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Editorial note:

With increasing prominence of the threat of antimicrobial resistance both internationally and locally, awareness and knowledge on the problem and prospects are essential, in order for rational application of control measures and monitoring of their effectiveness. In this issue of the Topical Update, Dr. Dominic Tsang and Dr. Christopher Lai present an updated overview of this important subject. We welcome any feedback or suggestion. Please direct them to Dr. Janice Lo (e-mail: janicelo@dh.gov.hk), Education Committee, The Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Antimicrobial resistance – a global health crisis

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End of modern medicine as we know it

The World Health Organization (WHO) described in 2001 antimicrobial resistance (AMR) as a global problem and an impending crisis. The apocalyptic term "Post-antibiotic era" was mentioned.[1] The situation did not improve since. In fact, it deteriorated. In the United Kingdom (UK) government-commissioned "Review of Antimicrobial Resistance" by Lord Jim O'Neill, it was estimated that 700,000 people died from AMR infections in 2016 in the UK alone, and that drug-resistant infections could cause 10 million human deaths annually by 2050, costing the world up to $100 trillion.[2] The Chief Medical Officer for England, Dame Professor Sally Davies, has predicted that unless tackled now, AMR could lead to the end of modern medicine as we know it. It could lead to routine operations and even childbirth becoming increasingly dangerous without the required antibiotics. In the UK, over 25,000 deaths a year are attributed to drug resistant infections.[3] European Commission estimated the costs associated with AMR infection at €1.5 billion annually.[4]

The driving force behind emergence and dissemination of AMR is directly related to the use of antibiotics, i.e. the antibiotic selection pressure.[5] It is recognized that non-human indiscriminate use of antibiotics in agriculture and animal husbandry to promote growth in animals and the consequential persistence of antibiotics in soil and aquatic environment select for AMR that could be disseminated widely.[6] Human overuse nonetheless needs to be controlled by dedicated efforts on strengthening regulations on over-the-counter purchase of prescription only antibiotics, enhancing training in antibiotic prescriptions,

monitoring compliance with antibiotic guideline and antibiotic stewardship programme (ASP).[7]

Concerted effort against AMR

Antibiotics on one hand is an agent required for life saving. But on the other, its usage and the resultant selective pressure have been recognized as the main drivers for AMR. Therefore, its use in human and non-human settings should be balanced against the risk of driving AMR. As such, antibiotic usage data has been linked to AMR surveillance data in the AMR containment strategy.[8,9]

There are already in place a few surveillance systems on AMR, covering healthy animals, diseased animals, food and humans in countries such as Canada, Denmark, Finland, Germany, Italy, Japan, USA, the Netherlands, Norway, France, and Sweden.[10]

The UK and China will establish the Global AMR Research Innovation Fund and encourage further investment from other governments and the private sector, helping to address AMR. The new fund will invite bids from industry, academia and other bodies. It aims to create international partnerships to build a global response and support new research to reduce the spread of antibiotic resistance.

The World Health Assembly in May 2015 endorsed a WHO global action plan to tackle antimicrobial resistance to ensure continuity of successful treatment and prevention of infectious diseases with effective and safe medicines.[11] The plan sets out five strategic objectives including: to improve awareness and understanding of antimicrobial resistance; to strengthen knowledge through surveillance and research; to reduce the incidence of infection; to optimize the use of antimicrobial agents; and to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions. Under each of the objectives, specific actions were listed out for member states as well as international partners to implement.

Hong Kong Strategy against Multidrug resistant organisms (MDROs)

The Hong Kong Strategy and Action Plan on Antimicrobial Resistance 2017-2022[12] was released in July 2017 with the goals to develop a territory-wide network on surveillance on AMR and antimicrobial use, promote appropriate therapeutic use of antimicrobials in human and animals and to promote research on diagnostic and related interventions. Six key areas were targeted in the plan, including strengthening knowledge, optimizing antimicrobial use, reducing infections, improving awareness, promoting research and fostering partnerships among stakeholders.

