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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 policymakers 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 to over 7,000 affiliated individuals in more than 100 countries. The material provided by APUA is designed for educational purposes only and should not be used or taken as medical advice. We encourage distribution with appropriate attribution to APUA. See previous editions of the Newsletter on the APUA website.

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Most antibiotic prescriptions occur in primary care settings where prescribing can be difficult for several reasons. Firstly, prescriptions are often empirical, without identification of the causal agent. Physicians are also guided by bacterial resistance rates but they are continually changing and physicians may not be aware of these changes. Finally, external factors, such as the physician’s working conditions, patient expectations and financial pressures within the healthcare system, may also influence antibiotic prescription practices.

Physicians can use clinical practice guidelines (CPGs) to facilitate prescription. CPGs are textual documents containing recommendations from a group of experts based on scientific evidence. However, they are difficult to use in clinical practice because of their complexity (large amounts of ambiguous and heterogeneous text). Clinical decision support systems (CDSS) have been developed to make CPG use easier. These systems implement CPGs in the form of “if/then” rules, e.g., if (otitis) then (amoxicillin). However, their rates of adoption by physicians are low because: (i) they do not have the necessary properties for only a limited number of well-defined patient profiles, and physicians may find it difficult to extrapolate the recommendations to their own patients; (ii) they display only the conclusion of CPGs, not the underlying rationale, and this can undermine physician confidence in these systems; (iii) they are often difficult to use / navigate.

We designed a CDSS for primary care, AntibioHelp®, to overcome these shortcomings. Navigation is based on usability principles and the decision process used to treat patients with infectious diseases:

On page 1, the physician selects the disease and patient profile. On page 2 (Figure 1), the physician can visualise the entire decision process in an “at-a-glance” interface. This interface, built according to a “space-filling approach” is divided into five areas:

- The Treemap representation (top, left), presents the possible alternatives with recommended action(s) in intuitive colours. Red boxes lead to a display of the antibiotics, and their level of recommendation.
- The two areas below the main area are optional (they simply explain the decision variables used in the main area).
- Hospitalisation criteria (top, right) are shown with a graphical summary, Mister VCM (e.g., a highlighted eye means that the patient should be hospitalised in case of ophthalmological problems). Detailed criteria can also be visualised.
- The area at the bottom right displays situations for which the recommendation cannot be applied.

Page 3 (Figure 2) is displayed only if the recommended action chosen on page 2 is “antibiotic prescription”. It displays both the recommended and non-recommended antibiotics, together with their properties, weighted by degree of importance. The properties displayed are those used by the experts writing CPGs to determine which antibiotic to recommend. This interface uses the “rainbow boxes” technique. Antibiotics are displayed in columns, and properties in coloured rectangular boxes. Antibiotics are separated into two groups:

- The antibiotics on the right (dark grey) should not be prescribed. The antibiotics on the left (light grey) can be prescribed. AntibioHelp® helps physicians choose the best one(s) by rating them and displaying their
properties. Advantageous properties are displayed in a green box (e.g. narrow spectrum). Disadvantageous properties are in an orange box (e.g. serious side effects). No box is displayed if the properties are unknown. Box height is proportional to the weight attributed by the experts in the CPGs as determined via artificial intelligence techniques; a preference model was learnt with a metaheuristic algorithm and applied to a knowledge base built from CPGs and the knowledge of antibiotic experts.

AntibioHelp® was assessed by physicians in two crossover studies. Visualisation of weighted antibiotic properties helped physicians to extrapolate recommendations to patients for whom CPGs provided no explicit recommendations (41% decrease in error rate, \( p \)-value=6\( \times \)10\(^{-13} \)). It also increased physician confidence in their prescriptions for these patients (+8%, \( p \)-value=0.02). The usability of AntibioHelp® was found to be excellent (System Usability Score = 81). Physicians particularly appreciated the rapidity of the response (< 3 interfaces displayed), the consistency of interfaces for all diseases, and the overview of the decision process in an “at-a-glance” interface.

AntibioHelp® could help to improve antibiotic prescriptions in primary care, by helping physicians to extrapolate recommendations for situations for which no recommendations exist in CPGs, through the visualisation of weighted antibiotic properties. It also increases GP confidence in the system, by displaying the entire decision process in an “at-a-glance” interface, together with the rationale underlying recommendations, and it can be easily and rapidly used by physicians.

In the future, AntibioHelp® will be connected to electronic health records and updated automatically through external resources, such as microbiological observatories, and drug databases. This automatic updating will inform physicians of advances in medical knowledge in real time (e.g. physicians could be alerted, in real time, of changes in bacterial resistance, by a red box for the property “bacterial resistance”). A randomised controlled trial will also be conducted, to assess the impact of AntibioHelp® on antibiotic prescription quality and bacterial resistance.

