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Reducing antimicrobial resistance through appropriate antibiotic usage in Singapore

Hsu L Y, Kwa A L, Lye D C, Chlebicki M P, Tan T Y, Ling M L, Wong S Y, Goh L G

ABSTRACT

Two alarming trends threaten the future utility of antimicrobial agents: rise of antimicrobial resistance and decline in development of new antibiotics. The continuing emergence and spread of antimicrobial-resistant microbes—a global public health issue—exacerbates the problem of paucity of new antimicrobial agents. Singapore's public sector hospitals currently have some of the highest rates of antimicrobial resistance worldwide, evolving with surprising speed over the past two decades. Because there was no systematic surveillance until fairly recently, this healthcare problem has not been emphasised. In contrast, it is difficult to assess the scale of antimicrobial resistance in the community in view of the lack of recent research, although indirect evidence suggests that this is also a source of concern. A panel comprising representatives from multiple professional healthcare societies was convened to address the issue of antimicrobial resistance in Singapore, focusing on the conservation of antibiotics against resistance. From a review of the medical literature, potentially successful strategies involve facilitating prudent and appropriate use of antimicrobial agents in tandem with other interventions in infection control. Presently, there is a lack of data on the appropriate use of antibiotics in Singapore. The recommendations of the panel are: The professions should look into ways and means to support systematic data collection on antibiotic use and appropriateness of use; The Ministry of Health should take a more active and positive role in regulating antibiotic usage; Hospitals should actively support effective antimicrobial stewardship programmes; Educators should coordinate programmes to give greater emphasis on appropriate antimicrobial prescription, and support good clinical practice; and, Local and regional branches of pharmaceutical companies should adopt the Pharmaceutical Research and Manufacturers of America's updated code of conduct on interactions with physicians as a step towards re-aligning the industry-physician relationship in the direction of educational and informational support.

Keywords: antibiotic usage, antibiotic surveillance, antimicrobial drug resistance, antimicrobial stewardship, clinical education, pharmaceutical industry

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INTRODUCTION

The discovery and development of antibiotics is widely acknowledged to be one of the most important public health interventions of the last century – it was placed second in a poll on "greatest medical advances since 1840", conducted by the British Medical Journal in 2007.[1] Countless lives and limbs have been saved by the use of antibiotics, and these drugs have been critical as ancillary treatment for the further development of surgical and cancer therapies. However, its impact has diminished dramatically with the advent of two alarming trends: the rise of antimicrobial resistance and the drying-up of the pharmaceutical antimicrobial development pipeline.[2] In view of these interlinked trends, one obvious strategy is to promote the prudent and appropriate use of antimicrobials in the clinical setting to retard the development of resistance and extend the viability of existing drugs. While this paper focuses mainly on the issue of uncontrolled and inappropriate antibiotic prescription in the local setting, it is important to appreciate that a concerted response—including strategies to spur the development of new antimicrobial agents—is key to resolving the current problems posed by antimicrobial resistance.

PARTICIPANTS

A multidisciplinary panel, comprising both public and private sector healthcare professionals from the specialties of infectious diseases, microbiology, pharmacy and family medicine, was convened to review the issue of antimicrobial usage and resistance locally, as well as to provide recommendations to facilitate the optimal use of antimicrobial agents in Singapore. A review of the medical literature was conducted, focusing on local antimicrobial resistance reports, international guidelines and original articles on appropriate antimicrobial use. Data were obtained from other sources where necessary, particularly the Ministry of Health, Singapore (MOH). This paper and its recommendations are endorsed by the following organisations: Society of Infectious Diseases

Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 5 Lower Kent Ridge Road, Singapore 119074

Hsu LY, MBBS, MPH, MRCP
Assistant Professor

Department of Community, Occupational and Family Medicine

Goh LG, MBBS, MMed, FCFP
Associate Professor

Department of Pharmacy, Singapore General Hospital, Outram Road, Singapore 169608

Kwa AL, PharmD, BCPS
Principal Pharmacist

Department of Infectious Diseases

Chlebicki MP, MD, ABIM
Consultant

Infection Control Unit

Ling ML, MBBS, FRCPA
Director

Department of Infectious Diseases, Communicable Disease Centre, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433

Lye DC, MBBS, FRACP
Consultant

Department of Laboratory Medicine, Changi General Hospital, 2 Simei Street 3, Singapore 529889

Tan TY, MBBCh, MRCPath
Consultant

Infectious Diseases Partners Pte Ltd, Gleneagles Medical Centre, 6 Napier Road, #10-03, Singapore 258499

Wong SY, MBBS, MMed, FAMS
Senior Consultant

Correspondence to:
Dr Hsu Li Yang
Tel: (65) 6779 5555
Fax: (65) 6779 5678
Email: mdchly@nus.edu.sg

(Singapore), Infection Control Association (Singapore), Singapore Society of Pathology, and Chapter of Infectious Disease Physicians, Academy of Medicine, Singapore.

