

CMEARTICLE

Ten-year narrative review on antimicrobial resistance in Singapore

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ABSTRACT Antimicrobial resistance (AMR) results in drug-resistant infections that are harder to treat, subsequently leading to increased morbidity and mortality. In 2008, we reviewed the problem of AMR in Singapore, limiting our discussion to the human healthcare sector. Ten years later, we revisit this issue again, reviewing current efforts to contain it in order to understand the progress made as well as current and emerging challenges. Although a significant amount of work has been done to control AMR and improve antibiotic prescribing in Singapore, most of it has focused on the hospital setting, with mixed impact. The role of antibiotic use and AMR in food animals and the environment – and the link to human health – is better understood today. This issue of AMR encompasses both human health as well as animal/food safety, and efforts to control it will need to continually evolve to maintain or improve on current gains.

Keywords: anti-bacterial agents/therapeutic use, antimicrobial stewardship, bacterial drug resistance, public health, Singapore

INTRODUCTION

Antimicrobial resistance (AMR), which results in drug-resistant infections that are harder to treat and attendant increased morbidity and mortality, is a slow but implacable evolutionary process that has been sped up by human activity in multiple sectors, particularly human health and agriculture.⁽¹⁻⁴⁾ In 2008, when the issue was less well known, we wrote a position paper on the problem of AMR in Singapore, limiting our discussion to the human healthcare sector.⁽⁵⁾

Several recommendations, as summarised in Table I, were made based on evidence and expert opinion available a decade ago that would facilitate the prudent and appropriate use of antibiotics.⁽⁵⁾ These included hospital- and ministry-level policies and interventions that resulted in enhanced surveillance, formal antimicrobial stewardship programmes (ASPs) in hospitals, and education on AMR.⁽⁵⁾ As seen in Table I, we observed that the majority of the recommendations made in 2008⁽⁵⁾ have been implemented over the past decade in local public sector hospitals, but not in private hospitals or the primary healthcare sector. All acute care public sector hospitals now have ASPs – primarily funded by the Ministry of Health (MOH) – and formal laboratory surveillance of key antibiotic-resistant bacteria isolated from patients attending public sector hospitals. Teaching of AMR to healthcare professionals and undergraduates is also increasingly emphasised.

Understanding of AMR has broadened, particularly with regard to the role of agriculture and the environment.⁽¹⁻⁴⁾ After ten years, it is timely that the issue of AMR and efforts to contain it in Singapore be reviewed again, in order to understand the progress made and the challenges that remain or have emerged over time.

AWARENESS AND POLICY-SETTING GOALS

Unlike a decade ago, AMR is widely recognised as a global public health threat today.⁽¹⁻⁴⁾ The threat of a post-antibiotic era ‘doomsday scenario’, where common infections or minor injuries can result in death, has been raised by the World Health Organization (WHO).⁽¹⁾ The United Kingdom’s Review on AMR estimated that by 2050, the continued rise in AMR could result in ten million deaths annually and an economic loss of USD 100 trillion.⁽²⁾ This is corroborated by a separate World Bank report conducted in 2016, which estimated that the impact of AMR would mirror that of the 2008 global financial crisis by 2050.⁽⁶⁾

In response, the World Health Assembly adopted a Global Action Plan for AMR in 2015, calling on each member state to develop and implement a corresponding context-specific multisectoral national plan.⁽³⁾ In the following year, at a special high-level meeting of the United Nations General Assembly, all member states pledged to dedicate themselves to a global response against this rising threat, adopting a ‘One Health’ approach.⁽⁴⁾

In line with this goal, Singapore launched its own National Strategic Action Plan on AMR in November 2017.⁽⁷⁾ The multisectoral plan, which was jointly developed by the MOH, the former Agri-Food and Veterinary Authority of Singapore (AVA), the National Environment Agency (NEA), and the national water agency PUB, sets a national ‘One Health’ framework to reduce the emergence and spread of drug-resistant micro-organisms through five core strategies: (a) surveillance and risk assessment, to enable timely and appropriate responses to be mounted; (b) research, to better understand AMR and provide information – where gaps in evidence exist – to

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Table I. Recommendations made in 2008 to reduce inappropriate antimicrobial usage and an assessment of their implementation over the past decade.