In terms of AMR surveillance, the overall resistance profiles of MDROs have all along been closely monitored in public hospitals under the Hospital Authority in Hong Kong.[13] Among the concerned MDROs, Gram positive organisms include methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE). Gram negative organisms include extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-E) and the WHO top priority organisms of carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).[14]

Trends in antibiotic resistant organisms

MRSA: In Hong Kong, MRSA bloodstream infection was made a key performance indicator (KPI) to gauge the performance of infection control practices in all public hospitals.[15] The corresponding MRSA bacteraemia rate was 0.18-0.19 per 1,000 acute bed days when the monitoring began in 2008 and declined gradually to 0.144 per 1,000 acute bed days in 2017. At the same time, MRSA constituted 43.1% among *S. aureus* isolated from local HA hospitals.

VRE: The total number of VRE cases detected remains below 50 a month since 2015, after an upsurge and successful control in the Queen Elizabeth Hospital in 2013 when the peak number of cases detected in a month reached 300.[16]

CRAB/multi-drug resistant *Acinetobacter baumannii* (MDRA) is commonly associated with patients with prolonged hospital stay and who required ventilator-assisted ventilation. These patients are also usually put on multiple antibiotics for the treatment of underlying infections.[17] Substantial environmental contamination with the resistant bacteria is frequent as a result of nursing care procedures, leading to explosive outbreaks which are difficult to abort unless attention is given to patient segregation and effective disinfection of instruments and environmental surfaces.[18,19]

ESBL-E began to emerge in late 1980s and peaked in UK in 2006 with 12% *E. coli* isolated from bacteraemic cases being ESBL positive. ESBL-E has been common locally, at 22% in 2017 compared to 24.3% since 2012. They are especially important as they commonly caused community-acquired as well as hospital-acquired infections. In fact, a local report showed 62% of imported chicken were found to be contaminated with ESBL-E.[20] Community carriage rates for ESBL-E are high in East Mediterranean areas and South East Asia, from 30-60%.[21,22] For treatment of ESBL-E infections, imipenem has been universally effective since its launch in 1987, and the same applies to meropenem, another carbapenem antibiotic which was launched in 1996.

CPE are members of the *Enterobacteriaceae* including *E. coli* and *Klebsiella species* which possess the gene on plasmids coding for the enzymes such as KPC, NDM and OXA-48 under the Ambler Classification on molecular class A, B or D respectively which enable them to inactivate carbapenem antibiotics and also other beta-lactams. CPE are usually multiply antibiotic resistant, therefore rendering limited options in treatment of their infections.[23] The emergence and subsequent spread of CPE followed human movement closely as exemplified by the clustering of KPC-CPE in New York, North-West England, Israel and the spreading of NDM-CPE to Sweden by a returning patient from New Delhi, India.[24-26] In Hong Kong, CPE cases were being increasingly detected, from 19 cases in 2011 to 473 cases in 2017. Active bacterial screening (ABS) of patients based on a set of consensus criteria in public hospitals including admission screening of all patients who have stayed in overseas hospitals in the past 12 months, suffering from antibiotic associated diarrhoea, staying in the same cubicle of a known CPE case, etc., helped to pick up an increasing number of CPE. Fortunately, most of the cases (90%) were asymptomatic carriers and did not require specific treatment. Of note, the number of confirmed CPE isolates in England in 2016 was more than 2,500 with KPC, NDM and OXA-48 predominant. Effective treatment options for CPE are few. The activities of ceftazidime and aztreonam with and without avibactam were tested against a large, contemporary, international collection of carbapenemase-producing Gram negative bacilli (CP-GNB) with diverse resistance mechanisms. Aztreonam-avibactam was active against all isolates except two NDM producers with elevated MICs of 8/4 and 16/4 mg/litre; ceftazidime-avibactam was active against all KPC-, IMI-, SME-, and most OXA-48 group-producing isolates (93%) but not metallo-β-lactamase producers. Among the older and contemporary antimicrobials, the most active were colistin, tigecycline, and fosfomycin, with overall susceptibilities of 88%, 79%, and 78%, respectively.[27] Among local CPE isolates, the resistance rate of colistin is around 5.8%.