THE SHRINKING ANTIMICROBIAL DEVELOPMENT PIPELINE

The reasons for the decline in research and development (R&D) of new antimicrobial agents have been described in detail in the Infectious Diseases Society of America's white paper in 2004.[3] Most importantly, the returns on investment on antimicrobial development are far too low compared with chronic disease and lifestyle medications.[3] Approximately USD 800 million and a period of ten years or longer are the industry averages for bringing a new drug to market, and this does not take into consideration the risks of post-approval adverse events or drugs that fail the R&D process.[3] Unlike chronic disease medications, novel antibiotics often then become drugs of last resort, held back in reserve by well-meaning clinicians and policy makers in a bid to retard the inevitable development of resistance. They are also quickly discontinued (average length of treatment between 5 and 14 days) in contrast to chronic disease medications.[3] Initiatives to address this gap are underway, especially in the United States (US), including multilevel and multimillion dollar funding efforts by the National Institute of Allergy and Infectious Diseases (NIAID) to develop therapies against drug-resistant bacteria.[4] However, even in the best-case scenario, it will be a decade or longer before these new antimicrobial agents enter the market.

RISING ANTIBIOTIC RESISTANCE

The continuing emergence and spread of antimicrobial-resistant microbes exacerbate the problem of paucity of new antimicrobial agents. Antimicrobial resistance is acknowledged to be a global public health issue, and is fuelled by four main factors:[2,3,5]

(1) Excessive use of antimicrobial agents in animal husbandry.
(2) Inappropriate and immoderate prescription of antimicrobial agents in clinical practice.
(3) Implementation failure of infection control practices in institutional settings.
(4) Globalisation with ease of travel/transport of both humans and agricultural products.

Multiple studies have shown that infections caused by antimicrobial-resistant microbes are associated with higher mortality, morbidity, costs, and prolonged hospital stay compared with infections caused by their drug-susceptible counterparts.[6-8]

DATA ON ANTIMICROBIAL RESISTANCE IN SINGAPORE

Singapore has not been spared from the global public health issue of rising antimicrobial resistance.

Public sector hospitals

Our public sector hospitals currently have some of the highest rates of antimicrobial resistance worldwide, and this has evolved with surprising speed over the past two decades. Because there was no systematic surveillance until fairly recently, this healthcare problem has not been emphasised.

Resistance in Gram-negative bacteria

Extended-spectrum beta-lactamases (ESBL)—bacterial enzymes that break down practically all cephalosporins and penicillins—were probably first detected locally in 1986,[9] and by 1992, approximately 39% of *Klebsiella* spp. at a large tertiary hospital tested positive for ESBL.[10] In 2006, a systematic survey of all local public hospitals showed that 36% and 18% of *Klebsiella* spp. and *Escherichia coli*, respectively, were resistant to third-generation cephalosporins.[11] During this same period, quinolone resistance in Enterobacteriaceae rose from 12% at a university hospital in 1991,[12] to almost 50% in 2006 among all local public hospitals.[11] Although Enterobacteriaceae are the predominant clinical isolates, antibiotic resistance in non-fermenting Gram-negative bacilli has also escalated. In 2006, 49.6% of all *Acinetobacter* strains were reported as resistant to the carbapenems,[11] and isolates resistant to all conventional antibiotics are not uncommon.

Resistance in Gram-positive bacteria

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been established in Singapore for at least 25 years.[13] By the 1990s, approximately 40% of *S. aureus* isolates were reported to be methicillin resistant, and this proportion has remained until today.[11] To add to the complexity, MRSA infections are beginning to establish a toehold in community-acquired infections[14] while MRSA isolates in hospitals may be subtly shifting towards low-level vancomycin resistance,[15] thereby adversely influencing therapeutic outcomes. Until recent times, Singapore was spared from circulating vancomycin resistance in enterococci. However, a significant outbreak of vancomycin-resistant *Enterococcus faecium* in 2005 changed the perception that Singapore was safe from this nosocomial pathogen.[16] While the overall prevalence remains low, ongoing surveillance demonstrates that

vancomycin-resistant enterococci (VRE) remains a very real threat in the at-risk population.[11]

