APUA® NEWSLETTER
International Society of Antimicrobial Chemotherapy
Spring 2019
Volume 37, No. 1

PUBLISHED SINCE 1983 BY THE ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

TABLE OF CONTENTS

APUA®

International Society of Antimicrobial Chemotherapy

"Preserving the Power of Antibiotics"

APUA / ISAC Merger Announcement

APUA recently took the difficult decision to relinquish its independent status and to merge its activities with the International Society of Antimicrobial Chemotherapy (ISAC). This move is tinged with sadness as it was prompted by Stuart Levy's retirement from Tufts University School of Medicine in Boston which has served as the operational base for APUA for almost four decades. Stuart's inspirational leadership of APUA will be sorely missed and we wish him all the very best in his retirement.

ISAC is delighted to bring APUA into its portfolio and to lead its regeneration. The Boards of the ISAC Antimicrobial Stewardship Working Group and APUA have merged to form a new APUA Board which will be chaired by Pierre Tattevin. Furthermore, members of APUA's Scientific Advisory Board and ISAC's Antimicrobial Stewardship Working Group have been invited to transfer their membership to the new APUA International Advisory Board.

APUA Board Members

APUA Chair
Pierre Tattevin (France)

APUA Vice-Chair
Geoff Coombs (Australia)

APUA Secretary
Mushira A. Enani (Saudi Arabia)

R. Gaynes (USA)

A. Ghafur (India)

S. Gharakhanian (USA)

S. Kanj (Lebanon)

C. Larkin (USA)

G. Levy Hara (Argentina)

F. MacKenzie (UK)

M. Riley (USA)

R. Saginur (Canada)

D. White (USA)

The Prudent Use of Antibiotics: Reason to Hope!

Pierre Tattevin

APUA Board Chairman

The Alliance for the Prudent Use of Antibiotics (APUA) recently merged with the International Society of Antimicrobial Chemotherapy (ISAC) to promote the better use of antibiotics, a fight of paramount importance.

Looking back at the activities of both organisations over the years, one may feel somewhat discouraged as antibacterial resistance is much worse than it was when ISAC was founded almost 60 years ago and when Stuart Levy began his long journey advocating for appropriate use of antibiotics 40 years ago. The sobering facts that meticillin-resistant *Staphylococcus aureus* (MRSA) and Extended Spectrum Beta-Lactamases (ESBL) producing Enterobacteriaceae are now regularly encountered in patients with no link to the healthcare system in many countries are a dramatic illustration of failure, despite numerous interventions undertaken. One should not give up however, as this demonstrates that the warnings raised by a few prophetic voices decades ago were absolutely right: overuse of antibiotics leads to the emergence of multidrug resistant (MDR) bacteria and this is not being matched by the development of new antibiotics. The most affected countries daily face the clinical impact of MDR with common infections only controlled by complex antibacterial treatment or, worse, are left with no active antibiotic. As with climate change, the proportion of non-believers has gradually decreased so now no observer can *bona fide* state that overuse of antibiotics is harmless.

Although the level of MDR in many parts of the world testifies that humans failed to preserve the efficacy of antibiotics, there are still reasons to hope. Firstly, several countries that implemented ambitious policies towards more appropriate use of antibiotics have demonstrated that MDR may be reversed within a few years, as could be predicted from the fast evolution of bacterial genes. Secondly, thanks to the free exchange of knowledge internationally via websites, meetings, publications and social media, innovative interventions have emerged with documented efficacy that could be replicated around the world. This has led to the development of 'antimicrobial stewardship' (AMS) interventions that have now full matured, as demonstrated by the multiplication of dedicated AMS sessions in medical conferences. Looking back at the dramatic development of the AMS concept over the last ten years, one may be optimistic that with more commitment and investment from stakeholders the payback will be substantial. Thirdly, as with climate change, the costs associated with the emergence of MDR have led major policymakers to strengthen regulation of antimicrobials across multiple sectors including human health, animal health and agriculture.

The most spectacular demonstration of this awareness was the high-level meeting on antimicrobial resistance (AMR) at the United Nations (UN) headquarters in 2016; this was only the fourth time a health issue has been addressed by the UN General Assembly. Noting that AMR threatens the achievement of sustainable development goals, member states committed to develop national AMR action plans based on the "Global Action Plan on Antimicrobial Resistance" developed in 2015 by the World Health Organization in collaboration with the Food and Agriculture Organisation of the UN and the World Organisation for Animal Health. National strategies for combating AMR were not only released in so-called 'wealthy countries' such as the USA (**Figure.** The CDC's "Get Smart About Antibiotics Week"), but also in some low- and middle-income countries, sometimes supported by multinational and/or private-public partnerships.

Of course, this is not the time for complacency. The current situation is very bad and must be seen for what it is in most parts of the world: a failure to prevent the emergence of MDR despite the early warnings of pioneers in the field such as Stuart Levy and colleagues when they founded APUA. The medical community, policy makers and general population were informed that overuse of antibiotics would lead to disaster but we did little, or not enough, resulting in the current dire levels of MDR in many parts in the world with unprecedented burdens and high human tolls. However, as detailed above, there are many reasons to hope so we may reasonably expect that within a few years, if we are successful in advocacy, effective multidisciplinary and multinational collaboration and in the implementation of interventions that have been shown to be successful we will reverse the trend. The APUA / ISAC merger is one step forward in that direction!

Jean-Francois Jabbour

Emergence of Antimicrobial Resistance in the Arab Countries

Jean-Francois Jabbour and Souha S. Kanj

Division of Infectious Diseases, Department of Internal Medicine
American University of Beirut Medical Center, Beirut, Lebanon

Souha S. Kanj

The impact of antimicrobial resistance (AMR) is a global issue of great concern. The prevalence of multidrug resistant (MDR) pathogens has increased worldwide, including in countries of the Arab league[1]. There is heavy international travel to these countries due to the large population of expatriates and to the annual pilgrimage to the holy city of Mecca, which contributes to the spread of AMR organisms such as MDR *Acinetobacter baumannii* and NDM producing *Escherichia coli*[2], with high rates of ceftazidime resistance and septicaemia episodes[2].

A recent review addressing some of the WHO MDR priority pathogens summarised the published literature over a period extending from 2008 and 2017 on the commonly encountered MDR pathogens from 14 countries of the Arab League[1] (**Figure**). Starting with extended-spectrum beta-lactamase (ESBL) producing bacteria, overall rates were reported as 25% in Kuwait, 17% in Qatar, 7% in Saudi Arabia, 4% in Oman, 66% in Palestinian territories, 54% in Syria, 47% in Iraq, 45% in Jordan, 31% in Lebanon, 55% in Egypt, 35% in Sudan, 9% in Tunisia and Morocco, and 14% in Algeria[1]. However, a much higher rate was observed in some institutes, such as one from Saudi Arabia that had 29% ESBL rates among *E. coli* and 65% among *Klebsiella pneumoniae*[2].

> ***"Incidence rates of ESBL-producing E. coli and K. pneumoniae among urinary tract infections and intra-abdominal infections from Lebanon and Jordan increased by about 20% from 2011 to 2015."***

Similarly, rates were recently reported from the Study for Monitoring Antimicrobial Resistance Trends (SMART), which found that the rates of ESBL-producing *E. coli* and *K. pneumoniae* among urinary tract infections and intra-abdominal infections from Lebanon and Jordan increased by about 20% from 2011 to 2015[3].

A wide range of resistance genes has been reported from ESBL-producing Enterobacteriaceae in the region. However, a predominance of the *ctx-M* gene was observed[1] with CTX-M-15 as the most prevalent enzyme produced in isolates from Lebanon and Jordan[3].