The "Find and Confine" Control strategy of AMR in HA hospitals

"**Find**": This is the single most important control measures aiming to uncover the carriage state of any asymptomatic carrier, especially of VRE and CPE, who could shed the MDRO in the excreta. This is commonly done by ABS in the form of admission screening based on high risk factors such as hospitalization in recent months, a history of exposure to a known case, prolonged hospital stay (e.g. for 14 days or more), development of antibiotic associated diarrhoea etc. The yield of ABS at present is not high, ranging from 0.6% to 1.4% (average 1.0%) based on 2017 CPE ABS data in one of the hospitals, but ABS has undoubtedly provided a substantial impact in mitigating otherwise uninterrupted dissemination of VRE and CPE in the hospital setting. The availability of commercial agar media with the function to differentiate CPEs after overnight

incubation has greatly facilitated ABS. Coupled with other rapid enzyme detection and PCR confirmation of CPE, which are also available commercially, the time to detection of CPE carriage in patients has been shortened to one to two days.

"**Confine**": It is an important part of standard precautions (SP) plus contact precautions (CP) in the care of a known MDRO case. A room with en-suite is the preferred placement especially for those who suffer from diarrhoea and therefore at a higher risk of transmission of MDROs. This is widely practiced in developed countries. When en-suite rooms are not available, segregation of MDRO carriers by "cohorting" patients carrying the same MDRO is a pragmatic alternative.

Hand hygiene (HH): Healthcare workers (HCWs) strictly observing proper HH, e.g. WHO 5 moments, is undoubtedly the most important and effective measure in aborting the dissemination of MDROs in healthcare setting. The use of alcohol handrub in place of hand washing in situations where soiling is minimal has greatly improved HH compliance. However, HH is an action governed by human behavior which unfortunately also suffers from all factors that affect our behavior, such as physical fatigue, forgetfulness, motivation, persistence, peer influence, etc. For the same reason, the reliability of HH compliance monitoring by direct observation is also limited by the well-known "Hawthorn effect" in that, as humans, we tend to perform when we are aware of being observed.[28] Further, in periods of high bed occupancy like influenza seasons, it is very hard to expect HCWs to fully comply with HH and as a consequence, these periods are more prone to cross transmission and outbreaks of MDROs. Apart from HCWs, patients and visitors are equally important in observing HH in order to avoid cross transmission. Similar moments of HH are being promoted for patients in local hospitals. In the long run, the development of a positive and motivated infection control culture and HH habit would not only maintain the cross transmission of MDROs at a low level but also mitigate the risk of other cross infections.

Environmental hygiene: The inanimate environment plays an important role in perpetuating the dissemination of MDROs in the hospital settings, especially VRE and MDRA.[29,30] High-touch (frequently touched) surfaces such as patients' privacy curtain, bed rails, door knobs, nursing trolleys, drip stands are often contaminated with the MDROs during outbreaks.[31] The conventional cleansing and disinfection by using diluted sodium hypochlorite solution, although effective, is labour intensive. Also, to ensure the cleaning procedure is meticulously performed, it is commonly monitored by the use of a surrogate marker (e.g. UV-fluorescent marker) to ensure satisfactory performance.[32] To circumvent such drawback, there are now plenty of effective new products on environmental disinfection, ranging from self-disinfecting surface coating sprays, hydrogen peroxide vapor, UV-C device, 2-in-1 disinfectant wipes to antimicrobial privacy curtains that could achieve effective decontamination with less labour. In a multi-centre study, 42.7% of standard hospital curtains were contaminated with MRSA and 42.3% with CRAB.[33] The use of disposable antibacterial privacy curtains, e.g. nanoparticle silver or quaternary ammonium impregnated curtains, have been shown to prolong the time to contamination and reduce the bio-burden even after extended usage in acute care setting.[34]