Community

There have been no recent studies of antibiotic resistance in the local community, and it is therefore difficult to assess the scale of this problem. However, there is some indirect evidence that antibiotic resistance in the community is a clear source of concern; besides non-systematic evidence of the spread of community-associated MRSA,[14] a recent study highlighted the carriage of ESBL-positive Enterobacteriaceae in up to 12% of more than 1,000 emergency department attendees, the majority of whom had no previous hospitalisations.[17] The only risk factor that was significantly associated with this phenomenon was recent consumption of oral antibiotics.[17]

ANTIBIOTIC USAGE IN SINGAPORE

Various international organisations have recommended that aggregated drug use at local and national levels should be monitored so as to better understand the relationship between drug use and resistance development.[18-20] This is now performed in Europe by the European Surveillance of Antimicrobial Consumption (ESAC) and in US institutions participating in the US Center for Disease Control and Prevention (CDC) National Healthcare Safety Network and ICARE projects. No such comprehensive surveillance programme exists in Singapore, although financial data on the sales of antimicrobial agents by pharmaceutical companies and public sector institutes are captured by IMS Health Incorporated and the MOH, respectively. The Network for Antimicrobial Resistance Surveillance (Singapore) (NARSS)—a voluntary group of healthcare professionals—has also started to capture antibiotic prescription data from the public sector hospitals since 2006.

Public sector

The public sector delivers approximately 20% and 80% of primary and tertiary healthcare, respectively.

Government polyclinics

The antimicrobial expenditure of government polyclinics constitutes approximately 1.3%–1.4% (SGD 303,126.07–SGD 333,550.00) of the entire drug budget, and has been decreasing over the period 2005–2007 [personal communication, MOH]. Antimicrobial use in this setting is controlled by the limited number of drugs available in the standard formulary under MOH.

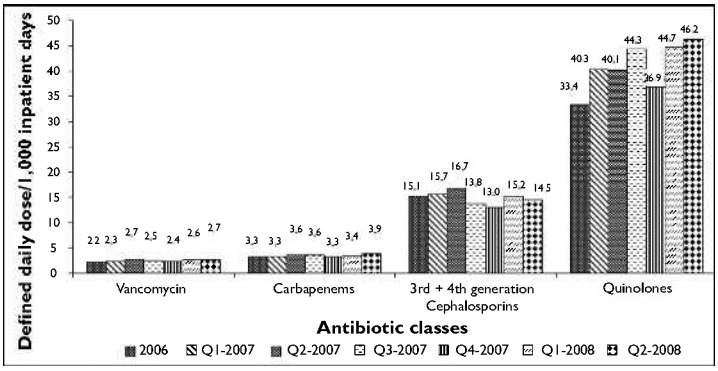

Fig. 1 Bar chart shows combined usage data of key antibiotic classes in local public hospitals according to defined daily dose per 1,000 patient-days.

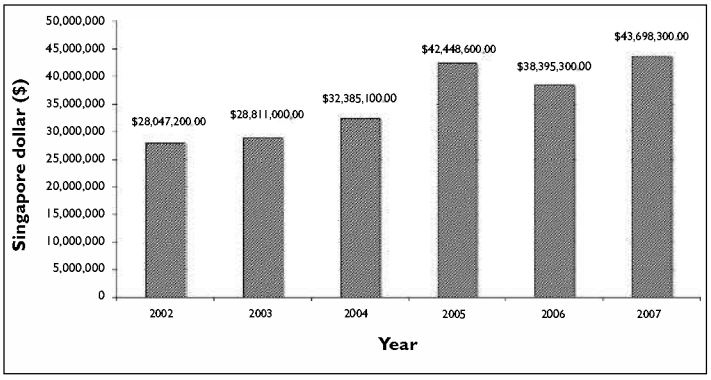

Fig. 2 Bar chart shows approximate overall sales of systemic antibiotics by pharmaceutical companies in Singapore to both private and public healthcare sectors. It does not include antifungal agents and topical antimicrobial agents (data from IMS Health reports).

Public sector hospitals

Antimicrobial expenditure of public sector hospitals has been rising steadily over the same period, constituting approximately 0.07%–18.6% (SGD 4,428.00–SGD 17,400,000.00) of the drug budget of these hospitals [personal communication, MOH]. The antibiotic usage data of public sector hospitals in terms of defined daily dose methodology as proposed by the World Health Organisation (WHO) is shown in Fig.1.

