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"Preserving the Power of Antibiotics"

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Emerging threats of antibiotics in the environment: what about the pharmaceutical industry?

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"Antibiotic resistance is no longer a prediction for the future."
The World Health Organization (WHO) 2014 report on Global Surveillance of Antimicrobial Resistance (AMR) revealed that: "It is happening right now, across the world, and it is putting at risk the ability to treat common infections in the community and hospitals"[1]. WHO and other eminent global health experts warn that we are at the dawn of a "post-antibiotic era". The UK Independent Review on AMR projects a worldwide death toll of 10 million people per annum by 2050, if resistance is left unchecked, with a cost of up to $100 trillion.

Several interconnected human, animal and environmental habitats can contribute to the emergence, evolution and spread of AMR. Better managing this problem includes taking steps to preserve the continued effectiveness of existing antimicrobials such as trying to eliminate their inappropriate use in both human and veterinary medicine. Despite publication of WHO guidelines recommending the discontinuation of the prescription of antibiotics as growth factors, many countries do not comply and even plan to increase the use of those antibiotics in intensive industrial farming[2]. Pollution from inadequate treatment of industrial, residential and farm waste increases the spread of resistant bacteria in the environment. Numerous countries and several international agencies have now included a "One Health Approach" within their action plans to fight AMR. "One Health" is defined as a concept and approach to "designing and implementing programmes, policies, legislation and research, in which multiple sectors communicate and work together to achieve better public health outcomes". This term is now globally recognised, having been widely used in the EU and in the 2016 United Nations Political Declaration on AMR[3].

The natural environment presents a transmission route and a reservoir for resistant microorganisms. It is well known that such bacteria and antibiotic resistance genes (ARG) are ubiquitous in nature: they can indeed be found in high concentrations in clinical, industrial and urban wastewater, as well as in animal husbandry. Moreover, the environments frequently contain very high levels of antibiotics and pharmaceuticals[4,5,6,7]. One of the very first to take an interest, Larsson *et al* analysed pharmaceuticals in the effluent from a wastewater treatment plant serving approximately 90 bulk drug manufacturers in Patancheru, near Hyderabad, India which is a major production site of generic drugs for the world market[8]. The samples contained by far the highest levels of pharmaceuticals reported in any effluent. The high levels of several broad-spectrum antibiotics raise concerns about resistance development. The concentration of the most abundant drug, ciprofloxacin (up to 31,000 µg/l), exceeds levels toxic to some bacteria by over 1000-fold. In 2017, Lübbert *et al* sampled different sites and wastewaters in an urban Indian territory where a major production area is also settled for the global bulk drug market: they found that all environmental sampling sites were contaminated with very high concentrations of antimicrobials, in particular moxifloxacin, voriconazole and fluconazole; and that microbiological analyses revealed an extensive presence of Extended Spectrum Beta Lactamase (ESBL), Carbapenemase Producing Enterobacteriaceae (CPE) and non-fermenters in more than 95% of the samples[7]. The relative abundance of total ARG was 30-fold higher in river sediments within the city, compared to upstream sites.

"Information about the origin of Active Pharmaceutical Ingredients and the finished products that end up on our pharmacy shelves is kept confidential by drug firms."

Despite those studies, few actions have been taken to improve the situation. It was not until 2011 that a European action plan against AMR mentioned the problem of pollution from production sites. In 2013, a directive required member states to develop a strategic approach against water pollution by pharmaceutical substances within two years. One of the measures envisaged plans to include environmental criteria in the guides to "Good Manufacturing Practice". However, the opacity is such that to date it is almost impossible to obtain manufacturing traceability and therefore it is actually difficult for a pharmaceutical firms to follow compliance with environmental standards. Information about the origin of Active Pharmaceutical Ingredients (APIs) and the finished products that end up on our pharmacy shelves is kept confidential by drug firms, which are unwilling to open up their supplier relationships to public scrutiny. Regulators, who could easily demand greater transparency from the pharmaceutical industry, have so far shied away from taking action[9].

Practical proposals could be made: hospitals could revise supply policies to integrate environmental clauses into their specifications for antimicrobial purchases. They could blacklist polluting companies and more legal means should allow agencies to sue companies for ecocide. Under these conditions, the question of the relocation of production factories must be asked by pharmacists and prescribers, who do not have an ethical vocation to be at the origin of the worldwide dissemination of AMR. The COVID-19 crisis, which also results in drug shortages, could be a trigger for this movement towards greater security of medicine supply.

However, these concerns no longer apply only to low- to middle– income countries (LMICs) where hygiene and sanitation may be lower. Czekalski *et al* showed increased levels of multi drug resistant (MDR) bacteria and ARGs after wastewater treatment and dissemination into Lake Geneva, in Switzerland[4]. Finally, it must be remembered that healthcare settings themselves may act as a potential reservoir for environmental pollution with MDR or even hospital-acquired outbreaks with MDR pathogens[10, 11, 12].

To conclude, we have to act on different scales in human medicine, in farms and in our environment, by limiting antibiotic consumptions and effluents, and improving surveillance and research in these areas. In 2018, WHO issued a public document whose target is to improve awareness and to educate any kind of healthcare worker to fight AMR[13]. And we can also get involved as a prescriber and a citizen, by asking for transparency on our antimicrobial market, and on the management of pharmaceutical industry effluents.
We should start acting rapidly to protect our whole world from the threat of AMR in every setting of our life.

