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Reducing antimicrobial resistance: a bold call to action

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In this edition of the Singapore Medical Journal, Hsu et al have issued a bold call to action on the problem of antimicrobial resistance in Singapore.[1] This takes the form of a position paper representing the major infectious diseases and clinical microbiology societies. To our knowledge, this is the second time that a group of professional societies has issued a position paper independent of the Ministry of Health, Singapore (MOH) and is a refreshing evidence of "medical activism" by civil society in Singapore. The first, published in the Annals of the Academy of Medicine, Singapore, by Chua et al, suggested roles for human immunodeficiency virus (HIV)-infected healthcare workers in Singapore.[2] This second document is a timely call for action on the problem of antimicrobial resistance. The authors argue for several measures: for enhanced data collection to document the scale and impact of the problem of antibiotic use and misuse; for the MOH to take an active role in regulating antibiotic use; for hospitals to support antimicrobial stewardship programmes; and finally for an update of the code of conduct regulating the relationship between the pharmaceutical industry and prescribing physicians.[1]

The paper begins with a summary of the data on antibiotic resistance in Singapore. While published studies have shown that the rate of antibiotic resistance in some Singapore hospitals is very high[3,4]—much higher than in Northern Europe or Scandinavia, for example—there have been some methodological questions about these data. Indeed, Ti et al showed that when true community-acquired urinary tract infections were teased out of an aggregated laboratory database, the actual proportion of isolates that were resistant to commonly-used antibiotics was much lower. They suggested that surveys based on laboratory data alone might lead to overestimations of the rate of antibiotic resistance and inappropriate empiric antibiotic choices.[5] Certain patients—those in intensive care units or those who have been exposed to broad spectrum antibiotics—are at risk of infection or colonisation with antibiotic-resistant pathogens. Data collected from hospitals represent skewed data. Perhaps one of the first positive outcomes of this position paper will be funding support from agencies, such as the National Medical Research Council or the MOH to obtain accurate information using internationally standardised definitions for the rates of antibiotic resistance in a range of different settings.

The position paper also makes a timely call for regulating the pharmaceutical industry in Singapore. It has been shown that it takes longer to sit down with a parent to explain to them that the child's infection is most likely caused by a virus that will not respond to antibiotics than to write a prescription.[6] In Singapore, the problem is compounded by the low utilisation of diagnostics in the community, especially point-of-care tests that can reliably demonstrate to patients the non-bacterial aetiologies of their illnesses. In Europe, these have been shown to be useful in reducing antibiotic prescriptions, while providing primary care practitioners the reassurance that they are not missing major bacterial infections.[7] Furthermore, the Singapore healthcare system is governed by a series of incentives which tend to reward "over-prescription" as some doctors derive a large proportion of their revenue from the sale of medications, including antibiotics. In Taiwan, inappropriate prescribing of antibiotics for common colds was found to be positively associated with dispensing by physicians or those with on-site pharmacies.[8] One potential good outcome of the recent steps to encourage bill itemisation is that it leads the public to recognise the intrinsic value of the professional services rendered; it may reduce the incentive to prescribe the newest (and most expensive) antibiotics. Once again, we are speculating; the data is still unavailable. Here is an area of study for the emerging field of health services research. Community health education is another area which can be looked into.

But do we have only ourselves, the doctors, to blame? More antibiotics are used in animal husbandry than in healthcare! Hsu et al pointed out that the proportion of antibiotics used in humans is a small fraction of the total amount of antibiotics used globally[9] – the majority of which are used as "growth promoters" in animal husbandry. In many countries in Europe, resistant Gram-positive bacteria have been linked to pig and other animal farming. In Singapore, methicillin-resistant *Staphylococcus aureus* (MRSA) has been identified in animals used in experimental surgery.[10] The direct links

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between antimicrobial use in agriculture and human antibiotic resistance have not been well established, perhaps because of the distance between animal microbiologists and human infectious diseases specialists in most settings. Singapore is uniquely positioned with a very tightly-regulated system of food and animal imports, and perhaps the next edition of this position paper could incorporate our veterinary colleagues. The Agri-Food and Veterinary Authority (AVA) may wish to take the lead in funding the research into the extent of antimicrobial resistant pathogens in our food supply. This is a research question with global implications. Singapore has the opportunity to answer this question, thanks to the nature of our food supply, our small size and the highly-sophisticated human and animal microbiology facilities available on the island.