**Funding:** Funding was obtained from the Agence Nationale de Sécurité du Médicament et des Produits de santé (ANSM). APP 2016—RaMIPA Project (Raisonner pour Mieux Prescrire les Antibiotiques [Reasoning for better antibiotic prescription]). Project leader: Dr Rosy Tsopra.

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10. Tsopra R et al. Helping GPs to extrapolate guideline recommendations to patients for whom there are no explicit recommendations, through the visualization of drug properties. The example of AntibioHelp® in bacterial diseases. J Am Med Inform Assoc 2019; doi: 10.1093/jamia/ocz057 [ahead of print]


Figure 2: Example of uncomplicated cystitis in a woman. In this case, the 12 antibiotics located on the left (light grey) can be prescribed. At a glance, we can see that one of them, fosfomycin trometamol, has the greatest total height of green boxes and the smallest total height of orange boxes. This antibiotic is therefore the most appropriate in this case. In the column header, we can see that this is the antibiotic recommended in rank 1 in the clinical practice guidelines. This interface can also be used for extrapolating recommendations to patients for whom CPG recommendations do not apply, e.g. for women with uncomplicated cystitis and a recent history of fluoroquinolone treatment. In such cases, the physician can tick the checkboxes at the bottom of the screen to grey out the antibiotics from classes that cannot be prescribed (in this case, quinolones). The physician can then see, at a glance, that there are six antibiotics with the necessary properties, including fosfomycin trometamol, which remains the most appropriate. See [10] for more details.
Antibiotic resistance (AMR) is a major public health problem. Indeed, experts estimate that in 2050, 10 million deaths will be attributable to AMR. It is now proven that the emergence of bacterial resistance is directly correlated with excessive use of antibiotics. ¹ A study analysing the trends and drivers of antibiotic consumption from 2000 to 2015 in 76 countries demonstrates that the latter increased by 65%. ² In order to fight AMR, in 2016 the World Health Organization (WHO) launched a global plan of action that covers several areas including the implementation and promotion of Antimicrobial Stewardship Programmes (ASP) and the monitoring of antibiotic consumption. ³

Until 2018, there was no national ASP in Tunisia. According to Klein et al., Tunisia is the second highest consumer of antibiotics in the world ² and national data on AMR are alarming. Tunisian multicentre data show that the resistance of E. coli strains to third-generation cephalosporins increased from 3.9% to 19.3% and resistance to ciprofloxacin increased from 13.5% to 25.6% between 2004 and 2017. During the same period, resistance of K. pneumoniae strains isolated from bloodstream infections to imipenem increased from 0 to 12.1%. ⁴ In our institution, a multidisciplinary university hospital with 850 beds, more than 30% of the pharmacy budget is spent on antibiotics. Regarding antibiotic mis-usage, we observed that 35.7% of inpatients are on antibacterials of which 45.8% patients received an inappropriate prescription.

Building on these findings, we started an ASP in July 2014. We took three major steps. The first step was the implementation of an antibiotic management team (AMT) with a part-time Infectious Diseases (ID) specialist. The role of the “Antibiotherapy Referent (AR)” was to provide antibiotic therapy advice to prescribers. The second step was to centralise all antibiotic advice requests. The third step was that all requests and responses were documented. Antibiotic therapy advice forms were created and AR responses were computer recorded.