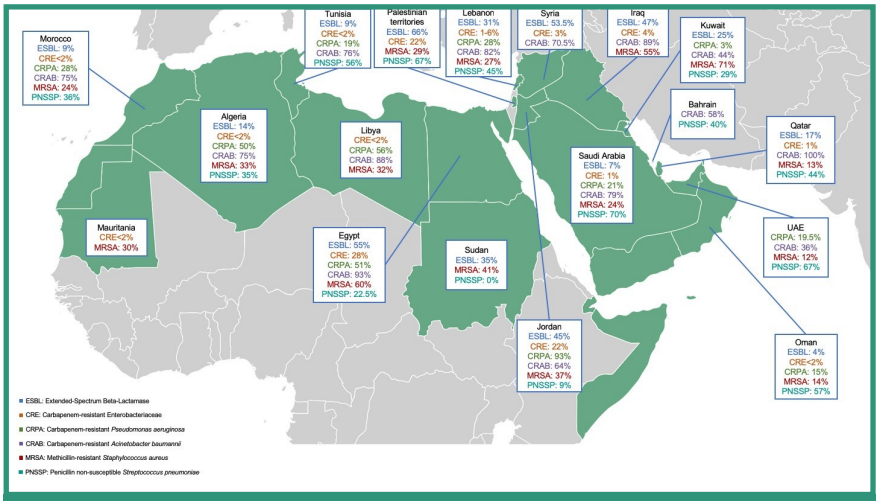
As for carbapenem-resistant Enterobacteriaceae (CRE), mostly *E. coli* and *Klebsiella* spp., their prevalence was found to be 1% in Saudi Arabia, Qatar and Lebanon, 3% in Syria, 4% in Iraq, 22% in Palestinian territories and Jordan, and 28% in Egypt[1]. Algeria, Libya, Morocco, Mauritania, Tunisia and Oman have a CRE prevalence of 2% or less[1]. More recently, many tertiary care centres across the region have observed an increase in the rate of CREs, reaching 7.3% in *Klebsiella* spp. and 5% in *E. coli* in a study from Lebanon[4].

The most commonly produced carbapenemases in countries of the Arab League were NDM-1 (46%), OXA-48-like (32%), or both (9%),[1,3] and only a few *K. pneumoniae* carbapenemase (KPC) enzymes in Jordan, Saudi Arabia and Egypt[5]. In addition, resistance to quinolones was seen in a recent report from Lebanese hospitals, where ciprofloxacin susceptibility decreased from 58% to 52% in two years[6]. Recent reports from the region described emerging resistance to colistin, where Enterobacteriaceae were found to carry the *mcr1* gene on conjugative plasmids[7]. As for carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) isolates, data from the Gulf Cooperation Council (GCC) showed a CRPA prevalence of 20% in the United Arab Emirates (UAE), 15% in Oman, 21% in Saudi Arabia, and 3% in Kuwait. In the Levant, Jordan had a percentage of 93%, and it was 28% in Lebanon. In the African countries the highest prevalence was found in Egypt (51%) and Libya (56%), followed by Algeria (50%), and the lowest prevalence was found in Tunisia (19%) and Morocco (28%)[1].

The production of metallo-β-lactamases (mostly VIM and IMP) is the most important mechanism of carbapenem resistance in *P. aeruginosa* throughout the Arab League countries[1]. Other rare enzymes were also reported, such as PME-1 from Qatar[8]. Mutations in *gyrA* and *parC* were reported from Lebanon, and mutation of *oprD* enhancing porin loss was identified in Lebanon and Algeria[1,9].

A recent study from the GCC countries found that the most prevalent carbapenemase-encoding gene was blaVIM (39%).[10] *Acinetobacter* spp. seen in this region are mostly hospital-acquired and MDR[11] and particularly carbapenem-resistant[6]. The highest

prevalence of carbapenem-resistant *A. baumannii* (CRAB) in the GCC is in Qatar (100%), followed by 79% in Saudi Arabia, 58% in Bahrain, 44% in Kuwait and 36% in the UAE[1]. In the Levant, the highest CRAB prevalence was reported in Iraq (89%) and Lebanon (82%), followed by Syria (70%) and Jordan (64%). In the African countries, Egypt (93%) and Libya (88%) reported the highest resistance prevalence, followed by Algeria (75%), Morocco (75%) and Tunisia (76%)[1].



Prevalence of the resistance of some of the WHO Priority pathogens in the countries of the Arab League

Most of the CRAB isolates in the GCC were found to harbor the *bla*$_{OXA51}$ gene and 91% of them were also positive for *bla*$_{OXA-23}$, which is the most predominant gene in Lebanon also[12]. Most countries report polyclonal spread with the predominant carbapenemases being OXA-23 and OXA-24 and are associated with high-level resistance. Rapid emergence of NDM1[1,12] is also reported. Recently, colistin resistance was reported in *A. baumannii* isolates[1].

Meticillin-resistant *Staphylococcus aureus* (MRSA) has been extensively reported as a hospital-acquired pathogen in most countries of the Arab league[1]. In the GCC, MRSA rates were found to be 24% in Saudi Arabia, 14% in Oman, 13% in Qatar and 12% in UAE. In Kuwait, MRSA was isolated from 71% of diabetic foot cultures. In the Levant, MRSA rates were found to be 27% in Lebanon, 29% in Palestinian territories, 37% in Jordan and 55% in Iraq. In the African countries, the lowest rate of MRSA was in Morocco (24%), followed by Mauritania (30%), Libya (32%), Algeria (33%), Sudan (41%) and Egypt (60%)[1]. There is a predominance in the SCC*mec* IV strain[13,14] and the Pantone Valentine Leukocidin gene.[14] More than 20% of strains harbored the *tst1* gene.

Penicillin non-susceptible *Streptococcus pneumoniae* (PNSSP) was reported from the region and pertained to invasive and non-invasive pneumococcal diseases, as well as from healthy carriers and Hajj pilgrims[1]. The highest rate of PNSSP from the GCC countries was in Saudi Arabia (70%), then UAE (67%), Oman (57%), Bahrain (40%), Qatar (44%) and Kuwait (29%). In the Levant, Palestinian territories reported 67% PNSSP, followed by Lebanon (45%) and Jordan (9%). In Africa, PNSSP rates were 56% in Tunisia, 36% in Morocco, 35% in Algeria, 22% in Egypt and none in Sudan[1]. Different serotypes exist in the region with the most common being 19F, 23F, 6B and 19A.[15]

It is clear that AMR is quite prevalent among most countries of the Arab League. While the Global Antimicrobial Resistance Surveillance System (GLASS) report will publish more representative data on the matter in the future, it is crucial to recognize the need for the standardization of microbiological methods and antimicrobial surveillance techniques in this region to accurately reflect the true burden of AMR and guide infection control and stewardship efforts.

References

1. Moghnieh, RA *et al*. Epidemiology of common resistant bacterial pathogens in the countries of the Arab League. *Lancet Infect Dis* 2018
2. Zowawi, HM *et al*. beta-Lactamase production in key Gram-Negative pathogen isolates from the Arabian Peninsula. *Clin Microbiol Rev* 2013
3. Hajj, A *et al*. Post Syrian war impact on susceptibility rates and trends in molecular characterization of *Enterobacteriaceae. Future Microbiol* 2018
4. Moussally, MZ *et al*. Prevalence of multidrug-resistant organisms at a tertiary care center in Lebanon, 2010-2016. Poster presented at *World Congress of Internal Medicine*, Cape Town, South Africa 2016
5. Zahedi Bialvaei, A *et al*. Dissemination of carbapenemases producing Gram negative bacteria in the Middle East. *Iran J Microbi* 2015
6. Chamoun, K *et al.* Surveillance of antimicrobial resistance in Lebanese hospitals: retrospective nationwide compiled data. *Int J Infect Dis* 2016
7. Sonnevend, A *et al*. Plasmid-mediated colistin resistance in Escherichia coli from the Arabian Peninsula. *J Med Microbiol* 2018
8. Zowawi, HM *et al*. PME-1-producing *Pseudomonas aeruginosa* in Qatar. *Antimicrob Agents Chemother* 2015
9. Salma, R *et al*. *gyrA* and *parC* mutations in quinolone-resistant clinical isolates of *Pseudomonas aeruginosa* from Nini Hospital in north Lebanon. *J Infect Chemother* 2013
10. Zowawi, HM *et al*. Identification of carbapenem-resistant Pseudomonas aeruginosa in selected hospitals of the Gulf Cooperation Council States: dominance of high-risk clones in the region. *J Med Microbiol* 2018
11. Kanafani, ZA *et al.* Ten-year surveillance study of ventilator-associated pneumonia at a tertiary care center in Lebanon. *J Infect Public Health* In Press
12. Kanj, SS *et al*. Increase in Prevalence of blaOXA-23-like Carbapenem Resistance-Encoding Gene Among Acinetobacter baumannii strains between 2007 and 2013 Outbreaks at a Tertiary Care Center in Lebanon. *J Infect Dev Ctries* 2018
13. Eed, EM *et al*. Phenotypic and molecular characterization of HA-MRSA in Taif hospitals, Saudi Arabia. *J Infect Dev Ctries* 2015
14. Sonnevend, A *et al*. Change in meticillin-resistant Staphylococcus aureus clones at a tertiary care hospital in the United Arab Emirates over a 5-year period. *J Clin Pathol* 2012
15. Memish, ZA *et al*. A cohort study of the impact and acquisition of naspharyngeal carriage of Streptococcus pneumoniae during the Hajj. *Travel Med Infect Dis* 2016

Superinfection: A forgotten quality measure of antimicrobial stewardship?