Recommendations	State of implementation
General	
Closing local data gaps in antimicrobial prescription and antimicrobial resistance (AMR), including:	
(a) Antimicrobial prescription data from the private and primary healthcare sectors.	Antimicrobial prescription data from private and primary healthcare sectors is not easily accessible nor compiled with public sector data.
(b) AMR data from the community and private hospitals.	AMR data from community hospitals and private hospitals is available at institutional level but not compiled or shared at the national level.
(c) Cost-effectiveness of different interventions for facilitating appropriate antibiotic use in the local framework.	Cost-effectiveness of different interventions is not well worked out.
(d) Patients' and healthcare providers' perceptions of antimicrobial prescription.	Patients' and healthcare providers' perceptions of antimicrobial prescription have been captured in a series of small studies.
(e) Impact of the pharmaceutical industry's actions on physician prescribing.	The impact of the pharmaceutical industry's actions on prescribing has been evaluated overseas.
Continued and improved surveillance and antimicrobial stewardship, with more focus on standardising definitions and communicating results and insights across institutions.	The formation of the National Antimicrobial Resistance Control Committee's National Antimicrobial Stewardship Expert Panel by the Ministry of Health (MOH) has resulted in improved surveillance in public sector acute hospitals, as well as better support for antimicrobial stewardship and communication of results and insights between public sector hospitals.
Regulators	
The MOH should take a more active and positive role in regulating antibiotic usage.	
(a) Enforce the establishment of antibiotic stewardship programmes (ASPs) in all hospitals, as with infection control programmes.	ASPs are now established in all public sector acute hospitals and some community hospitals, although not in private hospitals.
(b) Award funding to public sector hospitals for ASPs in proportion to the savings from public healthcare subsidies.	Funding has been made available to public sector acute hospitals for the establishment and maintenance of ASPs.
(c) Facilitate the sharing of laboratory and prescription data from private and public laboratories and pharmacies for surveillance purposes.	Laboratory and prescription data from the public healthcare sector is now collated by the National Antimicrobial Resistance Control Committee (NARCC) for surveillance purposes. Private hospital and laboratory data remains largely unavailable for such purposes.
(d) Re-examine the current situation where general practitioners and private specialists may have a financial incentive to prescribe more and expensive antibiotics.	This has not been re-examined.
(e) Support research or quality improvement projects on finding effective ways of improving antibiotic prescription at healthcare facilities.	More research has been performed and research funding made available for these purposes.
(f) Coordinate collaborative work among public and private hospitals in improving antimicrobial stewardship.	This has not been addressed.
(g) Track prescribing practices at hospitals through standardised and agreed metrics in the form of process and outcome measures, e.g. <i>Clostridium difficile</i> rates, AMR rates and drug usage.	For public sector acute hospitals, this has now been standardised under NARCC.
(h) Regulate the interactions between pharmaceutical industries and doctors, in particular promoting stringent disclosure requirements and restrictions as proposed internationally.	No new regulations have been established regarding interactions between pharmaceutical industries and doctors, but self-regulation, to a large part, has occurred.
(i) Promote the use of healthcare information technology (e.g. computerised surveillance and computerised decision support systems) to help improve prescription practices.	Healthcare information technology has been deployed at some public sector acute hospitals to assist in both surveillance and prescription of antibiotics.
The MOH can support local and/or regional research in the development of new antimicrobial agents.	Different research institutions have conducted research on discovering and/or developing new antimicrobial agents, although none have yet reached the stage of clinical trials.

(Contd...)

Table I. (Contd...)

Recommendations	State of implementation
Hospitals	
Hospital administrators and leaders should actively support ASP efforts. This is critical to the success of ASPs.	Public sector hospital leaders are now generally strong supporters of ASPs.
Hospitals should provide administrative and financial support for and recognition of multidisciplinary ASPs. Such programmes should be recognised as being part of an overarching attempt to limit AMR and nosocomial infections. Therefore, the role of infection control efforts in this area should be recognised and supported as well.	These efforts are now well supported in most public sector acute hospitals but not yet in private hospitals.
Hospital ASPs should collaborate actively with Infection Control and Pharmaceutical and Therapeutics committees.	This has generally been achieved at many public sector hospitals.
ASPs should monitor and audit their work regularly and improve on their interventions over time.	This has generally been achieved at many public sector hospitals' ASPs.
Educators	
At the undergraduate university level, medical and pharmacy education should be coordinated to give greater emphasis to appropriate antimicrobial prescription and the threat of AMR.	This has gradually been implemented over the years, particularly by infectious disease physicians and pharmacists teaching in local universities.
At the postgraduate level, industry-sponsored programmes should be limited. Professional bodies and societies should educate on and implement good clinical practices in antimicrobial usage.	A combination of self-regulation by pharmaceutical industries and local public sector hospitals has resulted in the limitation of industry-sponsored programmes associated with antimicrobial agents. Local professional societies have made attempts to educate healthcare professionals on antimicrobial usage and resistance.
Together with the Health Promotion Board and professional bodies/societies, the MOH should step up its attempts to educate the public and physicians regarding appropriate antibiotic usage. A shift in perception and expectations for both patients and providers is required in this area.	This is now an action item in the National Strategic Action Plan on AMR.
Pharmaceutical industry	
Local and regional branches of pharmaceutical industries should adopt the Pharmaceutical Research and Manufacturers of America's updated code of conduct on interactions with physicians.	The pharmaceutical industry in Singapore is now in compliance with the code of conduct, particularly in the public sector, where hospitals have imposed limits on physicians' interactions with the industry.

support the other core strategies; (c) education, to increase awareness and understanding of AMR; (d) prevention and control of infection, to stop transmission of resistant organisms in healthcare settings and the community; and (e) optimisation of antimicrobial use, to slow the emergence of resistance and minimise healthcare costs.