This paper describes AR activity from 1 July 2014 to 31 December 2018. During the study period, 3,872 requests were registered. The requests came from surgical departments (1,742 / 45% cases), medical departments (1,587 / 41% cases) and emergency and intensive care wards (543 / 14% cases). ID requests were made by senior doctors (1,641 / 42.4% cases), specialist trainees (948 / 24.5% cases) and generalist trainees (1,283 / 33.1% cases). To respond to requests, AR consulted patients’ medical records (3,016 / 77.9% cases) and moved to the patients’ beds (759 / 19.6% cases). In 97 cases (2.5%), antibiotic advice was given by phone call. Among all requests, 78.1% (n=3,024) were on antibiotic therapy management, 10.3% (n=399) were on the patient transfer and 8.2% (n=318) were on diagnostic advice (Figure). It is worth noting that the main reason for antibiotic management requests is antibiotic therapy adjustment which represents 66.1% (1,999 requests) of all the requests (3,024). The AR was asked to initiate antibiotics in 798 cases (26.4%) while discontinuation of antibiotic therapy was requested in 227 (7.5%) (Table). The AR’s intervention resulted in cessation / avoidance of antibiotic therapy in 419 cases (13.8%). When an antibiotic adjustment was recommended (1,363 cases), de-escalation was proposed in 409 cases (30%). Finally, concordance between prescriber requests and AR’s advice was 65.5%.
Our findings manifested by worrying antibiotic consumption data, AMR and the demand from antibiotic prescribers for ID advice show a real need for the implementation of an ASP in our hospital. This need affects all medical and surgical wards and all categories of physicians from trainees to senior doctors. We have noticed that trainees made the highest number of requests reaching 57.6% while senior doctor requests represent 42.4% of all the cases. We have shown that ASP can reduce antibiotic consumption and hospitalisation length-of-stay. Reduced antimicrobial use contributes to a reduction in mortality. Moreover, ASP leads to reduced AMR. Molina et al., proved that an education-based ASP was effective in decreasing the mortality rate of multidrug bloodstream infection through sustained reduction in antibiotic use. The goal of an ASP is to improve antimicrobial use. This involves choosing the right drug for the appropriate diagnosis, the correct dose and the adequate duration of treatment. Creation of an AMT is crucial to a successful ASP. Its mission is to devise a strategy for rational use of antibiotics. In our local context, an ID specialist acted as the AR. His decisions are more likely to be accepted and applied by prescriber physicians due to his in-depth knowledge and expertise in the field of antibiotic therapy but the fact that he is part-time is an obstacle to better ASP implementation. In fact, face-to-face interaction was largely impossible due to AR time constraints and advice was mostly provided in patients’ records. Our referent chose a post-prescription approach which gives prescribers the option to request advice or not to. A pre-prescription approach is a better means of controlling antibiotic consumption but is less accepted by prescribers. Indeed, it allows the physician to benefit from the expert knowledge of the AR before antibiotic prescription. However, it requires the recruitment of full-time and well-trained AMT.

Regardless of the chosen approach, experience in different countries shows that the presence of an antibiotic therapy referent results in better patient treatment and is cost-effective. We found 65.5% concordance between requests and referent opinion. However, we were unable to check that the AR advice has been followed in cases of discordant opinions.

In conclusion, our experience shows that there is a need for the implementation of a full-time multidisciplinary ASP team. We also believe that a pre-prescription approach and the implementation of patients’ electronic medical records will allow the proper use of antimicrobials in a cost-effective way. Therefore, institutional support is needed for a successful ASP.

References
Antibiotic Stewardship to Control MRSA: is it possible?

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Much attention is given to the rising carbapenemase problem across the globe but MRSA continues to be a major burden with few countries successful in its control. One exception is the UK where hospital strains were so prevalent at the turn of the century that their control became an important campaign factor in the government elections in 2005. At that time, major public concern about the dangers of hospital-acquired MRSA led to a national hand hygiene campaign, government funding for admission screening and improvements to hospital hygiene standards. The general attitude to MRSA at that time was that it was a hygiene / infection, prevention & control (IPC) issue. Several high profile UK publications suggested some reduction in MRSA rates after these measures were introduced but also suggested that much of the decline was due to natural strain variation. In the USA too, IPC measures and universal chlorhexidine decontamination (particularly targeting ICU patients) were introduced with some success.

The real success in MRSA control in the UK came after the introduction of antibiotic restriction policies to control a nationwide epidemic of C. difficile, predominately epidemic strains 001 and 027. These were unusually antibiotic resistant strains, resistant not only to the cephalosporins (as are all strains of C. difficile) but also to the quinolones and macrolides. Earlier work from our centre in Scotland demonstrated it was these antibiotic classes that were driving the MRSA epidemic which was caused by E15 and which had its epicentre in the ICU. This was soon replaced however, by E15 in the rest of the hospital. Recently we stopped ICU chlorhexidine bathing (unless patients screen positive for MRSA) as we have seen a build-up of QAC genes linked to AMR on mobile elements in epidemic strain of S. epidermidis, which is a worrying feature.

Analysis of antibiotic use data has allowed us to establish non-linear associations with resistance and the identification of thresholds of consumption, as originally postulated by APUA’s founder, Stuart Levy. It is apparent that there are no safe prescribing levels of cephalosporins in relation to MRSA. Reasonable levels of quinolone, macrolide and co-amoxiclav prescribing can be maintained even in the presence of resistant epidemic strains. It is only when prescribing thresholds are exceeded that it is cost effective for carriage of the key resistant genes that give strains survival value. Thresholds were also identified for (a) bed occupancy (more than 80% was a tipping point for increased MRSA), (b) proportion of patients screened on admission, (c) number of MRSA patients admitted, (d) length of stay and