Khalid Eljaaly[1,2] and Mushira A. Enani[3]

[1]Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; [2]College of Pharmacy, University of Arizona, Tucson, AZ; [3]Medical Specialties Department, Section of Infectious Diseases, King Fahad Medical City, Riyadh, Saudi Arabia

Khalid Eljaaly **Mushira A. Enani**

Monitoring evidence of adverse events related to antibiotics was recommended by the 2016 Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) guidelines for implementing antibiotic stewardship programmes (ASP).[1] The guidelines however, have not addressed superinfections and which antibiotics are associated with higher risk of superinfections. This is likely due to limited data. Major concerns for the use of broad spectrum antibiotics include the emergence of superinfection during therapy.[2] Longer duration of antibiotics for ventilator-associated pneumonia (VAP) was associated with increased rates of susceptible and multidrug resistant superinfection.[3] The recommended antipseudomonal carbapenems for nosocomial pneumonia are imipenem and meropenem based on the current clinical practice guidelines but they should be reserved.[3] The authors hypothesised that these carbapenems might cause higher rates of superinfection attributed to their relatively broader spectrum of activity compared to other agents. Randomised controlled trials (RCTs) decrease the chance of selection bias but unfortunately do not consistently report superinfection rates and each is likely underpowered for detection of a statistically significant difference in occurrence of superinfections. Therefore, a meta-analysis was conducted with the aim of comparing the rate of superinfection between pneumonia patients who received imipenem or meropenem compared to non-carbapenem antibiotics.

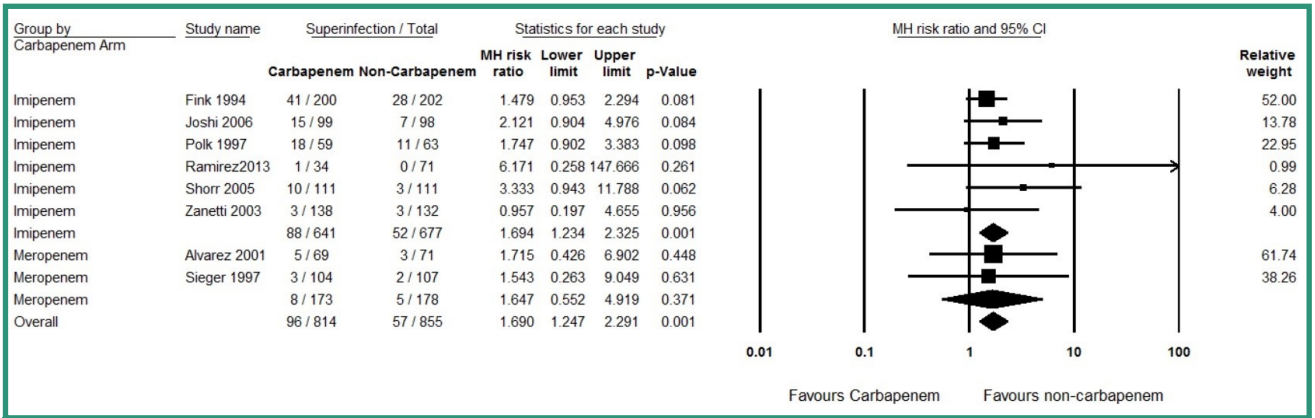
"Pneumonia treatment with imipenem associated with higher superinfection rates compared with non-carbapenem treatment."

Two researchers independently searched PubMed, Embase and Cochrane Library databases as well as the ClinicalTrials.gov and ClinicalTrialsRegister.eu websites without restriction of date or language until 25 February 2017 and performed the data extraction. The authors included RCTs of hospitalised adults with pneumonia that reported rates of superinfection and compared either imipenem or meropenem versus non-carbapenems. Superinfection was defined as isolation of a new pathogen after starting study antibiotic therapy and at least one of the following to reduce the likelihood of colonisation: symptoms and signs of infection and requiring treatment. The primary outcome was the superinfection rate based on the intention-to-treat (ITT) analysis. The secondary outcome was the superinfection rate among Clinically Evaluable (CE) patients. Subgroup analyses were done based on carbapenem type and pathogen according to the ITT principle and on presence of blinding. In addition, they analysed superinfection rates of carbapenems versus other antipseudomonal beta-lactams. Heterogeneity (I^2) was calculated using Cochrans's chi-squared test and risk ratios (RRs) with 95% confidence intervals (CIs) using random-effects models.

The search process identified 431 articles and eight RCTs (total of 1,874 patients) were included.[4-11] Based on ITT-analysis, the mean of superinfection was 11.79% (range, 2.88-30.51%) in the carbapenem group vs. 6.67% (range, 0-17.46%) in the non-carbapenem group. A statistically higher risk of superinfection (RR=1.69, 95% CI 1.25-2.29, p<0.001, I^2=0%) was associated with the two carbapenems compared to non-carbapenems **(Figure)**. In comparison with non-carbapenems, subgroup analysis showed that superinfection with imipenem was significantly higher (RR=1.69 [95% CI 1.23-2.33]; p<0.001; I^2=0%), while it was non-significant with meropenem (RR=1.65 [95% CI 0.55-4.92]; p=0.371; I^2=0%) (**Figure)**. The results did not change in subgroup analysis based on blinding and after restricting comparison group to anti-pseudomonal beta-lactams.

The difference was also statistically significant for CE-patients (RR=1.61 [95% CI 1.08-2.39]; p=0.018; I^2=0%). Only three studies reported the organisms causing superinfection[5,6,10]. *Pseudomonas aeruginosa* caused a statistically higher superinfection in the carbapenem group versus the fluoroquinolones group (RR=3.638 [95% CI 1.382-9.580]; p=0.047; I^2=0%; Q=0.009). There was no significant difference with other pathogens. However, it was not reported in any of the studies included if the bacteria causing superinfection were susceptible or resistant to the study antibiotic.

This is the first meta-analysis of RCTs showing higher risk of superinfection with carbapenems, especially imipenem, compared to other antibiotics including anti-



Forest plot showing the risk ratios of superinfection based on intent to treat analysis for patients receiving carbapenem versus non-carbapenem. Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios.

pseudomonal agents. Antibiotics change the normal protective microflora and its ecological balance in the body, leading to opportunistic pathogens overgrowth and superinfections.[12] It is a common clinical question to ask if carbapenem use causes more superinfections than other beta-lactam alternatives. The results provide support for using other antipseudomonal beta-lactams and reserving carbapenems for scenarios when they are really needed. A limitation of this meta-analysis is that superinfection was not characterised in all the studies included and thus superinfection may refer to fungal infection or the development of drug-resistant bacteria. Only three studies reported the organisms causing superinfection.[4,5,9] In this meta-analysis, the definition of superinfection was a clinical definition that took into account the development of symptoms and/or signs of infection and the need for treatment. This was done to reduce the possibility of colonisation, which is another dimension of antibiotic use. However, not all studies defined superinfection uniformly. For meropenem, only a few studies were included (post-hoc power calculation: 14.5%) and the pooled superinfection rate was not precise because the CI was wide. Another drawback is the fact that the imipenem studies were funded by the comparative drug manufacturers[5-9,11] and the two meropenem studies[4,10] were funded by the meropenem manufacturer. Thus, the presence of bias in reporting could not be entirely excluded.

In conclusion, a meta-analysis of pneumonia data of RCTs showed significantly higher superinfection with imipenem compared to non-carbapenems. Larger sample size is likely needed to determine if the same results apply to meropenem. This additional adverse outcome of carbapenem use provides added evidence to support reserving these valuable agents for the treatment of pneumonia caused by multidrug resistant organisms. Antibiotic stewardship programmes should seek to reduce unnecessary use of carbapenems.