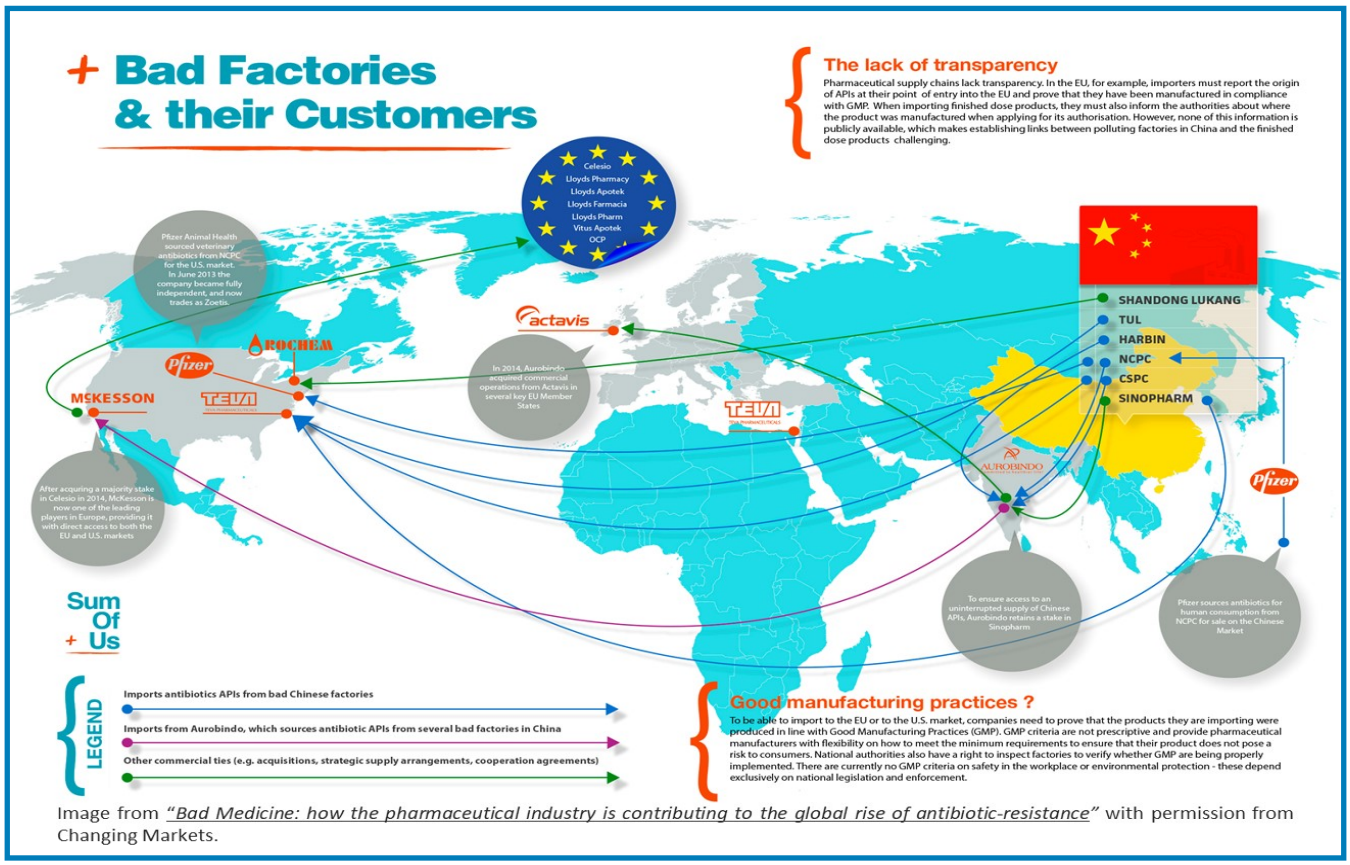
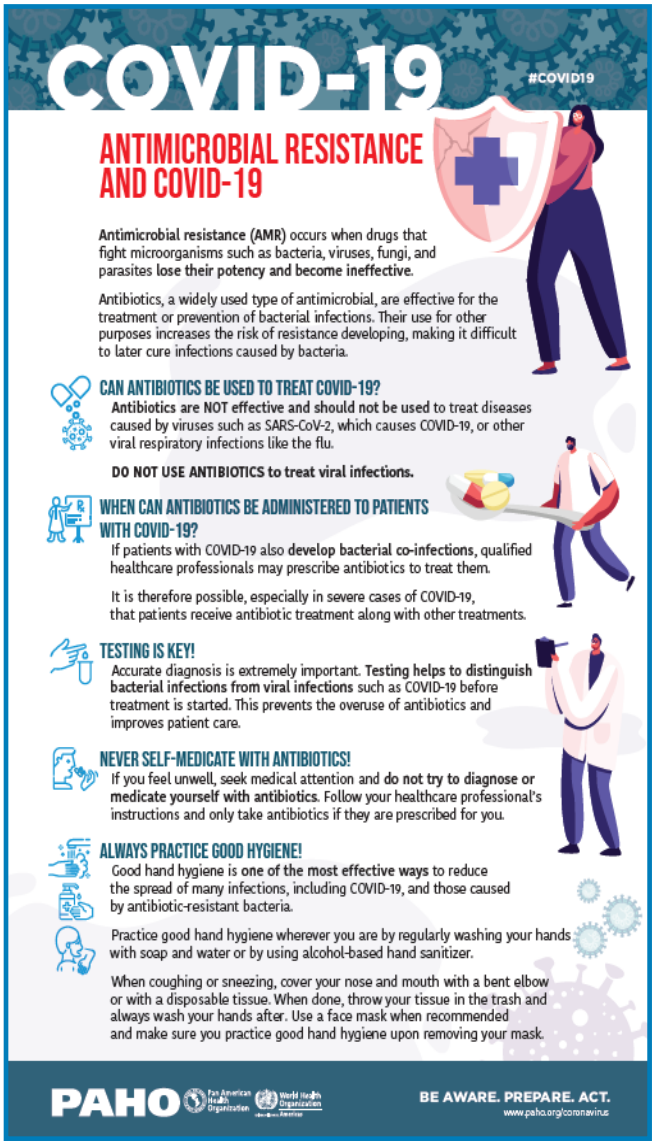


Image from *"Bad Medicine: how the pharmaceutical industry is contributing to the global rise of antibiotic-resistance"* with permission from Changing Markets.

References

1. World Health Organization. Antimicrobial resistance: global report on Surveillance. April 2014
2. Aidara-Kane A *et al*. World Health Organization (WHO) guidelines on use of medically important antimicrobials in food-producing animals. *Antimicrob Resist Infecti Control.* 2018;7:7
3. European Commission. A European One Health Action Plan against Antimicrobial Resistance (AMR). 2017
4. Czekalski N *et al.* Increased Levels of Multiresistant Bacteria and Resistance Genes after Wastewater Treatment and Their Dissemination into Lake Geneva, Switzerland. *Front Microbiol*. 2012;3:106
5. Larsson DGJ. Pollution from drug manufacturing: review and perspectives. *Philos Trans R Soc B Biol Sci*. 2014;369:20130571
6. Waseem H *et al*. Antimicrobial Resistance in the Environment. *Water Environ Res* 2017;89:921–941
7. Lübbert C *et al*. Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. *Infection* 2017;45:479–491
8. Larsson DGJ *et al*. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Hazard Mater*. 2007;148:751–755
9. Changing markets and Ecostorm. Impacts of pharmaceutical pollution on communities and environment in India. February 2016
10. Ory J *et al.* Ciprofloxacin residue and antibiotic-resistant biofilm bacteria in hospital effluent. *Environ Pollut*. 2016;214:635-645
12. Carling PC. Wastewater drains: epidemiology and interventions in 23 carbapenem- resistant organism outbreaks. *Infect Control Hosp Epidemiol* 2018;39:972–979
11. Marathe NP *et al*. Sewage effluent from an Indian hospital harbors novel carbapenemases and integron- borne antibiotic resistance genes. *Microbiome*. 2019;7:97
13. World Health Organization. WHO competency framework for health workers' education and training on antimicrobial resistance. 2018



Events

GARDP | Developing antibiotics for children
Medical need and regulatory challenges
28 October 2020 | Webinar

World Antimicrobial Awareness Week 2020
18—24 November 2020

National OPAT Conference 2020
2 December 2020 | Virtual Event
A global overview of drug development and effective use through diagnostics, stewardship and shared learning.

BSAC Spring Conference 2021
1 March 2021
50 years of BSAC. Details to follow

Association of Medical Microbiology & Infectious Diseases Canada Annual Conference
25—30 April 2021 | Virtual Event

18th Asia Pacific Congress of Clinical Microbiology & Infection
11—13 November 2021 | Singapore

19th International Symposium on Staphylococci and Staphylococcal Infections
28—31 August 2022 | Perth, Australia
ISSSI 2022 will cover many interdisciplinary subjects regarding staphylococci and staphylococcal infections.

