TWN Series on
Antimicrobial Resistance
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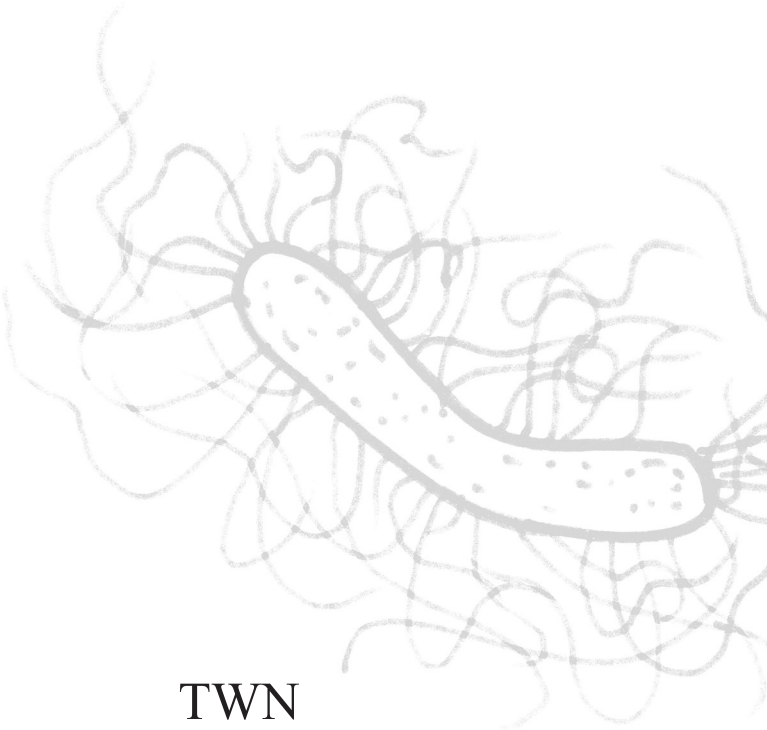
Factors That Get in the Way of Appropriate Use of Antimicrobial Medicines in Humans

Beverley Snell



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Factors That Get in the Way of Appropriate Use of Antimicrobial Medicines in Humans: Examination of Studies of Antimicrobial Use Against Defined Principles and Strategies for Good Antimicrobial Use

Beverley Snell

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Note

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Summary

THE Therapeutic Guidelines Australia principles of good antimicrobial prescribing, the Australian Commission on Safety and Quality in Health Care (ACSQHC) recommendations and the key Strategic Objectives of the World Health Organization (WHO) template for developing an Antimicrobial Resistance Plan are presented.

Studies of antimicrobial prescribing and consumer knowledge about antimicrobials from Lao PDR, Cambodia, the Philippines, Taiwan, Malaysia, India, Sri Lanka, Thailand, Oman, Australia, Pakistan, China, Solomon Islands and Fiji are examined to identify issues that contribute to sub-optimal or appropriate prescribing and use of antimicrobials in humans compared with the accepted principles. Factors contributing to sub-optimal understanding and use include absence of regulatory control of prescribing, sale and distribution of antimicrobials; absence of regulatory control of health practitioners; absence of political will; financing structures that depend on funds from the sale of expensive medicines; private practices that profit from the sales of medicines; absence of well-functioning Medicines and Therapeutics Committees; prescribers' lack of knowledge of the appropriate treatments for specific organisms and of antimicrobial therapy in general; prescribers' perceptions of community expectations; community attitudes and expectations; absence of laboratory diagnostic tests to guide prescribing and inefficient laboratory practices; poor stock management to ensure reliable supplies of the right antimicrobial medicines, laboratory reagents, and infection prevention and control consumables; and absence of records across the whole system.

Australia was shown to be one country having all factors in place to enable best use of antimicrobials, and independent not-for-profit bodies are also in place in the country to facilitate improvement of prescribing and use of antimicrobial medicines. But even there, there is still much room for improvement.

