



Newsletter

Volume 41, No. 1 • Spring 2023

In this issue...

2 - 3 A new resistance combatting strategy Robin Patel

International Society of Antimicrobial Chemotherapy

4-5 Antimicrobial treatment of *Pseudomonas* aeruginosa severe sepsis

Johnny Zakhour, Sima L. Sharara, Joya-Rita Hindy, Sara F. Haddad, Souha S. Kanj

6

7

HAPPY PATIENT project: an update

Carl Llor, Lars Bjerrum, Pierre Tattevin

The ISAC Early Career Working Group: providing support to the next generation of researchers

Jinxin Zhao, Yu-Wei Lin, Nusaibah Abdul Rahim, Iris Minichmayr

ISAC / APUA News

- 8 9 Antimicrobial resistance in the news
- 10-13 ISAC / APUA news
- 14 About ISAC / APUA







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A new resistance combatting strategy



Based on the Hamao Umezawa Memorial Award (HUMA) lecture at the ICC, Australia, November 2022

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The global antimicrobial resistance (AMR) crisis is a major Creative use of technology can help; fortunately, we are in threat to human health. In a recently published article, the a technology revolution. There have been major advances Antimicrobial Resistance Collaborators estimated that in the application of proteomics, nucleic acid amplification 4.95 million deaths were associated with bacterial AMR in tests and sequencing-based diagnostics, microbial imaging, 2019¹. These numbers are predicted to increase year by microbial metabolomics and advanced host response year. AMR has changed the way medicine is practiced. For assessment for infectious diseases in recent years, and example, infections previously treated with oral antibiotics point-of-care diagnostics are in the process of transforming now require injectable treatment and, because whether an where testing can be done (including at non-traditional antimicrobial resistant bacterium may be involved is often sites and in the home). In my view, we need to rethink unknown when therapy is initiated, unnecessarily broad- approaches to the challenge of AMR by practicing medicine spectrum antibiotics are oftentimes prescribed, or in a more modern way using better diagnostics to inform alternatively, the prescribed regimen may not even treat antimicrobial therapy. the infection because of unrecognised underlying resistance. In addition, antibiotics are frequently Modern diagnostic tests can help curb emergence of AMR administered to patients who do not need them because by informing improved use of antibiotics (a patient and they do not have a bacterial infection.

societal benefit), leading to avoidance of unneeded testing and treatment (a patient benefit), decreasing transmission

AMR involves hundreds of microbial species, dozens of of infectious diseases (a societal benefit) and informing new

antimicrobial agents and a multitude of clinical syndromes (e.g., pneumonia, urinary tract intra-abdominal infection, infection). The WHO's Priority Pathogens List for new antibiotics and the United States Centers for Disease Control and Prevention's



discoveries and better delivery of healthcare (which will have future benefits). A decade ago, the first large multiplex PCR panel was cleared / approved by the United States Food and Drug Administration (FDA) for testing positive blood culture bottles. Our team executed a

"urgent", listings, albeit slightly different, of resistant bacteria, but do that its implementation would reduce unneeded use of not comprehensively list all possible species or resistance- antibiotics and more quickly get patients with drugtypes involved. While development of new antibiotics and resistant infections on appropriate antibiotic therapy². In antimicrobial stewardship are essential to address this study, results of multiplex panel testing were provided evolving situation, better diagnostics and appropriate use with interpretive comments with therapeutic guidance, an thereof are an additional strategy that needs to be better approach recently supported by a recommendation from incorporated.

medicine (Figure 1), taught to medical students and applied was blaKPC, for which there were no detections²; due to infection (step 1: based on history, physical controlled study evaluated rapid microbial imaging-based examination, initial tests); what the causative pathogen(s) phenotypic susceptibility testing for patients with blood molecular testing for microorganisms); and finally, which time to first antibiotic modification was faster with the treatment should be administered (step 3: based on culture rapid test for all antibiotics and Gram-negative antibiotics, -based antimicrobial susceptibility testing). This classic with antibiotic escalation being faster for antimicrobialapproach, although intellectually interesting, is at once resistant infections⁴. contributing to the AMR crisis and failing because of it.

"serious" and "concerning" threats provide randomised controlled clinical trial of this panel showing the Diagnostics Committee of the Antibacterial Resistance Leadership Group³. In the multiplex PCR panel study, the The classic three-step diagnostic paradigm used in clinical only Gram-negative resistance marker included in the panel by medical professionals throughout the world, involves accordingly, effects on antibiotic use in Gram-negative asking whether a patient's clinical presentation could be bacteraemia were minimal. A second randomised might be (step 2: based on culture, serologic testing, cultures positive for Gram-negative bacilli; in that study,

The blood culture diagnostics highlighted above (although performed after incubation of blood cultures) illustrate an important pathway forward that is, detecting microorganisms and immediately defining their clinically relevant antibiotic susceptibility. This has been



transformation of healthcare). Beyond eliminating a third step, in the future, the first two steps (shown in yellow and green) will likely be consolidated to one.

microorganisms and directly call out ideal therapy in a single step (Figure 2), socalled, microbial "theranostics". То move forward, we need continued development of better diagnostics combined with changes in the way healthcare is delivered, facilitated by

SA SSTI assay (which detects Staphylococcus aureus and methicillin resistance / susceptibility) and MTB/RIF assay (which detects Mycobacterium tuberculosis and rifampin resistance /susceptibility). Our group recently described an 2. assay for detection of Helicobacter pylori and associated / susceptibility⁵, clarithromycin resistance and 3. Mycoplasma pneumoniae and associated azithromycin resistance / susceptibility⁶; assays to detect ciprofloxacin 4. resistance / susceptibility in Neisseria gonorrhoeae and azithromycin resistance in Mycoplasma genitalium are other examples of this approach.