In July 2018, the WHO released a report on action against AMR at the country level.⁽⁸⁾ The report was based on submissions of a country self-assessment questionnaire, summarising national progress on the strategic objectives in the Global Action Plan.^(3,9) The topics assessed included human health, animal production, food safety concerns, plant production and the environment. A total of 154 countries were included in the report, showing much international effort to tackle AMR. Singapore was reported to have achieved most of the strategic objectives, especially for human health.⁽¹⁰⁾ Some gaps were identified, including better antibiotic stewardship, surveillance, education and awareness, and research on areas involving animal and plant health, as well as the environment.⁽¹⁰⁾

CHANGES IN ANTIMICROBIAL RESISTANCE EPIDEMIOLOGY OVER A DECADE

Global perspective

The first global surveillance report published by the WHO in 2014 showed high rates of AMR in almost all WHO regions, although updated data is not available from several countries. Asia had the highest rates of third-generation cephalosporin-resistant Enterobacteriaceae.⁽¹¹⁾ The vast majority of third-generation cephalosporin resistance in Enterobacteriaceae is due to the production of extended-spectrum beta-lactamases (ESBLs) and, to a lesser extent, AmpC beta-lactamases.⁽¹¹⁾ This is not just a problem within hospitals, as the incidence of ESBL infections is also increasing rapidly in the community setting, with ESBL-producing Enterobacteriaceae faecal colonisation rates among healthy individuals reported at 14% or higher worldwide.^(12,13)

The widespread use of carbapenems, largely directed against possible and proven ESBL-producing Enterobacteriaceae infections, likely promoted the selection and subsequent dissemination of multiple different mechanisms of carbapenem

resistance among Enterobacteriaceae.⁽¹⁴⁾ In South and Southeast Asia, carbapenem-resistant Enterobacteriaceae (CRE) has been reported in virtually every country, possibly exceeding 10% of all hospital-cultured Enterobacteriaceae in South Asian countries.⁽¹⁵⁾ More recently, transmissible resistance to colistin, one of the few available drugs for treating carbapenem-resistant Gram-negative infections, has also surfaced. Plasmid-mediated *mcr* (*mobilised colistin resistance*) genes were first described in *Escherichia coli* (*E. coli*) isolated from food animals in China in 2015. They were subsequently found in clinical isolates in various parts of the world, including Singapore.^(16,17)

Methicillin-resistant *Staphylococcus aureus* (*S. aureus*) (MRSA) was initially considered a purely nosocomial pathogen. This changed significantly with the emergence and establishment of community-associated MRSA (CA-MRSA).⁽¹⁸⁾ Moreover, recent reports suggest that CA-MRSA is taking over healthcare-associated MRSA as a cause of endemic healthcare-acquired infections at many hospitals around the world.⁽¹⁹⁾

Other than in humans, these drug-resistant organisms have also been found in animals and the environment. ESBL-producing Enterobacteriaceae have been reported in livestock and wildlife.^(20,21) Reports of livestock-associated MRSA, which are genetically distinct from human isolates, have steadily increased.⁽¹⁸⁾ This is probably due to the overcrowded conditions of food animals in most commercial farms, along with extensive use of antibiotics as growth promoters, prophylaxis or metaphylaxis.⁽²²⁾ The problem is exacerbated by the complicated exchange of antibiotic resistance genes between human, livestock and environmental pools, either via direct contact or through the food chain by contact with or ingestion of animal food products.⁽²¹⁾

Local perspective

Multidrug-resistant organisms have also been reported in Singapore. The diversity in the epidemiology of these drug-resistant organisms is likely the consequence of Singapore's strategic geographical location at international crossroads.