Chapter 1

Principles and Strategies to Encourage Best Use of Antimicrobial Medicines

APPROPRIATE use of antimicrobials involves knowledge and practices in line with the principles of good antimicrobial use within a supportive enabling framework.

The Australian independent not-for-profit organization Therapeutic Guidelines,[1] in its *Therapeutic Guidelines: Antibiotic* (Version 15, 2014), has provided a comprehensive guide to good antimicrobial prescribing in humans.

The World Health Organization (WHO) template for development of National Antimicrobial Resistance (AMR) Plans provides recommendations for strategies for building an environment that will improve the use of antimicrobials and minimize the development of AMR. Some structural systems that are needed to support the appropriate use of antimicrobials are also identified. In addition, a legislative framework is necessary to regulate the use of antimicrobial medicines (Plumet, 2017).

Principles of appropriate antimicrobial prescribing[2]

Appropriate antimicrobial prescribing practice includes the following (*Therapeutic Guidelines: Antibiotic*, 2014):

1. Clarification of the indication for antimicrobial therapy
2. Consideration of appropriate microbiological assessment and, if indicated, collection of specimens *before* the first dose of antimicrobial

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1 https://www.tg.org.au

2 This section is based on material from https://tgldcdp.tg.org.au/viewTopic?topicfile=antimicrobial-use-principles#toc_d1e123.

3. Selection of an antimicrobial for the specified indication that is consistent with appropriate clinical guideline recommendations: consider the required spectrum of activity, potential adverse effects, drug interactions and cost, as well as patient factors such as history of antimicrobial hypersensitivity, recent antimicrobial use, and pregnancy and breastfeeding. (This point highlights the need for up-to-date standard treatment guidelines which are based on laboratory surveillance specific for the setting. The guidelines determine the next two points.)
4. Selection of the appropriate dose, frequency and route; consider the severity and site of infection, as well as pharmacokinetic and pharmacodynamic parameters that influence dosage regimens
5. Prescribing for the appropriate duration; consider specifying a review or stop date.

In addition, the following should also be undertaken:

- Clearly document all antimicrobial therapy in the patient's medical records and/or medication chart. Documentation should include the indication and the intended duration of therapy before further review or cessation.
- When an antimicrobial is prescribed, provide information about the indication and the intended plan for antimicrobial therapy and the potential adverse effects to the patient or the patient's carer.

Therapeutic Guidelines: Antibiotic (2014) also provides detailed guidance for all types of antimicrobial use together with an introduction to antimicrobial stewardship.

In Australia, the Australian Commission on Safety and Quality in Health Care (ACSQHC) recommends five essential strategies and other activities for effective antimicrobial stewardship which are arguably relevant to most national settings:

- Implementing clinical guidelines that are consistent with the latest version of *Therapeutic Guidelines: Antibiotic* and that incorporate local microbiology and antimicrobial susceptibility patterns

- Establishing formulary restriction and approval systems that include restriction of broad-spectrum and later-generation antimicrobials to patients in whom their use is clinically justified
- Ensuring laboratories use selective reporting of susceptibility results consistent with hospital or health service antimicrobial treatment guidelines
- Reviewing antimicrobial prescribing, with intervention and direct feedback to the prescriber. At a minimum, this should include doctors working in intensive care
- Monitoring performance of antimicrobial prescribing by collecting and reporting unit- or ward-specific usage data, auditing antimicrobial use, and using indicators for the quality use of medicines.

Other activities that can be undertaken according to local priorities and resources include:

- Educating prescribers, pharmacists and nurses about good antimicrobial prescribing practice and antimicrobial resistance
- Using point-of-care interventions, including:
  – streamlining or de-escalation of therapy
  – dose optimization
  – parenteral-to-oral conversion
- Using information technology such as electronic prescribing with clinical decision support and/or online approval systems for restricted antimicrobials
- Publishing hospital- or health service-specific antimicrobial susceptibility data annually.