Reducing overuse of antibiotics: It is imperative to maintain the use of antibiotic at the minimum essential level in order to prevent the emergence of resistance.[34] Education and training at an early stage of the medical curriculum is critical in establishing the concept and skills in prudent antibiotic use. Guideline such as the local IMPACT guideline on antibiotic use is indispensable in providing the guidance on the right indications, choice, dose, route, and duration of antibiotic use. In addition, antibiotic stewardship program (ASP) has been widely practiced and proven to be effective in ensuring appropriate use of antibiotics.[35] Locally, a multi-disciplinary team of clinical microbiologists, physicians, pharmacists and infection control nurses has been put in place in all HA hospitals to provide concurrent feedback on the use of targeted "big-gun" antibiotics. The percentage of appropriate use stays at above 80% in general and feedbacks on antibiotic use are welcomed in most of the cases.

Another very important aspect in the control of AMR is diagnostic support in infection.[36] The rapid isolation and identification of an aetiological agent lends strong support in the continuation of antibiotic treatment, or its discontinuation in the absence of any evidence of infection. This is made possible with the introduction of molecular platforms such as 16S ribosomal RNA PCR and metagenomic studies.[37]

Surrogate biomarker of infection, in particular procalcitonin (PCT) which exhibits greater specificity than other proinflammatory markers such as C reactive protein (CRP) helps in identifying patients with sepsis and can be used for diagnosing infections, especially ventilator-associated pneumonia (VAP).[38,39] The short half-life (25-30 hours in plasma) of PCT and its absence in healthy state make it the preferred biomarker for bacterial infections. PCT levels <0.15 ng/mL make a diagnosis of significant bacterial infection unlikely.

The outlook of the challenges from AMR

The outcome in our battle against MDROs depends on how successful we are in preserving the efficacy of our existing antibiotics for treatment of infections and the result of our search for new antibiotics. Both require resources, efforts and dedication. While preserving existing effective antibiotics demands the aforementioned One Health approach, research breakthroughs arguably provide us the only hope in winning the battle against MDROs and to ensure effective treatment of infections for the continual practice of modern medicine.

Not long ago, researchers have identified from a soil sample a new cell wall inhibitor, teixobactin, from a previously unknown Gram-negative bacterium that lives in soil but which cannot be cultured in the laboratory using standard technique.[40] The researchers used the "Ichip", an isolation chamber, in which a soil sample is diluted with agar and a single bacterial cell in a chamber is then placed in soil where the bacteria could access to nutrients and growth factors. The teixobactin identified has excellent activity against Gram-positive pathogens including MRSA, *Clostridium difficile*, *Bacillus anthracis* and *Mycobacterium tuberculosis*. Another recent breakthrough was reported[41] on accessing hidden natural products (NP) made by bacteria not by culturing but by sequencing, bioinformatics analysis and heterologous expression of biosynthetic gene clusters captured on DNA extracted from environmental samples. Such technique has led to the discovery of malacidins, a distinctive class of antibiotics which are active against MRSA infections without selection for resistance under the laboratory conditions. These discoveries are definitely good news given the great potential for more to be discovered by using these innovative technologies. Of course, there are still tests to be done before they could become clinically useful, but at least these discoveries through our human creative and innovative minds are holding promise in the battle against AMR. Meanwhile, we must not be distracted away from the momentum in tackling the rapidly deteriorating AMR situation.