Beyond nucleic acid amplification-based microbial 6 detection and gene- or mutation-based characterisation of resistance, microbial sequencing directly from clinical 7. specimens is being developed, and can theoretically both detect the infecting organism(s) and characterise resistance / susceptibility to clinically relevant antibiotics. In a case report, for example, Mycoplasma salivarium was identified as a cause of periprosthetic joint infection, using shotgun metagenomic sequencing, with simultaneous detection of a mutation associated with macrolide ^{10. Cunningham SA et al.} Core genome multilocus sequence typing and antibiotic resistance'. The possibility of going from microbial sequence data to near-full recapitulation of results of phenotypic susceptibility may be realised in the future, especially with improved understanding of resistance mechanisms and advanced analytics⁸⁻¹¹. This may in turn facilitate rapid full recapitulation of phenotypic susceptibility testing in a clinically actionable way, directly from clinical specimens^{12, 13}. In addition, deep sequencing may allow simultaneous assessment of microorganisms and host response, helping with interpretation of clinical significance of detected microorganisms^{14, 15}.

Finally, in addition to transforming clinical practice and optimising use of antibiotics, improved diagnostics may deliver new findings, as illustrated by the surprising discoveries of Borrelia mayonii¹⁶, Yersinia rochesterensis¹⁷, and the cause of hyperammonemia syndrome in lung 18. Wang X et al. Ureaplasma parvum causes hyperammonemia in a transplant recipients - Ureaplasma urealyticum and Ureaplasma parvum¹⁸⁻²⁰.

In summary, because of improved diagnostic testing, we 20. Bharat A et al. Disseminated Ureaplasma infection as a cause of fatal are positioned to undo the classic (and slow) diagnostic paradigm (Figure 1), using diagnostics that detect

delivered by tests such as the GeneXpert (Cepheid) MRSA/ better diagnostics and necessary to harness their value.

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Antimicrobial treatment of Pseudomonas aeruginosa severe sepsis

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Introduction

Pseudomonas aeruginosa (P. aeruginosa) is a major cause combinations of nosocomial infections, particularly bloodstream and ticarcillin-clavulanate), antipseudomonal cephalosporins respiratory infections, with a high mortality rate of up to (ceftazidime, 30%¹. It has intrinsic resistance to many antimicrobials and antipseudomonal carbapenems (doripenem, meropenem, can quickly develop resistance to most available imipenem). If possible, cephalosporins should be favoured antibiotics². With the spread of highly resistant strains, the over carbapenems for their higher potency, narrower risk of inappropriate empiric treatment is increasing, and spectrum, and lower tendency to induce resistance⁸. has been correlated with increased mortality, especially in Antipseudomonal AG (gentamicin, tobramycin, amikacin) severe infections like sepsis³. Difficult to treat (DTR) should only be used in combination therapy except for P. *aeruginosa* is a recent definition that indicates resistance urinary tract infections (UTIs)⁹. piperacillin-tazobactam, ceftazidime, to meropenem, imipenem-cilastatin aztreonam, quinolones, and is used in most current guidelines⁴.

Empirical Antimicrobial Treatment (EAT)

EAT in severe sepsis should be chosen according to the patient's allergies, comorbidities, primary site of infection, prior antibiotic exposure, and most importantly, local susceptibility patterns.

Combination therapy for *P. aeruginosa* sepsis may decrease the risk of inadequate EAT by combining mechanisms of action. However, the evidence regarding the efficacy of combination EAT is conflicting. While one Cochrane review comparing beta lactam monotherapy and combination with

(BL/BLI) (piperacillin-tazobactam and cefepime and cefoperazone) and

Levofloxacin and cefepime, ciprofloxacin are currently the only available oral treatment and options for *P. aeruginosa* and should be spared for oral transitioning. Emergence of resistance is possible and should be highly suspected in patients who worsen despite appropriate therapy⁸.

P. aeruginosa resistant to first line therapy

P. aeruginosa may acquire resistance to carbapenems through various mechanisms such as production of a carbapenemase, outer membrane protein modification or efflux pumps (Table). The potential of co-resistance to multiple first-line agents, especially, between ceftazidime, piperacillin-tazobactam and meropenem is high. In those

aminoglycoside an (AG) showed similar mortality for patients with P. aeruginosa sepsis, another recent meta -analysis evaluating allmortality cause showed survival improved with combination $EAT^{5,6}$.

	C/T	CAZ/AVI	IMP/REL	Cefiderocol	Plazomicin	Fosfomycin	Colistin
Carbapenemase							
Class A (KPC)	No	Yes	Yes	Yes	Yes	Yes	Yes
Class B (MBL)	No	No	No	Yes	Variable	Yes	Yes
Class D (OXA)	No	Yes	No	Yes	Yes	Yes	Yes
OprD	Yes	Yes	Yes	Yes			
MexAB	Yes	No	Yes	Yes			
MexXY	Yes	No	Yes	Yes			
Table 1. Treatment options for Carbapenem-resistant <i>P. aeruginosa</i> according to mechanism of resistance. C/T, Ceftolozane-Tazobactam; CAZ/AVI, Ceftazidime- avibactam: IMP/REL. Imipenem-cilastatin-relebactam							

cases, escalation to secondwill line agents likelv outcomes¹⁰. improve Second-line agents include **BL-BLI** novel like ceftolozane-tazobactam (C/ T), ceftazidime / avibactam (CAZ/AVI) and imipenemcilastatin/relebactam (IMI/ REL) or the siderophore cephalosporin, cefiderocol².

Given the rise of antimicrobial resistance

(AMR), combination EAT should be highly considered in cases of severe sepsis to avoid inappropriate EAT'. Two different mechanisms of action should be combined, typically a backbone beta-lactam and a fluoroquinolone (FQ) or preferably, an AG. Prompt de-escalation to monotherapy with a narrower spectrum is highly advised once susceptibility results are available and source control is achieved.

