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Impact of COVID-19 on antimicrobial resistance in Taiwan

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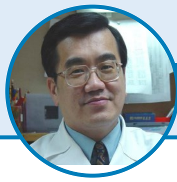

Po-Ren Hsueh

Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) at the end of 2019, its associated disease, coronavirus disease 2019 (COVID-19), has affected more than 144 million people and resulted in more than 3 million deaths across 223 countries[1]. During the COVID-19 pandemic, overuse of antibiotics has occurred due to the following reasons:

1. Both SARS CoV-2 infection and community-acquired bacterial pneumonia share similar presentations, such as cough, fever, and radiological infiltrates.
2. The lack of effective anti-SARS CoV-2 treatments.
3. Potential bacterial coinfection, fungal, or other secondary infection along with COVID-19, but the incidence of this is low[2].

Therefore, the issue of increasing antimicrobial resistance (AMR) following the high rate of antibiotic utilisation for patients with COVID-19, particularly in severe cases, should be seriously considered[2].

In contrast to many other countries with an intense impact of COVID-19, Taiwan is relatively safe, wherein only 1,100 patients have been confirmed with SARS CoV-2 infection as of April 27, 2021 and 12 of them have succumbed to the disease[3]. The successful control of COVID-19 in Taiwan could be attributed to the aggressive efforts and preemptive deployment of response actions preventing rapid disease spread[4]. Even in such a scenario, a recent study reported a high consumption of antibiotics in the National Taiwan University Hospital, a 2500-bed medical center that provides primary and tertiary care in northern Taiwan in January–September 2020 compared with January–September 20192. These included ß-lactam / ß-lactamase inhibitor combinations, quinolones, carbapenems, colistin, tigecycline, fosfomycin, glycopeptides, linezolid, and daptomycin Moreover, increased levofloxacin resistance in *Streptococcus pyogenes*, ciprofloxacin resistance in non-Typhi *Salmonella* species, ampicillin-sulbactam, imipenem, and levofloxacin resistance in *Acinetobacter baumannii* complex isolates has been observed in the National Taiwan University Hospital[2]. However, we wondered whether the situation in a single hospital could be generalised to all other hospitals in Taiwan. Therefore, we conducted the analysis using the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) database and database from Taiwan Healthcare-associated Infection and Antimicrobial Resistance Surveillance System (THAS) established by the Taiwan Centers for Disease Control.

SMART

SMART has been used to monitor the *in vitro* AMR of non-duplicate clinically important bacteria, including *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Salmonella* spp., *Shigella* spp., *Neisseria gonorrhea, A. baumannii* complex*, Pseudomonas aeruginosa, Campylobacter* spp.*,* and *Haemophilus influenzae*, which have been isolated from hospitals throughout Taiwan since 2017[5,6]. In this study, we analysed data on antimicrobial susceptibility and major resistance mechanisms, especially those underlying carbapenemase resistance, of clinically important bacteria isolated from 18 hospitals in Taiwan in 2019 and 2020.

Increasing proportions of methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium*, ertapenem-nonsusceptible *K. pneumoniae*, imipenem-nonsusceptible *P. aeruginosa* and imipenem-nonsusceptible *A. baumannii* complex were observed (**Figure 1**). In contrast, decreasing proportions of ertapenem-nonsusceptible *E. coli*, colistin-non-wild-type (NWT) *E. coli*, colistin-NWT *K. pneumoniae* and colistin-NWT non-typhoid *Salmonella* spp. were observed (**Figure 1**). Decreasing rates of carbapenem resistance from 2019 to 2020 were observed for both *E. coli* (1.4% [6/421] to 0.9% [3/335]) and *K. pneumoniae* (12.2% [45/370] to 11.1% [35/316]). Among the carbapenem-resistant *E. coli* isolates, only one was found to carry the carbapenemase-encoding gene $bla_{\text{KPC-17}}$ in 2019. Among the carbapenem-resistant *K. pneumoniae* isolates, 19 and 17 isolates in 2019 and 2020, respectively, were found to carry carbapenemase-encoding genes. bla_{KPC} was the most common carbapenemase-encoding gene, and in particular, $bla_{\text{KPC-2}}$ was the most common KPC gene.

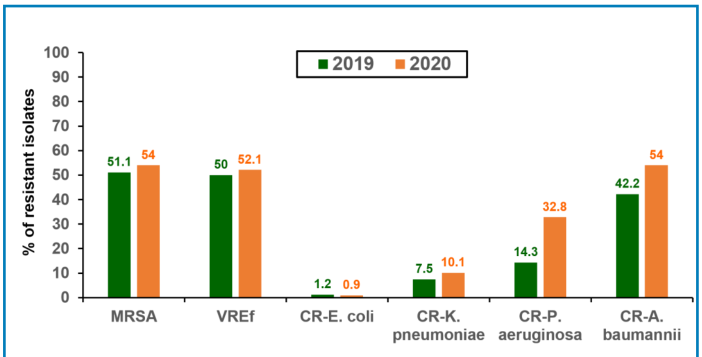

Figure 1. The proportions of clinically important multidrug-resistant organisms associated with bloodstream infection, as recorded in the SMART database, in 2019 and 2020. MRSA. Methicillin-resistant *S. aureus*; VREf, vancomycin-resistant *E. faecium*; CR, carbapenem-resistant.

THAS

In addition to applying SMART, we also assessed the change in AMR before and after the COVID-19 outbreak using an open access database, Taiwan Nosocomial Infection Surveillance System (TNIS), which was launched by the Taiwan Centers for

Disease Control in 2007 and renamed to THAS on 4 February 2020[7]. This system aims to monitor the occurrence of healthcare-associated infections (HAIs) and assess the epidemiologic trends of HAIs. Moreover, this system also provides antimicrobial susceptibility data from the reporting hospitals, including medical centers (n = 22) and regional hospitals (n = 84), across different regions in Taiwan. This study used the recent report of THAS[7], which presents the surveillance data of HAIs and associated AMR until September 2020, for analysis.