References

1. Barlam TF *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016
2. Bliziotis IA *et al*. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2005
3. Kalil AC *et al*. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016
4. Lerma FA *et al*. Efficacy of Meropenem as Monotherapy in the Treatment of Ventilator-Associated Pneumonia. *J Chemother* 2001
5. Fink MP *et al*. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. The Severe Pneumonia Study Group. *Antimicrob Agents Chemother* 1994
6. Joshi M *et al*. Comparison of piperacillin/tazobactam and imipenem/cilastatin, both in combination with tobramycin, administered every 6 h for treatment of nosocomial pneumonia. *Respir Med* 2006
7. Polk HC *et al.* Treatment of pneumonia in mechanically ventilated trauma patients. Results of a prospective trial. *Arch Surg* 1997
8. Ramirez J *et al.* Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother* 2013
9. Shorr AF *et al*. Levofloxacin for treatment of ventilator-associated pneumonia: a subgroup analysis from a randomized trial. *Clin Infect Dis* 2005
10. Sieger B *et al*. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med* 1997
11. Zanetti G *et al*. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* 2003
12. Sullivan A Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infect Dis* 2001
13. Masterton RG. Carbapenems in serious infections: maximizing the power, minimizing resistance. *Clin Microbiol Infect* 1999
14. Paul M *et al*. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* 2004

Colistin-Resistant Superbugs and Poultry Politics!

Abdul Ghafur

Coordinator, Chennai Declaration on AMR; Consultant in Infectious Diseases and Clinical Microbiology, Apollo Cancer Institute, Chennai

The ancient Indian scripture *Manusmriti* forbids eating food in which hair or bugs have fallen and food that belongs to a miser, a thief, a cruel man, a liar and a doctor! The list is so long that it mentions almost every food we are expected not to eat, with a notable exception – food that contains colistin-resistant superbugs!

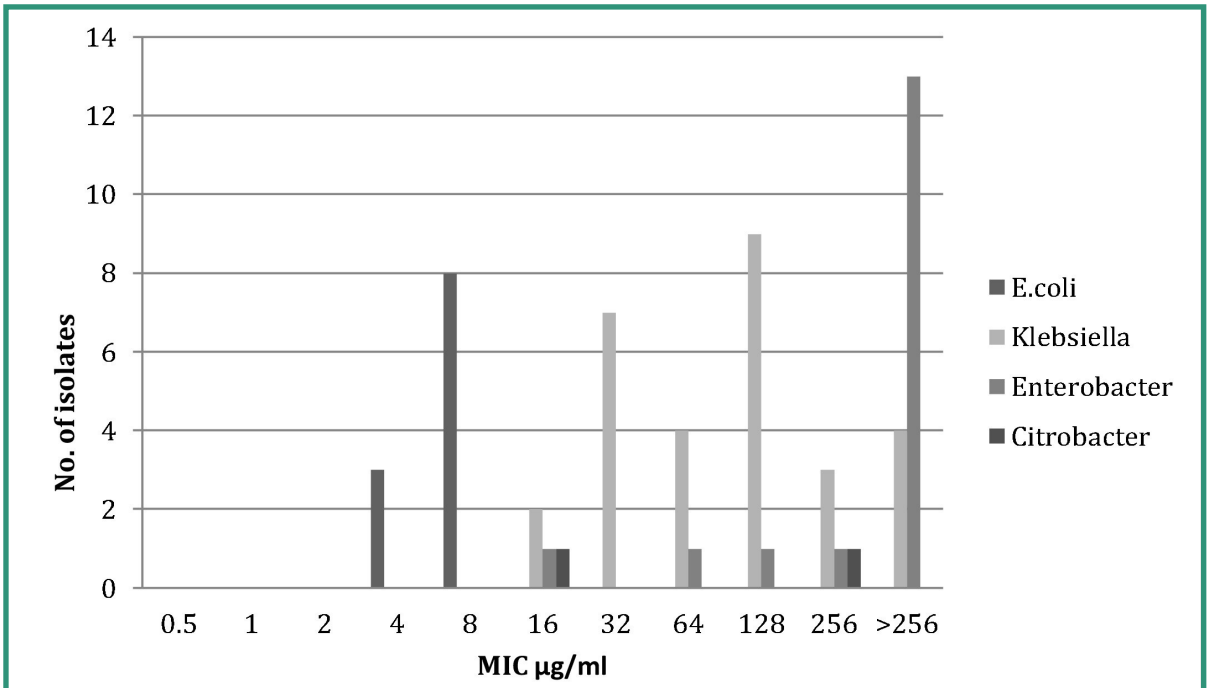
Manusmriti is a compilation of discourses given by Manu, an ancient Indian Guru, 300 BC. Antibiotics are a phenomenon belonging to the current eon, the *Kaliyuga* – where evil and quarrel reign! Colistin is an antibiotic discovered in 1959 which went out of fashion in the 1980s due to the unfriendly attitude of this molecule on human kidneys. Safer antibiotics such as carbapenems replaced colistin and turned out to be the favourite in the armamentarium, fostering extensive usage of this more expensive and more attractive molecule. As expected, extensively drug resistant Gram-negative bacteria (XDR GNB) spread their devilish tentacles across the world, with high mortality rates among the affected patients, especially those undergoing cancer chemotherapy and transplants. The world finally remembered the old sweetheart – colistin. The renewed love and affection towards colistin resulted in worldwide extensive usage of this molecule and hence the spread of colistin-resistant bacteria, with literally no active drug, emerging sensitive on the antibiogram display.

> ***"Usage of colistin as a growth promoter must be banned urgently."***

Pan drug resistance, or possible pan drug resistance is indeed the result of extensive colistin usage in the human world. Genes coding for colistin resistance (alterations in *mgrB , phoP/Q, pmr A/B*) are situated in the chromosomal part of the bacteria and as such, are less transmissible. Colistin-resistant bacteria were sporadic and we anticipated them to remain sporadic forever. Until a few years ago, a cluster of patients with colistin-resistant bacterial infections could easily be contained with very good infection control practices. The appearance of the plasmid mediated *mcr-1* gene and its variations dramatically changed the scenario. More than thirty countries reported the presence of *mcr* positive bacteria in human, food and environmental samples in just three years. Though the *mcr* gene is a well-reported cause of colistin resistance in human *Enterobacteriaceae* isolates, especially in *E.coli*, the gene does not explain the rapid dissemination of colistin resistance in *Klebsiella spp* in humans. *mcr* and its variants are rare in *Klebsiella* of human origin. Then how could *Klebsiella* change their behaviour from sporadicity to clonality and unleash havoc across the world? The answer… insertion sequences!

Insertion sequences (IS) help the alterations in *mgrB* or other similar genes to lose their celibacy and turn into highly promiscuous elements, moving out of the chromosome to plasmids and then to other bacteria. Plenty of publications are now available on the role of IS in the dissemination of colistin-resistant *Klebsiella spp* in healthcare institutions.[1-3]

mcr and its variants are less significant in clinical practice. Most colistin-resistant infections in hospitals across the world are due to *Klebsiella* (without mcr) and not *E. coli* with *mcr.* If the *mcr* gene in colistin-resistant *Enterobacteriaceae* could be of poultry origin, then why couldn't the *mgrB* mutations in *Klebsiella* have an indirect poultry connection? If *mgr B* mutations and IS are present in human *Klebisella*, naturally these elements should be present in *Klebisella* of food origin. If so, consumption of food containing *Klebsiella* with colistin resistance due to *mgrB* mutation could transmit these gene alterations to human *Klebsiella*. The first step in proving the hypothesis is to look for *mgrB* mutations in food *Klebsiella*. For the first time in global literature, our team of researchers from Chennai and Vellore, India, reported the presence of insertional inactivation of *mgrB* gene coding for colistin resistance in *Klebsiella* of food origin.[4] The paper has inspired scientists across the world to search for chromosomal mutations and insertional inactivation in food *Klebsiella* and, of late, at least one more publication has enriched the literature.[5] We have also identified human intestinal carriage of food born *Klebsiella* with *mgrB* mutations and insertional inactivation (unpublished data), further corroborating the food hypothesis. Can the human intestinal coexistence of carbapenem-resistant colistin sensitive bacteria of human origin and the colistin-resistant carbapenem sensitive *Klebsiella* of food origin, result in transmission of *mgrB* mutations and colistin resistance, generating possible pan drug resistance? This is quite possible – but we do need further evidence to prove the hypothesis.



Colistin minimum inhibitory concentration (MIC) distribution of bacterial isolates from food samples in Chennai, India.

Our paper, quite incidentally, is also the first Indian paper on the presence of colistin-resistant bacteria in raw food samples. We could also detect the presence of *E.coli* with *mcr* genes, though we were more excited about the *Klebsiella* with *mgrB* mutations and insertional inactivation!