A Multidisciplinary, French-speaking course on Antimicrobial Stewardship in Africa: the MUFASA Project

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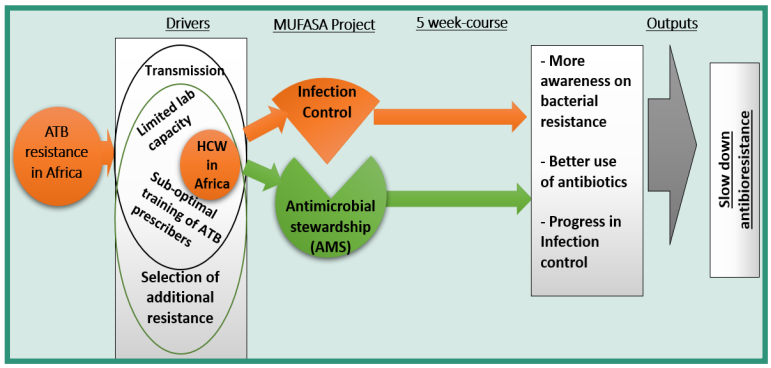
The "Multidisciplinary, French-speaking course on Antimicrobial Stewardship in Africa" (MUFASA) is a capacity building project to raise awareness and provide basic skills to healthcare workers who may promote antimicrobial stewardship (AMS) in sub-Saharan Africa.

The emergence of antimicrobial resistance (AMR) is a public health issue worldwide and may be of special concern in countries with limited access to microbiological documentation, sub-optimal surveillance of antibiotic use / bacterial resistance, uncontrolled use of broad-spectrum antibiotics and repeated unavailability of antibiotics[1]. Low- and middle-income countries, including most of sub-Saharan Africa, fulfil all these criteria[2]. Although robust data on AMR in sub-Saharan African remain scarce[3], especially in the community[4], the high prevalence of faecal carriage of multidrug-resistant bacteria in travellers returning from Africa in the absence of any additional risk factor[5], provides robust evidence that Africa is disproportionately affected by this scourge.



To address this public health issue, various initiatives have emerged in recent years including massive open online courses[6], lobbying for dedicated funding[7,8] and innovative networking activities, including toolboxes and guidelines to support developing AMS programmes within hospitals in developing countries[1,9-12]. However, healthcare workers active in the field have almost no opportunity for practical training including direct exchanges with peers and experts in the field[13-15].

Annually since 2017, the MUFASA project gathers 50—55 healthcare workers from 15—20 sub-Saharan African countries during five consecutive weeks to develop their awareness and skills on the development and the implementation of AMS programmes in Africa.

Objectives

1. To raise awareness on the extent of AMR in Africa, its determinants and what may be done in the field to reverse these trends.
2. To provide basic knowledge about microbiology, infection control, as well as infectious diseases diagnosis, treatment and prevention, so that the participants will be empowered to promote AMS in their own environment.
3. To develop skills for the design and implementation of AMS programmes taking into account local context and potential collaborators.
4. To train the participants in communication and advocacy of AMR and AMS so their training will benefit themselves and also their colleagues and their patients when performing their routine activities.

We expect i) a better use of antibiotics not only by the participants when they return from the course, but also by their peers and students through the trickle-down effect; and ii) progress in infection control to reduce the emergence of AMR in sub-Saharan Africa.

Assessment of Need

Due to the scarcity of data available on AMS programmes[11] and AMR[3,4] in Africa, baseline data were limited when the MUFASA project was initiated. In addition, initial metrics were crippled by the broad heterogeneity not only from one country to another but also according to the settings (community vs hospital, primary care vs referral centres, rural vs urban, etc.). The need for intensive efforts on AMS programmes in Africa was evident for all experts in the field[8], even in the absence of reliable quantitative baseline data for most countries.

Target Audience

Specific attention is paid to include a broad spectrum of healthcare workers involved in AMS (e.g. physicians from various medical specialties, pharmacists,

biologists, nurses, midwives and hospital administrators). In each country, key opinion leaders and stakeholders are invited to participate either directly in the course and / or in selecting candidates. Selecting candidates takes into account the quality and the background of the candidates, their contribution to fighting AMR, the needs of each participating country, with a fair balance regarding gender, religion, countries and age.

The MUFASA project trains participants from sub-Saharan African, French-speaking countries including Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Cote d'Ivoire, Democratic Republic of Congo, Gabon, Guinea, Bissau Guinea, Equatorial Guinea, Mali, Mauritania, Niger, Rwanda, Senegal and Togo. Participation is not restricted to French-speaking countries but as the training is performed in French, candidates who are not able to speak and understand French cannot be selected. As we aim to impact AMS at the country level, enhancing the trickle-down process of the knowledge, we prioritise key opinion leaders and / or healthcare workers who fight AMR in their country and positively influence their peers.

Participants of the 3rd Multidisciplinary, French-speaking course on Antimicrobial Stewardship in Africa, Bobo Dioulasso, Burkina Faso, 2019

The participants, their colleagues, the patients they manage, the community healthcare settings in which they work and their relatives all benefit from the MUFASA project because AMR is transmissible. AMR is a public health issue and impacts the population as a whole, in line with the One Health approach. Hence, AMS programmes, if successful, will be beneficial to the population as a whole.

Innovation

The MUFASA project presents four major assets:

1. It deals with a neglected target, in terms of intervention for AMS programmes: healthcare workers in French-speaking countries of sub-Saharan Africa.
2. This project builds upon a robust collaborative experience within the same partners, of three consecutive courses on AMS, in 2017, 2018 and 2019 which were highly successful, despite limited support, at a lower scale than the MUFASA project (see: Announcement of French-speaking AMS training in Africa and 2018 programme)
3. Burkina Faso has engaged in a voluntary monitoring of country progress on AMR (see the website)
4. Gathering healthcare workers from different sub-Saharan Africa countries with faculty members from Africa and Europe will stimulate interactive activities that engage learners, help them reflect on current practices with their peers and identify the gap between their current performance and the gold standard.

Funding

The MUFASA project is supported by the French Society of Infectious Diseases (*Société de Pathologie Infectieuse de Langue Française*), the University Nazi Boni of Bobo Dioulasso (Burkina Faso), the Ministry of Health of Burkina Faso, Mérieux Fondation (France), ICI-Santé (Public Health Technical Support Agency, Ouagadougou, Burkina Faso), the University of Montpellier (France) and the West African Organization on Health (*Organisation Ouest Africaine de la Santé, OOAS,* Bobo Dioulasso, Burkina Faso).