References

1. World Health Organization. WHO global strategy for containment of antimicrobial resistance [Internet]. Geneva: World Health Organization; 2001 [cited 2018 May]. Available from: http://www.who.int/drugresistance/WHO_Global_Strategy.htm/en/

2. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London: Review on Antimicrobial Resistance; 2016 May 19 [cited 2018 May]. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

3. McKie R. 'Antibiotic apocalypse': doctors sound alarm over drug resistance [Internet]. London: The Guardian; 2017 Oct 8 [cited 2018 May]. Available from https://www.theguardian.com/society/2017/oct/08/world-faces-antibiotic-apocalypse-says-chief-medical-officer

4. Rodier G. European strategic action plan on antibiotic resistance 2011–2016. [Internet] Copenhagen: WHO Regional Office for Europe; 2011 Sep [cited 2018 May]. Available from

http://www.euro.who.int/__data/assets/pdf_file/0011/148988/RC61_Pres_Rodier_antibiotic_resistance.pdf

5. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev [Internet]. 2010 [cited 2010 Sep];74(3):417-33. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=20805405

6. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. Clin Microbiol Rev [Internet]. 2011 [cited 2011 Oct];24(4):718-33. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=21976606

7. Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc [Internet]. 2011 [cited 2011 Nov];86(11):1113-23. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=22033257

8. World Health Organization. Global antimicrobial resistance surveillance system (GLASS) report: Early implementation 2016-2017 [Internet]. Geneva: World Health Organization; 2018 Jan 29 [cited 2018 May]. Available from: http://www.who.int/glass/resources/publications/early-implementation-report/en/

9. Johnson I, Hansen A, Bi P. The challenges of implementing an integrated One Health surveillance system in Australia. Zoonoses Public Health [Internet]. 2018 [cited 2018 02];65(1):e229-e236. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=29226606

10. Silley P, Simjee S, Schwarz S. Surveillance and monitoring of antimicrobial resistance and antibiotic consumption in humans and animals. Rev Sci Tech [Internet]. 2012 [cited 2012 Apr];31(1):105-20. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=22849271

11. World Health Organization. Global action plan on antimicrobial resistance [Internet]. Geneva: World Health Organization; 2015 [cited 2018 May]. Available from: http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/

12. Centre for Health Protection. Hong Kong Strategy and Action Plan on Antimicrobial Resistance [Internet]. Hong Kong: Centre for Health Protection; 2018 May [cited 2018 May]. Available from: https://www.chp.gov.hk/en/static/49301.html

13. Lai CK, Chuang WM, Kong MY, Siu HK, Tsang DN. Antimicrobial susceptibility in hospitals in Hong Kong: The current status 2009-2011. J Glob Antimicrob Resist [Internet]. 2014 [cited 2014 Dec];2(4):225-231. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=27873680

14. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed [Internet]. Geneva: World Health Organization; 2017 Feb 27 [cited 2018 May]. Available from: http://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

15. Leung PY. Making the Control of MRSA a Key Performance Indicator. Medical Diary [Internet]. 2011 Apr [cited 2018 May]; 16(4): 14. Available from: http://www.fmshk.org/database/hkmd/mdapril2011fullpage2.pdf

16. Lai CK, Wong SY, Lee SS, Siu HK, Chiu CY, Tsang DN, Ip MP, Hung CT. A hospital-wide screening programme to control an outbreak of vancomycin-resistant enterococci in a large tertiary hospital in Hong Kong. HONG KONG MED. J. [Internet]. 2017 [cited 2017 Apr];23(2):140-9. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=28232642

17. Huang H, Chen B, Liu G, Ran J, Lian X, Huang X, Wang N, Huang Z. A multi-center study on the risk factors of infection caused by multi-drug resistant Acinetobacter baumannii. BMC Infect Dis [Internet]. 2018 [cited 2018 01 05];18(1):11. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet].