Targeted therapy for P. aeruginosa sepsis P. aeruginosa sensitive to first line agents

First-line beta-lactam agents for P. aeruginosa coverage include beta-lactam / beta-lactamase-inhibitor

C/T has a high affinity to all penicillin-binding proteins (PBP) of P. aeruginosa and has been approved for complicated intra-abdominal infections (cIAI), UTIs, and hospitalacquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Favourable outcomes have been reported in clinical trials comparing C/T to other agents for P. aeruginosa HAP including VAP, cIAI, and UTIs. CAZ/AVI has also been approved by the FDA and EMA for the treatment of UTIs, cIAI and infections with resistant Gram-negative pathogens. C/T and CAZ/AVI have been considered key therapeutic agents and have greatly improved outcomes in patients with DTR P. aeruginosa. However, resistance to them has Conclusion started emerging¹¹.

Infectious Diseases (ESCMID) suggest treatment with C/T patients' outcomes and spared the adverse events of older treatment with either C/T, CAZ/AVI, or imipenem/ inappropriate antimicrobial therapy and prompt derelebactam for DTR P. aeruginosa infections outside the escalation when susceptibility results are available. urinary tract⁴. Although C/T is favoured over CAZ/AVI for *P*. aeruginosa, susceptibility to both agents should be References obtained as there are C/T-resistant CAZ/AVI-susceptible 1. Zakhour J et al. Antimicrobial Treatment of Pseudomonas aeruginosa strains¹³. Real world evidence has confirmed the efficacy of both¹.

Cefiderocol is recommended as an alternative to novel BL/ BLI by IDSA. Although there is concern about higher 4. Tamma PD et al. Infectious Diseases Society of America Antimicrobialmortality due to the CREDIBLE-CR trial's results, the number of patients with *P. aeruginosa* in that trial was small, hence, these findings may not be generalisable¹⁴. Cefiderocol remains an option, especially given its activity against metallo-beta lactamases (MBL).

significant concern. Aztreonam may resist hydrolysis by MBLs making it an attractive agent in combination with 7. CAZ/AVI¹⁵.

Although many guidelines recommend against the use of 8. Carmeli Y et al. Emergence of antibiotic-resistant Pseudomonas polymyxins they might be the only option for the treatment of DTR strains in low resource settings. Although intravenous Fosfomycin may be active against DTR P. aeruginosa, monotherapy is only indicated for cases of uncomplicated UTIs due to the risk of emergence of resistance¹⁶.

A single agent, preferably a beta-lactam, should be chosen for DTR isolates since definitive combination therapy has ^{11. Tamma PD} et al. Modifiable Risk Factors for the Emergence of not been shown to improve outcomes and may increase costs and adverse events¹.

Important key elements of therapy

The pharmacokinetics of most antimicrobials are altered 13. Teo JQM et al. Ceftolozane/Tazobactam Resistance and Mechanisms in following the hemodynamic changes of severe sepsis. Critically ill patients may require dose adjustments. For C/ T, higher doses (3g every 8 hours) are recommended in critically ill patients to maintain bactericidal serum concentration¹⁷.

Extended infusion (EI) of beta lactams may help achieve a 15. Lee M et al. Activity of aztreonam in combination with ceftazidimemore sustainable serum concentration and decrease the length of stay¹⁸. It is also recommended by IDSA and ESCMID for the treatment of non-susceptible strains⁴.

The duration of treatment should consider the primary site of infection, the patient's underlying comorbidities, source ^{17. Ruiz J et al.} Ceftolozane/Tazobactam Dosing Requirements Against control, susceptibility results, inflammatory biomarkers, and clinical response. Two to three weeks is currently 18. Thabit AK et al. The pharmacodynamics of prolonged infusion b-lactams recommended especially for immunocompromised patients and patients with pneumonia who are at risk of recurrence with shorter regimens¹⁹.

The burden of *P. aeruginosa* severe sepsis is worsened by The European Society of Clinical Microbiology and resistant strains. Novel treatment options have improved as the single first choice for severe DTR pseudomonal toxic drugs like polymyxins. Combination empiric therapy infections like severe sepsis¹². IDSA recommends should be initiated in critically ill patients to avoid

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HAPPY PATIENT project: an update

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Funded by the European Union, HAPPY PATIENT (The Health The first audit of the HAPPY PATIENT project took place a Patient-Centred Perspective) is led by the Catalan Health study was carried out (September 2021 - February 2022) to in five European countries.

appropriately and how to improve communication skills.

These intervention meetings started in September with a specific "train the trainees" course led by Sara-Anna Davies, The data that HAPPY PATIENT is collecting has already María Rodríguez Barragán, Nieves Barragán and Lucías Arias revealed a major part of the challenges European health as members of the Spanish Society of Family and Community Medicine (semFYC) and its Working Group Programme on these communication tools try to resolve doubts based on the Communication and Health.

Participants of the HAPPY PATIENT training sessions had the together with the rest of the consortium, have been opportunity to discuss the results of the first audit. All responsible for formatting the communication materials participants will be able to use the tools experts have presented to coincide with the European Day for the Prudent developed. Experts from five European countries (Spain, Use of Antibiotics (November 2022). Greece, France, Poland and Lithuania) have participated in a DELPHI study to establish a set of communication tools to The six HAPPY PATIENT communication materials address the achieve the prudent use of antibiotics. The idea is to keep doubts and problems that may exist at different levels of care, health professionals and patients informed and improve from Primary Care to Nursing homes through to Pharmacies, communication. The materials are limited to the work of the and offer handy knowledge guides specially designed for use HAPPY PATIENT European project, are available in different by professionals who carry out their activity in each one of languages and provide reliable, helpful and contrasted these areas. information on antimicrobial resistance (AMR) and prescriptions.