References

1. Levy Hara G *et al*. Ten key points for the appropriate use of antibiotics in hospitalised patients: a consensus from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy. *Int J Antimicrob Agents*. 2016;48:239-46
2. Cox JA *et al.* Antibiotic stewardship in low- and middle-income countries: the same but different? *Clin Microbiol Infect.* 2017;23:812-8
3. Okeke IN *et al.* Growing problem of multidrug-resistant enteric pathogens in Africa. *Emerg Infect Dis.* 2007;13:1640-6
4. Ouedraogo AS *et al.* Emergence and spread of antibiotic resistance in West Africa: contributing factors and threat assessment. *Med Sante Trop*. 2017;27:147-54
5. Ruppe E *et al*. High Rate of Acquisition but Short Duration of Carriage of Multidrug-Resistant Enterobacteriaceae After Travel to the Tropics. *Clin Infect Dis*. 2015;61:593-600
6. Sneddon J *et al.* Development and impact of a massive open online course (MOOC) for antimicrobial stewardship. *J Antimicrob Chemother*. 2018;73:1091-7
7. Mendelson M *et al.* JA. A Global Antimicrobial Conservation Fund for Low- and Middle-Income Countries. *Int J Infect Dis*. 2016;51:70-2
8. Laxminarayan R *et al*. UN High-Level Meeting on antimicrobials--what do we need? *Lancet*. 2016;388:218-20
9. Goff DA *et al*. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. *Lancet Infect Dis*. 2017;17:e56-e63
10. Howard P *et al.* ESGAP inventory of target indicators assessing antibiotic prescriptions: a cross-sectional survey. J Antimicrob Chemother. 2017;72:2910-4
11. Howard P *et al.* An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemotherapy. 2015;70:1245-55
12. Pulcini C *et al.* Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. Clin *Microbiol Infect*. 2019;25:20-25
13. Davey P *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. *The Cochrane database of systematic reviews.* 2017;2:Cd003543
14. Castan B *et al.* [Antibiotic stewardship: A 2017 update]. Med Mal Infect. 2017;47:439-42
15. Ouedraogo AS *et al*. High prevalence of extended-spectrum ss-lactamase producing enterobacteriaceae among clinical isolates in Burkina Faso. BMC Infect Dis. 2016;16:326

Bacteriophages: when history can save the future

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It is undeniable that we live amidst an era of grave antimicrobial resistance (AMR). It is estimated that there are 700,000 deaths per year due to multidrug-resistant organisms (MDRO) infections and by 2050, 10 million people will die annually from infections by MDRO[1]. The antimicrobial crisis was highlighted by the World Health Organization (WHO) in two recent reports on preclinical and clinical antibacterial pipelines. Currently, 32 antibiotics in the clinical pipeline that target WHO's priority pathogens have little benefit compared to existing ones, and only two are active against difficult-to-treat Gram-negative bacteria[2]. In light of the devastating toll caused by MDRO, the world is in dire need of an alternative to antibiotics.

In recent years, combatting AMR focussed on the introduction of new antibiotics in the pipeline, the use of combination therapy, the re-introduction of old antibiotics and other antimicrobial stewardship (AMS) efforts. Bacteriophages present a different therapy concept that may play a role in dealing with the AMR crisis while supporting AMS principles.

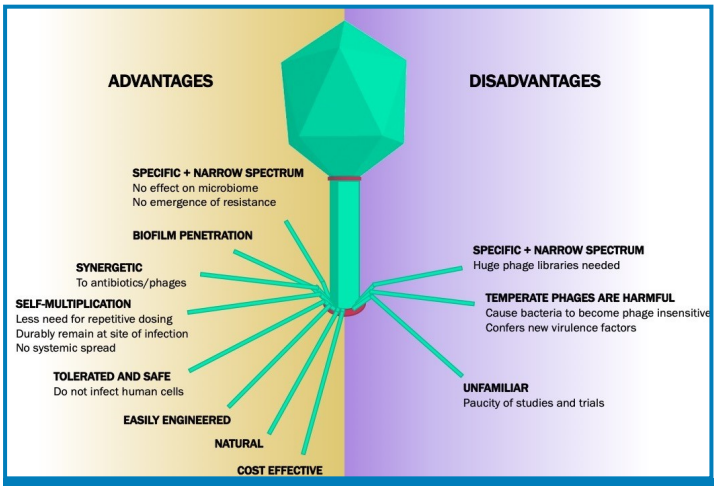


Figure: Advantages and disadvantages of bacteriophage therapy

Bacteriophages are viruses that infect and replicate only in bacterial cells and are highly abundant in nature. The first encounter with bacteriophages dates back to 1906, when Félix d'Hérelle discovered these peculiar viruses and began experimenting with them, ultimately coining the term "bacteriophage" (or "to eat bacteria")[3]. During World War I, d'Hérelle concocted phage preparations to treat soldiers with dysentery and later collaborated with George Eliava to found the Bacteriophage Institute (now known as the Eliava Institute) in Tbilisi, Georgia in the 1940s. d'Hérelle's discovery spread to the Western world and research was ongoing globally[3]. However, the discovery of penicillin after World War II caused the interest in phages to dwindle in the West and the era of antibiotics took off. After 80 years, and with the emergence of AMR, scientists regained interest in bacteriophages. They have already been approved in the food industry[4], agriculture[5] and in the treatment of infections caused by MDRO in many Eastern European countries[6]. Currently, the biggest phage libraries are in Tbilisi and Wroclaw.

All bacteriophages are composed of a nucleic acid genome that can be single- or double-stranded DNA or RNA, and a protein capsid encapsulates the genome. Tail fibers are engaged to initiate binding and match a specific receptor on the bacterial cell wall[7]. Thus, a single bacteriophage can infect a limited number of bacterial strains, and this property determines its absolute specificity.

Phages are divided according to their biological cycles: virulent (or lytic) and temperate (or lysogenic) bacteriophages. Virulent bacteriophages inject the genome inside the bacterial cell, which redirects the bacteria to produce and release new virions that will lyse and kill the bacteria. The newly formed bacteriophages would then infect other bacterial cells[8]. In contrast, temperate bacteriophages integrate their genetic material into the host bacterium without inducing the production of new phages. The host cell becomes a prophage, or a carrier, which transmits the viral genome to daughter cells with each mitotic division. Under certain conditions, the viral genome from the prophage can be detached from the bacterial DNA and induce entry into the lytic stage[8]. Only virulent bacteriophages can be used in the clinical setting as they are able to kill bacteria.

The application of phage therapy is currently being investigated worldwide, with more than 20 registered clinical trials for different infection sites and with different phage formulations, such as whole genome, engineered phages or phage lysins[9].

Phage therapy has been used in various infectious diseases. Most studies that have addressed skin and soft tissue infections showed favourable results, such as treating infected venous ulcers[10,11] and burns infected with MDR *Pseudomonas aeruginosa* (MDRPA)[12]. However, some studies failed to prove effectiveness.

This was partly explained by the low dose and instability of the bacteriophage preparation, which could have led to decreased viral titres throughout the treatment period[13].

Bacteriophages were also studied in respiratory infections, particularly in cystic fibrosis (CF) patients and lung transplant recipients with recurrent infections caused by MDRO, where no other therapeutic modalities were efficacious. In one study, aerosolised bacteriophages were administered and both the bacterial concentration in the respiratory secretions and the antibiotic need were reduced[14]. Real-life experience with intravenous phage therapy showed promising results in a CF patient with recurrent MDRPA[15] and a disseminated *Mycobacterium abscessus* infection following lung transplant[16].

Device-related infections, such as left ventricular assist devices (LVAD)[17] and aortic graft infections[18], are often challenging to treat due to biofilm formation. Therapeutic concentrations of antibiotics are unable to penetrate biofilms because of poor permeability and the inability to metabolize its constituents[18]. The phage OMKO1 was demonstrated to reach *P. aeruginosa* strains inside the biofilm successfully and was able to replicate within the bacterial cells, leading to the biofilm disruption. This property is synergistic with antibiotics as it would allow therapeutic concentrations of the antibiotics to reach target bacteria in the biofilm[18].