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=29304746

18. Markogiannakis A, Fildisis G, Tsiplakou S, Ikonomidis A, Koutsoukou A, Pournaras S, Manolis EN, Baltopoulos G, Tsakris A. Cross-transmission of multidrug-resistant Acinetobacter baumannii clonal strains causing episodes of sepsis in a trauma intensive care unit. Infect Control Hosp Epidemiol [Internet]. 2008 [cited 2008 May];29(5):410-7. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=18419362

19. Apisarnthanarak A, Pinitchai U, Thongphubeth K, Yuekyen C, Warren DK, Fraser VJ, Thammasat University Pandrug-Resistant Acinetobacter baumannii Control Group. A multifaceted intervention to reduce pandrug-resistant Acinetobacter baumannii colonization and infection in 3 intensive care units in a Thai tertiary care center: a 3-year study. Clin Infect Dis [Internet]. 2008 [cited 2008 Sep 15];47(6):760-7. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=18684100

20. Consumer Council. 測試 100 款生雞翼及全雞 6 成驗出 ESBL 耐藥細菌 [Internet]. Hong Kong: Consumer Council; 2016 Dec 15 [cited 2018 May]. Available from: https://www.consumer.org.hk/ws_chi/choice/482/chicken-and-antibiotics.html

21. Barreto Miranda I, Ignatius R, Pfuller R, Friedrich-Janicke B, Steiner F, Paland M, Dieckmann S, Schaufler K, Wieler LH, Guenther S, Mockenhaupt FP. High carriage rate of ESBL-producing Enterobacteriaceae at presentation and follow-up among travellers with gastrointestinal complaints returning from India and Southeast Asia. J Travel Med [Internet]. 2016 [cited 2016 Feb];23(2):tav024. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=26858272

22. Woerther PL, Andremont A, Kantele A. Travel-acquired ESBL-producing Enterobacteriaceae: impact of colonization at individual and community level. J Travel Med [Internet]. 2017 [cited 2017 Apr 01];24(suppl_1):S29-S34. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=28520999

23. Hrabak J, Chudackova E, Papagiannitsis CC. Detection of carbapenemases in Enterobacteriaceae: a challenge for diagnostic microbiological laboratories. Clin Microbiol Infect [Internet]. 2014 [cited 2014 Sep];20(9):839-53. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=24813781

24. Woodford N, Tierno PM Jr, Young K, Tysall L, Palepou MF, Ward E, Painter RE, Suber DF, Shungu D, Silver LL, Inglima K, Kornblum J, Livermore DM. Outbreak of Klebsiella pneumoniae producing a new carbapenem-hydrolyzing class A beta-lactamase, KPC-3, in a New York Medical Center. Antimicrob Agents Chemother [Internet]. 2004 [cited 2004 Dec];48(12):4793-9. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15561858

25. Samra Z, Ofir O, Lishtzinsky Y, Madar-Shapiro L, Bishara J. Outbreak of carbapenem-resistant Klebsiella pneumoniae producing KPC-3 in a tertiary medical centre in Israel. Int J Antimicrob Agents [Internet]. 2007 [cited 2007 Dec];30(6):525-9. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17931835

26. Khong WX, Xia E, Marimuthu K, Xu W, Teo YY, Tan EL, Neo S, Krishnan PU, Ang BS, Lye DC, Chow AL, Ong RT, Ng OT. Local transmission and global dissemination of New Delhi Metallo-Beta-Lactamase (NDM): a whole genome analysis. BMC Genomics [Internet]. 2016 [cited 2016 06 13];17452. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=27297071

27. Vasoo S, Cunningham SA, Cole NC, Kohner PC, Menon SR, Krause KM, Harris KA, De PP, Koh TH, Patel R. In Vitro Activities of Ceftazidime-Avibactam, Aztreonam-Avibactam, and a Panel of Older and Contemporary Antimicrobial Agents against Carbapenemase-

Producing Gram-Negative Bacilli. Antimicrob Agents Chemother [Internet]. 2015 [cited 2015 Dec];59(12):7842-6. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=26392487

28. Srigley JA, Furness CD, Baker GR, Gardam M. Quantification of the Hawthorne effect in hand hygiene compliance monitoring using an electronic monitoring system: a retrospective cohort study. BMJ Qual Saf [Internet]. 2014 [cited 2014 Dec];23(12):974-80. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=25002555