ESBL and AmpC beta-lactamase-producing Enterobacteriaceae were first documented in 1986 and 2003, respectively, in Singapore.^(23,24) In 2006, 30.3% and 19.6% of hospital isolates of *Klebsiella* spp. and *E. coli*, respectively, were ESBL producers, with 5.6% and 8.5% of each type of bacteria also producing AmpC.⁽²⁵⁾ These rates have remained relatively stable over the past decade in local hospitals. However, two dissimilar surveys in 2006 by Young et al and 2016 (Alex Cook et al, personal communication) showed a marked difference in community rectal carriage of ESBL-producing Enterobacteriaceae (6.3% in 2006 vs. 26.0% in 2016), which appears to signify an increasing trend despite the differing methodology of the studies.⁽²⁶⁾

Of greater concern is the growing threat of CRE. Rare in 2008, CRE was at that time due almost entirely to a combination of ESBL or AmpC beta-lactamases production combined with drug impermeability due to porin loss.⁽²⁴⁾ The introduction of carbapenemase-producing Enterobacteriaceae (CP-CRE) – with diverse plasmid-borne enzymes such as NDM, KPC and OXA-48-like variants – into local hospitals in rapid succession since

2010 has changed the local dynamic drastically.^(27,28) In a study conducted in Singapore General Hospital, the largest hospital in Singapore, carbapenem resistance rates among *Klebsiella pneumoniae* and *E. coli* increased from 2% and 0% to 12% and 5%, respectively, between 2011 and 2015.⁽²⁹⁾ From 2010 to 2013, NDM was the most frequently detected gene (57.3%), followed by OXA-48-like (24.2%) and KPC (13.7%) genes,⁽³⁰⁾ although the situation can change rapidly. Fortunately, CP-CRE rates appear to have stabilised in the past two years.⁽³¹⁾ Antibiotic resistance in non-fermenting Gram-negative bacteria is also of concern. From 2011 to 2015, the prevalence of carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* has remained stable at approximately 50% and 10%, respectively.⁽²⁹⁾

MRSA emerged in Singapore in the 1970s,⁽³²⁾ becoming endemic in local healthcare facilities, with 35.3% of all *S. aureus* isolates reported to be methicillin-resistant in 2006.⁽³³⁾ Apart from acute care hospitals, intermediate-term and long-term care facilities are also important reservoirs for MRSA. In 2014, the prevalence of MRSA was found to be significantly higher in intermediate (29.9%) and long-term (20.4%) care facilities than in acute care hospitals (11.8%), as reported in a recent study.⁽³⁴⁾ The organism has also been sporadically reported in the community as well as in local food and animals.⁽³⁵⁻³⁷⁾ The MOH, working with public sector hospitals, has stepped up measures to track and control the rates of MRSA, which have since fallen considerably from over a decade ago.⁽³⁸⁾ However, MRSA rates in private sector hospitals are not publicly available.

Vancomycin-resistant *Enterococcus* (VRE) was first reported in Singapore in 1994 but remained rare until two significant outbreaks in 2004 and 2005.⁽³⁹⁾ A passive laboratory surveillance programme from 2006 to 2010 concluded that 0.4%–0.7% of all clinical enterococcal isolates were resistant to vancomycin over these five years, with the overall incidence density of VRE remaining stable over time.⁽⁴⁰⁾ Unfortunately, resistance to the few antibiotics with activity against VRE has started to emerge, and VRE carriage rates appear to have increased since 2010.^(41,42)

LOCAL SURVEILLANCE

In the human healthcare sector, the Network for Antimicrobial Resistance Surveillance (Singapore) – an informal collaboration between public sector clinical microbiologists, pharmacists and infectious diseases physicians that was established in 2005 – was the first local multi-hospital group to elucidate the scale of antibiotic drug resistance and prescription in the local setting.⁽³³⁾ Participation in this programme was voluntary, resulting in gaps in the data collected. The network published reports until 2011, several of which took the form of academic publications.⁽⁴³⁻⁴⁵⁾

In 2009, the MOH formally established the National Antimicrobial Taskforce (NAT) – consisting of infectious disease physicians, microbiologists, infection control physicians, nurses and pharmacists – to formulate and implement measures to monitor the use of antibiotics as well as AMR rates. The NAT was also tasked with recommending measures to prevent and limit the incidence of such infections. The NAT has published annual reports on public sector hospital AMR and antibiotic

prescribing rates since 2012, but these are not publicly available. In 2014, the NAT was reorganised into the National Antimicrobial Resistance Control Committee (NARCC), for surveillance of AMR and antibiotic prescribing, and the National Infection Prevention and Control Committee, for providing national guidelines on infection prevention in the healthcare setting.

Surveillance on AMR and antimicrobial prescribing has been patchy in the animal and food sectors in Singapore. Academic projects implemented prior to 2018 were primarily independent and one-off.^(35,46,47) With the announcement of the National Strategic Action Plan against AMR, however, representatives of the MOH, AVA, NEA and PUB have made an effort to initiate AMR surveillance in the animal, food and environmental sectors, and this information will be incorporated into a joint 'One Health' report along with the NARCC annual reports in the near future.