Most of the data that enables us to be very confident of the reasons for the successful control of MRSA in North-East Scotland comes from more than 20 years’ worth of antibiotic resistance / use data. The same phenomena may be evident elsewhere in the UK, but other antibiotic resistance / use databases are less complete. Our early ICU intervention [Fig 1] with chlorhexidine bathing commenced in 2001 and was successful in controlling E16, which had its epicentre in the ICU. This was soon replaced however, by E15 in the rest of the hospital. Recently we stopped ICU chlorhexidine bathing (unless patients screen positive for MRSA) as we have seen a build-up of QAC genes linked to AMR on mobile elements in epidemic strain of S. epidermidis, which is a worrying feature.
levels of hand hygiene gel use. Antibiotic use thresholds vary with several factors e.g. susceptibility of patients (older patients require lower thresholds of antibiotic use to control epidemic strains of MRSA and C. difficile).

Success in MRSA control has not needed much resource; there was no use of molecular screening methods or expensive publicity campaigns. It simply requires government oversight and committed senior hospital management; co-ordination by existing IPC and AMS teams. Total antibiotic use was not reduced. Rather, substitution of key drug classes with gentamicin, cotrimoxazole, tetracyclines and narrow spectrum penicillins enabled more diversity in prescribing with limited increase in resistance to these agents. Additionally, there has been reduced mortality, not least from the control of MRSA bacteraemia. Given the well-known human and economic costs of MRSA why doesn’t the world make more of an effort to control it? Control is not expensive. Moreover, epidemic strains of MRSA don’t usually replace MSSA, but are an additional burden of infection. Outside Northern Europe, hospitals commonly cite MRSA rates of 50%, implying a doubling of S. aureus infections. This is certainly worth addressing!

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2. Lawes T et al. Turning the tide or riding the waves? Impacts of antibiotic stewardship and infection control on MRSA strain dynamics in a Scottish region over 16 years: non-linear time series analysis. BMJ Open 2015;5:e006596
The need for an open access global directed antimicrobial treatment guideline

Heiman Wertheim
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The World Health Organization (WHO) recently stated that resistance to antimicrobials means ‘an end to modern medicine as we know it’. Antimicrobial resistance (AMR) leading to treatment failure of common infections is the greatest contemporary challenge in infectious diseases. The causes of AMR are complex, with inappropriate antimicrobial use in humans and animals as a key factor. The problem is particularly pressing in low- and middle-income countries (LMICs), where the high burden of infectious disease is compounded by treatment failures and due, in part, to AMR. Importantly, many doctors in LMICs have little or no access to simple, up-to-date and contextualised treatment guidelines that would provide them with the best available evidence on how to treat a specific disease, whether it is susceptible or resistant to available drugs. Up to date and evidence-based antibiotic treatment guidelines, are essential to facilitate appropriate use of antibiotics but such a tool, which would require significant effort and input from experts to compile, is not available for most prescribers around the globe. WHO will release a syndromic, empiric treatment guideline. For directed therapies however, there is still a need. A recent study illustrated that only a few guidelines around the world include local etiological or resistance data.

Currently, online antimicrobial treatment guidelines are either commercial (payment required), restricted access or in a static format that cannot be easily adapted or updated. Furthermore, most guidelines have been developed for high-income countries and are often not applicable to LMIC settings or are confined to specific patient groups (e.g. HIV/AIDS-patients, TB and paediatric). There is clearly a need for a core directed antimicrobial treatment guideline that can be adapted by anyone, anywhere in the world, comparable to the world wide availability of Wikipedia in multiple languages.

“There is clearly a need for a core directed antimicrobial treatment guideline that can be adapted by anyone, anywhere in the world, comparable to the world wide availability of Wikipedia in multiple languages”

ISAC, APUA and their stakeholders are in a key position to pull this off as they have sufficient expertise in their global networks. For the development of this open access Directed Treatment Guide, an international core editorial team needs to be formed with broad access to networks of infectious disease experts (including paediatrics and representatives of other relevant specialist groups). We envision a crowd sourcing project which includes expertise from resource-constrained settings and contributions will largely be done through acknowledging contributors for intellectual input. The crowd sourcing nature of this project will allow it to continue and be updated after the duration of this project. WHO supports such an initiative, which is highly relevant for worldwide acceptability and application. ISAC, APUA and stakeholders discussed this project during ECCMID in Amsterdam in 2019. There is broad support of this initiative and over the coming months we will develop what is meant by directed therapy.