Urinary tract infections caused by MDRO are increasing. The first trial with phage therapy against resistant uropathogens is currently underway in Russia. (ClinicalTrials.gov Identifier: NCT03140085).

To date, the evidence indicates that bacteriophage therapy is very safe with little disadvantages (Figure). Theoretically, there are no bacteria that cannot be lysed by at least one bacteriophage. The specificity of bacteriophages offers an advantage compared to antibiotics because the former will not affect the microbiome[19]. They are natural products that are well -tolerated and easily administered. They can also be easily engineered to increase their effectiveness. On the other hand, the unfamiliarity with bacteriophages engenders hesitation, calling for rigorous studies to guide future therapy.

As interest in bacteriophages is growing, scientists and clinicians are increasingly considering their use in clinical practice. Major western universities, such as the University of California, San Diego and others, have already established centres for engineered bacteriophages. In addition, pharmaceutical companies are closely following the development in the field to decide on whether this area would be worth investing in for the future. The increasing knowledge of these microorganisms will soon provide us with a clearer picture of their clinical application. It is now time to consider what history might have provided as a solution to the inevitable rise in AMR.

References

1. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. *Review on Antimicrobial Resistance* 2016
2. The antimicrobial crisis: enough advocacy, more action. *The Lancet* 2020;25;395:247
3. Chanishvili N. Phage therapy—history from Twort and d'Herelle through Soviet experience to current approaches. *Adv Virus Res* 2012;83:3–40
4. Moye ZD *et al*. Bacteriophage Applications for Food Production and Processing. *Viruses* 2018;10:205
5. Svircev A *et al*. Framing the Future with Bacteriophages in Agriculture. *Viruses*. 2018;25:10
6. Furfaro LL *et al*. Bacteriophage Therapy: Clinical Trials and Regulatory Hurdles. *Front Cell Infect Microbiol* 2018;8:376
7. Elbreki M *et al.* Bacteriophages and Their Derivatives as Biotherapeutic Agents in Disease Prevention and Treatment. *Journal of Viruses* 2014
8. Salmond GPC *et al*. A century of the phage: past, present and future. *Nat Rev Microbiol* 2015;13:777–86
9. Gill JJ *et al*. Bacteriophages and phage-derived products as antibacterial therapeutics. *Expert Opin Ther Pat* 2007;1;17:1341–50
10. Markoishvili K *et al*. A novel sustained-release matrix based on biodegradable poly(ester amide)s and impregnated with bacteriophages and an antibiotic shows promise in management of infected venous stasis ulcers and other poorly healing wounds. *Int J Dermatol* 2002;41:453–8
11. Rhoads DD *et al*. Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial. J *Wound Care* 2009;18:240–3
12. Abul-Hassan H *et al*. Bacteriophage Therapy of Pseudomonas Burn Wound Sepsis. *Ann Mediterr Burns Club* 1990;3:262–264
13. Jault P *et al*. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect Dis* 2019;19:35–45
14. Kutateladze M *et al.* Bacteriophages as potential new therapeutics to replace or supplement antibiotics. *Trends Biotechnol* 2010;28:591–5
15. Law N *et al.* Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant Pseudomonas aeruginosa infection in a cystic fibrosis patient. Infection. 2019;47:665–8
16. Dedrick RM, *et al*. Engineered bacteriophages for treatment of a patient with a disseminated drug resistant Mycobacterium abscessus. *Nat Med* 2019;25:730–3
17. Aslam S *et al.* Novel bacteriophage therapy for treatment of left ventricular assist device infection. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 2019;38:475–6
18. Chan BK *et al*. Phage treatment of an aortic graft infected with Pseudomonas aeruginosa. *Evol Med Public Health* 2018;2018:60–6
19. Domingo-Calap P *et al*. Bacteriophages: Protagonists of a Post-Antibiotic Era. *Antibiotics* 2018;7:66

Antibiotic Resistance in the News

Antimicrobial resistance centre renamed after APUA founder, Stuart Levy

The Center for Integrated Management of Antimicrobial Resistance, a collaborative effort supported by Tufts University and Tufts Medical Center, has been renamed the Stuart B. Levy Center for Integrated Management of Antimicrobial Resistance (Levy CIMAR) in tribute to APUA founder and antibiotic resistance pioneer, Stuart Levy.

Levy CIMAR builds on Levy's work and takes a One Health approach to antimicrobial resistance (AMR) research, policy recommendations and educational programmes. A virtual event to celebrate the renaming was attended by colleagues, friends and family. Read the full story on "Tufts Now".

Study reveals >50% of COVID-19 patients received antibiotics

Out of 1,705 COVID-19 patients from 38 Michigan hospitals, 56.6% were prescribed antibiotics amidst concern they had a coinfection. However, according to the *Clinical Infectious Diseases* study, only 3.5% had a confirmed community-onset bacterial coinfection. Antibiotic use different greatly across hospitals – from 27%-84%. The authors conclude that reducing COVID-19 test turnaround time and supporting stewardship could improve antibiotic use.

AMS in the ICU during COVID-19—back to the 90s?

The use of antimicrobial drugs during COVID-19 highlights the importance of upholding antimicrobial stewardship (AMS) principles according to a new paper published in *Intensive Care Medicine*. Many AMS strategies developed and implemented in the past decade have been ignored as the pandemic spread and although it is challenging to apply the concepts used outside of pandemics, rational infection management remains of utmost importance. The authors outline the challenges in applying AMS concepts, offer potential solutions and identify research priorities for strengthen AMS during COVID-19.

Study reveals widespread broad-spectrum antibiotic use in COVID-19 patients

The authors of an article published in *Journal of Antimicrobial Chemotherapy* used a 16-question survey to investigate antibiotic prescribing practices in COVID-19 patients who received antibiotic therapy for suspected or confirmed bacterial superinfection of the lung or sepsis. The survey, completed by 166 participants across 82 hospitals, found 61.8% reported the existence of local guidelines for antibiotic use in COVID-19 patients but 82.9% stated they did not differ from local community-acquired pneumonia guidelines. Clinical presentation was recognised as the most important reason for starting antibiotics. Combinations of β-lactams and macrolides or fluoroquinolones were reported by 52.4% of respondents. In the intensive care unit, piperacillin / tazobactam was the most commonly prescribed antibiotic. The mean reported duration of antibiotic treatment was 7.12 days. Implementation of antimicrobial stewardship principles is warranted to mitigate the negative consequences of antibiotic therapy.

Inappropriate antibiotic therapy for bloodstream infections

A retrospective study published in *The Lancet Infectious Diseases* analysed electronic health records from 131 US hospitals and included 21,608 patients with bloodstream infections (BSI) who received empirical antibiotic therapy. Of these patients, 4,165 received discordant empirical antibiotic therapy. Discordant empirical therapy was shown to be independently associated with increase risk of mortality, a relationship that was unaffected by the presence or absence of resistance or sepsis or septic shock. Most incidences of discordant empirical antibiotic therapy and associated deaths occurred among patients with bloodstream infections caused by *Staphylococcus aureus* or Enterobacterales.