LOCAL RESEARCH

Research is critical to fill in evidence gaps in AMR by generating new knowledge. This includes identifying risk factors for the emergence and spread of resistant organisms, and ways to stop their progress. This information will support relevant policymakers and organisations in making decisions on the appropriate actions necessary to combat AMR. There has been an increase in research activities and collaboration between various research groups in recent years, largely supported by the public sector in Singapore.

The National Research Foundation is currently funding a SGD 30-million research project in AMR over five years.⁽⁴⁸⁾ This project, helmed by the Singapore-MIT Alliance for Research and Technology, is being conducted by an interdisciplinary research group (IRG) in partnerships with universities and research institutions in Singapore.⁽⁴⁹⁾ The IRG seeks to identify new mechanisms of AMR to develop new drugs and drug delivery technologies, and to exploit host immunity to kill resistant microbes. It is also interested in developing new therapeutic diagnostic methods that are fast, cheap and easy to administer.

On a smaller scale, the National Medical Research Council (NMRC) is currently funding an SGD 5-million four-year collaborative grant on AMR.⁽⁵⁰⁾ The grant programme, Collaborative Solutions Targeting Antimicrobial Resistance Threats in the Health System (CoSTAR-HS), is a collaboration between three major hospitals in Singapore. CoSTAR-HS focuses on health systems and is looking to develop new diagnostic methods for identification of resistance mechanisms in microbes, new assessments for infection control strategies, optimisation of ASPs, and research into health systems and behavioural drivers of AMR. In addition to the above, multiple individual research grants have been given out by the NMRC, MOH and Agency for Science, Technology and Research for a variety of independent research efforts into AMR over the past decade.

Other than research on human health, it is also important to focus on animals, food and the environment. Although there is ongoing research in these sectors, much more work is needed to develop new vaccines, drugs, animal management systems and husbandry practices.^(46,51) In addition, there is a need to understand how antibiotics may contribute to the selection and

spread of drug-resistant organisms in the natural environment. This information is necessary to better control the transmission of drug-resistant organisms between the human, animal, food and environment sectors.

One critical piece that is missing in Singapore is an estimate of the socioeconomic impact of AMR at the local level. While a number of macro- and microeconomic studies have been published,^(2,6,52) these do not include the unique features of our healthcare system nor our reliance on food importation; a more accurate local assessment would enable better financing estimates for the control of AMR in Singapore.

EDUCATION ON ANTIMICROBIAL RESISTANCE AND ANTIBIOTIC PRESCRIBING

As misconceptions about appropriate antibiotic use and the consequences of misusing antibiotics are common,⁽⁵³⁾ education is needed to guide people towards a correct, unified understanding and perception of AMR, including its impact on society. Education serves two main purposes: (a) to let the target audience recognise that AMR is an urgent issue that needs to be acted upon; and (b) to equip them with the right knowledge to effectively participate in activities against AMR.

Education for healthcare and veterinary professionals should include appropriate antibiotic usage, contributors to AMR and infection control issues. These are currently included in the education curricula of many undergraduate and graduate healthcare professional programmes. Ongoing continuing education keeps professionals up to date as new evidence on AMR emerges. Training workshops can also be conducted. For example, in the area of antimicrobial stewardship, the annual Singapore Antimicrobial Stewardship Training introduces local and regional participants to best practices and skills that are needed to establish ASPs.⁽⁵⁴⁾

In addition to knowledge and skills, promoting behavioural changes in practice is also important and should be guided by sociobehavioural understanding of the target audience. A local focus group study was conducted to explore hospital physicians' perceptions of and attitudes toward their ASP.⁽⁵⁵⁾ Two reasons identified for poor acceptance of ASP recommendations were lack of awareness of the ASP team and lack of trust in them. These could potentially be addressed through improved communication with the various hospital departments via educational roadshows, regular reports on their antibiotic prescription trends, and published evidence that ASP recommendations specific to their department are advantageous to their patients.⁽⁵⁶⁻⁶⁰⁾

Patients' attitudes and expectations often influence physicians' antibiotic prescribing practices,⁽⁵³⁾ reinforcing the need for public education to increase awareness about the issue of AMR and appropriate antibiotic use. Since 2016, Singapore has been actively participating in the annual World Antibiotic Awareness Week, supported by the WHO every November, by reaching out to the public at various public forums, hospitals and national libraries.^(61,62) In 2017, the MOH and Health Promotion Board organised a social campaign called F.I.G.H.T., focusing

on the general prevention of infection to fight the spread of influenza and other infectious diseases.⁽⁶³⁾ Most recently, the issue of antibiotics overprescription was featured in the local newspapers.^(64,65) The articles highlighted the results of a recent national point prevalence study (PPS) stating that more than half the patients in acute hospitals were on at least one antibiotic, a much higher proportion compared to inpatients in European hospitals.⁽⁶⁶⁾

Emphasis should also be placed on education in the agriculture and biopharmaceutical sectors, although these are small in Singapore. End-users of veterinary medicines such as farmers should know how to responsibly use antibiotics in farm animals. Pharmaceutical industries, farms and hospitals involved in the disposal of waste should be educated on proper waste management to reduce the discharge of antibiotics into the environment, reinforced by local regulatory controls.