First, the summary of AMR in the clinical isolates causing HAIs in intensive care units (ICUs) collected between January and September 2020 showed that the carbapenem resistance rates of clinical isolates of *A. baumannii, Enterobacterales, E. coli, K. pneumoniae, and P. aeruginosa* were 75.3%, 26.1%, 1.9%, 44.4%, and 22.6%, respectively. The vancomycin resistance rates of *Enterococcus* species and *E. faecium* were 45.0% and 68.1%, respectively. The methicillin resistance rate of *S. aureus* was 56.9% (**Figure 2**). Second, the findings in regional hospitals' ICUs showed that the carbapenem resistance rates of clinical isolates of *A. baumannii, Enterobacterales, E. coli, K. pneumoniae, and P. aeruginosa* were 78.1%, 20.3%, 4.5%, 34.3%, and 20.3%, respectively. The vancomycin-resistance rates of *Enterococcus* species and *E. faecium* were 40.8% and 60.8%, respectively. The methicillin resistance rate of *S. aureus* was 65.1% (**Figure 2**). Third, evaluation of the changes in the AMR rate between 2019 and three-fourths of the year 2020 showed that the carbapenem resistance rates of *A. baumannii, Enterobacterales* and *K. pneumoniae* had increased in the medical centers from 2019 to 2020. In contrast, the AMR rate decreased from 2019 to 2020 (**Figure 2**). Finally, a similar trend was observed with the regional hospitals. The carbapenem resistance rates of *A. baumannii*, *Enterobacterales*, *K. pneumoniae* and *P. aeruginosa* increased, but their rate of resistance to other antibiotics decreased (**Figure 2**).

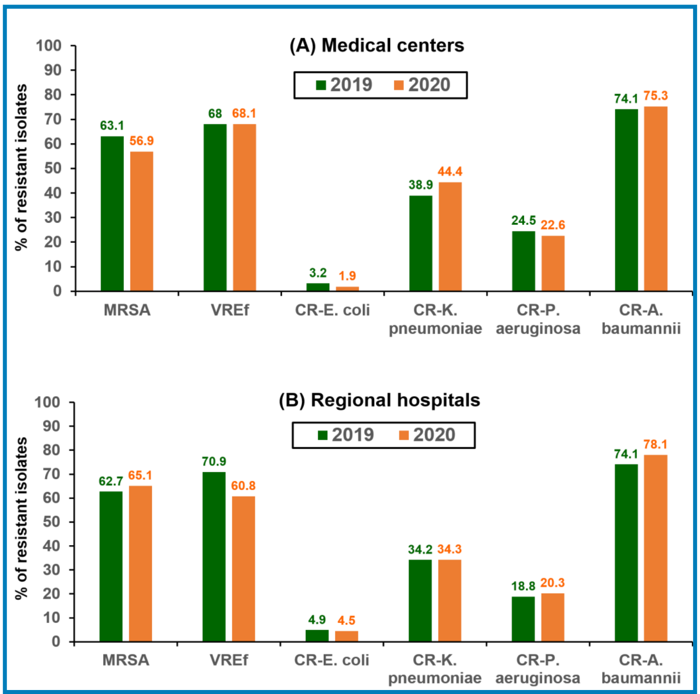

Figure 2. The rates of incidence of common multidrug-resistant organisms in intensive care units of (A) medical centers (n = 22) and (B) regional hospitals (n = 84), as reported in the Taiwan Healthcare-Associated Infection and Antimicrobial Resistance Surveillance System (THAS) in 2019 and 2020. MRSA. Methicillin-resistant *S. aureus*; VREf, vancomycin-resistant *E. faecium*; CR, carbapenem-resistant.

Overall, the increase in the carbapenem resistance rate in the THAS report was much lower than that obtained with SMART. These differences could be due to the different clinical settings considered for compiling these two databases. THAS included 22 medical centers and 84 regional hospitals, focusing on ICUs including medical, surgical, and mixed ICUs, and cardiac care units. Moreover, most hospitals in THAS did not care for patients with COVID-19; hence, the impact of the COVID-19 pandemic on the changes in AMR rate could be diluted in the THAS report and was not as large as that observed with SMART, wherein all the 18 hospitals were involved in caring for patients with COVID-19, especially the critical cases.

Conclusions

Based on our analysis using SMART and THAS, we found that the carbapenem resistance rate of clinical bacterial isolates increased from 2019 to 2020, especially using SMART. The cause was multifactorial, specifically because of the high rate of antimicrobial agent utilisation with a relatively low rate of coinfection or secondary infection in patients with COVID-19. Appropriate prescription and optimised use of antimicrobials according to the principles of antimicrobial stewardship (AMS) programmes, together with quality diagnosis and aggressive infection control measures, may prevent the occurrence of infections of multidrug-resistant organisms during COVID-19. Clinicians should continue following appropriate antibiotic prescription practices according to the AMS programmes, especially with the use of carbapenem in Taiwan. In addition, regular monitoring of AMR data in every hospital would help establish an epidemiologic database for clinicians' reference for prescribing antimicrobial agents. Our findings were based on only a short-term surveillance. Therefore, further long-term assessment of the impact of COVID-19 on AMR is warranted.

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Successful prevention of antimicrobial resistance in animals: a retrospective country case study of Sweden

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According to EU monitoring, Sweden has the lowest use of antibiotics in animals of the EU Member States and the occurrence of antibiotic resistance (AMR) is among the lowest in Europe[1,2]. In a recent study published in the scientific journal *Antibiotics,* we identified key factors behind this favorable situation[3]. The study was inspired by the Global Action Plan by the OIE, FAO and WHO[4] and the EU One Health Action Plan against AMR[5], postulating that lessons learned from successful strategies in individual countries could be valuable for other countries[5]. The study focused on the situation in food producing animals in Sweden and is based on data since the early 1900s. Here we summarise findings in the study by briefly presenting actions taken within the two areas:

1. **Antibiotic use / AMR**
2. **Prevention / control of infectious diseases**

In addition, we present some supporting facts and the major key factors identified in the study. References cited in the study are available in the full publication in *Antibiotics*[3].

Antibiotic use and resistance

Since the mid-1950s, when antibiotics became commonly available for use in animals, prudent use and the risks of AMR have frequently been highlighted by veterinary practitioners and researchers in Sweden. It was recognised early that antibiotics are important tools for the treatment of bacterial infections and that they need to be protected and not considered miracle drugs for dramatically improving animal production.