The paper inspired widespread discussion on the growth promotional use of colistin in the poultry industry and its implications on the healthcare system.[6-8] Colistin is extensively used in poultry and aqua farming in India, though the exact magnitude of the usage is not yet available. India imports at least 200 tonnes of colistin, worth $1,648,612 every year, to be used as growth promoter.[9] More than 95% of the import is from China. The Chinese Government has already banned the use of colistin in animal feed since November 2016. China still exports and India still imports colistin for growth promotional use. Though there is a rule specifying withdrawal period of antibiotics before processing food-producing animals, currently India has no regulations to prevent antibiotic usage as a growth promoter.

Considering the public health impact of the extensive spread of colistin-resistant bacteria in food samples, with subsequent potential gut colonisation and clinical infection; usage of colistin as a growth promoter must be banned urgently.[4] The Chennai Declaration of Medical Societies in India and India's AMR National Action plan have made clear cut recommendations to ban the usage of antibiotics as growth promoters in livestock and aqua farming.[4,10]

Since publication of our paper, the Indian Ministry of Health and other relevant ministries have fast tracked efforts to ban growth promotion use of colistin and a rule regarding this is in its final stage. Indian data inspires Indian action!

Manusmriti certainly advised against eating food offered or touched by doctors! The text was unequivocally right and eminently futuristic in this regard. Hand hygiene compliance rate among doctors was not considerably better in 300BC than in 2019 AD!

References

1. Cannatelli A *et al*. In vivo emergence of colistin resistance in Klebsiella pneumoniae producing KPC-type carbapenemase mediated by insertional inactivation of the PhoQ/PhoP mgrB regulator. *Antimicrob Agents Chemother* 2013
2. Lopez-Camacho *et al*. Genomic analysis of the emergence and evolution of multidrug resistance during a Klebsiella pneumoniae outbreak including carbapenem and colistin resistance. *J Antimicrob Chemother* 2014
3. Laurent Poirel *et al*. The mgrB gene as a key target for acquired resistance to colistin in *Klebsiella* pneumonia. *J Antimicrob Chemother* 2015
4. Ghafur A *et al*. Detection of chromosomal and plasmid-mediated mechanisms of colistin resistance in *Escherichia coli* and *Klebsiella pneumoniae* from Indian food samples. *J Glob Antimicrob Resist* 2019
5. Pishnian Z *et al*. Prevalence and molecular determinants of colistin resistance among commensal Enterobacteriaceae isolated from poultry in northwest of Iran. *Gut Pathog* 2019
6. Kannan, R. Waiter, there's bacteria in my salad! *The Hindu.* Published: 21 Dec 2018
7. Sharma DC. New study finds antibiotic resistant gene in fresh food samples. *The Hindu*. Published: 25 Apr 2018.
8. Prasad P. Mechanism of colistin resistance in Klebsiella bacteria unraveled. *The Hindu*. Published: 29 Sept 2018
9. Import analysis of colistin sulphate: Zauba Technologies and Data Services. Accessed: 12 Jan 2018
10. Ghafur A D et al. The Chennai declaration: A roadmap to tackle the challenge of antimicrobial resistance. *Indian J Cancer* 2013

Epidemiology of Colistin Resistant & ESBL producing Gram-negative bacilli in Lebanese Chicken and Swine Farms

Iman Dandachi
Department of Biomedical Sciences, Faculty of Medicine and Medical Sciences, Univ. of Balamand, Amioun, Lebanon

Jean-Marc Rolain
Aix Marseille University, IHU-Méditerranée Infection, Marseille, France

Ziad Daoud
Department of Biomedical Sciences, Faculty of Medicine and Medical Sciences, Univ. of Balamand, Amioun, Lebanon; Antimicrobial Stewardship Program, Saint George Hospital-UMC, Beirut.

The rise of multidrug resistance in Gram-negative bacilli is nowadays considered a serious challenge encountered by healthcare professionals. Resistance in Gram-negative bacilli is mainly mediated via the production of extended spectrum beta-lactamases (ESBL), AmpC beta-lactamases and carbapenemases. Genes encoding these enzymes are often co-localised on plasmids harbouring resistance genes to other commonly prescribed antibiotics in human medicine such as aminoglycosides and quinolones[1]. Infections with these multidrug-resistant organisms (MDROs) could thus pose therapeutic challenges when encountered. This is currently emphasised with the recent emergence of colistin resistance in Gram-negative bacilli. Before 2015, colistin resistance was thought to be only mediated through chromosomal mutations that lead to the alteration of the lipid A subunit of the lipopolysaccharides chain[2]. However, in 2016 Liu *et al*. reported the first detection of a transferable phosphoenolamine transferase named *mcr-1* gene in *E. coli* strains isolated from pigs and meat. Thereafter, *mcr* variants became heavily reported in humans and animals across all continents.[3]

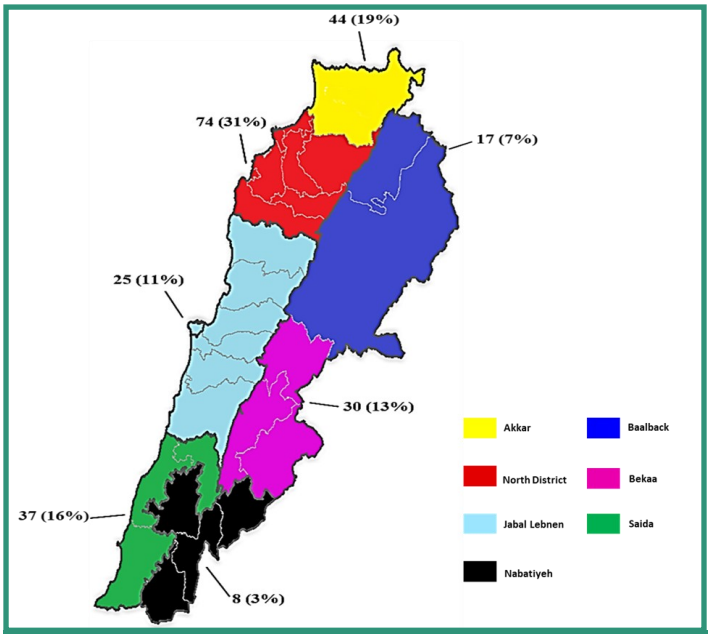


Figure. Prevalence of MDROs in Lebanese poultry farms. Prevalence is expressed as the "Number of isolates (%)"

Nowadays, farm animals are considered a reservoir of antimicrobial resistance. The major public health concern about MDROs spread in animals is their potential transmission to humans. Once transmitted, these organisms can cause infections with limited therapeutic options, especially those cross-resistant to antibiotics frequently used in human medicine. In Lebanon, the dissemination of MDROs in the clinical setting is well documented[4] however, studies addressing multidrug resistance in animals remain scarce. In collaboration with the Ministry of Agriculture, we undertook this study with the aim of determining the prevalence of extended-spectrum cephalosporin and colistin-resistant Gram-negative bacilli in Lebanese chicken and swine farms.

Between August and December 2015, 981 faecal swabs were obtained from 49 poultry farms distributed across Lebanon. In May 2017, 114 faecal samples were collected from swine farms located in south Lebanon. Separate media supplemented with cefotaxime, ertapenem, and colistin were used for the screening of resistant organisms. Double-disk synergy test, AmpC disk test and Carba NP test were performed to detect ESBL, AmpC and carbapenemase producers, respectively. Detection of beta-lactamase and *mcr* genes was performed using real-time polymerase chain reaction.