PREVENTION AND CONTROL OF INFECTION IN SINGAPORE

Effective infection prevention and control (IPC) measures are required to minimise infection risks and limit the emergence and spread of drug-resistant organisms among humans and animals, which ultimately reduces the usage of antibiotics. Vaccination is occasionally overlooked as an intervention against AMR. However, the prevention of viral or bacterial infections that could lead to healthcare visits correspondingly reduces opportunities for antibiotic prescription. In 2017, MOH established the National Adult Immunisation Schedule to facilitate the uptake of important vaccinations such as influenza and pneumococcal vaccines among adults.⁽⁶⁷⁾ These recommendations are not mandatory, and measures to monitor and encourage vaccine uptake are necessary.

IPC programmes are mandated for all hospitals as part of hospital licensing. National guidelines for IPCs have recently been published by the National Infection Prevention and Control Committee and help to establish standards and guidance to prevent the spread of infections, including from multidrug-resistant organisms.⁽⁶⁸⁾ Hospitals must report infection control indicators routinely to the MOH for detection of any peculiar trends.

In the animal sector, the Singapore Food Agency (SFA) enforces strict biosecurity requirements and good animal husbandry/aquaculture practices to reduce the occurrence of infectious diseases in animals, although testing for multidrug-resistant organisms in food is not routinely performed.

OPTIMISATION OF ANTIMICROBIAL PRESCRIPTION AND USE

Community and veterinary prescription of antibiotics

There remains a gap in knowledge about the amount and appropriateness of antibiotic prescribing in the primary healthcare setting in Singapore, although it is likely that improvements can be made.⁽⁵³⁾ A similar gap exists for antibiotics prescribed in local veterinary and agricultural practices. In these settings, in addition to attempts to improve data capture, strategies to improve prescribing practices in the community – such as guidelines

for antibiotic prescription and incentives to encourage proper antibiotic usage – should be developed to tackle the issue of inappropriate prescribing. The use of antibiotics in veterinary medicine could be governed by regulations, while guidelines would encourage the prudent use of antibiotics in livestock and veterinary medicine.

Hospital antibiotic prescription

Data from the acute care hospitals suggests that antibiotic usage is high: in a national PPS conducted in 2015, 51% of 5,415 patients from 13 private and public acute hospitals were on at least one systemic antibiotic.⁽⁶⁶⁾ This was significantly higher than comparable results from a global PPS that reported 37.2% and 39% in other Asian and European settings, respectively.⁽⁶⁹⁾ The national study also found that 12.8% of the prescriptions were for surgical prophylaxis, the majority of which were prescribed for more than one day, a practice that is non-evidence-based.⁽⁶⁶⁾ Unfortunately, appropriateness of antibiotic prescriptions was not assessed as it was beyond the scope of this national PPS, although public hospitals – such as KK Women's and Children's Hospital – have reported that broad-spectrum antibiotics such as carbapenems were appropriately prescribed up to 90% of the time.⁽⁷⁰⁾

Antimicrobial stewardship programmes in Singapore

ASPs aim to optimise antibiotic use through multi-pronged strategies, including pre-authorisation, prospective audit with intervention and feedback, and, more recently, the use of computerised clinical decision support systems (CDSSs) to improve antibiotic prescribing at the time of prescribing.⁽⁷¹⁾ In 2011, MOH provided SGD 20 million to fund the development of ASPs in Singapore's public acute care hospitals. This fund was used for the provision of ASP teams – consisting of infectious diseases physicians, microbiologists, infectious diseases pharmacists and executives – as well as the development of CDSSs. Guidelines for training and practice of antimicrobial stewardship were introduced the year after in order to ensure a consistent standard of delivery.⁽⁷²⁾

Since then, numerous studies from various institutions have reported that ASPs were able to improve the appropriateness of antibiotic prescriptions and reduce the duration of antibiotic use without compromising patient safety.⁽⁵⁶⁻⁶⁰⁾ Acceptance of ASP recommendations was associated with shorter lengths of stay, decreases in mortality and re-admissions, and substantial cost savings for patients, although ASPs on their own were notably unsuccessful in significantly decreasing the incidence of AMR in local hospitals.⁽⁷³⁻⁷⁵⁾

The first local CDSS, ARUS-C (Antibiotic Resistance Utilisation and Surveillance-Control), was developed by Tan Tock Seng Hospital in 2009, prior to MOH's ASP funding – which spurred attempts to adopt ARUS-C or develop new CDSSs after 2011.⁽⁷⁶⁾ By using appropriate algorithms, CDSSs could potentially provide patient-specific, evidence-based antibiotic recommendations at the point of prescribing, an advantage that is potentially magnified by the availability of other patient data

within electronic medical records such as drug allergies, culture results, and renal and/or liver function.