The HAPPY PATIENT project aims to reduce the unnecessary prescription of antibiotics in five countries of the European Union which have worrying consumption levels. To achieve • Interventions covering the results of the first audit in the this, the consortium is developing various interventions with health professionals with multiple levels of care in the continent where these drugs are prescribed (Primary Care, Primary Care Emergency Services, Nursing Homes and Community Pharmacies).

In this first phase of the project, Lithuania and Spain have contributed the most participants - 105 and 109 respectively. Poland has contributed 80 participants, France has contributed 58 and Greece has contributed 54.

By medical specialties, family doctors or general practitioners • have so far contributed 146 participants (almost 40% of the community pharmacies have total). contributed • approximately 30% of participants, and, the other levels of care contributing participants have been the emergency • Preparation of the second audit will start in February 2023. services of the first level of care and nursing homes (30%).

Alliance for Prudent Prescription and Yield of Antibiotics from between February and May 2022. Previously, a qualitative Institute (ICS) and the IDIAPJGol Research Institute, and it develop communication tools. To optimise the results and seeks to reduce unnecessary prescription of antibiotics by 40% achieve the objectives, the HAPPY PATIENT consortium used an adaptation of the DELPHI methodology, where a panel of experts prioritised predefined misconceptions regarding the To achieve this goal, a total of 406 participants have been use of antimicrobials. This methodology, which includes participating in several intervention meetings of the HAPPY feedback and dialogue between the different experts, resulted PATIENT European project on how to use antibiotics more in the messages to be used in the communication tools developed in HAPPY PATIENT.

> professionals face when prescribing antibiotics. Therefore, evidence collected so far. Based on these differences and peculiarities, the University of Copenhagen and the semFYC,

Keynotes of ongoing activity

- By the end of 2022, interventions were made in three countries. In January 2023, the remaining two interventions were completed.
- four settings in five different countries with feedback and discussion of these results and an intervention in a courseworkshop to improve communication taught by two professionals trained by the semFYC Communication and Health Group (training course for trainers carried out during the month of September 2022).
- Preparation of e-learning material with clinical cases, questions and communication videos uploaded on the Moodle E-learning platform.
- Preparation of specific publications based on the results of the first audit.
- Results of antibiotic inappropriateness for each setting in the different countries.



The ISAC Early Career Working Group: providing support to the next generation of researchers

Jinxin Zhao, Yu-Wei Lin, Nusaibah Abdul Rahim, Iris Minichmayr

The ISAC Early Career Working Group Officers

There has never been a more critical time than now for the organised by the EC Working Group. next generation of researchers, clinicians and clinical pressing challenges due to current global health and biodiversity threats and, in turn, requires next-generation scientists to be fully engaged in continuous advanced training during the early stages of their careers. With the support of the International Society of Antimicrobial Chemotherapy ISAC Young Ambassadors should become a member of an (ISAC) Executive Committee, we have established this affiliated society of ISAC in their country, although the aims of international collaboration amongst early-career researchers these may vary depending on the needs of each location and

research and serve as a platform for communication between early-career and senior scientists. Aligning with aims of ISAC, the ISAC Early Career (EC) Working Group aims to promote continuous education for young scientists and the general public to advance training in the science of antimicrobial infections. Importantly, we intend to provide opportunities for young experts worldwide to build long-lasting networks for collaboration.

actively involved in ISAC's programmes. As of 2022, its members were from 18 countries, reflecting the global importance of ISAC and the ISAC EC Working Group for facilitating outreach, networking, collaboration and advanced itself, are supported as they continue their journey with the training for the next generation of scientists working in society and can become involved with its other committees. infectious diseases.

In 2022, the ISAC EC Working Group successfully held a workshop for early-career scientists at the 32nd International Congress of Antimicrobial Chemotherapy (ICC). It included scientific presentations by ISAC / ICC Travel Grant awardees as well as a panel discussion by Professor Robin Patel. Following this event, the EC Working Group assisted in the early-career researchers session at the 1st International Conference on Antimicrobial Computational Pharmacology (ICAComP). Some of the EC Working Group's leadership team (Drs Nusaibah Abdul Rahim and Yu-Wei Lin) shared their experiences with other attendees.

In addition, the group is organising a monthly webinar series that will focus on 'When pharmacometrics and systems pharmacology meet infectious diseases' to provide members and attendees with cutting-edge techniques and their applications in the field of infectious diseases. Visit the ISAC YouTube Channel to watch the three webinars already

pharmacists in the field of antimicrobial chemotherapy, in the The ISAC EC Working Group is also planning other early stages of their careers, to keep up with novel techniques programmes and activities, which will be implemented very and to ensure a timely response in meeting current global soon. Once of its exciting programmes aims to foster the next health threats. Infectious diseases, as a discipline, is facing global generation of scientists by establishing academic and clinical collectives that will bring together researchers, clinical pharmacists and clinicians to form the ISAC International Young Ambassadors Programme.

that will help to address the challenges in antimicrobial community. In general, early-career researchers engaged in

The ISAC Early Career **Working Group** represents the interests of young ISAC members in the field of infectious diseases.

this programme will have the opportunity to develop essential skills outside the training curriculum; including teamwork, scientific writing, improvement of communication skills, participating in and organising meetings, and expanding personal and professional networks. If you are interested in becoming an ISAC Young Ambassador of your country, please email your CV and a letter of support to earlycareer@isac.world.

The ISAC EC Working Group will also work with ISAC Since its establishment, the ISAC EC Working Group has been committee members to feature in journals and newsletters relevant to ISAC and have a presence on the website to share information on activities and opportunities. This will ensure that early-career researchers are able to engage with ISAC

> Building on ISAC's notable successes in promoting education and research, together, we aim to advance the education and training of the next generation of professionals in the field of infectious diseases. Through the ISAC partnership, we hope to contribute to advancing both the quality and quantity of education, which will be a substantial investment for the future of infectious disease research.