In 1986, the use of antibiotics for growth promotion (AGP) was banned in Sweden. This put the focus on disease prevention by other means, including measures for improved management, feeding and housing of animals. The use of antibiotics and sustainable animal production became, and still are, important issues on the political agenda and for consumers, which has promoted sustained efforts for a prudent use of antibiotics.

Access to data on the occurrence of AMR, since the late 1950s, and on antibiotic sales, since 1980, has been used to formulate policies, guidelines and legislation and for evaluating the effects of actions taken. This has transformed a general awareness of AMR into concrete knowledge on prudent use and into concrete actions to mitigate emergence of AMR.

During more recent years, actions have been taken to counteract the spread of bacteria with AMR of specific importance. For example, the implementation of a policy on the treatment of mastitis in dairy cows in 1995 reduced the occurrence of penicillin resistant *S. aureus* from 10% to 1%. Another example is an outbreak of tiamulin-resistant *Brachyspira hyodysenteriae* in pig herds in 2016 which was actively curbed. This organism causes swine dysentery, and tiamulin is vital for treatment. Other examples are control of imported animals to minimise the risk of introduction and spread of *E. coli* resistant to extended-spectrum cephalosporins in broiler production and methicillin-resistant *Staphylococcus aureus* in pig production. Also, legislation is in place to mitigate the spread of bacteria with specific AMR in animals, for example carbapenemase-producing Enterobacteriaceae (CPE).

Prevention and control of infectious diseases

For the substantial efforts required for eradication of major epizootic diseases (**Table 1**), State veterinary leadership, veterinary infrastructure and regional veterinary laboratory capacity were established early in Sweden. These later became valuable tools in the prevention of other infectious diseases, including endemic disease. Already in 1945, industry-led animal health counselling services were initiated and in 1969 a regulatory implementation of organised health controls transformed the industry-led health services into coordinated and focused activities. As a result, important endemic diseases could be controlled or eradicated through joint action by the government and the industry.

Hygiene and biosecurity routines on farms and in feed production were implemented early through the control and eradication programmes. Due to a limited and controlled import, and trade within the country, of animals, genes and feed ingredients the introduction and spread of several infectious diseases has been prevented.

Farmers enrolled in organised health controls and organised health services, are provided with farm-specific advice on the management and prevention of diseases through access to veterinary expertise and regular visits by veterinarians. Such visits are also important for compliance with policies and recommendations on biosecurity, the use of antibiotics and good agricultural practice .

Stringent animal welfare regulations are also considered to have improved animal health and decreased the need for antibiotic treatment.

Cooperation in problem solving

Using regulatory and financial tools, the competent authority has facilitated control of infectious diseases and AMR. Cooperation between relevant stakeholders has enabled mutual understanding of the need for and benefits of implementing measures to prevent and control infectious diseases and to counteract AMR. A One Health perspective is taken into account by a cooperation between national authorities in the human and animal sectors facilitating the control of zoonotic diseases and AMR.

Early actions

It is interesting to note that in three areas of major importance for counteracting AMR, Sweden took control actions long before other countries. The control and eradication of several diseases, for example, *Salmonella* infections, Bovine tuberculosis and brucellosis, was initiated early (**Table 1**). A successful control of *Salmonella* has resulted in a virtually salmonella-free animal and feed production. The control was initiated more than 60 years ago following an outbreak which caused the death of 90 people and more than 9,000 cases of illness. In 1980, Sweden became one of the first countries in the world to publish data on sales of antibiotics, and in 1986, also the first country to ban the use of AGPs. Sweden was also comparatively early in setting up a national monitoring programme for AMR in animals (2000).

Summary

Data and experiences in Sweden show that it is possible to combine high productivity in animal production with a restricted use of antibiotics. The major key factors explaining the success of Swedish prevention of AMR are:

- Early insight and continuous awareness of risks associated with AMR and the need for prudent use of antibiotics.
- Early access to data on antibiotic sales and AMR making it possible to focus on activities of concern.
- Early and longstanding efforts to prevent, control and when possible eradicate infectious diseases has reduced the need for antibiotics.

Legal structures, strategies and policies established under government leadership and in cooperation between stakeholder

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Year	Disease	Animal Species	Comments
1924–27	Foot and mouth disease (FMD)	Cattle	11,002 herds infected.
1938–40	FMD	Cattle	7293 herds infected.
1940	Classical swine fever (CSF)	Pigs	230 herds infected.
1943–44	CSF	Pigs	445 herds infected.
1950–56	Paratuberculosis	Cattle	Beef cattle, 830 animals seropositive.
1951–52	FMD	Cattle	562 herds, 1 million cattle vaccinated.
1953	Salmonella epidemic	Mainly cattle	9000 human cases, 90 deaths.
1956–57	Porcine brucellosis	Pigs	76 herds infected.
1956–57	Anthrax	Cattle/pigs	19 cattle herds/68 pig herds infected.
1960	FMD	Cattle	6 herds infected.
1993	Paratuberculosis	Cattle	53 beef cattle herds infected.
1991–97	Bovine tuberculosis	Farmed deer	13 herds infected.
1995–96	Newcastle disease (ND)	Poultry	650 flocks tested; 1.75 million birds/eggs destroyed.
2007	Porcine reproductive and respiratory syndrome (PRRS)	Pigs	7 herds infected, modified stamping out.
2008–09	Bluetongue	Cattle	30 outbreaks in different regions, 2.7 million cattle vaccinated.
2010–20	Highly pathogenic avian influenza and ND	Poultry	2 and 5 outbreaks, respectively.
2010–20	Anthrax	Cattle	12 outbreaks.
In addition: National eradication programme of diseases widely spread following early imports of breeding animals:			
1934-1958	Bovine tuberculosis	Cattle	1937; macroscopic lesions in 30 % of slaughtered cattle (indicating 60-70 % being infected)
1944-1962	Bovine brucellosis	Cattle	1944; 16 000 (6 %) cattle herds infected

Table 1. Significant outbreaks of major epizootic diseases in Sweden for 1900–2020. Adapted from [3].

Authors' note

Professor Stuart Levy, the founder of APUA, had a great commitment for the use of antimicrobials in animals and was a key person when WHO in 1997/98 recommended to phase out the use of antibiotics for growth promotion. Professor Levy during the years acknowledged data and experiences from Sweden and it is therefore a privilege to present these data in the APUA newsletter.