British Poultry Council report on sustainable use of antibiotics

The British Poultry Council's (BPC) antimicrobial stewardship (AMS) report highlights progress made regarding antibiotic use by the UK poultry meat sector in the last seven years. The BPC AMS has helped achieve a 76% reduction in the total use of antibiotics and 97.3% reduction in the use of critically important antibiotics. In 2019, the sector used 19.7 tonnes of antibiotics which accounts for 9.33% of total antibiotics licensed for food producing animals (Source VMD). British BPC Chief Executive, Richard Griffiths, said: "With poultry being half the meat eaten in the UK, the BPC's AMS plays a vital role in delivering good bird health and welfare; ensuring the sustainable and responsible use of antibiotics, safeguarding the efficacy of antibiotics, and helping produce food consumers trust."

Sweden tackles reducing antibiotics in food-producing animals

Together with companies, academia, authorities, industry and civil society, Axfoundation, an independent not for profit organisation, has developed Antibiotics 2.0 – a tool for the food industry to set requirements for suppliers of meat, dairy and seafood in terms of antibiotic use and animal welfare. The original version was developed in 2013 and a stricter version of the criteria was published in Autumn 2020. The updated version also includes a questionnaire to support buyers in their dialogues with suppliers.

Barriers to outpatient antibiotic stewardship

Pew Charitable Trusts and the American Medical Association conducted a national survey of 1,550 primary care physicians to better understand the attitude of doctors toward antibiotic resistance (AMR), inappropriate antibiotic prescribing and need for / impact of antimicrobial stewardship (AMS). Although physicians recognise AMR and inappropriate prescribing, 55% did not see a problem in their own practices and 60% of respondents believe they prescribe antibiotics more appropriately than their peers. The lack of recognition of their own contribution to inappropriate antibiotic prescribing could be a barrier to implementing AMS initiatives. Respondents strongly supported patient education as an AMS initiative and indicated that a wide range of approaches carried out by health care stakeholders could spur AMS implementation at the practice level. Overall, the survey found a clear need to improve antibiotic prescribing in outpatient health care settings.

WHO guidelines against universal recommendation of mass drug administration of azithromycin

New WHO guidelines on mass drug administration (MDA) of azithromycin to children under five years old recommends a targeted approach for MDA-azithromycin for prevention of childhood mortality in low- to middle- income countries.

The second recommendation offers guidance on a highly selective set of conditions in which MDA-azithromycin might be considered. The evidence-based guidelines focussed on three randomized trials looking at the effect of MDA-azithromycin in children. All studies reporting that MDA-azithromycin had an impact on mortality were conducted in sub-Saharan African countries with high under-five child mortality rates. Two out of three of the showed that MDA-azithromycin led to reduced child mortality.

Animal health professionals crucial in fight against AMR

The American Veterinary Medical Association (AVMA) has released its inaugural report on Antimicrobial Resistant Pathogens Affecting Animal Health in the United States which details the impact of AMR bacteria on different animal species across the country and the antimicrobial stewardship efforts that can be used by vets, producers, breeders and animal owners to curb the rise of AMR. Species include cats and dogs, cattle, chicken and turkeys, fish and shrimp, sheep and goats, horses and swine. Each species has a host-specific summary that identifies pathogens of concern, resistance profiles and prevention actions.

Paediatric antibiotic prescribing in Germany decreases

Authors of a study published in *Eurosurveillance* assessed recent trends in outpatient antibiotic prescribing in children in Germany aged between 0-14 years old (n = 9,389,183) from 2010 - 2018. Prescription rates were calculated by age group (0-1, 2-5, 6-9 and 10-14). Across all age groups, prescriptions decreased significantly by 43% with the largest reduction noted in the 0-1 and 2-5 age groups. Cephalosporins accounted for 32% of prescribed antibiotics. Although the reductions are significant, prescription rates of cephalosporins remains high in Germany compared with other European countries suggesting frequent first-line use of these substances for common respiratory infection.

Study suggests need to introduce safe antibiotic thresholds in sewage

New research published in *Communications Biology* indicates that current thresholds may not be sufficient to prevent evolution of resistance. The authors tested five antibiotics grouped within three commonly-used classes of antibiotics – macrolides (azithromycin, clarithromycin and erythromycin) fluoroquinolones (ciprofloxacin) and tetracycline. The macrolides and ciprofloxacin are included on the European Commission Water Framework Directive's Priority Substances Watch List due to concerns about their toxicity to aquatic life. The team investigated the lowest concentrations at which resistance to antibiotics evolved in complex communities of bacteria present in wastewater and found ciprofloxacin concentrations similar to those found in the environment did drive increased antibiotic resistance, whereas macrolides did not. This suggests that thresholds specific to the need to be set specific to the type of antibiotic need to be set.

FDA to expand efforts to track AMR in foodborne pathogens

The National Antimicrobial Resistance Monitoring System (NARMS) is a collaboration between the U.S. Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the U.S. Food and Drug Administration (FDA), and state and local health departments to monitor resistance in enteric bacteria from humans, retail meats and food-producing animals. Under a new strategic 5-year plan, the scope of NARMS will include more bacterial pathogens, more animal species and resistant bacteria found in the environment. The plan emphasises a more One Health perspective. The efforts will include collaboration with the Environmental Protection Agency to monitor surface waters for antibiotic-resistant pathogens, the creation of a testing programme for resistant bacteria in animal feed and pet food and the addition of routine surveillance testing of seafood products and imported foods.

Report outlines ideas to improve UK's AMR response

The latest report from Reform, a think tank for the public sector, looks at the UK's role and contribution to the global response on antimicrobial resistance (AMR). The report, which contains a foreword from Professor Dame Sally Davies, UK Special Envoy on AMR, acknowledges progress achieved by the UK to tackle AMR and outlines areas in need of attention. It advises the Government to harness the lessons from the COVID-19 crisis to inform its approach to AMR. In particular, the pandemic's impact on increased public awareness of infection prevention and control, the crucial role of rapid diagnostics, antibiotics and vaccines, and the importance of prompt, wide-reaching and coordinated policy action for addressing public health challenges.

Antibiotics linked to higher risk of inflammatory bowel disease

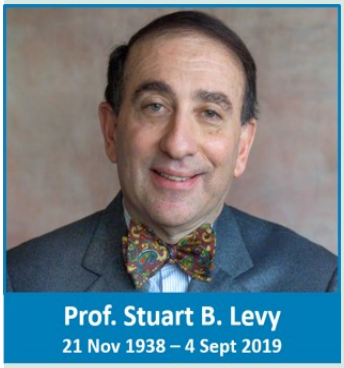
A study published in *The Lancet Gastroenterology and Hepatology* showed antibiotics are associated with an increased risk of inflammatory bowel disease (IBD). The authors identified 23,982 new patients living in Sweden over the age of 16 with IBD (15,951 ulcerative colitis, 7,898 Crohn's disease, 133 unclassified IBD) and compared them with 28,732 siblings and 117,827 controls. The increased risk of IBD was nearly two times higher in those who had previously used antibiotics versus those who had not. The increased risk was noted for both ulcerative colitis and Crohn's disease with the highest estimates corresponding to broad-spectrum antibiotics.

Study on global impact of antibiotic waste

The University of the West of Scotland is teaming up with the Indian Institute of Technology to assess antibiotic pollution and its role in fuelling antimicrobial resistance.