There is considerable inappropriate use of antimicrobials worldwide, often due to lack of knowledge and lack of access to evidence and updated guidelines. Providing access to a comprehensive, open access, up-to-date and evidence based knowledge-base that outlines how to treat a particular infectious disease is key to improving treatment outcomes.
worldwide. In addition, the availability of global evidence-based guidelines may help local professional bodies of health care workers to advocate for the availability of essential antimicrobial drugs. They may also be the starting base for local guidelines, adapted to the best available local evidence. Moreover, this tool will provide a much needed reference standard for the assessment and improvement of local prescribing practices, as well as a benchmark against which future antimicrobial stewardship interventions can be assessed. Finally, this guideline will define key diagnostic decision points to determine treatment, and provide an authoritative platform to inform WHO and other international health organisations.

References

Don’t miss the 31st International Congress of Antimicrobial Chemotherapy—4th Gulf Congress of Clinical Microbiology & Infectious Disease (31st ICC—4th GCCMID) is taking place in Dubai from 6-9 November 2019!

Register now to join some of the world’s most renowned experts specialising in infectious diseases, antimicrobial chemotherapy, infection control, and clinical microbiology.

Submit abstracts / apply for ISAC Travel Grants by 27 August!

ISAC member society applicants who submit an abstract and are under 35 years old are invited to apply for an ISAC Travel Grant. Successful applicants will receive 1,000 USD towards travel to Dubai and hotel accommodation as well as free congress registration. See the website for more details.

Programme Highlights

Plenary Lectures

- **In Vitro Veritas - Susceptibility Testing in the 21st Century**
  John Turner, 2019 HUMA Awardee, Australia

- **E-learning and Innovative Educational Solutions for Global Antimicrobial Stewardship**
  Dilip Nathwani, United Kingdom

- **Update on MERS CoV infection: How Close are we to Controlling It?**
  Yaseen Arabi, Saudi Arabia

- **Access Barriers to Effective Antibiotics**
  Ramanan Laxminarayan, United States

- **AMR in the Gulf Region: Where Are We Heading?**
  Hanan Baithy, Saudi Arabia

Keynote Lectures

- **Emerging and Vector-Borne Infections and their Prevention**
  Mohammed Al Haemi, Saudi Arabia

- **Reactive Oxygen - A Novel Antimicrobial**
  Matthew Dryden, United Kingdom

- **Sepsis**
  Huwaiin Abdulaadit Alawadih, United Arab Emirates

- **Forgotten and Novel Antimicrobials**
  Po-Ren Hsuah, ISAC President, Taiwan

- **Infectious Diseases and Displaced Persons**
  Salah Al Awady, Oman

- **Antimicrobial Stewardship: An Experience from UAE**
  Khuloud Bin Rafiea, United Arab Emirates
APUA Bulgaria
Action plan to combat antimicrobial resistance in Bulgaria (2020-2024)
Following years of preparation and revision, the Bulgarian action plan to combat antimicrobial resistance (AMR) is now ready. It has been prepared by an expert group within the Ministry of Health (MH) including representatives from leading institutions in human medicine (the majority of whom are APUA members), veterinary medicine and environmental science. Two strategic aims and five strategic tasks have been identified:

Aims:
- Antimicrobial stewardship (AMS): prudent use of antibiotics.
- Surveillance of AMR with implementation of epidemiological control measures.

Strategic tasks:
- Improve awareness and knowledge of AMR through education.
- Increase and strengthen research and effective communication of scientific data.
- Strengthen infection prevention and control.
- Promote AMS and increase surveillance and control of antibiotic consumption.
- Promote innovations to develop new antimicrobial agents and new diagnostic technologies.

Managing the containment of AMR requires a complex (one-health) approach by all parties for sustained reduced emergence and spread of antibiotic resistant strains. Implementing concrete measures and actions in different areas such as legislation, education, competent use, control, awareness and research is required. The most important interventions are:
1. Increase societal awareness and knowledge of AMR.
2. Achieve a basic knowledge of antibiotics, antimicrobial chemotherapy, AMR and AMS in higher education across various medical disciplines through improved educative programmes.
3. Strengthen the capacity of microbiology laboratories, dealing with AMRS in human, veterinary, food and environmental sectors (availability of tests and methods for rapid diagnosis); build a net-reference centre/laboratories; participate in national, European and international research projects.
4. Establish AMS teams in ambulatory and hospital care as a Government policy.
5. Increase awareness and knowledge of AMR and infection control in people working in animal husbandry and the food chain.
6. Improved pharmaceutical services: provide all necessary antimicrobial agents for human and veterinary use; reliable system for surveillance of antibiotic consumption in ambulatory, hospital and veterinary sectors; greater control of over the counter sales. Legislative interventions are required: promote state mechanisms for delivering clinically important antibiotics that are now unavailable in the country drug market; control the use of antibiotics that contribute significantly to development and spread of particular resistance mechanisms; ensure that patients with XDR-infection will be treated with reserve / newest antibiotics (despite the high cost).
7. Improved infection prevention and control measures in hospitals e.g. enough isolation rooms in hospitals, obligatory screening procedures for pan-drug and XDR-microorganisms etc.