Unfortunately, the CDSSs set up in Singapore had limited success in improving antibiotic prescribing: only 63%–67% of the antibiotic recommendations from the various CDSSs were accepted.^(55,77) Another attempt to adopt ARUS-C at another local hospital failed entirely, with the hospital's senior management pulling the plug after a short trial period. Understanding physician behaviour when using CDSS, integrating CDSS into the work process in a user-friendly manner and education on its proper usage are important to optimise uptake and acceptance.

Since 2011, ASPs have been implemented in all public acute care hospitals in Singapore. They have not been established in private hospitals and are present in only a couple of community hospitals.

Future steps to optimise prescription in hospitals

ASPs should ideally be established in both public and private hospitals, which might require a regulatory approach similar to that used for infection prevention programmes in Singapore. One possibility for established ASPs is to shift from antibiotic-specific audits to syndrome-specific audits. This is an effective way to improve prescribing, as the intervention message can be focused, with clinical guidelines and algorithms reinforced.⁽⁷¹⁾ Syndrome-specific audits could then be regularly evaluated to identify new areas for targeted interventions based on local needs.⁽⁷¹⁾

The recently established National Collaborative Prescribing Programme trains experienced pharmacists and advanced practice nurses to legally prescribe medicines and order tests, without requiring a doctor's countersignature.⁽⁷⁸⁾ This could possibly change the landscape of ASPs, with ASP pharmacists taking on a more active role to ensure appropriate antibiotic prescriptions or to order further investigations for the team.

New technology can be harnessed to improve patient care and the use of antibiotics. A National Electronic Health Records (NEHR) system, set up in 2011, has been collating patient health records across different healthcare providers.⁽⁷⁹⁾ The NEHR allows healthcare professionals to have a holistic and longitudinal view of patients' healthcare histories. As the number of institutions participating in the NEHR increases, including general practitioner clinics, we can expect more seamless care for patients, as all previous laboratory and radiological investigations as well as prior antibiotic usage would be readily available. This enormous amount of data could potentially be harnessed for machine learning and artificial intelligence to identify potentially inappropriate prescriptions as well as improve prescribing via the development of superior versions of current-day CDSSs.^(80,81)

CONCLUSION

AMR has gained considerable recognition as a major global public health threat. The position paper published in this journal a decade ago was limited in scope, focusing on human health and antibiotic prescribing in particular. A more nuanced understanding of AMR as a 'One Health' issue has emerged since then, and considerable work has gone into controlling AMR and

improving antibiotic prescribing in Singapore, although this has been largely focused in the public hospital setting. The actual impact on the control of AMR has been mixed, with better control of MRSA coupled with a global rise in Gram-negative resistance that has also affected local hospitals and the community.

More efforts for AMR control are required in the human health, animal and environment sectors. These gaps are recognised in Singapore's National Strategic Action Plan against AMR, which has also led to the formation of a new entity – the AMR Coordinating Office based at the National Centre for Infectious Diseases – to track and coordinate national efforts.

Other potential future steps towards the control of AMR in Singapore include expanding surveillance and educational efforts directed towards the private healthcare sector, the community and the agricultural/veterinary sectors; improving vaccination rates and other aspects of IPC in hospitals and community; continued research funding, particularly for estimating the socioeconomic impact of AMR at the local level; improving the delivery of ASPs; and harnessing new technology, including artificial intelligence, to improve antibiotic prescribing.

Because AMR is an evolutionary process, the implementation of policies to control AMR as a 'One Health' effort similarly needs to continually evolve in order to maintain or improve on current gains. This will require persistently strong political will and a motivated workforce in Singapore.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201908A)