In 2015, out of 981 faecal swabs collected, 203 (21%) showed bacterial growth on the selective medium

supplemented with cefotaxime (**Figure**)[5]. In total, 235 strains were isolated: 217 were identified as *E. coli* (92%), 8 as *K. pneumoniae* (3%), 3 as *P. mirabilis* (1%) and 3 as *E. cloacae* (1%). Multilocus sequence typing (MLST) analysis of *E. coli* isolates showed the presence of different sequence types distributed across the country: ST156, ST5470, ST354, ST155 and ST3224. The phenotypic tests revealed that 44%, 28% and 20% of the strains were AmpC, ESBL, AmpC/ESBL producers, respectively. The putative TEM gene was detected in 83% of the isolates, SHV in 20%, CTX-M in 53% and CMY AmpC b-lactamase gene in 65%. Moreover, during this surveillance study, an *mcr-1*-positive colistin-resistant *E. coli* strain was isolated from the south of Lebanon[6]. This *E. coli* isolate was an ESBL producer harbouring the TEM-135-like gene. MLST analysis revealed that this strain is of the sequence type ST515. This ST differs from those previously reported in *E. coli* isolates harbouring the *mcr-1* gene in food-producing animals[6]. As for the swine farms, out of 114 faecal samples, 76 showed growth on the medium with cefotaxime. In total, 111 strains were isolated with 94% being *E. coli*[7]. Phenotypic tests showed that 98, 6 and 7 strains were ESBL, AmpC, and ESBL/AmpC producers, respectively. CTX-M and CMY were the main beta-lactamase genes detected. In parallel, on the medium supplemented with colistin, 19 samples showed growth. From these, 23 colistin-resistant *E. coli* strains harbouring the *mcr-1* gene were isolated (**Table**). [4]

	Isolate	Colistin MIC (µg/ml)	AMP	FOX	ATM	CTX	TZP	FEP	AUG	CAZ	Carb	GNT	SXT	CIP	TGC	*bla* genes
Farm 1	*E.coli* (1)	8	R	S	S	S	S	S	S	S	S	S	R	R	S	
	E.coli (2)	4	R	S	S	S	S	S	R	S	S	S	R	R	S	
	E.coli (3)	8	R	S	S	S	S	S	S	S	S	S	R	R	S	
	E.coli (4)	16	R	S	S	S	S	S	S	S	S	R	R	R	S	
	E.coli (5)	8	R	S	S	S	S	S	R	S	S	R	R	R	S	
	E.coli (6)	8	R	S	S	S	S	S	S	S	S	R	R	R	S	
	E.coli (7)	8	R	S	S	S	S	S	S	S	S	R	R	R	S	
	E.coli (8)	4	R	S	S	S	S	S	R	S	S	R	R	R	S	
	E.coli (9)	4	R	S	S	S	S	S	S	S	S	R	R	R	S	
	E.coli (10)	4	R	R	S	S	S	S	R	S	S	R	R	S	S	SHV/TEM
Farm 2	*E.coli* (11)	8	R	S	S	S	S	S	R	S	S	S	R	S	S	
	E.coli (12)	8	R	S	S	S	S	S	S	S	S	S	R	R	S	
	E.coli (13)	8	R	S	S	S	S	S	S	S	S	S	R	R	S	
	E.coli (14)	8	R	S	S	S	S	S	S	S	S	S	S	S	S	
	E.coli (15)	8	R	R	S	S	S	S	R	S	S	S	S	S	S	SHV/TEM
Farm 3	*E.coli* (16)	8	R	S	S	S	S	S	R	S	S	R	R	R	S	
	E.coli (17)	8	R	S	S	S	S	S	R	S	S	R	R	R	S	
	E.coli (18)	4	R	S	S	S	S	S	S	S	S	S	R	R	S	
	E.coli (19)	8	R	S	S	S	S	S	S	S	S	S	R	S	S	
	E.coli (20)	8	R	S	S	S	S	S	S	S	S	S	R	S	S	
	E.coli (21)	16	R	R	S	S	S	S	R	R	S	S	R	S	S	CTX-M/SHV/TEM
	E.coli (22)	8	R	S	S	S	S	S	S	S	S	S	S	R	S	
	E.coli (23)	up 256	R	S	S	R	S	R	S	R	S	S	S	R	S	CTX-M/SHV/TEM

Table. Resistance profiles of mcr-1 colistin-resistant *E. coli* strains isolated from the Lebanese swine farms

Our work illustrates the current epidemiology of multidrug resistant Gram negative bacilli in Lebanese chicken farms. ESBL and AmpC producers cross-resistant to antibiotics used in human medicine are highly prevalent across the territory. As demonstrated by Olaitan et al., *mcr-1*-harbouring strains can be readily spread from animals to the human gut and thus our finding sparks concerns over the transmission of *mcr-1* strains to the Lebanese community. Nowadays, carbapenem-resistant isolates are disseminated in the clinical and community settings in Lebanon. This dissemination has necessitated the frequent use of colistin in Lebanese hospitals. Therefore, it is expected that *mcr-1* strains, when transmitted from animals to humans in Lebanon, will be easily selected and further diffused by the selective pressure applied by the use of colistin and other antibiotics in clinical settings[7]. Surveillance studies addressing the current epidemiology of colistin resistance are thus warranted in Lebanon. In addition, the usage of colistin in veterinary medicine should be re-evaluated, as unpublished data have revealed its heavy use in animals in Lebanon.

References

1. Ruppe E *et al*. Mechanisms of antimicrobial resistance in Gram-negative bacilli. *Ann Intensive Care* 2015
2. Baron S *et al*. Molecular mechanisms of polymyxin resistance: knowns and unknowns. *Int J Antimicrob Agents* 2016
3. Liu YY *et al*. Emergence of plasmid-mediated colistin resistance mechanism *MCR-1* in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 2016
4. Dandachi I *et al*. Prevalence of Extended-Spectrum Beta-Lactamase-Producing Gram-negative bacilli and Emergence of *mcr-1* Colistin Resistance Gene in Lebanese Swine Farms. *Microb Drug Resist* 2018
5. Dandachi I *et al*. Prevalence and Characterization of Multidrug-Resistant Gram-negative bacilli Isolated From Lebanese Poultry: A Nationwide Study. *Front Microbiol* 2018
6. Dandachi I *et al*. First Detection of *mcr-1* plasmid mediated colistin resistant *E.coli* in Lebanese poultry. *J Glob Antimicrob Resist* 2018
7. Olaitan AO *et al*. Clonal transmission of a colistin-resistant *Escherichia coli* from a domesticated pig to a human in Laos. *J Antimicrob Chemother* 2015 Dec

An overview of antimicrobial stewardship programmes in Latin America

Gabriel Levy Hara

Infectious Diseases Unit, Hospital Carlos G Durand, Buenos Aires, Argentina. Independent Advisor for Studies of use of antibiotics and Antimicrobial Stewardship Programs in Latin America, PAHO/WHO

Antimicrobial stewardship programmes (ASPs) are relatively new in Latin America compared with other parts of the world such as Australia, the USA and Europe. However, around three years ago some individual hospitals in various Latin American countries began to create ASPs in the absence of official policies and support from national governments. [1, 2]

The first international survey evaluating the existence of ASPs was conducted jointly by the International Society of Chemotherapy (ISAC) Antimicrobial Stewardship (AMS) Working Group and the ESCMID Study Group for Antibiotic Policies (ESGAP) in 2012 and included 103 responses from Latin American countries.[3] Most responders were from Argentina (39), Peru (18), Brazil (9), Venezuela (9), Chile (8), Colombia (6) and Uruguay (5). More than half were teaching, tertiary care hospitals. Overall, 46% Latin American Countries already had an ASP compared with 66% in Europe, 67% in the USA and 56% in the "rest of the world". In general, ASPs were fairly new in Latin America (median duration was three years). Brazil (67%), Chile (88%) and Colombia (83%) had more ASPs in place, although figures were too small to establish real comparisons between countries. The main stated objectives of ASPs were comparable with the rest of the world: to reduce or stabilise resistance (87%), reduce the amount of antibiotic prescribing (53%) and improve clinical outcomes (49%). In contrast, dedicated weekly hours of AMS team members were different from other regions. For example, Latin American hospitals reported a mean of 9 hours of a pharmacist with experience in antimicrobials or infectious diseases (ID) (world mean = 18 hours), 12 hours of ID physician (world mean = 10 hours), and 7 hours of a clinical microbiologist (world mean = 9 hours). Similar to other low- and middle-income regions however, nurses had a critical role: 14 hours / week dedicated to the ASP, compared with a mean of 6 hours world-wide. The main barriers reported to delivering a functional and effective ASP were the lack of personnel or funding, opposition from prescribers, lack of information technology support and/or ability to get data and other higher-priority initiatives. These obstacles were similar to the rest of the world.

> ***"ASP major components are leadership, human resources, microbiology laboratories and robust pharmacy services."***

Recent progress in the Americas

The World Health Organization (WHO) and its regional office for the Americas, the Pan-American Health Organization (PAHO), have approved action plans for the containment of antimicrobial resistance (AMR)[4]. The design of the National Action Plans in collaboration with the WHO Global Action Plan proposal is currently advanced in most Latin American countries.

In September 2017, PAHO began a project to implement ASPs in Latin America. This initiative began with contacting the identified focal point from the Ministry of Health (MOH) in every country interested in participating in the project, requesting the selection of five to ten hospitals initially.