Cystic fibrosis antibiotic susceptibility testing

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Cystic fibrosis (CF) is a chronic, progressive, life-limiting genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene[1]. Most CF patients suffer from acute pulmonary exacerbations resulting in progressive lung disease due to the production of thick immobile secretions, airway inflammation, chronic and recurrent infections[1, 2]. Therefore, the cornerstone of CF management is the use of mucoactive drugs and antibiotics with the goal of improving symptoms while suppressing the resident bacterial population[2]. Long term antibiotic therapy leads to infecting / colonising organisms becoming resistant to more and more antibiotics making treatment difficult[3]. Similarly, problems with antimicrobial allergy or intolerance pose challenges for appropriate antimicrobial therapy. Therefore, extended antimicrobial susceptibility testing (AST) is employed — quantitative, evidence-based *in vitro* AST results can guide prescribing of antimicrobials[4].

The Cystic Fibrosis Antibiotic Susceptibility Service (CFASS) has been funded by "NHS National Services Scotland" since 1999. It is based at the Microbiology Department in Aberdeen Royal Infirmary, Scotland and provides extended antimicrobial susceptibility testing using a minimum of six pairs of antimicrobials with results ranked in order of their *in vitro* effectiveness. The service is available for use by all Scottish CF clinicians / clinics and accepts multidrug-resistant Gram-negative microorganisms isolated from the respiratory tracts of adult individuals with CF. Microorganisms which are not multidrug-resistant are also accepted for testing where there is difficulty locally in determining appropriate antimicrobial therapy due to allergy or intolerance.

In our 20 year experience and in agreement with CF epidemiology, the most received isolate is *Pseudomonas aeruginosa* (54.31%) followed by *Burkholderia cepacia complex* (22.54%). In CF patients, *P. aeruginosa* is the most commonly isolated pathogen; more than 70% are colonised with this bacterium by the age of 25[5, 6]. This is due to its ubiquitous presence in the environment[7] and the ability to phenotypically and genotypically adapt itself to the CF lung environment. An innate adaptation of *P. aeruginosa* which enables its establishment in the airways is the ability to switch from planktonic to a biofilm mode of growth. This greatly impedes the efficacy of antibiotics due to reduced growth rate of biofilm bacterial cells and the presence of an anaerobic environment[3]. Other adaptations used by *P. aeruginosa* is the ability to exist as metabolically dormant persister cells or hypermutator strains due to increased mutation rates from defects in DNA repair / error systems[3]. The inability to eradicate these organisms from the airways and the development of resistance are the reasons combination testing is employed in CF management.

Synergy testing is an *in vitro* assessment of the interaction of two antimicrobial agents to determine if the effect of the combination is greater than the sum of their individual activities, hence classified as synergistic.[8] Data from 11,695 combination tests showed that most combinations had no interaction with only 9.8% synergy and 1.4% antagonistic combinations observed. Notably, **Table 1** shows that c.50% synergistic combinations were observed in *Stenotrophomonas maltophilia* (15.7%) compared with *P. aeruginosa* (8.4%). Furthermore, our data suggest that synergy in *S. maltophilia* primarily results from the addition of ticarcillin / clavulanate (44.94%): combination with aztreonam resulted in 50% synergy. Ciprofloxacin and ceftolozane / tazobactam was the most synergistic combination in *P. aeruginosa*. The reasons for these are unclear; research is necessary to unravel the underlying causes of species / drug synergistic interactions.

Organism ID	Total Isolates (%)	Synergy*(%)#	No interaction*(%)#	Antagonism*(%)#	Top Synergistic combination
P. aeruginosa	1089 (54.31%)	504 (8.4)	5435 (90.5)	65 (1.1)	Ciprofloxacin + Ceftolozane/ Tazobactam
Pseudomonas spp.	139 (6.93%)	51 (6.7)	708 (92.5)	6 (0.8)	Ciprofloxacin + Piperacillin/ Tazobactam
S. maltophilia	176 (8.78%)	178 (15.7)	930 (81.8)	29 (2.6)	Ticarcillin/Clavulanate + Aztreonam
B. cepacia complex	452 (22.54%)	333 (11.0)	2638 (87.4)	49 (1.6)	Tobramycin + Ceftazidime
Achromobacter spp.	117 (5.84%)	80 (10.4)	669 (87.0)	20 (2.6)	Ceftazidime + Imipenem

Table 1. Summary of isolate combination testing interpreted using FICI
* number of isolates; # percentage of isolate

Synergy testing methodology varies widely in complexity and interpretation and there is a lack of standardidation[8]. There is currently no clear consensus on the gold standard for assessing synergy; methods are time-consuming and labour-intensive with up to 25% discrepant results compared with the commercial Etest method used in most clinical laboratories[8]. The clinical relevance of synergy testing is questioned due to a lack of data.[8] Only one study used the multiple-combination bactericidal test method alone in a randomised, double-blind trial to show that CF patients who were treated with combination antibiotic regimens for pulmonary exacerbation did not exhibit significantly improved outcomes[9]. Due to insufficient evidence, the UK Cystic Fibrosis Foundation guidelines recommend that synergy testing should not be done in CF patients[10] but research has shown that it is still currently in use in the management of pulmonary exacerbations[11,12]. Due to limited treatment options resulting from increasingly resistant bacteria, we believe there is an urgent need for further research to understand which synergy methods are predictive of clinical efficacy. This should lead to identification of an evidence-based, gold standard method for carrying out and interpreting synergy testing. Additional interpretative criteria should be explored when comparing the *in vitro* effectiveness of antimicrobial combinations. This should include the susceptibility breakpoint index[13] proposed by our laboratory, which may be more clinically relevant than the fractional inhibitory concentration index (FICI) as it is a measure of clinically relevant concentrations. **Figure 1** demonstrates that similar median susceptible breakpoint index (SBPI) values were observed for most isolates except *B. cepacia* complex. We also advocate rigorous quality control and exploration of avenues such as automation and / or the manufacture of synergy panels[14] to simplify methods for use in the clinical laboratory.