Private sector

The private sector delivers approximately 80% of the primary care of Singapore and 20% of the tertiary healthcare. Currently, there is no readily available data on antimicrobial usage in this sector. It is conceivable that this sector contributes to the increase in value of antibiotic sales by pharmaceutical companies locally as collated by IMS Health and is shown in Fig. 2.

APPROPRIATENESS OF PRESCRIPTION

More relevant than financial or prescription data is the question of whether antimicrobial agents are appropriately

prescribed. Previous studies performed elsewhere suggest that up to one-third or more of antibiotic usage in hospitals is inappropriate.[21,22] There is a paucity of such data in Singapore, although vancomycin and carbapenem audits conducted at the Singapore General Hospital in 2005 found that 23.5% and 44%, respectively, were inappropriately prescribed.[23] There is therefore a need for such surveys to be conducted both in the primary care sector as well as in the hospital sector.

ROLE OF THE PHARMACEUTICAL INDUSTRY

There is increasing international concern about the influence of the pharmaceutical industry on physician prescription. The evidence is clear—despite many physicians' claims otherwise—that such relationships influence prescribing behaviour, and potentially in negative ways.[24] Attempts to self-regulate this by physician bodies have not been successful, leading to interventions by administrators and policy-makers worldwide.[25] Intense lobbying in the US led to changes in the "Code on Interactions with Healthcare Professionals" by the Pharmaceutical Research and Manufacturers of America (PhRMA).[26] This will take effect from January 2009, and includes stricter guidelines on industry-physician relationships. It is important to note that this code only pertains to the US, and is voluntary in nature.

No study has been conducted in Singapore with regard to the influence of the pharmaceutical industry on local prescribing behaviour. The Singapore Association of Pharmaceutical Industries (SAPI) has a code of marketing practices,[27] but this is considerably less strict than PhRMA's code, and not all pharmaceutical companies operating in Singapore belong to SAPI. The Singapore Medical Council provides guidance on such interactions as part of its ethical code; however, these are mainly codes of behaviour and are largely not enforced except with regard to advertisement.[28]

INTERVENTIONS FOR OPTIMISING ANTI-MICROBIAL PRESCRIPTION

Since the 1980s, there have been more than 300 reports in the medical literature proposing a range of interventions designed to reduce inappropriate antibiotic prescribing. The vast majority was undertaken in the hospital setting. Comprehensive systematic reviews summarising these interventions were published recently, concluding that the majority of high-quality studies had demonstrated that such interventions could improve antimicrobial prescription in hospitals, and reduce the incidence of antimicrobial resistance and/or hospital-acquired infections.[20,29-31] Effective antimicrobial stewardship programmes (ASPs) were also financially self-supporting and resulted in considerable annual savings as a consequence of decreasing antimicrobial usage. In general, however, recognition of ASPs as a priority area by patient advocacy groups, key decision-makers, and government are crucial to successful and sustainable implementation.[32]

Hospital setting

Traditionally, two core strategies provide the foundation for hospital-based ASPs:

(1) Prospective audit with intervention and feedback.

(2) Formulary restriction and pre-authorisation.

Other supplementary interventions include: use of guidelines and clinical pathways, education, parenteral to oral antibiotic conversion, among others.[20] In general, restrictive interventions were more effective and had greater immediate impact than persuasive interventions.[29] However, they were less acceptable to healthcare providers and were more likely to meet with substantial resistance upon introduction.[29] Few of these strategies can be translated successfully into the primary healthcare sector.

With the development of information technology, computerised decision support systems (CDSS) were established that were also effective in improving appropriateness of antibiotic use without adversely impacting patient outcomes.[33-35] The key feature of any CDSS for antibiotic prescription is integration of patients' microbiological culture results with antibiotic guidelines and prescription tools. Desirable safety features comprise allergy and therapeutic duplication checks as well as renal dose adjustment. Importantly the CDSS must be part of the work process of doctors and be as user-friendly as possible in order to optimise uptake and acceptance. The ability to audit the entire prescribing process is critical to ensure patient safety and assess performance of the CDSS.