The plan contains a detailed operational section that outlines delivery times, responsible persons, finances and criteria for assessing performance. Initially, it will be widely discussed and forwarded to different ministers for coordination before it is presented to the Council of Ministers.

For more information on APUA Bulgaria’s activities / publications, see the APUA Bulgaria webpage.

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APUA Kenya
Antimicrobial Stewardship
- Completed a point prevalence survey on antibiotic use in 3 major hospitals in Kenya and an additional 3 high volume hospitals covered through partnerships with graduate student research.
- Development of National Antimicrobial Stewardship Guidelines is in progress due for completion by end of July 2019.
- Establishment of Stewardship Programmes in hospitals (piloting has been ongoing since January 2018 in 5 county hospitals in Kenya).
- Review of antibiotics import data is in progress since January 2019 through the National Medicines Regulatory Authority alongside the mapping of medicines along the veterinary supply chain.

Major challenges: Inadequate resources to support the development and implementation of the National Guidelines for Antimicrobial Stewardship at a National level.
Combination antibiotic therapy could defeat ‘superbugs’
A study in *Nature Microbiology* has shown that specific antibiotic drug combinations can destroy multidrug-resistant bacteria that demonstrate heteroresistance.

Weiss *et al.* examined 104 bacterial isolates from a CDC-supported surveillance programme in Georgia (Multi-site Gram-negative Surveillance Initiative), that tracks multi-drug-resistant carbapenem-resistant *Enterobacteriaceae* superbugs. They found 88% were heteroresistant to at least two antibiotics. Further, the study shows that this heteroresistance may also provide an opportunity for combination therapy – if bacteria were heteroresistant to two different bacteria, two drugs used in combination killed the bacteria more effectively.

Grant to help Tanzania combat AMR
The American Society for Microbiology (ASM) and the Fleming Fund will lead a one-health partnership with the Southern Africa Centre for Infectious Disease Surveillance (SACIDS) and Africare to strengthen Tanzania’s national antimicrobial resistance (AMR) surveillance strategy. The consortium aims to:
- Train microbiologists to conduct required AMR surveillance testing.
- Improve access to laboratory supplies.
- Strengthen antimicrobial stewardship.
- Foster interdisciplinary collaboration.
- Standardise quality assurance in laboratory testing.
- Promote the understanding of appropriate antimicrobial use.
- Increase the number of health facilities that routinely do culture and antimicrobial drug susceptibility tests.

2nd Dutch Ministerial Conference on AMR
The second Ministerial Conference on AMR was held in the Netherlands in June to discuss progress made since the first ministerial conference on AMR in 2014 and to further accelerate the implementation of the Global Action Plan on AMR. It was sponsored by the World Health Organization (WHO), Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE). The full congress report is now available.

Multi-Partner Trust Fund launched to combat global AMR
A joint effort by the Food and Agriculture Organization (FAO), the World Organisation for Animal Health (OIE) and WHO – has launched an AMR Multi-Partner Trust Fund, supported by an initial contribution of US$5 million from the Government of the Netherlands. The Trust Fund has a five-year scope and aims to increase efforts to support countries to counter the immediate threat of AMR.

The immediate funding appeal is for US$70 million to support countries and the implementation of the Tripartite AMR Workplan 2019—2020.

GARDP “5 by 25” initiative
The Global Antibiotic Research and Development Partnership (GARDP) is calling upon the global community to support its goal to develop and deliver five new treatments to address antibiotic resistant infections by 2025 (‘5 by 25’).

As an integral element of WHO’s Global Action Plan on AMR, GARDP is calling on Member States, philanthropic and other global organisations to support ‘5 by 25’ and contribute towards its target of €500m. GARDP announced it will launch its business plan to deliver its ‘5 by 25’ goal on 28 October 2019 at the World Health Summit in Berlin.

WHO list of critically important antimicrobials
WHO has identified “Highest Priority Critically Important Antimicrobials” in the WHO list of critically important antimicrobials for human medicine (WHO CIA list). The CIA list is intended to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine. The “Highest Priority Critically Important Antimicrobials” are: quinolones, 3rd and higher generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

Long delays prescribing new antibiotics hinder market for needed drugs
A survey into how 132 U.S. hospitals prescribed six new antibiotics from 2014-2018 found that the average time to prescribe one of the new drugs was 398 days. The results, published in *Diagnostic Microbiology and Infectious Disease*, showed that the average time varied from less than two weeks to more than four years and varied by region. The delay may threaten the supply or discourage future development of needed drugs.