The *kick-off* included a point prevalence survey of antibiotic use (PAHO/WHO HAMU PPS 2018), adapted from the methodology proposed by WHO in 2017[4]. Once hospitals are selected by the MOH, teleconferences to present the overall project are held. During these initial meetings, participants exchange ideas on the following: previous experiences in AMS; revised benefits and objectives of ASPs; members of the AMS team; strategies to co-opt prescribers overall the facility; sensitisation of stakeholders and possible strategies to implement the programme according to each hospital setting and baseline situation. One of the key messages is that implementing an ASP requires time, patience and the recognition that we need to take a step-by-step approach for every issue (e.g., strategies, interventions, indicators, etc).

Simultaneously with the preparation and training to perform the antibiotic point prevalence survey, a baseline check-list related to AMS is requested. This tool includes questions regarding core elements of ASP as a hospital situation, authority support, team members, the existence (or not) of any AMS strategies, clinical practice guidelines, training on antimicrobial use, indicators of antimicrobial consumption, etc. In the second part of the check-list, coordinators are requested to propose which interventions (for example, related to prescription control, education, guidelines) they would be able to implement in their scenario. Later in the process of ASP implementation, virtual meetings

are held to discuss advances in the programmes and the main barriers. The involvement of many hospitals from the same country contributes to synergistic working: those with more advanced ASPs provide their experience and potential solutions to those who are just beginning.

By March 2019, there are more than 30 ASPs being implemented across El Salvador, Costa Rica, Perú, Paraguay and Cuba. Mexico is recruiting facilities to begin these projects. During this first year of the PAHO project it has been evident that, in general, stewardship initiatives are well-received by prescribers. There are essentially two prescription-based strategies to control antimicrobial use: pre-authorization and post-prescription review[5]. Considering that the majority of hospitals are taking their first steps they are incorporating a pre-authorisation strategy for prescribing certain antimicrobials (usually, third generation cephalosporins, piperacillin/tazobactam, carabapenems, colistin, fosfomycin, tigecycline, linezolid and new antifungal agents – equinochandins, voriconazole and lipid formulations of amphotericins). Audit and feedback or joint wards rounds are not in general use, despite their well-known benefits.

The main barriers observed both in the baseline checklists as well as in the follow-up virtual meetings are similar to those reported in most low- and middle-income economies on a global scale: [3,7, 8]

- Low institutional awareness regarding the problem of AMR and the need for prudent use of these agents.
- Scarcity of available human resources to work on AMS.
- Variable degrees of resources assigned to clinical microbiology laboratories.
- Absence of involvement and commitment of hospital pharmacies in AMS initiatives.
- Training on proper use of antimicrobials is usually limited and not continuous, due to a low number of health care workers in the AMS team. Then, incidental education predominates over structured and programmed interventions.

Recommendations for implementing antimicrobial stewardship programmes in the region

By November 2018, during the World Antibiotic Awareness Week, PAHO, together with the Global Health Consortium (GHC) of the Florida International University (FIU), launched the Recommendations for Implementing Antimicrobial Stewardship Programmes in Latin America and the Caribbean: Manual for Public Health Decision-Makers[6]. Its aim is to collaborate with Public Health authorities in their fight against AMR. This manual examines the concept and benefits of ASPs, and describes their major components: leadership, human resources, microbiology laboratories, and robust pharmacy services. Specific interventions are described, as are the ethical and legal issues related to these programmes. Primary health care interventions are given special attention as over 90% of antimicrobial use occurs at the community level, where high antibiotic use may reflect over-prescription, easy access through over-the-counter sales and, more recently, Internet sales, which are widespread in many countries.

Conclusions

The journey has just begun and initial experiences and reactions suggest that results will be very positive, as long as the programmes are consistent and sustainable over time. Involvement and support from National Health Authorities is necessary along with the provision of human and material resources needed to control antimicrobial use, monitor the operation of the programmes, conduct audits with feedback to prescribers and managers, training programmes and locally adapted guidelines. Antimicrobial Stewardship Teams might have the chance to select indicators and measure certain outcomes. Clinical microbiology laboratories should be strengthened and a well-functioning network to refer clinical samples to improve diagnosis must be developed.

The improvement in using these non-renewable therapeutic agents, the reduction in AMR, hospital length of stay, adverse effects and attributable death without doubts justify the initial investments in human and material resources.

References

1. Levy Hara G *et al*. Antimicrobial stewardship programs in Latin American hospitals. In: *Developments in emerging and existing infectious diseases. Antimicrobial Stewardship*. Elsevier 2017

2. Van Dijck C *et al*. Antibiotic stewardship interventions in hospitals in low-and middle-income countries: a systematic review. *Bull World Health Organ* 2018

3. Howard P *et al*. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother* 2015

4. WHO methodology for point prevalence survey on antibiotic use in hospitals. Geneva: World Health Organization 2018.

5. Pan American Health Organization/World Health Organization. *Plan of Action on Antimicrobial Resistance. 54th Directing Council of PAHO, 67th meeting of the WHO Regional Committee for the Americas* 2015

6. Pan American Health Organization. Florida International University. *Recommendations for Implementing Antimicrobial Stewardship Programs in Latin America and the Caribbean: Manual for Public Health Decision-Makers* 2018

7. Levy Hara G. Antimicrobial stewardship in hospitals: Does it work and can we do it? *J Glob Antimicrob Resist* 2014.

8. Cox JA *et al*. Antibiotic stewardship in low- and middle-income countries: the same but different? *Clin Microbiol Infect* 2017

Antibiotic Resistance in the News

Dr Hanan Balkhy - WHO Assistant Director General

Dr Balkhy, based in Saudi Arabia, is the new WHO Assistant Director General for Antimicrobial Resistance.

She will present a keynote lecture on Antimicrobial Resistance in the Gulf Region during the 31st ICC – 4th GCCMID in Dubai in November 2019.

AMR in Europe continues to increase

A new report by The European Centre for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA) confirmed that antimicrobial resistance in diseases such as campylobacteriosis and salmonellosis is increasing.

- Most countries reported high to extremely high resistance levels to ciprofloxacin and tetracyclines in *Campylobacter jejuni* isolates from humans.
- Multidrug resistance is high (28%) in *Salmonella* in humans and animals. Two isolates of *S. typhimurium* were resistant to eight of nine tested substances.
- *S. kentucky* from humans exhibited high-level resistance to ciprofloxacin in addition to a high prevalence of ESBL.

Antibiotics sourced from insects?

A study in *Nature Communications* investigated the antimicrobial activity of natural products from *Streptomyces* associated with insects. Investigators tested 2,003 *Streptomyces* strains against 27 microbes (bacteria and fungi) including clinically relevant pathogens. *Streptomyces* associated with insects exhibited significantly greater inhibitory activity than soil or plant *Streptomyces*.

Cyphomycin, a new molecule active against multidrug resistant fungal pathogens was extracted from a *Streptomyces* isolated from an ant and shows promise.

Pet Industry Joint Advisory Council releases recommendations for combatting AMR

The guide includes a set of principles for all sectors of the pet care community and provides expert advice and best management practices on topics including antibiotic use, sanitation, hygiene and zoonotic disease prevention.

Omadacycline treats pneumonia and skin infections

Two *New England Journal of Medicine* papers describe Omadacycline, a new once-daily IV / oral aminomethylcycline agent, effective in treating community-based pneumonia and bacterial skin infections. Both studies show it was non-inferior to a comparator antimicrobial with similar safety profiles.

The U.S. FDA has approved omadacycline since reviewing the findings.

Funding for UK-China partnerships against AMR

The UK Department of Health and Social Care (DHSC) / Innovate UK will award £20 million for AMR research, including bilateral research between DHSC's Global AMR Innovation Fund (GAMRIF) and the Chinese Ministry of Science and Technology (MoST).

GAMRIF's UK-China competition supports new innovations addressing AMR in humans and animals. UK and Chinese companies and research organisations will partner to conduct novel research that neither country could carry out alone and includes 14 projects covering novel diagnostics, therapeutics, animal feed and opportunities from traditional Chinese medicine for treating or preventing infectious bacterial disease.

Funding for Commonwealth partnerships to improve AMS

The Commonwealth Partnerships for Antimicrobial Stewardship (AMS) scheme has selected 12 projects to run across Uganda, Tanzania, Ghana and Zambia.