> Throughout the year, you can stay connected with the ISAC EC Working Group via our social media platforms (Twitter / LinkedIn / Website) By signing up to our social platforms, you will be the first to hear about what is coming up, and you can also contribute with ideas and feedback. What are you waiting for? Get involved now!

> The ISAC EC Working Group is always happy to welcome new members; both students and early-career scientists. If you are interested in joining the ISAC EC Working Group, please email your CV to and earlycareer@isac.world

Antibiotic Resistance in the News

UN calls to reduce pollution to decrease AMR

A new report from the UN Environment Programme (Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance ([AMR]) highlights that AMR cannot be addressed separately from the triple planetary crisis of climate change, biodiversity loss, and pollution and waste. As well as presenting a comprehensive overview of scientific findings, it calls for priority action to address key pollution sources from poor sanitation, sewage; community and municipal wastes; healthcare delivery; pharmaceutical manufacturing; intensive crop, and terrestrial and aquatic animal production sectors.

Using a 'One Health' approach to AMR will not only help reduce the risk and burden of AMR on societies but will also help address the triple planetary crisis.

Antibiotics in food-producing animals to increase by 2030

Authors of a study in <u>PLOS Global Public Health</u> used statistical models and country reports of veterinary antimicrobial usage (AMU), regional totals of AMU from the World Organization for Animal Health (WOAH), and on-farm AMU surveys, to estimate global antimicrobial usage in food-producing animals between 2020 and 2030 in 229 countries.

Based on current trends, global AMU is predicted to increase by 8% from 99,502 tonnes in 2020 to 107,472 tonnes by 2030.

In 2020, China, Brazil, India, USA and Australia were the top five AMU consumers, accounting for 58% of global AMU. By continent, Asia had the highest consumption (59%), 56% of which was from China alone. Africa, Oceania and South America, despite lower absolute AMU, were predicted to have higher relative increases of AMU (25%, 16% and 14% respectively).

By class, Tetracyclines were the most used antimicrobial (33,305 tonnes) and use is predicted to increase by 9% by 2030. This varied by country. Of note, Pakistan exhibited the highest consumption of penicillin.

Prospective audit and feedback in COVID-19 patients

Researchers of a <u>Lancet Microbe study</u> assessed the efficacy of prospective audit and feedback within an antimicrobial stewardship programme (ASP) for adults hospitalised in Edmonton, Canada, for the treatment of COVID-19 pneumonia. Patients were randomly assigned to the prospective audit and feedback plus standard of care group or the standard of care alone group.

301 audit and feedback events were recorded in the intervention group and 215 recommendations were made, of which 84% were accepted. Recommendations included discontinuing antibiotics when no bacterial infection was suspected or confirmed, or shortening the duration of therapy in alignment with guidelines.

Despite lower antibiotic use in the intervention group than in the control group (364·9 vs 384·2 days per 1,000 patient days), there was no impact on the clinical condition of patients which shows that prospective audit and feedback is safe and effective in optimising and reducing antibiotic use in adults admitted to hospital with COVID-19.

AMR high in patients with COVID-19 and bacterial infections

Authors of a study in the <u>Lancet Microbe</u> performed a systematic review and meta-analysis of bacterial co-infections (identified within \leq 48 h of presentation) and secondary infections (>48 h after presentation) in outpatients or hospitalised patients with COVID-19. Authors included 148 studies (362,976 patients) from over 40 countries. The prevalence of bacterial co-infection was low at 5.3%, whereas the prevalence of secondary bacterial infection was higher at 18.4%. Patients in ICUs were at higher risk of bacterial infection than general hospitalised populations (38.9% vs8.4%).

42 of the studies included comprehensive data for the prevalence of antimicrobial resistance (AMR) amongst bacterial infections. Amongst people with bacterial infections, the proportion of infections that were resistant to antimicrobials was 60.8% and the proportion of isolates that were resistant was 37.5%. Compared with the Americas region, the odds of antibiotic-resistant isolates were higher in studies done in the Eastern Mediterranean, South-East Asia and Western Pacific regions. Increased AMR was associated with a low-income or middle-income setting, being in an intensive care unit, interleukin-6 inhibitor use and diabetes.

Assessment of AMR national action plans

Several countries have national action plans (NAPs) for guiding national strategy and action on antimicrobial resistance (AMR) but this is the first comprehensive analysis of the plans. Using a governance framework containing 18 domains and 54 indicators, the authors of a study in <u>Lancet Infectious Diseases</u> reviewed 114 NAPs, looking at three main areas: policy design, implementation tools, and, monitoring and evaluation.

Using a scale of 0 – 100 (worst to best), the mean antimicrobial AMR governance score was 51 with considerable variance between countries. Norway had the highest score (85) and the Federated States of Micronesia had the lowest (28). The highest scoring domain was participation (83) and the lowest scoring domains were accountability (30) and feedback mechanism (30). Domains relating to policy design and implementation tools scored similarly (55/54), whereas monitoring and evaluation efforts were lower (38). This is an area which needs to be improved for continuous understanding of national and international progress. These data suggest that the international response might not correspond with the scale / severity of AMR.

New WHO antibiotic book on common infections

The <u>WHO</u> AWaRe (Access, Watch, Reserve) antibiotic book provides short, clinical guidance on the management of 30 of the most common infections (adults and children), including recommendations for empiric antibiotic treatment at the first clinical presentation and when a "no antibiotic" approach is appropriate. Guidance is also given on the dosage and the treatment duration.

The AWaRe book is intended for all health care workers who prescribe and dispense antibiotics in high-, middle- and lowincome settings in both the primary health care and the facility / hospital setting. The information included in the book supports the recommendations for antibiotics listed on the WHO Model Lists of Essential Medicines and Essential Medicines Children and the WHO AWaRe classification of antibiotics.