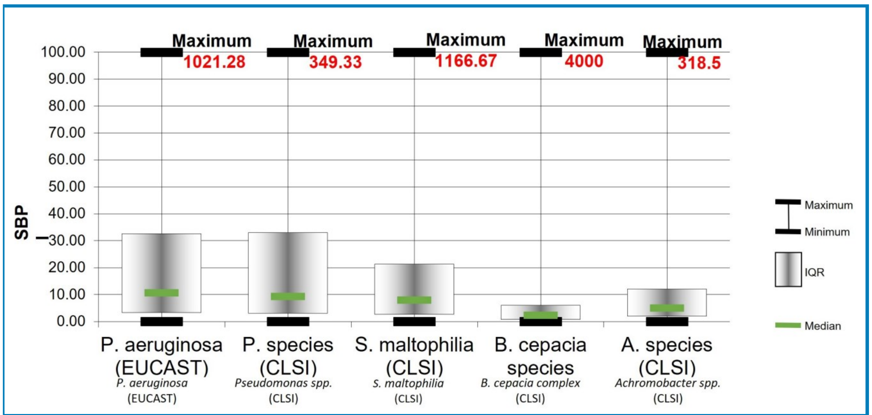

Figure 1. Susceptibility Breakpoint Indices (SBPI) for CFASS referred isolates. SBPI interquartile range denoted by the grey box, median, green line while maximum and minimum values are represented by the thick black line. P. aeruginosa was interpreted using the EUCAST guidelines for all antibiotics while CLSI was used for other species.

Despite evidence that a decrease in AST frequency is not associated with poorer outcomes[15] or lack of predictive value[16], it is still used in the management of CF. We asked service users if the AST report helped in the management or initial choice of antibiotics. 40% of respondents stated that reports helped in the initial choice of antibiotic treatment for infective exacerbations (**Figure 2**). Zemanick *et al*[4] reported that AST is rarely used to guide initial antibiotic choice and changed only when there was a lack of clinical response to current treatment: whilst we agree with this statement, we hypothesise that an AST report helps reaffirm the initial choice of antibiotics although it does not necessarily result in a change. When we explored whether there was a relationship between existing treatment and clinical progress, divergent results were seen. This suggest that assessment of clinical progress is subjective and clearer definitions should be included in CF pulmonary exacerbation management when assessing the effectiveness of treatment.

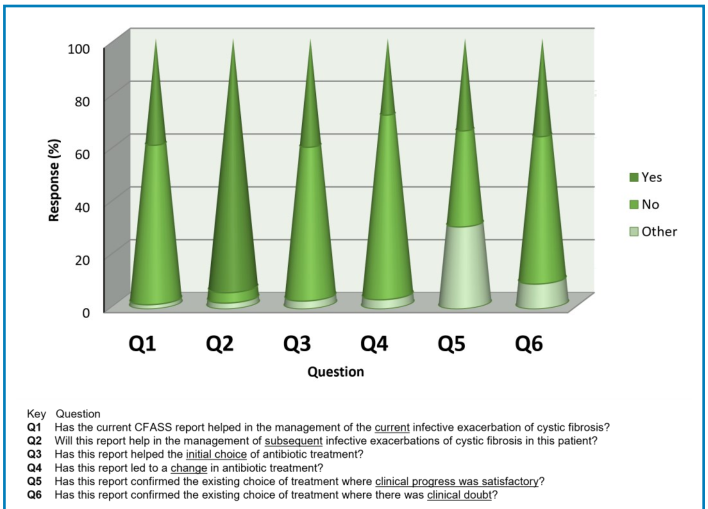

Figure 2. Clinician responses to CFASS feedback questionnaires. Combination susceptibility feedback responses (yes, no, or other) were grouped as six questions (Q1-6). A total of 817 feedback responses were received by the service.

In conclusion, AST results appear not to influence treatment decisions, but our survey identified it is an important resource for clinicians: 94% of respondents proposed to use AST reports in the management of subsequent pulmonary exacerbations.

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Antibiotic Resistance in the News

Children's antibiotic prescriptions decrease during pandemic
Research published in *Paediatrics* shows a decline in drug prescriptions for children (0 – 19 years) during COVID-19.
The authors used the IQVIA National Prescription Audit which contains monthly dispensing counts from 92% of US retail pharmacies to assess changes in prescriptions dispensed to US children during 2018–2020. The authors categorised 231 drugs into three groups (acute infections, chronic diseases and other).
During the first eight months of the pandemic, there was a 27% reduction across *all* prescriptions but a 57% decrease in antibiotic prescriptions, comparable with the same period in 2019.
"The decrease in antibiotic dispensing most likely reflects reductions in infections, such as colds and strep throat, due to COVID-19 risk-mitigation measures like social distancing and face masks," said author, Prof. Chua.
Whether reductions in prescribing infection-related drugs will continue needs to be monitored going forward.

Antibiotic resistant bacteria in dog food
Authors of a new study analysed 55 samples of dog food (wet, dry, semi-wet, raw frozen and treats) for enterococci from supermarkets and pet shops across Porto, Portugal. Most brands analysed are commercially available worldwide. 30 / 55 samples contained enterococci while it was found in *all* of the raw food samples. More than 40% of the enterococci were resistant to erythromycin, tetracycline, quinupristin-dalfopristin, streptomycin, gentamicin, chloramphenicol, ampicillin or ciprofloxacin. There was also some resistance to vancomycin and teicoplanin (2% each) and 23% of the enterococci were resistant to linezolid, a last resort antibiotic used when other drugs have failed.
"The trend for feeding dogs raw food may be fuelling the spread of antibiotic resistant-bacteria", the researchers said.

New guidance for veterinary antibiotics
The U.S. Food and Drug Administration's (FDA) Center for Veterinary Medicine has finalised guidance for the agricultural industry to bring all medically important antibiotics used in food-producing animals under veterinary oversight.
Previously, a veterinary prescription was required only for some injectable products as well as for antibiotics used in feed and water. Guidance for Industry #263 (GFI #263) extends this requirement to cover all drugs administered through any route. This will allow the agency to strengthen antibiotic stewardship and protect public health against antibiotic resistance.
The voluntary process outlined in this guidance will help ensure new animal drugs containing antimicrobials of human importance are administered only under veterinary oversight and only for therapeutic uses.
The new policy will be fully implemented in June 2023.