The research aims to assess the impact of increasing levels of antibiotic pollution entering waterways and the role that plays in enabling bacteria to resist the effects of medication. It also aims to design effective measures for monitoring antibiotic levels and removing them from waste. The interdisciplinary team comprises experts on sensor technologies, water treatment, remediation, environmental microbiology and meta-omics, geochemistry and waste management. It will also involve policy and industrial regulatory experts to help shape policy and improve regulatory control.

APUA News



Remembering Stuart Levy

It has been just one year since Stuart Levy passed away but it already seems so long ago. Since then, the world has been confronted with an unprecedented pandemic situation which has kept us all so busy that we hardly find time to relax.

Stuart left us just before a small virus would lead to one of the most dramatic revolutions in our society. Many paradigms have been changed at a pace none of us would have expected. The economic, educational, cultural activities, work, leisure, sports, national and international exchanges, and many other pillars of our modern civilisation, have been jeopardised.

Looking back to the special tribute newsletter we wrote collectively one year ago, under the flag of APUA as a tribute to Professor Stuart Levy and his key publications, feels like a return to our roots. Most of the topics covered in these pages remain contemporary and of high value. We will most likely see the end of the COVID-19 pandemic, hopefully before the second anniversary of Stuart Levy's death, and we will then have to boost actions for better use of antibiotics worldwide, a topic sadly neglected over the last months. By that time, all the basics and principles established by Stuart Levy and others will help us to rebuild our collective actions and thrive.
Meanwhile, we hope you all keep safe so that we have the pleasure to meet again!

New APUA Article on AMS

APUA Board members, ISAC Executive Committee members and other antimicrobial stewardship (AMS) experts, co-authored an article on advocacy for increased international efforts for AMS in low– to middle– income countries (LMICs).

The article, published in *Frontiers of Medicine*, found that AMS programmes effective in high-income (HIC) countries may not perform as well in LMICs. Despite the need to individually tailor AMS programmes in LMICs, international collaborations remain highly valuable through the dissemination of high-quality documents and educational material, that may be shared, adapted where needed and adopted worldwide.

New APUA Board Member

APUA is delighted to welcome new member, Jeroen Schouten, to the APUA Board.

Jeroen is an Intensive Care Physician and Senior Researcher at IQ Health Care, Radboud University, Nijmegen Medical Centre in the Netherlands.

He is also is a member of Dutch guideline committees for community-acquired pneumonia, sepsis and antibiotic stewardship for the Dutch Working Group for Antibiotic Policies (SWAB). Additionally, Jeroen is currently Chair of European Study Group for Antimicrobial Stewardship (ESGAP) and Chair of the Antimicrobial Stewardship Programme at Radboudmc.

With his expertise in Antimicrobial Stewardship, Jeroen will be a great addition to the team.

New APUA Nepal Newsletter

APUA-Nepal
Alliance for the Prudent Use of Antibiotics

APUA Nepal has published its own newsletter annually since 2009 to update its members about recent activities, the antimicrobial resistance (AMR) scenario in Nepal and the latest advances in the field of AMR. The 17th issue has just been published and includes an update on the sensitivity patterns of common isolates in urine and blood from hospitals of in Nepal.

Recent activities

- Publication and distribution of Vol 16 of APUA-Nepal Newsletter to different medical colleges and hospitals.
- Participation in a high-level advocacy meeting on national antimicrobial consumption monitoring, Ministry of Health and Populations Nepal (MOHP) /World Health Organization (WHO), July 2019.
- Participation in National Action Plan-AMR (draft) workshop, MOHP / WHO, August 2019.
- Participation in launching Health Workers' Education and Training on AMR: Curricula Guide, WHO, October 2019.
- Participation in National Action Plan-AMR finalisation workshop, MOHP/WHO, November 2019.

We also request anyone working in the field to join us and become a member of APUA Nepal.

ISAC Society News

ISAC COVID-19 Symposium

ISAC invites you to join its free, live webinar, **COVID-19: Around the World in 80+ Minutes.** This unique webinar will bring you a global view of the pandemic from those on the frontline in diverse parts of the world. It will cover aspects of epidemiology and genomics, screening, control, treatment and consequences of infection. The speakers, all leaders in their fields, have a unique perspective of how the pandemic affects their region. Each session will be 15 minutes and we invite you to comment online. We plan to incorporate the presentations and discussion into an ISAC Academy web tutorial. We look forward to seeing you on the webinar.

The webinar will take place on **25 November 2020** at **noon (12.00) GMT.** **Click here to register.**

New dates 32nd International Congress of Antimicrobial Chemotherapy (ICC)

Due to the current COVID-19 situation, the ICC which was scheduled to take place in November 2021 will now take place from **26—30 November 2022**. The meeting will take place in Perth, Australia.

The meeting is co-hosted by the Australian Society for Antimicrobials (ASA) and is also in affiliation with Asian Pacific Society for Clinical Microbiology and Infection (APSCMI). Register your interest at www.32ICC.org

New ISAC Member Societies

We are delighted to announce three new ISAC Member Societies:

1. The Danish Society for Clinical Microbiology (DSKM)

President: Michael Pedersen

DSKM is the Danish specialist scientific society for clinical microbiology. For more information on DSKM, visit the website.

2. Ghana AMR Platform

President: Martha Gyansa-Lutterodt

The Ghana AMR platform is a multi-stakeholder platform of all entities affected and or impacted by the AMR phenomenon. It is part of the governance structure for the implementation of the National Action Plan (NAP).

3. Iranian Society for Medical Bacteriology (ISMB)

President: Abdolaziz Rastegar lari

ISMB works to provide a platform for proper communication amongst bacteriologists for better research and education. Visit the society's website.

Honorary doctorate for Souha Kanj

Professor Souha Kanj, ISAC Executive Committee member and APUA Board member, received an honorary doctorate from Radboud University, Nijmegen, the Netherlands, at the university's 97th anniversary ceremony.

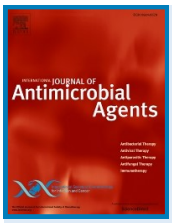
Souha has been head of the Infectious Diseases Department at the American University of Beirut Medical Center in Lebanon since 1998. She also holds an appointment at Duke University Medical Center in America.

Souha is an authority on the issue of global antibiotic resistance and published the first overview of antibiotic resistance in the Arab world. Notably, Souha was the first woman in the Arab world to lead an Infectious Diseases Department. Her work has led to Lebanon conforming to the World Health Organization (WHO) Guidelines for Hand Hygiene. She is directly involved in the fight against COVID-19 in Lebanon and is active within the WHO. She often works under difficult conditions in Beirut, which has not only been struck by an economic crisis, but also by the COVID-19 pandemic and most recently by a devastating explosion.

Watch Souha's inspiring acceptance speech here.

JGAR Dispatches

A new dispatches section has been launched in ISAC's open access journal, Journal of Global Antimicrobial Resistance (JGAR). "SARS CoV-2 Dispatches" welcomes short articles (up to 750 words) of relevant data and experiences on the pathogenesis, diagnosis, clinical management, epidemiology and surveillance of SARS-CoV-2.