Ambulatory/primary healthcare setting

Given a certain level of technology, CDSS may also be employed successfully in the outpatient and primary healthcare setting.[35] However, other interventions in this setting have had more varied impact, and many interventions used in the hospital setting are ill-suited to a primary healthcare setting. Clinical practice guidelines for appropriate use of antibiotics have been developed for primary care worldwide.[36,37] One of these documents is the MOH Clinical Practice Guidelines on Antibiotic

Use in Adults, 2006.[36] It is important to note that interventions focusing on physician education alone have rarely succeeded, and success has mainly been achieved with strategies that target education at both "supply" (physicians) and "demand" (patients and community), resulting in a sustained cultural change.[37]

RECOMMENDATIONS

In conclusion, antimicrobial resistance is a major public health issue worldwide and in Singapore. Although there are gaps in the data, there is sufficient evidence that the problem is pervasive in Singapore, and one purpose of this position paper is to sound the alarm on the seriousness of antibiotic resistance locally. Under the current circumstances, lack of data or confirmation should not be an excuse for inaction.

The following recommendations are put forth by the panel to reduce inappropriate antimicrobial usage and ultimately, antimicrobial resistance in the local context. A concerted, multilevel approach with public-private partnership is the ideal, but individual efforts in this area should also be supported.

General

(1) Ways and means to support systematic data collection should be explored to provide the data to close the current local gaps in information with regard to antimicrobial prescription and resistance. These gaps include:
   (a) Antimicrobial prescription data from the private and primary healthcare sectors.
   (b) Antimicrobial resistance data from the community and private hospitals.
   (c) Cost-effectiveness of different interventions for facilitating appropriate antibiotic use in the local framework.
   (d) Patients' and healthcare providers' perceptions on antimicrobial prescription.
   (e) Impact of the pharmaceutical industry's actions on physician prescribing.

(2) Existing programmes in surveillance and antimicrobial stewardship should continue, with more effort made towards standardising definitions and communicating results and insights across institutions.

Regulators

(3) MOH should take a more active and positive role in regulating antibiotic usage. The following measures should be considered:
   (a) Enforce the establishment of ASPs in all hospitals, just as in the case with infection control programmes. ASPs may be part of, or separate from, existing infection control programmes.
   (b) Award funding to the public sector hospitals for ASPs in proportion to the savings made from public healthcare subsidies.
   (c) Facilitate the sharing of laboratory and prescription data from private and public laboratories and pharmacies for surveillance purposes.
   (d) Re-examine the current situation, where general practitioners and private specialists may have a financial incentive to prescribe more and expensive antibiotics.
   (e) Support research or quality improvement projects on finding effective mechanisms of control at the healthcare facilities.
   (f) Coordinate collaborative work among public and private hospitals in improving antimicrobial stewardship (similar to the successful IHI collaborative work on various improvement programmes in the US).
   (g) Track prescribing practices in the country, e.g. through standardised and agreed metrics for hospitals in the form of process and outcome measures, e.g. *Clostridium difficile* rates, antimicrobial resistance rates, drug usage computed as defined daily doses (for comparison with international figures).
   (h) Regulate the interactions between pharmaceutical industries and doctors, in particular promote stringent disclosure requirements and restrictions as proposed internationally.[25,26]
   (i) Promote the use of healthcare information technology (e.g. computer surveillance and CDSS) to help improve prescription practices. This could be part of the future national Electronic Health Records system announced by the health minister at the JAMA-NUHS CME conference.[38]

(4) MOH can also support local and/or regional research in the development of new antimicrobial agents in line with US NIAID efforts.[4]

Hospitals

(5) Hospitals should provide administrative and financial support for and recognition of multidisciplinary ASPs. Beyond the immediate possible cost savings, such programmes should be recognised as being part of an overarching attempt to limit antimicrobial resistance and nosocomial infections. Therefore the role of infection control efforts by other individuals in

this area should be recognised and supported as well.

(6) Although the panel does not recommend any specific interventions per se, it is important that ASPs should monitor and audit their work regularly, and improve on its interventions over time.

(7) Hospital ASPs should collaborate actively with Infection Control and Pharmaceutical and Therapeutics Committees or their equivalent.

(8) Hospital administrators and leaders should actively support ASP efforts. This is critical to the success of ASPs. It is desirable that ASP functions under Infection Control, Quality or Patient Safety.

Educators

(9) At the undergraduate university level, medical and pharmacy education should be coordinated to give greater emphasis on appropriate antimicrobial prescription and the threat of antimicrobial resistance.

(10) At the postgraduate level, industry-sponsored programmes should be limited. Professional bodies and societies should undertake to educate and implement good clinical practices in antimicrobial usage.

(11) Together with the Health Promotion Board and professional bodies/societies, 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.

Pharmaceutical industry

(12) Local and regional branches of pharmaceutical industries should adopt the PhRMA's updated code of conduct on interactions with physicians.[26] While the panel recognises that the code falls short of being ideal, it marks an important advance over previous iterations in managing physician-industry interactions.

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