AMR resistance stable in the Netherlands
NethMap/MARAN 2021 is an annual report in which various organisations jointly present data on antibiotic use and resistance in the Netherlands, for both humans and animals. Despite the increase in ICU admissions due to the pandemic, more bacteria did not develop resistance in 2020 in the Netherlands. In addition, the number of bacteria that are resistant to various antibiotics at the same time remained the same.
Lessening resistance may be due to implementation of COVID-19 measures, such as social distancing and working from home because many infectious diseases spread by social contacts occurred less frequently.
The pandemic also influenced antibiotic use – in outpatients, the total systemic use decreased by 10.5% from 2019 to 2020.
Antibiotic use and resistance in animals and resistance in human foodborne pathogens was also analysed.
The quantity of antibiotics sold in 2020 for farm animals increased slightly by 2% since 2019. However, since 2009, the sale of antibiotics has decreased by almost 70%. This was reflected in the reduction of the level of resistance in some bacterial species in livestock, particularly for ESBLs in poultry and chicken meat. Almost no antibiotics that are crucial for treating infections in humans have been used for farm animals in recent years.

Shorter course of antibiotics for UTIs in men
A new study published in *JAMA* supports a 7-day course of antibiotics as an alternative to a 14-day course for men with urinary tract infections (UTIs).
The authors randomised 272 men from two US Veterans Affairs medical centres with presumed symptomatic UTIs with no fever into two groups. The men were treated with ciprofloxacin or trimethoprim/sulfamethoxazole for either 7 or 14 days. 93.1% on the 7-day course and 90.2% on the 14-day course were successfully treated.
Recurrence of UTI symptoms occurred in 9.9% in the 7-day group versus 12.9% in the 14-day group. Adverse events occurred in 20.6% in the 7-day group versus 24.3% in the 14-day group.

AMR public discussion survey
The "Tripartite"—The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) – is conducting a public discussion to collect views from different stakeholders on the substantial elements of the proposed "Antimicrobial Resistance (AMR) Multi-Stakeholder Partnership Platform" (the Platform).
The Tripartite is interested in hearing opinions to shape the foundations of the Platform together, responding to the needs of stakeholders and combatting AMR as a critical global threat across the human-animal-plant-environment interface. The Tripartite hopes this is the starting point for global, collective action.
Please complete the survey by 18 September 2021.

Variation in antimicrobial use across Europe

The authors of a report published in *Frontiers in Pharmacology* analysed data on antibiotic consumption and use from 30 countries in the European Surveillance of Antibiotic Consumption Network (ESAC-Net) and 15 countries in the WHO Europe Antimicrobial Medicines Consumption (AMC) Network.

Total antibiotic consumption was similar across both networks (20.0 defined daily doses [DDD] per 1,000 inhabitants per day in ESAC-Net countries and 19.6 DDD for WHO Europe AMC Network countries).

Large variations were observed across countries in both networks, ranging from 8.9 DDD per 1,000 inhabitants per day in Azerbaijan to 34.1 DDD in Greece.

Consumption of Watch antibiotics, antibiotics not recommended for routine use, ranged from 34% (Bosnia and Herzegovina) to 69% (Uzbekistan) in the WHO Europe AMC Network countries and 13% (Iceland) to 61% (Slovakia) in ESAC-Net countries. This suggests an area for improved prescribing.

Effective national policies to deal with AMR vary across countries in both ESAC-Net and the WHO Europe AMC Network. Reliable data are needed to describe patterns of AMC and to monitor the evolution of AMR. Standardised methods of data collection and analysis and the application of common metrics and indicators facilitate benchmarking across settings, countries and regions.

OIE Report on Antimicrobial Agents Intended for Use in Animals

The fifth report from World Organisation for Animal Health (OIE) which collects global data on antimicrobial usage in animals found a 34% decrease in antimicrobial use from 2015 – 2017.

Of the 160 countries submitting data, 70% did not use any antimicrobial agents for growth promotion, regardless of the presence or absence of legislation or regulations. 50% of countries reporting the use of antimicrobials as growth promoters do not have a regulatory framework.

The most frequently listed antimicrobial agent was bacitracin, followed by flavomycin and avilamycin.

The decrease in antimicrobial quantities biomass in all OIE Regions represents countries' commitment to the responsible use of antimicrobials in animals at the country level.

Fast food restaurants scored on antibiotics in beef policies

The sixth annual Chain Reaction Scorecard grades the top 20 US fast food restaurants on reducing antibiotic use in their beef supply chains. The five previous editions of the Scorecard documented how top restaurant chains have helped transform antibiotic use practices in the chicken industry by sourcing chicken produced without the routine use of antibiotics. This has not yet happened in the beef, pork or turkey industries.

In this report, surveyed companies made little progress transitioning to responsible antibiotic use in their beef supplies in 2020, with the exception of Wendy's, an American international fast food chain. Wendy's committed to prohibiting the routine use of medically important antibiotics in its beef supply chain by the end of 2030.

E. coli resistance increasing

The rate of *Escherichia coli* (*E. coli*) antibiotic resistance has continued to increase despite reductions in unnecessary antibiotic prescribing in general practice in England according to a new study in *The Lancet Infectious Diseases*.

This authors assessed patterns in broad-spectrum prescribing and antibiotic resistance in *E. coli* bacteraemia isolates before and after the implementation of the National Health Service (NHS) England Quality Premium (Quality Premium). Quality Premium is an antimicrobial stewardship intervention implemented in 2015 - 016 that provides financial rewards to Clinical Commissioning Groups to reduce antibiotic prescribing.

The authors analysed monthly prescribing data from 6,882 GP practices in England between 2013—2018. By the end of 2018, antibiotic prescribing had reduced by 57% compared with the counterfactual situation (i.e., had the Quality Premium not been implemented). The Quality Premium objective of reducing the prescribing rate was achieved for co-amoxiclav and levofloxacin but not for ciprofloxacin, ofloxacin or levofloxacin.

In the same period, a 12% reduction in the resistance rate was noted since implementation of the Quality Premium. Although this effect was sustained until the end of the study period, the overall trend remained on an upward trajectory. On examination of the long-term effect following implementation of the Quality Premium, there was an increase in the number of isolates resistant to at least one of the five broad-spectrum antibiotics tested.