Urban wildlife may add to AMR threat
A study in *Lancet Planetary Health* found that urban wildlife in Nairobi has a high burden of clinically relevant AMR bacteria. Faecal samples were collected from 75 species of wildlife from the household / perimeter of 99 households across Nairobi. The team cultured *Escherichia coli* from the specimens and tested a single isolate from each sample for sensitivity to 13 antibiotics. This was compared against samples from livestock, humans and the environment. The authors conclude that wildlife that interacts closely with humans, livestock, and both human and livestock waste within households are exposed to more antimicrobial resistant phenotypes. They could therefore act as conduits for the dissemination of clinically relevant antimicrobial resistance to the wider environment.

Australia to launch 20-year plan to combat AMR
The Australian Government has published a consultation paper which seeks stakeholder feedback on Australia’s five-year antimicrobial resistance strategy (published in 2015) and sets out plans for a future strategy. According to the paper, the strategy should have a clear 20-year aspirational vision, with shorter-term action plans.
Development of new antibiotics encouraged with new pharmaceutical payment system
The National Health Service (NHS) in the UK will test the world’s first ‘subscription’ style model that pays pharmaceutical companies upfront for drugs based on their usefulness to the NHS. The new trial will be led by the National Institute for Health and Care Excellence (NICE), NHS England and NHS Improvement. The trial is calling for companies to identify products to be considered for the initial phase of the test. Findings will be shared globally so that other healthcare systems can test similar models.

Antibiotics in rivers vastly exceed ‘safe’ level
A new study by researchers at the University of York, UK, looked for 14 commonly used antibiotics in rivers in 72 countries across six continents and found antibiotics at 65% of the sites. The Kirtankhola River in Bangladesh contained the highest antibiotic level of any site with concentrations of Metronidazole 300 times greater than the ‘safe’ level. The team said that the ‘safe’ limits were most frequently exceeded in Asia and Africa but sites in Europe, North America and South America also had concerning levels. Trimethoprim, an antibiotic primarily used to treat urinary tract infections, was the most prevalent which was detected at 307 of the 711 sites tested.

Antibiotic reduction: no negative impact on Dutch famers
The reduction in antibiotic sales of 63% between 2009 and 2017 in the Netherlands did not have a negative impact on Dutch farmers according to a recent policy paper on Economics of antibiotic usage on Dutch farms. It also summarised the following:
- To improve animal health (which made a reduction in antibiotic usage possible) farmers used a variety of relatively easy and cheap measures. These included more attention to hygiene, use of pain killers and anti-inflammatory agents or more preventive vaccinations.
- International cost competitiveness of Dutch broiler and pig farms was not hampered by the reduction in antibiotic usage. The deterioration of the cost competitiveness in especially sow farms was caused by other factors, e.g. an increase of environmental costs.

Antibacterial agent found in toothpaste could increase osteoporosis
A study published in The Journal of Clinical Endocrinology & Metabolism found that women exposed to triclosan, an antibacterial agent found in soaps, toothpastes and cleaning products, could have a greater risk of osteoporosis.

The study examined 2005-10 National Health and Nutrition Examination Survey data to find an association between concentrations of triclosan in urine and osteoporosis in 1,848 U.S. women aged 20 and older. Researchers found triclosan concentrations were negatively associated with bone mineral density and positively associated with osteoporosis. However, the authors say future prospective studies are needed to validate the findings.

U.S. Biodefense, Preparedness, and Implications of Antimicrobial Resistance for National Security
The United States House Committee on Oversight and Reform Subcommittee on National Security held a hearing in June on “U.S. Biodefense, Preparedness, and Implications of Antimicrobial Resistance for National Security.”
Center for Integrated Management of Antimicrobial Resistance Director Helen Boucher and three other experts testified at the hearing to help the subcommittee examine the readiness of the U.S. government and healthcare system, including hospitals and emergency professionals, to respond to naturally-occurring pandemics and biological attacks. The subcommittee will investigate the growing threat of antimicrobial-resistance, as well as the implications of this challenge for U.S. national security. Watch the full hearing here.

Colistin use banned in India
The Indian Government has banned the use of colistin on farms after an investigation revealed it was being widely used as a growth promoter in livestock. The Ministry of Health issued a notification prohibiting the “manufacture, sale and distribution of the drug and its formulations for food-producing animals, poultry, aqua farming and animal feed supplements” because such use is “likely to involve risk to human beings”. That also means the drug cannot be used as a veterinary medicine for farm animals. The ban follows recommendations earlier this year by India’s top drug advisory body, the Drugs Technical Advisory Board and the National Antimicrobial Resistance Action Plan committee.