Carriers of MDR bacteria at higher risk of infection

Authors of a systematic review in the <u>Lancet Infectious Diseases</u> aimed to determine if carriers of multidrug-resistant Gramnegative bacteria (MDR-GNB) or vancomycin-resistant enterococci (VRE) in the intestinal tract were at higher risk of developing infection during hospital admission.

The review covered data from 44 cohort studies from 14 countries from 1995 – 2022. Overall, 14,049 carriers were included in the meta-analysis: 5,015 VRE carriers and 9,034 MDR-GNB carriers.

The authors found the risk of infection with MDR-GNB is on average 14% within 30 days in hospitalised patients (19% for patients with carbapenem-resistant *Enterobacterales* [CRE] and 8% for VRE). These differences are important for guiding infection control strategies, such as screening and adjustment of antibiotic treatment to colonisation status.

The risk is considered high when compared to "clean" postsurgery infections which only is 1–3% at 30 days and comparable with surgical site infections after contaminated or "dirty" surgical procedures (18–25%).

Antibiotics can increase risk of IBD in older adults

Frequent antibiotic use for gut infections increases the risk of developing inflammatory bowel disease (IBD) in adults aged \geq 40 years according to a study in <u>Gut</u>.

Data on 6,104,245 Danish citizens who had not been diagnosed with IBD aged ≥ 10 years from 2000 – 2018 were included. During this period, 36,017 new cases of ulcerative colitis (UC) and 16,881 new cases of Crohn's disease (CD) were diagnosed. Of the individuals included, 90.9% received at least one course of antibiotics. Authors studied the timing, dose and class of antibiotics to determine if these impacted IBD development.

Antibiotic use was associated with an increased risk of IBD as compared with no antibiotic use for all age groups, although the greatest association was in those aged over 40. Those aged 10-40 were 28% more likely to be diagnosed with IBD versus 48% of 40-60 year olds. This risk was highest in the years immediately following antibiotic use (1 - 2 years), persisted across antibiotic classes affecting the gastrointestinal microbiome and was associated with the development of both UC and CD.

GLASS report shows increase in BSIs

The fifth <u>WHO Global Antimicrobial Resistance and Use</u> <u>Surveillance System (GLASS)</u> report summarises 2020 data on antimicrobial resistance (AMR) rates in common bacteria from countries, territories and areas. This version of the report brings new features, including analyses of population testing coverage or AMR trends. For the first time, the report presents 2020 data on AMC at the national level. A new interactive dashboard allow users to explore AMR and AMC global data, country profiles and download the data.

Of note, although most resistance trends have remained stable over the past four years, bloodstream infections due to resistant *Escherichia coli* and *Salmonella* spp. and resistant gonorrhoea infections increased by at least 15% compared to rates in 2017. More research is needed to identify the reasons behind the observed AMR increase.

Scale to asses AMR awareness

Authors of an article in <u>Journal of Antimicrobial Chemotherapy</u> used a 23-item antibiotic resistance (ABR) scale to assess ABR awareness amongst human healthcare practitioners (HHCP) and animal healthcare practitioners (AHCP) licensed to prescribe and dispense antibiotics in Ghana, Nigeria, Tanzania, Vietnam, Thailand and Peru. The scale, a self-administered questionnaires, comprised four modules: demographics, ABR awareness, practice items and context items.

Overall, 941 HCPs (625 human and 316 animal) were included. The ABR awareness scale had high-reliability coefficients (0.88 for human and 0.90 for animal HCPs) but performed better within countries than across countries.

Using a scale of 0-100, median ABR awareness scores were 54.6–63.5 for human HCPs and 55.2–63.8 for animal HCPs. Physicians and veterinarians scored higher than other HCPs in every country tested. Around two-thirds of respondents felt the information received on ABR was not adequate to inform their day-to-day practice. More than 95% of HCPs were interested in receiving information or training on ABR and antimicrobial stewardship.

Using the scale alongside context questions and objective measurement of practices is recommended to inform interventions to improve antibiotic use.

Appropriate antibiotics for BSIs lowers mortality risk

A study published in <u>JAMA Open Network</u> found appropriate antimicrobial therapy is associated with lower in-hospital mortality in patients with bloodstream infections (BSIs).

The analysis included 32,100 adult patients with BSIs from 183 US hospitals who received at least one new antimicrobial within two days after blood samples were collected during hospitalisation. Patients were divided into three infection groups: gram-negative rods (GNRs [46.6%]), gram-positive cocci (GPC [52.5%]) or *Candida* species (0.9%). Patients were further divided into those who did, and those who did not receive appropriate initial antimicrobial therapy. Appropriate antibiotic therapy use was 94.4% for GNRs, 97.0% for GPC and 65.1% for *Candida* species. The most common pathogens were *Escherichia coli* (58.4%) and *Staphylococcus aureus* (31.8%).

In-hospital mortality rates for the appropriate antimicrobial group versus the inappropriate empirical therapy group were 12.8% vs 20.7% for GNR, 14.8% vs 21.1% for GPC and 23.7% vs 34.3% for *Candida* species.

Global study on AMS programmes

A study in <u>JAMA Open Network</u> found a positive association between antimicrobial stewardship programmes (ASP) and antibiotic use globally in both hospital and nonhospital settings.

Authors analysed 52 studies (40 conducted in high income countries and 12 in low- and middle income countries) comprising 1,794,889 participants to determine the link between ASPs and antimicrobial consumption.

ASPs were associated with a 10% reduction in antibiotic prescriptions and a 28% reduction in antibiotic consumption. For settings, the largest reduction in antibiotic consumption associated with ASPs, was in paediatric hospitals at 21%. A 28% reduction was observed in World Health Organization watch groups antibiotics with high resistance potential.