	True	False
1. Antibiotic-resistant bacteria in livestock and the environment have no impact on human health.	<input type="checkbox"/>	<input type="checkbox"/>
2. Human activity and antibiotic use have been the most important factors contributing to the issue of antimicrobial resistance today.	<input type="checkbox"/>	<input type="checkbox"/>
3. The impact of antimicrobial resistance at the global level, if left unchecked, has been estimated at several million deaths each year by the year 2050, with a financial cost equivalent to the 2008 financial crisis.	<input type="checkbox"/>	<input type="checkbox"/>
4. There is universal acceptance at the country level that action against antimicrobial resistance is critical and necessary.	<input type="checkbox"/>	<input type="checkbox"/>
5. There is ongoing and regularly updated global surveillance on the prevalence of antibiotic prescription and antibiotic-resistant bacteria in all countries.	<input type="checkbox"/>	<input type="checkbox"/>
6. Methicillin-resistant <i>Staphylococcus aureus</i> has now been identified in both the community setting and in animals in Singapore.	<input type="checkbox"/>	<input type="checkbox"/>
7. Extended-spectrum beta-lactamase-producing Enterobacteriaceae have not yet emerged as a cause of community-acquired infections in Singapore.	<input type="checkbox"/>	<input type="checkbox"/>
8. The antibiotic-resistant bacteria currently of greatest concern in Singapore hospitals is carbapenem-resistant Enterobacteriaceae.	<input type="checkbox"/>	<input type="checkbox"/>
9. The incidence of infections caused by carbapenem-resistant <i>Pseudomonas aeruginosa</i> (<i>P. aeruginosa</i>) has increased over the past few years in Singapore hospitals, with more than 30% of <i>P. aeruginosa</i> clinical isolates being resistant to carbapenems.	<input type="checkbox"/>	<input type="checkbox"/>
10. Vancomycin-resistant enterococci are currently the most prevalent antibiotic-resistant bacteria causing drug-resistant infections in Singapore.	<input type="checkbox"/>	<input type="checkbox"/>
11. The socioeconomic impact of antimicrobial resistance in Singapore has been calculated and is used to guide policies to control the issue here.	<input type="checkbox"/>	<input type="checkbox"/>
12. Better infection control policies, including good hand hygiene, are key to preventing the spread of antibiotic-resistant bacteria in the hospital setting.	<input type="checkbox"/>	<input type="checkbox"/>
13. Infection control programmes are mandated as part of hospital licensing for both public and private hospitals in Singapore.	<input type="checkbox"/>	<input type="checkbox"/>
14. Antibiotic stewardship programmes are mandated in Singapore hospitals as part of hospital licensing by the Ministry of Health.	<input type="checkbox"/>	<input type="checkbox"/>
15. The Singapore Food Agency (former the Agri-Food and Veterinary Authority of Singapore) reinforces good animal husbandry practices but does not routinely test livestock products for antibiotic-resistant bacteria.	<input type="checkbox"/>	<input type="checkbox"/>
16. Influenza and pneumococcal vaccinations may reduce antibiotic prescription at the population level.	<input type="checkbox"/>	<input type="checkbox"/>
17. Patients' attitudes and expectations may influence physicians' antibiotic prescription preferences, and represent an area where more efforts can be made to reduce antibiotic-seeking behaviour.	<input type="checkbox"/>	<input type="checkbox"/>
18. The use of computerised decision support systems to provide recommendations to physicians prescribing antibiotics has been universally accepted in Singapore hospitals.	<input type="checkbox"/>	<input type="checkbox"/>
19. Acceptance of antibiotic stewardship recommendations in Singapore public hospitals has generally been associated with positive patient outcomes.	<input type="checkbox"/>	<input type="checkbox"/>
20. Antibiotic stewardship programmes have significantly reduced the incidence of drug-resistant infections in Singapore hospitals.	<input type="checkbox"/>	<input type="checkbox"/>

Doctor's particulars:

Name in full: _____ MCR no.: _____
 Specialty: _____ Email: _____

SUBMISSION INSTRUCTIONS:

Visit the SMJ website: <http://www.smj.org.sg/current-issue> and select the appropriate quiz. You will be redirected to the SMA login page.

For SMA member: (1) Log in with your username and password (if you do not know your password, please click on 'Forgot your password?'). (2) Select your answers for each quiz and click 'Submit'.

For non-SMA member: (1) Create an SMJ CME account, or log in with your SMJ CME username and password (for returning users). (2) Make payment of SGD 21.40 (inclusive of 7% GST) via PayPal to access this month's quizzes. (3) Select your answers for each quiz and click 'Submit'.

RESULTS:

(1) Answers will be published online in the SMJ October 2019 issue. (2) The MCR numbers of successful candidates will be posted online at the SMJ website by 10 October 2019. (3) Passing mark is 60%. No mark will be deducted for incorrect answers. (4) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council. (5) One CME point is awarded for successful candidates. (6) SMC credits CME points according to the month of publication of the CME article (i.e. points awarded for a quiz published in the December 2017 issue will be credited for the month of December 2017, even if the deadline is in January 2018).

Deadline for submission (August 2019 SMJ 3B CME programme): 12 noon, 3 October 2019.