Antibiotic Prescribing for urinary tract infections (UTIs)
A new draft guideline from the National Institute for Health and Care Excellence (NICE) and Public Health England sets out an antimicrobial prescribing strategy for lower UTIs (cystitis). It also aims to optimise antibiotic use and reduce antibiotic resistance. The draft guideline is is expected to be formalised in January 2019.

Robots to help produce new antibiotics
In a study in PLOS Biology, a team from The University of Manchester in the UK has engineered a common gut bacterium to produce a new class of antibiotics, known as class II polyketides, by using robotics. The antibiotics are also produced by soil bacteria but the naturally-produced Escherichia coli (E. coli) bacteria are difficult to work with as they grow in dense clumps that are incompatible with the automated robotic systems used for modern biotechnology research. By transferring the production machinery from the soil bacteria into E. coli, this class of antibiotics is accessible for much more rapid exploration.

By combining the bacterial production machinery with enzymes from plants and fungi, it was possible to produce new chemical compounds not previously seen in nature. Using this plug-and-play platform, it will now be possible to explore and engineer polyketides using robotic systems to develop new and diversified polyketides in an automated, rapid and versatile fashion.
## Publications of Interest

- **World Health Organization:** Monitoring and evaluation of the global action plan on antimicrobial resistance: Framework and recommended indicators. May 2019
- **Chemical disarming of isoniazid resistance in *Mycobacterium tuberculosis.*** Flentie K *et al.* *PNAS* 2019;116:10510-10517
- **Wildlife is overlooked in the epidemiology of medically important antimicrobial resistant bacteria.** Dolejska M *et al.* *Antimicrob Agents Chemother* 2019; accepted online
- **Low prevalence of zoonotic multidrug-resistant bacteria in veterinarians in a country with prudent use of antimicrobials in animals.** Verkola M *et al.* *Zoonoses Public Health* 2019; ahead of print
- **One-Day Point Prevalence of Healthcare-Associated Infections and Antimicrobial Use in four Countries of Latin America.** Huerta-Gutierrez, R *et al.* *Int J Infect Dis* 2019; ahead of print
- **New Drugs for Multidrug-Resistant Gram-Negative Organisms: Time for Stewardship.** Jean S-S *et al.* *Drugs* 2019; 79:705-714
- **Seasonal variation in antimicrobial resistance rates of community-acquired *Escherichia coli* bloodstream isolates:** Ramsey EG *et al.* *Int J Antimicrob Agents.* 2019; 54;:1-7

## Events

### 2019 World Dental Congress
4-7 September 2019, San Francisco, CA.
This year’s dental congress will host a session entitled 'The Role of Dentists and Dental teams in Mitigating Antibiotics Resistance'

### Global Vaccination Summit
12 September 2019, Brussels, Belgium
The European Commission and World Health Organisation will co-host the summit which will demonstrate EU leadership for global commitment to vaccination, boost political commitment towards eliminating vaccine preventable diseases and engage leaders from the scientific, medical, and political communities, as well as, across industry, philanthropy and civil society.

### CDDEP Awards in Antimicrobial Resistance
Center for Disease Dynamics, Economics & Policy (CDDEP) AMR awards will sponsor two individuals for the best-accepted abstracts for the 19th International Congress on Infectious Diseases (ICID) addressing AMR in low- or middle-income countries. The awards consist of travel, accommodation and registration expenses for the 19th ICID in Kuala Lumpur, 20 -23 February, 2020. Submit your abstract addressing AMR in LMICs by 25 October 2019

### Decennial International Conference on Healthcare-Associated Infections
Atlanta, GA 26 -30 March 2020
Global Solutions to Antibiotic Resistance in Healthcare

### International Symposium on Staphylococci and Staphylococcal Infections (ISSSI) 2020
23 -26 August 2020, Perth, Australia
ISSSI 2020 will cover many interdisciplinary subjects regarding staphylococci and staphylococcal infections. Sessions will be presented by the world’s leading experts in each of the research fields. Oral and poster sessions will be an integral part of the programme as well, and all delegates are invited to submit abstracts.
To launch the merger of APUA and the International Society of Antimicrobial Chemotherapy (ISAC), a reception was held during ECCMID in Amsterdam in April 2019.

The Reception was well attended by affiliates of both APUA and ISAC - thank you to those of you who were able to attend. Visit www.apua.org to see more photos from the event.