The impact assessment of ASPs in resource-limited settings, where antibiotic use is high, remains scarce.

Society News

New ISAC President



We are delighted to announce **Professor Geoff Coombs** as the new President of ISAC.

Prof. Coombs is the Chair of Public Health at the School of Veterinary and Life Sciences, Murdoch University and the Senior Clinical Scientist for PathWest Laboratory Medicine, Western Australia, Fiona Stanley Hospital. He has served on ISAC's Executive Committee since 2013.

Prof. Coombs will build upon the success of previous ISAC President, Prof. Andreas Voss, in helping ISAC achieve its aims of increasing knowledge of antimicrobial chemotherapy and tackling antibiotic resistance around the world.

We would like to thank Prof. Voss for his strong leadership and wisdom over the last three years throughout the pandemic, which were some of ISAC's most challenging and productive years.

New ISAC Executive Committee

We welcome **Souha Kanj** to the Board of Directors as ISAC President-Elect and **Heiman Wertheim** as ISAC Treasurer. We are also pleased to welcome four new members to the ISAC Executive Committee:

Fatma Amer (Egypt), Dale Fisher (Singapore), David Jenkins (UK) and Patricia Muñoz (Spain).

The new ISAC Executive Committee looks as follows:



New IJAA Editor in Chief

2023 marks a crucial editorial transition for the *International Journal of Antimicrobial Agents (IJAA)*.

At the end of 2022, Jean-Marc Rolain stepped down as Editor -in-Chief after eight years in this position. He has been succeeded by Jian Li, who officially took over on 1st January 2023.

Jean-Marc was appointed as Editor-in-Chief of *IJAA* in 2015 and guided the journal through a remarkable transformation. His work and dedication to the journal contributed to building firm foundations for its future.

We now have the privilege of welcoming Jian Li, who is committed to continuing the journal's aims to maintain high standards of academic quality and integrity. Jean-Marc and Jian have worked together on a detailed handover plan since October 2022 to ensure continuity for the journal.

ISAC and Elsevier sincerely thank Jean-Marc for his dedication and service and to each of you for your continuous

efforts and support for IJAA and its community. We would also like to take this opportunity to thank Dr Sophie Baron for her excellent work as Editorial Assistant to Jean-Marc and we welcome Dr Sue Nang who will provide editorial support to Jian going forward.



ISAC / APUA antibiotic cards

The Alliance for the Prudent Use of Antibiotics (APUA) is proud to announce the availability of 'Antibiotic cards' for some of the main antibiotics currently in use with further cards to follow. This project, initiated by Mushira Enani, aims to provide a summary of the main characteristics of selected antibiotics. These antibiotic cards have been primarily designed to assist prescribers in the selection of the most appropriate antibiotic, with optimal dosages, and to provide guidance to those who take care of patients who receive antibiotics.

These antibiotic cards have been produced by members of the APUA board and are freely available through our website. They share a common design, focusing on their antimicrobial spectrum, main indications dosing, and adverse events. We hope that you will find them useful and that these antibiotic cards will contribute to better use of antibiotics worldwide, the primary goal of APUA. Click here to download the cards or click the individual images below.



ISAC Project Grants



ISAC is now accepting Project Grant applications to fund antimicrobial research in low- to middle- income countries (LMICs) from ISAC Member Society applicants Applications are invited for grants between **£10,000** and **£20,000.** Apply here.

Aim of Research Project

Applicants are required to demonstrate that ISAC funds will be utilised for a clearly defined piece of research, which will have an identifiable outcome on completion of the work. At least one country involved must be an LMIC country.

Research projects should address one of the three following areas:

- 1. What are feasible & effective prevention strategies to prevent transmission of (resistant) pathogens in I low resource settings?
- 2. What basic laboratory support does a healthcare system minimally need to tackle infectious diseases?
- 3. How do we improve antimicrobial use worldwide to ensure it is delivered only to those who need it?



Deadline to apply: 1 September 2023

Recent awardees

In the previous call for applications, four excellent projects were chosen to be awarded grants:

- ◆ Carriage of antimicrobial resistance in Fiji associated with ◆ Impact of rapid diagnostic testing for chlamydia and gonorrhea in Kumi, Uganda recent exposure to international healthcare (CARE-Fiji) Anton Peleg and Tracey Young-Sharma The Alfred Hospital and Monash University, Australia / Colonial War Memorial Hospital, Fiji Improving the management of lower respiratory tract
- infections in children in Sri Lanka Phoebe Williams and Gayana Subasinghe

Sydney Children's Hospital, Australia / University of Kelaniya, Sri Lanka

- **Erik Schaftenaar and Alex Abal** St. Antonius Hospital, the Netherlands / Kumi Hospital, Uganda
- Evolution on lung-chip drives dose optimisation of
- antibiotic combination therapies: a systems and computational approach

Jinxin Zhao and Nusaibah Abdul Rahim

Monash University, Australia / University of Malaya, Malaysia

32nd International Congress of Antimicrobial Chemotherapy (ICC)



On-demand recordings

ISAC is pleased to share the recordings of the plenary and keynote sessions presented at the 32nd International Congress of Antimicrobial Chemotherapy (ICC) in Perth, Australia by top speakers in the field of infectious diseases and antimicrobial chemotherapy.

View ISAC's YouTube Channel (@ISACAPUA) to watch the presentations.

ICC Abstracts

The Abstracts from the 32nd ICC have been published in ISAC's journal, the Journal of Global Antimicrobial Resistance (JGAR). All abstracts are open access and freely available. Congratulations to all colleagues on their published abstracts. Read all the abstracts here.