The scheme is funded by the Department of Health and Social Care's Fleming Fund which has committed £1.3 million in UK aid to support new or existing partnerships between NHS trusts and UK health institutions, and their counterparts across four African Commonwealth countries.

WHO — cultural context approach to tackle AMR

The World Health Organisation (WHO) has released a policy brief outlining cultural factors as one of the biggest obstacles in tackling AMR. The brief examines how the prescription and use of antibacterials, the transmission of resistance and the regulation and funding of research are influenced by cultural, social and commercial, as well as biological and technological factors.

River drug pollution 10 - 20 times higher over 20 years

Pharmaceuticals are increasingly found in rivers at levels damaging to ecosystems. Dutch researchers developed a model to assess the aquatic risk of ciprofloxacin and carbamazepine in fresh water systems worldwide.

A study, in *Environmental Research Letters*, found that between 1995 and 2015 levels of ciprofloxacin in freshwater ecoregions have increased 10-20 fold. The environmental risk is particularly high in densely populated and dry areas. The study predictions underestimated the actual risk which is much higher.

Antibiotic nasal gel shows no adverse effects in healthy volunteers in phase I trial

An antibiotic nasal gel designed to prevent post-surgical *S. aureus* infections has passed through a phase I trial.
The drug, exeporfinium chloride, was developed by Destiny Pharma and tested in 35 healthy volunteers with different doses of the daily gel treatment for 21 days. The gel was significantly less irritating for the volunteers' skin than the placebo, distilled water. There were no side effects and none of the antibiotic reached the bloodstream. Potential indications include pneumonia, bacterial eye infections and diabetic foot ulcers.

Vitamin D helps clear MDR TB

A meta-analysis published in *European Respiratory Journal*, presented data from 1,850 patients with pulmonary TB in eight countries. When added to antibiotic treatment, vitamin D was found to speed up the clearance of MDR TB specifically. Overall, no acceleration was seen in the study population as a whole (both susceptible and MDR TB). The authors state the results provide a rationale to carry out new clinical trials to see if vitamin D can benefit patients who are taking standard antibiotics for MDR TB.

Antimicrobial used in toothpaste reduces antibiotic efficacy by up to 100 times

A study in *Antimicrobial Agents and Chemotherapy* found that exposure to triclosan which is used in many common products e.g. toothpaste, soap and baby toys, increased *E.coli* and MRSA tolerance to antibacterials by up to 10,000 fold *in vitro* and reduced antibiotic efficacy up to 100-fold.

A mouse model investigating antibiotic treatment for UTIs found that triclosan significantly increased numbers of surviving bacteria.

The study highlights the need to re-evaluate the costs and benefits of the prophylactic use of triclosan and other bacteriostatic compounds.

Indian "Superbug" found in the Arctic Wilderness

Antimicrobial resistant genes have been found in what is considered as Earth's last pristine environment according to a study published in *Environment International*. DNA from 40 samples of soil at eight locations in Svalbard was sequenced and 131 antibiotic-resistant genes were found including bla_{NDM-1}.

The AMR genes were brought in from outside sources – most likely human sewage or bird droppings.

Indian Critical Care Medicine Society Publish Guidelines on Antibiotic Use in ICUs

Antibiotic prescribing guidelines have been published by the Indian Critical Care Medicine Society (ICCMS) in the *Indian Journal of Critical Care Medicine.* They provide scenario-based recommendations and aim to combat multidrug resistance in the Indian population .

ICCMS will present the guidelines to the health ministry, Indian Council of Medical Research and circulate them to all medical associations and government hospitals.

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. The following speakers are confirmed:

Plenary Speakers
Dilip Nathwani
Hanan Balkhy
John Turnidge
Ramanan Laxminarayan
Yaseen Arabi

Keynote Speakers
Marion Koopmans
Matthew Dryden
Mohammed Al Hazmi
Po-Ren Hsueh
Salah Al Awaidy

Visit http://icc-gccmid2019.com/ to register, submit your abstract or apply for a travel grant.

Publications of Interest

World Organisation for Animal Health (OIE) Annual Report on Antimicrobial Agents Intended for Use in Animals

WHO Methodology for Point Prevalence Survey on Antibiotic Use in Hospitals

UK One Health Report: Joint Report on Antibiotic Use and Antibiotic Resistance, 2013-2017

UK 20-year Vision for Antimicrobial Resistance: How the UK will contribute to containing and controlling antimicrobial resistance (AMR) by 2040

Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early implementation 2017-2018

Recommendations for Implementing Antimicrobial Stewardship Programs in Latin America and the Caribbean: Manual for Public Health Decision-Makers

WHO Proof-of-Principle Antimicrobial Resistance Routine Diagnostics Surveillance Project (PoP project) (2018)

WHO Central Asian and Eastern European Surveillance of Antimicrobial Resistance. Annual report 2018 (2018)

ReAct Report: When the Drugs Don't Work: Antibiotic Resistance as a Global Development Problem

Impact of psychologically tailored hand hygiene interventions on nosocomial infections with multidrug-resistant organisms: results of the cluster-randomized controlled trial PSYGIENE. von Lengerke *et al*. *Antimicrob Resist Infect Contro*l 2019 Feb

Investigating the cultural and contextual determinants of antimicrobial stewardship programmes across low-, middle- and high-income countries—A qualitative study. Charani *et al*. *PLoS One* 2019 Jan

Implementation of antibiotic stewardship in different settings - results of an international survey. Charani *et al. Antimicrob Resist Infect Control*. 2019 Feb

Decolonization to Reduce Postdischarge Infection Risk among MRSA Carriers. Huang *et al. N* Engl J Med 2019 Feb

In vitro activity of the novel oral antimicrobial SMT-571, with a new mechanism of action, against MDR and XDR Neisseria gonorrhoeae: future treatment option for gonorrhoea? Jacobsson *et al*. *J Antimicrob Chemother. 2019 Feb*

Pan American Health Organization (PAHO): Recommendations for Implementing Antimicrobial Stewardship Programs in Latin America and the Caribbean: Manual for Public Health Decision-Makers, 2018

APUA Chapter News

APUA Nepal

APUA Nepal recently published its 15th newsletter highlighting the following successful initiatives since its inception:

- National Antibiotic Policy added to the National Drug Policy in 2001.
- National Antibiotic Treatment Guidelines published by MOH in 2014.
- Hospital-based AMR surveillance data published since 2004.

APUA Russia

Along with The Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC), APUA Russia has:

- Established programmes for interregional / national AMR monitoring (RosNet).
- Developed Russian National Guidelines for AMR testing and harmonised with EUCAST Guidelines
- 2017 - 2019: held 2 International Congresses and 5 regional conferences on antimicrobial therapy.

Planned activities:

- XXI International Congresses on Antimicrobial Therapy in Moscow (22-24 May 2019)
- Russian-Chinese Congress on Antimicrobial Therapy (17-18 Oct 2019)

Additional education activity includes

- Graduate educational courses on bacteriology and clinical pharmacology for bacteriologists and clinicians
- The first internet centre of distance education on antimicrobial chemotherapy in Russia
- All-Russian educational project "Diagnosis, treatment, prevention of infections caused by MDR microorganisms"

APUA Lebanon

Selected Activities 2015-2018

- With American Society for Microbiology (ASM) and the Smithsonian National Museum of Natural History (DC): Exhibition in "Byblos-Lebanon" aimed at increasing awareness of transmission of infection and bacterial resistance between humans, animals, and the environment.
- With WHO and the Lebanese Ministry of Public Health: Six workshops to train clinical microbiologists from 20 Lebanese hospitals on WHONET software.
- Signed MoU with the Ministry of Agriculture to collaborate in research activities about the spread of antimicrobial resistant organisms in Lebanese farm animals.
- Five-day course on "Epidemiology of Measurement of Resistance".
- Joint event with ASM: "Standardisation of antimicrobial susceptibility course".
- Joint event with ASM, the Ministry of Public Health (Lebanon) and WHO: "WHONET workshop for PULSENET/AMR laboratory network on Foodborne diseases."
- Three workshops for children on microbial principles and hygiene.
- APUA-Lebanon chapter is sponsoring two microbiological studies in Lebanon:
  1. Nationwide study, in collaboration with the Lebanese Society for Infectious Diseases and Clinical Microbiology, to determine susceptibility profiles of *Candida* spp .
  2. In collaboration with GSK: Analyse susceptibility profiles of *S. pneumonia* and *H. influenzae* in Lebanon and other Mediterranean countries.