29. Chemaly RF, Simmons S, Dale C Jr, Ghantoji SS, Rodriguez M, Gubb J, Stachowiak J, Stibich M. The role of the healthcare environment in the spread of multidrug-resistant organisms: update on current best practices for containment. Ther. adv. infect. dis. [Internet]. 2014 [cited 2014 Jun];2(3-4):79-90. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=25469234

30. Tan TY, Tan JS, Tay H, Chua GH, Ng LS, Syahidah N. Multidrug-resistant organisms in a routine ward environment: differential propensity for environmental dissemination and implications for infection control. J Med Microbiol [Internet]. 2013 [cited 2013 May];62(Pt 5):766-72. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=23393110

31. Dancer SJ. Controlling hospital-acquired infection: focus on the role of the environment and new technologies for decontamination. Clin Microbiol Rev [Internet]. 2014 [cited 2014 Oct];27(4):665-90. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=25278571

32. Ling ML, Apisarnthanarak A, Thu le TA, Villanueva V, Pandjaitan C, Yusof MY. APSIC Guidelines for environmental cleaning and decontamination. Antimicrob. resist. infect. control [Internet]. 2015 [cited 2015];458. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=26719796

33. Shek K, Patidar R, Kohja Z, Liu S, Gawaziuk JP, Gawthrop M, Kumar A, Logsetty S. Rate of contamination of hospital privacy curtains on a burns and plastic surgery ward: a cross-sectional study. J Hosp Infect [Internet]. 2017 [cited 2017 May];96(1):54-58. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=28413115

34. Canton R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. FEMS Microbiol Rev [Internet]. 2011 [cited 2011 Sep];35(5):977-91. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=21722146

35. Plachouras D, Hopkins S. Antimicrobial stewardship: we know it works; time to make sure it is in place everywhere. Cochrane Database Syst Rev [Internet]. 2017 [cited 2017 02 09];2ED000119. In: Ovid MEDLINE(R) Revisions [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medc&NEWS=N&AN=28211043

36. Center for Infectious Disease Research and Policy (CIDRAP). ASP Policy Update: Rapid Diagnostic Testing in Antimicrobial Stewardship [Internet]. Minneapolis: University of Minnesota; 2017 Oct [cited 2018 May]. Available from: http://www.cidrap.umn.edu/asp/policy-update/policy-update-october-2017

37. Bogaert D, van Belkum A. Antibiotic treatment and stewardship in the era of microbiota-oriented diagnostics. Eur J Clin Microbiol Infect Dis [Internet]. 2018 [cited 2018 05];37(5):795-798. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=29411188

38. Stolz D, Smyrnios N, Eggimann P, Pargger H, Thakkar N, Siegemund M, Marsch S, Azzola A, Rakic J, Mueller B, Tamm M. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J [Internet]. 2009 [cited 2009 Dec];34(6):1364-75. In: Ovid MEDLINE(R) [Internet].

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=19797133

39. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Bhatnagar N, Annane D, Reinhart K, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Lima SS, Maravic-Stojkovic V, Verduri A, Cao B, Shehabi Y, Beishuizen A, Jensen JS, Corti C, Van Oers JA, Falsey AR, de Jong E, Oliveira CF, Beghe B, Briel M, Mueller B. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev [Internet]. 2017 [cited 2017 10 12];10CD007498. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=29025194

40. Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, Mueller A, Schaberle TF, Hughes DE, Epstein S, Jones M, Lazarides L, Steadman VA, Cohen DR, Felix CR, Fetterman KA, Millett WP, Nitti AG, Zullo AM, Chen C, Lewis K. A new antibiotic kills pathogens without detectable resistance. Nature [Internet]. 2015 [cited 2015 Jan 22];517(7535):455-9. In: Ovid MEDLINE(R) [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=25561178

41. Hover BM, Kim SH, Katz M, Charlop-Powers Z, Owen JG, Ternei MA, Maniko J, Estrela AB, Molina H, Park S, Perlin DS, Brady SF. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. Nat. microbiol. [Internet]. 2018 [cited 2018 Apr];3(4):415-422. In: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations [Internet]. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=294343