IJAA Editor's Choice

Each month, Jean-Marc Rolain selects Editor's Choice articles for International Journal of Antimicrobial Agents (IJAA). Two articles were selected for the November issue. Read them for free:

1. Fosfomycin for Bacterial Prostatitis: A Review
2. New insights concerning *Acinetobacter* genomic island -related elements

New article by ISAC's IPC Working Group

The Infection Prevention & Control (IPC) Working Group assessed the perceptions of infection preventionists on the current global IPC preparedness measures for COVID-19. The authors conducted a cross-sectional, self-administered web-based survey study to gain a rapid insight into the preparedness of healthcare facilities and investigate current global practices and perceptions among IPC professionals concerning the prevention and control of COVID-19. The results are published in ISAC journal, *Journal of Global Antimicrobial Resistance*

New article by ISAC Rapid Diagnostics & Biomarkers Working Group

Novel rapid diagnostic tests (RDTs) offer huge potential to optimise clinical care and improve patient outcomes. In this study, the authors aimed to assess the current patterns of use around the world, identify issues for successful implementation and suggest best practice advice on introducing new tests. An electronic survey was devised by ISAC's Rapid Diagnostics and Biomarkers Working Group focussing on the availability, structure and impact of RDTs around the world. The results were published in the *European Journal of Clinical Microbiology and Infectious Disease.*

International Medical Association Bulgaria (IMAB) 30th Jubilee Annual Assembly

IMAB celebrated its 30th Jubilee in Varna, Bulgaria, 18-20 October 2020. The online forum attracted over 300 participants from 12 countries. 280 papers were presented in online sessions, with abstracts and discussions in round-tables via e-mail. The IMAB Jubilee Assembly proved that there were no barriers for colleagues, friends and members. The spirit of IMAB and its Jubilee Annual forum is a great example of how scientific meetings can occur in the time of COVID-19.

ASA: Antimicrobials Online

In lieu of a face to face annual scientific meeting, ISAC Member Society, Australian Society for Antimicrobials (ASA), has established Antimicrobials Online, an educational platform designed to facilitate the acquisition and dissemination of knowledge in the field of antimicrobials and to encourage communication and cooperation between those actively engaged.

Antimicrobials Online will typically provide monthly live 60 to 90 minutes educational sessions. All presentations will be recorded and will be available to all financial ASA members. In addition to the ASA educational sessions, ASA Foundation Members will hold industry sessions similar to the successful breakfast and lunch industry sessions held at the Society's annual scientific meeting.

Antimicrobials Online will provide peer-reviewed interactive poster sessions and networking opportunities for members. A virtual poster presentation will enable showcasing of research and discussion with colleagues.

The first session is a EUCAST Workshop which will take place on Thursday 12 November 2020.

ISAC Project Grants

Applications for grants to support antimicrobial research from ISAC Member Society applicants in low– to middle– income countries have now closed.
Interest was high and applications are now being reviewed by an independent panel of experts. Applicants will be contacted in due course. Thank you to everyone who applied.

About APUA

Founded in 1981 by Prof. Stuart B. Levy as a global non-profit organisation, APUA's mission is to maximise the effectiveness of antimicrobial treatment by promoting appropriate antimicrobial use and containing drug resistance. It was the first organisation to address antibiotic preservation and continues to provide a strong voice in the field despite the subsequent emergence of many other organisations and groups addressing a topic which has become a specialty in its own right; that of "antibiotic stewardship".

APUA has affiliated Chapters in 19 countries. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, healthcare providers, consumers and policy makers worldwide.

Prof. Levy's retirement was announced towards the end of 2018. This was an opportunity for the APUA Board to review its leadership and governance and it took the opportunity to seek a partner organisation with which to synergise. This led to the merger of APUA with the International Society of Antimicrobial Chemotherapy (ISAC), effective from February 2019.

About ISAC

ISAC was founded as a non-profit organisation in 1961 and, in response to the dynamic nature of the subject matter, has focused most recently on antimicrobial stewardship and antimicrobial resistance.

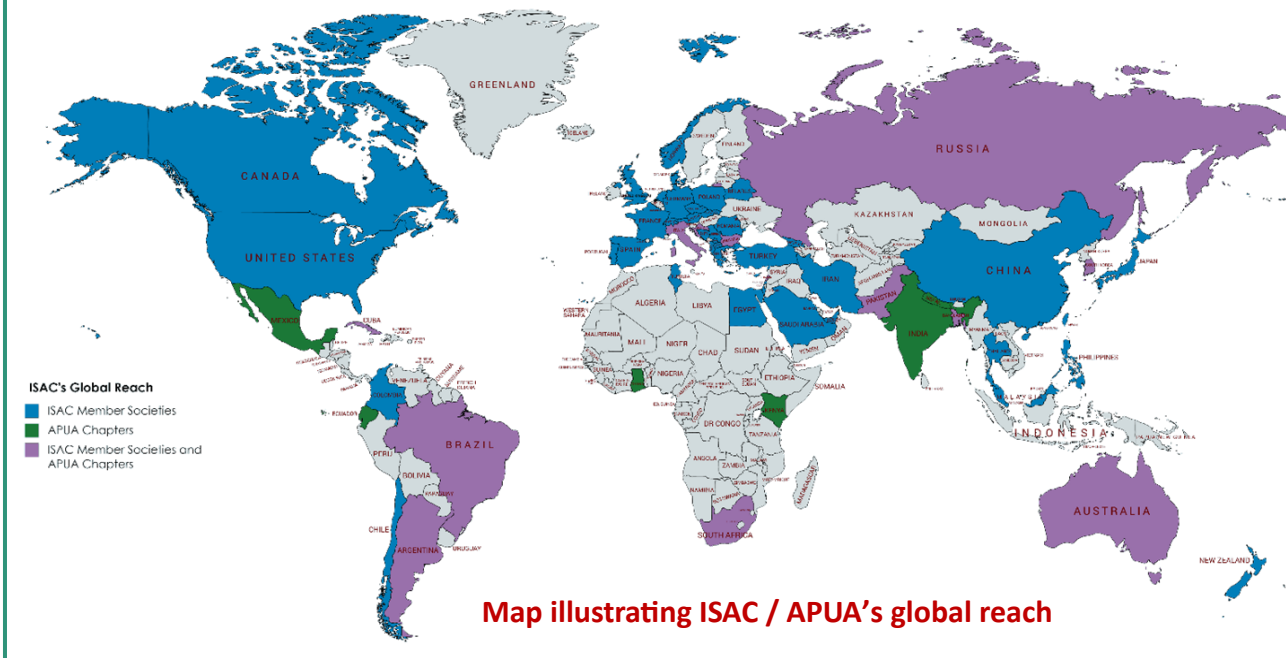
ISAC is a federation of affiliated Member Societies which aims to increase the knowledge of antimicrobial chemotherapy and combat antibiotic resistance around the world.

ISAC currently has a worldwide membership of 92 national and regional societies, which in turn have over 50,000 individual members.

ISAC has two society journals:

- International Journal of Antimicrobial Agents (IJAA)
- Journal of Global Antimicrobial Resistance (JGAR) - gold open access

ISAC's scientific congress, International Congress of Antimicrobial Chemotherapy (ICC), is held every two years and it is now in its 32nd year.



Map illustrating ISAC / APUA's global reach