ISAC Webinars

ISAC hosts free, educational webinars as part of the ISAC Academy on a variety of infectious disease-related topics in collaboration with its Working Groups and Member Societies. Watch ISAC's webinars on the ISAC YouTube Channel





ISAC offers free E-modules as part of the ISAC Academy series of short courses on infection topics. Participants receive a certificate of

Fever in returning travellers

This module was developed by ISAC's Immunisations & Vaccines Working Group, led by Dr David McIntosh, Prof. Robert Steffen and Prof. Blaise Genton.

The course is aimed at healthcare professionals interested in learning more about managing fever in returning travellers. It contains case studies as well as methods of infection prevention including vaccination,

vector control and chemoprophylaxis. Users will receive a certification upon completion. Access the module here.

Respiratory tract infections and antimicrobial resistance

This module explores the causes of Respiratory Tract Infections (RTIs), the epidemiological effect of the SARS CoV-2 pandemic on RTIs and antimicrobial prescribing. It also explores antimicrobial resistance (AMR) and diagnostics and the role of vaccines in reducing antimicrobial resistance. Access the module here.



Future congresses





ISAC CEO awarded Leader of the Year

ISAC's Chief Executive Officer, Fiona MacKenzie, was recently sat on most of the National COVID-19 operational, strategic

announced as recipient of the prestigious national award "National Health Service (NHS) Scotland Leader of the Year".

Fiona has fulfilled the unique role of national lead for SARS CoV-2 diagnostic testing across all National Health Service (NHS) Microbiology Virology / laboratories in the 15 regions of Scotland

throughout the pandemic. She demonstrated exceptional leadership in coordinating the rapid rollout and sustained provision of COVID-19 testing across NHS Scotland and also



and policy groups. She served as the linchpin providing linkage between the NHS, Scottish Government, Health Protection Scotland, NHS National Procurement and a large number of commercial companies. Stakeholders and colleagues alike respect, trust and admire

accolade, stating that "without her, NHS Scotland's diagnostic response to the pandemic would not have been the success that it has been".

In memoriam

person of many passions, skills and talent.

Above all else, he was a beloved husband, father, son, brother His most lasting legacies will perhaps be related to the and grandfather. His family wrote "that he completed his humanitarian work he initiated and actively participated in earthly journey" and announced his passing "with great across many countries and cultures around the world,

sorrow, but also with much joy over his life's work and over his legacy of strong personal faith and dedication to serving the poor, believing that today he is watching over us from the Kingdom of Heaven". The family announcement quoted Matthew 25; 34 – 36; "Then the King will say to those on his right hand, 'Come, you whom my Father has blessed,

you made me welcome.' "

the enormous esteem and affection in which he was held and hand the depth of compassion he had for those less fortunate; would have surprised such a humble and gentle man. During he was greeted with huge affection and reverence by some of the service, it was said that his scientific and humanitarian the homeless men of the city who he personally helped to feed activities were guided by his Christian values and it was clear and clothe. that he was a bright, shining national treasure with a tribute Vladimir was an extraordinary person with a kind heart who recorded from Slovakia's Prime Minister.

global expert on tropical and infectious diseases, and as a to his family, friends and colleagues.

It is with great sadness that we shared news of the passing of skilled administrator at universities in his home country of Professor Vladimir Krcmery on 20 December at the age of 62. Slovakia where he supported many trainees and students. He was an eminent and highly respected colleague and a Indeed, he founded the St. Elizabeth University of Health and Social Work in Bratislava.

including establishment of medical facilities across the developing world, including in Kenya, Cambodia and Haiti.

Vladimir displayed incredible humility, generosity and humour and was always a pleasure to know and socialise with.

Vladimir was a valued member of the ISAC Executive Committee from 2015 - 2019, a

take as your heritage the kingdom prepared for you since the leader of the ISAC Working Group on Infections in Catastrophic foundation of the world. For I was hungry and you gave me Areas until his death, and a friend who always had incredible food, I was thirsty and you gave me drink, I was a stranger and inspirational stories to share at the numerous ISAC meetings he attended. He hosted a memorable ISAC Executive The scale and grandeur of Vladimir's funeral service reflected Committee meeting in Bratislava when some witnessed first-

leaves behind a huge legacy and will be greatly missed by all Vladimir's international colleagues knew him best as a leading who knew him. ISAC members send their deepest condolences

Fiona and nominated her for this





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 95 national and regional societies, which in turn have over 60,000 individual members. <u>Visit www.ISAC.world to see how your society can become an ISAC Member Society</u>.

ISAC has **22 Working Groups** on specialist subjects which are engaged in advancing scientific knowledge in antimicrobial chemotherapy, clinical microbiology and infectious diseases through various activities. To join an ISAC Working Group, please email Fee Johnstone, ISAC Executive Assistant (secretariat@ISAC.world) with a brief C.V.

ISAC has two society **journals**:

• International Journal of Antimicrobial Agents (IJAA) (impact factor: 15.441)

• Journal of Global Antimicrobial Resistance (JGAR) - gold open access (impact factor: 4.349)

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

For more information on ISAC, visit <u>www. ISAC.world</u> or scan the QR code.

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".

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.

The new international APUA Board meets regularly and aims to build on the work achieved by Prof. Levy and his excellent team of associates.

Visit www.APUA.org for more information or scan the QR code.

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Since 1983, the APUA Newsletter has been a continuous source of non-commercial information disseminated without charge to healthcare practitioners, researchers, and policy-makers worldwide. The Newsletter carries up-to-date scientific and clinical information on prudent antibiotic use, antibiotic access and effectiveness, and management of antibiotic resistance. The publication is distributed in more than in more than 100 countries. The material provided by ISAC / APUA is designed for educational purposes only and should not be used or taken as medical advice. We encourage distribution with appropriate attribution to ISAC / APUA. See previous editions of the Newsletter on the APUA website.

*ISAC welcomes contributions. Please send us your article ideas. All content may be edited for style and length. Please email <u>secretariat@ISAC.world</u>

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