Re-introduction of the PASTEUR Act

The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act (PASTEUR Act) (H.R. 8920 and S. 4760) sets out a subscription model for developing new antibiotics in the US.

Under the PASTEUR Act, the federal government would provide financial incentives to develop new antimicrobial drugs. A similar approach is already being explored successfully in the United Kingdom.

Financial models which integrate the appropriate use and stewardship of antibiotics is a critical goal for preserving the long-term effectiveness of novel antibiotics.

The bill also prioritizes investment in hospital antimicrobial stewardship programs through a new grant.

Funding to develop national surveillance network

Pathogen Surveillance in Agriculture, Food and the Environment (PATH-SAFE), a major programme of pathogen surveillance, has been awarded UK Government funding of £19.2 million.

The project brings together various agencies including Food Standards Agency (FSA), Food Standards Scotland (FSS) and Public Health England (PHE) to test the application of genomic technologies in the surveillance of foodborne pathogens and antimicrobial resistant microbes in the UK. It aims to adopt a One Health approach to surveillance.

The heart of this 'virtual' network will be a new database that will permit the analysis, storage and sharing of pathogen sequence and source data, collected from multiple locations across the UK by both government and public organisations.

Society News

ISAC / APUA Combined 100th Anniversary

2021 marks 100 combined years of fighting infectious diseases (ID) and antimicrobial resistance (AMR) for ISAC and APUA.

ISAC, originally the International Society of Chemotherapy for Infection and Cancer (ISC), was founded in 1961 at a time when the specialties of antimicrobial and anti-cancer chemotherapy were intrinsically linked. Since then, they have diverged to become independent specialties in their own right and, over time, the society oriented towards antimicrobial rather than anti-cancer chemotherapy. This focus led to the society's current name, the International Society of Antimicrobial Chemotherapy (ISAC). ISAC, a federation of Member Societies, now has 92 Members around the world which in turn have over 60,000 individual members.

In 1981, Stuart Levy founded the Alliance for the Prudent Use of Antibiotics (APUA); the first organisation to address antibiotic preservation; a topic which has become a specialty in its own right; that of "antibiotic stewardship". Coinciding with Stuart's retirement, APUA took the decision to merge with ISAC in 2019, given ISAC's further refining of its focus towards antimicrobial stewardship and antimicrobial resistance.

Plans to celebrate the combined 100th anniversary were being made for ISAC's biennial International Congress of Chemotherapy (ICC) due to be held in Perth, Australia in November 2021. The COVID-19 pandemic means the 32nd ICC will now take place in 2022 and face-to-face celebrations are deferred until then. It is important nonetheless, to mark the fact that 2021 is the 100th anniversary year. A number of friends and colleagues of both ISAC and APUA have recorded short reflective messages are posted on ISAC.world and social media as they are uploaded culminating in a webinar presenting the history of ISAC later in 2021, to be presented by Professor Alasdair Geddes.

If you would like to record a short video, please email Fee at secretariat@ISAC.world.

ISAC AMR Project Grants—deadline approaching

ISAC is now accepting Project Grant applications to fund antimicrobial research in low- to middle- income countries from ISAC Member Society applicants**

Applications are invited for grants between **£5,000** and **£10,000.**

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 a low- to middle- income country.

Research projects should address one of the three following areas:

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

Project Criteria

- Projects can last up to 24 months.
- 6-monthly updates are required.
- Funds can be used for staff or materials.
- At least two institutions should be involved in the project.
- At least one institution should be from a low- or middle-income country.

Eligibility of applicants

- Principal applicant must be a member of an ISAC Member Society. (See website for all member societies)
- Other applicants do not need to be a member of an ISAC Member Society.
- The principal applicant must be the principal investigator on the intended research.
- At least one country involved must be a low- to middle-income country.

Deadline: 1 September 2021

Find out more at ISAC.world

**If you are not a member of an ISAC Member Society but are a member of another relevant society, email secretariat@ISAC.world to find out how to join for free.

ISAC Webinars

Rapid diagnostics & biomarkers at the heart of patient management

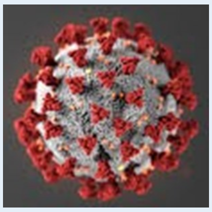
Provision of medicine is transforming due to the amount of research and development in novel diagnostics and technologies. In this webinar, ISAC's Rapid Diagnostics & Biomarkers Working Group aims to provide a number of short presentations on how rapid and novel diagnostics and technologies and their application can impact clinical practice and the provision of microbiology, infectious disease, antimicrobial stewardship and infection control services.

We hope the webinar will be informative and generate interesting discussions, future research and collaboration.

The full programme will follow soon—visit ISAC.world

Confirmed Speakers

Dr Kordo Saeed (UK); Dr Eric Howard Gluck (USA); Dr Stephen Poole (UK); Prof. Philipp Schütz (Switzerland); Dr Peter Laszlo Kanizsai (Hungary); Prof. Heiman Wertheim (the Netherlands)



COVID-19 Webinar Series

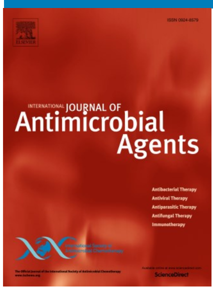
The fifth instalment in ISAC's COVID-19 series on **Long COVID** is coming on **28 September 2021**.

More details will follow—please keep an eye on the website.

Click the links below to watch the other four webinars in the series:

COVID-19 Effective Treatments COVID-19 Variants COVID-19 Vaccines COVID-19: Around the World

IJAA and JGAR Impact Factors Increase



We are delighted to announce that the latest journal impact factors have been announced:

- JGAR has increased from 2.706 to **4.035**
- IJAA has increased from 4.621 to **5.283**

Congratulations to Jean-Marc Rolain (Editor in Chief) and Sophie Baron (Editorial Assistant) for leading IJAA and Stefania Stefani (Editor in Chief) and Simona Purrello (Editorial Assistant) for leading JGAR. Thank you also to the Section Editors, the editorial team and to everyone who has contributed to the success of both journals.

New Executive Committee Member

We are pleased to introduce Jinxin Zhao (Chair and founder of the ISAC Early Career Working Group) as an ex officio member of the ISAC Executive Committee.