The most controversial aspect of this position paper, however, is the risk that it might be used to justify antibiotic restriction. To our knowledge, antibiotic restriction per se has never been shown to sustain reductions in antibiotic resistance. The most highly-quoted successful example of antibiotic resistance control in Finland was published in the New England Journal of Medicine.[11] The authors showed that a national effort to restrict macrolide prescribing reduced the rate of erythromycin resistance in group A streptococci from 16% to 8%. However, subsequent more detailed analyses revealed that the effect was more the result of the behaviour of a single circulating clone of erythromycin-resistant streptococci.[12] Another well-documented study done in New York showed that restriction of third generation cephalosporins led to a marked reduction in cephalosporin resistance,[13] but unfortunately, as an unintended consequence, prescribing of carbapenems (imipenem and meropenem) went up and the problem of cephalosporin resistance was replaced by carbapenem resistance, which is an even bigger problem to deal with. This phenomenon was described by Burke in an accompanying editorial as "squeezing the balloon", where "constraining one end causes the other end to bulge; addressing the problem of antibiotic resistance by limiting the use of one class of compounds may be counteracted by corresponding changes in prescribing and drug resistance that are even more ominous".[14] While there is no doubt that antibiotic use drives antibiotic resistance by selecting out resistant mutants and creating the milieu in which resistant bacteria can thrive, there is no universal consensus that restriction is going to solve the problem. Indeed, the guidelines on antimicrobial stewardship recently issued by the Infectious Diseases Society of America together with the Society for Healthcare Epidemiology in America have stated that, "the use of pre-authorisation requirements as a means of controlling antimicrobial resistance is less clear than formulary restriction, because a long-term beneficial impact on resistance has not been established, and in some circumstances, use may simply shift to an alternative agent with resulting increased resistance".[15]

Anecdotal evidence also suggests that antibiotic restriction policies are easily circumvented through use of the "right words" when talking with the person doing the restriction – usually an infectious diseases trainee. LaRosa et al documented how clinicians waited for the magic hour of 10 pm, when the infectious diseases trainee no longer had to approve the antibiotics, to order restricted antibiotics in their large teaching hospital.[16] Singapore clinicians are likely to take similar innovative approaches to do what they think is best for their own patients – prescribing the latest and broadest spectrum antibiotics without necessarily being too concerned about the ecological impact of their choices on the hospital flora in general.

Other approaches that have been tried include the use of information systems which provide rapid online suggestions. In Utah, a very sophisticated decision support system offers the prescribing clinician in the hospital and the clinic, a choice of antibiotics beginning with the most likely to be effective, based on the patient's past microbiological history, established guidelines, local microbial flora and a risk assessment tool.[17] The early stages of such a system are being developed in Singapore, and we are sure that clinicians would welcome the widespread use of this tool which preserves their autonomy yet integrates the best existing information to suggest effective care for their patients. Again, this is something that will hopefully be given an impetus by this position paper.[1]

As hospital clinicians faced with drug-resistant pathogens on a daily basis, our views are understandably skewed. While appreciating that community-level resistance is unlikely to be as severe, we are aware that we have little good data to work on. We accept, however, that the problem faced by hospital clinicians is severe enough to warrant action, and, on the basis of international recommendations, recognise that antibiotic stewardship should be a "must-have" programme for a hospital that sees itself as responsible and patient-centred.

Antibiotic stewardship should be seen as part and parcel of an overarching strategy to control antibiotic resistance, one that incorporates strengthening infection control and building a safer infrastructure in our hospitals

and clinics. We would like to commend the authors, Hsu et al, for taking the effort to mobilise the professional societies to support the publication of this position paper.[1] We look forward to high quality research to better understand the causes, cures, costs and complications of this pressing problem.

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