Jinxin Zhao is a Postdoctoral Research Fellow in the Biomedicine Discovery Institute, Monash University, Australia. Jinxin obtained his B.Sc. and M.Sc.Eng. at Shandong University, China and PhD (antimicrobial systems pharmacology) at Monash University. He comes with over seven years of experience in Antimicrobial Systems Pharmacology, Genome-scale metabolic modelling and Bioinformatics. His research is highly relevant to global public health, where multidrug-resistant is one of the three greatest global threats to human health. His research focuses on developing novel efficacious therapies against life-threatening infections caused by this problematic Gram-negative 'superbug' which is resistant to all other antibiotics.

If you want to join ISAC's Early Career Working Group, email your CV to Fee Johnstone (secretariat@ISAC.world).

See the group's webpage for more details.

Call for members—Zoonoses group

ISAC is looking to appoint the new Officers to lead and reinvigorate the Zoonoses Working Group.

An ISAC Working Group is a group of clinicians / scientists / investigators who organise themselves under the auspices of ISAC with the objective of studying a defined area within clinical microbiology and / or infectious diseases in line with ISAC's aims and objectives. The aim of the Zoonoses Working Group is to provide an international platform for promoting and encouraging the effective exchange of information about research and development activities in the zoonoses field (of any etiology: bacterial, viral, parasitic).

There are four positions available:

Chair, Vice Chair, Secretary, Treasurer

All Officers should be professionally active and will commit to driving this important Working Group. The Officers will be fully supported by ISAC Executive Assistant, Fee Johnstone, in taking the group forward.

If you have the relevant experience and are interested in applying for any of the Officer positions, please email your CV to Fee (secretariat@ISAC.world

International Congress of Antimicrobial Chemotherapy (ICC)

The 32nd ICC, co-hosted by ISAC and the Antimicrobial Society of Antimicrobials (ASA) will be held in Perth in November 2022. The Scientific Program Committee, co-chaired by Serhat Unal (ISAC) and John Turnidge (ASA), is currently finalising the programme. In addition to five plenary and six keynote sessions, 24 symposia are planned. Many of the symposium sessions will have two invited speakers (one regional and one international) and two proffered papers. Workshops and poster sessions are also scheduled. Further information on the congress, including travel awards, will be available on the meeting's website towards the end of 2021. Register your interest at www.32icc.org

Applications open for HUMA Award nominations

ISAC is now accepting applications from Member Societies for the Hamao Umezawa Memorial Award (HUMA).

The Hamao Umezawa Memorial Award (HUMA), generously sponsored by the Microbial Chemistry Research Foundation of Japan, is the highest award given by ISAC.

Professor Umezawa had an outstanding career and made many key discoveries in the fields of antibiotics, anticancer drugs and immunomodulators over many years.

Purpose

The HUMA is intended to honour individual researchers, scientists or clinicians who have made outstanding contributions in the field of antimicrobial chemotherapy. The award may be given for individual pieces of meritorious work or to honour an exceptional career in antimicrobial chemotherapy

Award

10,000 Swiss Francs, a certificate and a medal will be bestowed upon the successful nominee at the 32nd ICC in Perth, Australia in 2022. The awardee will also receive a funded place at the Congress and will be expected to deliver a 40-minute lecture. A list of previous awardees, along with their lecture titles, may be found on the ISAC website.

Nomination Procedure

- Nominations are invited from ISAC Member Societies.
- Nominees may either work in the scientific arena or in the area of patient care.
- Member Societies should E-mail a letter stating the reasons for the nomination accompanied by a curriculum vitae (CV), bibliography and electronic copies of key publications representing the candidate's work.
- Resubmission of an application made in a previous year should be accompanied by an updated CV and bibliography.

The above requirements (letter of nominations, CV of candidate and key publications) should be sent electronically to Dr Fiona MacKenzie, ISAC Chief Executive Officer via secretariat@ISAC.world.

Deadline to submit nominations is 31 October 2021.

Asia Pacific Congress of Clinical Microbiology & Infection (APCCMI)

APCCMI is the biennial conference for the Asia Pacific Society of Clinical Microbiology and Infection (APSCMI).

Postponed from 2020, APCCMI will take place as a hybrid event from 11—13 November 2021 in Singapore.

Whether you choose to join APCCMI online or in Singapore, you can save 10% on the registration fee when you register as a group (minimum 10 participants). If you register before **26 September 2021**, you will also save up to 100 SGD.

Register now.

APSCMI / Institut Mérieux Young Investigator Award

The Institut Mérieux and its entities have been committed for many years in the fight against infectious diseases in particular the issues with antimicrobial resistance (AMR). To provide an incentive for promising young investigators working in these fields, Institut Mérieux has decided to allocate several awards worldwide to researchers or clinicians at the beginning of their carrier in recognition of a major achievement having significant impact. The Young Investigator Award will be launched together with APSCMI for researchers or clinicians in the Asia-Pacific Region.

Selection criteria:

- Researchers and / or clinicians currently serving on a full-time basis in hospitals / research institutions / teaching institutions in countries in the Asia-Pacific region.
- Candidates will have < 10 years of either clinical practice experience or < 10 years of working experience in clinical microbiology after their M.D / PhD.
- Involved and made significant contribution to a research work on AMR, antimicrobial stewardship, innovative methods in faster microbiology diagnosis, innovative methods in using clinical microbiology information for infection prevention and control, clinical education / awareness programmes for combating AMR, innovative approach for surveillance on infectious diseases (including multi-drug resistant organisms but not limited to), or any similar work in the field of infectious diseases.
- Having collaborations with researchers / clinicians from other countries of the Asia-Pacific region.
- Indicators of impact from the work could be either publication (s) in prominent international journals and / or implementation of guidelines / protocols having led to significant improvements in the field.

Download an application form here.

The deadline to submit is 5 October 2021.

Find out more on APSCMI.net—the new APSMCI website.

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. Visit the website to see how your society can become an ISAC Member Society.

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. Visit the website for more information

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.

For more information on ISAC, visit www. ISAC.world

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.

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 the APUA website for more information.

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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 secretariat@ISAC.world

Newsletter Editorial Team: Fiona MacKenzie (Managing Editor) and Fee Johnstone (Editorial Assistant)