In the community, antimicrobial stewardship should involve the development of antimicrobial policies appropriate to prescribers' practices, and facilitation of these policies by state- and national-level support organizations, such as NPS MedicineWise (in Australia).[3]

[3] NPS MedicineWise is a government-supported independent not-for-profit organization that provides resources to enable health professionals and consumers to make and act on the best decisions about medicines, medical tests, health technologies and other options for better health and economic outcomes. For more on this organization, see the section on 'The Australian setting' in Chapter 3.

Development of National Antimicrobial Resistance Plans

The Strategic Objectives provided in the WHO template for developing National AMR Plans (WHO, 2016) are:

- Strategic Objective 1: 'Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.'
- Strategic Objective 2: 'Strengthen the knowledge and evidence base through surveillance and research.'
- Strategic Objective 3: 'Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures.'
- Strategic Objective 4: 'Optimize the use of antimicrobial medicines in human and animal health.'
- Strategic Objective 5: 'Develop the economic case for sustainable investment ... and increase investment in new medicines, diagnostic tools, vaccines and other interventions.'

Notably, in all the above principles, there is no mention of the need for a national regulatory framework, which is a crucial requirement.

Chapter 2

Analysis of Studies Focussing on the Use of Antimicrobial Medicines

WITH the above sets of principles and AMR Plan strategies in mind, we examined studies to identify factors that have an impact on the use of antimicrobial medicines. Other issues contributing to sub-optimal antimicrobial use that are not mentioned above were also identified. Positive examples that others can learn from were noted as well.

Community perceptions

First, we looked at studies that examine community perceptions about antibiotics. The WHO AMR Plan template lists this area under Strategic Objective 1.

Many studies have demonstrated that knowledge and perceptions of patients/community members are inaccurate, but do those perceptions have an impact on actual use?

In **Fiji**, knowledge about antibiotics was assessed in a nationally representative study sample of 5,000 Fijian community participants in 2015 (Mataika and Yim, 2015). It was found that education was highly correlated with knowledge of antibiotics, with those having completed lower levels of education stating less knowledge of what antibiotics were. The terms ‘amoxycillin’ or ‘penicillin’ were more known and recognized than the term ‘antibiotics’. Large numbers of participants still used antibiotics for viral infections such as a cold or flu. Antibiotics were used to treat headache, dengue, asthma, pregnancy and pain. Antibiotics were sometimes obtained without prescriptions from retail pharmacies (illegally) and they were frequently shared among family and friends. Despite knowing what antibiotics were, 67.1% of the surveyed population did not know what antimicrobial resistance was. A separate Fijian study asking doctors why they prescribe antibiotics when they are not necessarily appropriate showed that doctors perceived patient

pressure as a reason (Pickmere et al., 2015). However, there are no Fijian studies that show that physicians *are* significantly influenced by patient pressure.

Studies in other country settings show that community/patient perceptions and expectations *do* have an impact on antibiotic use both through prescriptions from authorized prescribers and also through access from other sources. Lao PDR studies have indicated that patient perceptions do have a serious impact on AB use.

Along with studies in other Mekong countries that show very wide use of antibiotics in the community before physicians are consulted, a report of studies in **Lao PDR** (Khennavong et al., 2011) of pre-treatment in Vientiane patients described antibiotic activity detected in urine samples prior to consultation with a doctor. In Vientiane, children had a higher frequency of estimated antibiotic pre-treatment than adults (60.0% versus 46.5%; $P < 0.001$). Antibiotics are widely available without prescription at private pharmacies in Laos. Dispensing of a single dose or an incomplete course is widespread.

Although Lao PDR appeared at the time to have lower levels of antibiotic resistance in comparison to adjacent countries (Phetsouvanh et al., 2006), extended-spectrum β-lactamase-positive *E. coli* and *Klebsiella pneumoniae* clinical isolates were present in Vientiane (Stoesser et al., 2009). The high frequency of antibiotic use in the community, as revealed by urinary antibiotic activity, may cause worsening drug resistance (Stoesser et al., 2009).

In **Cambodia**, 775 children of median age 4.6 years attending an outpatient department were investigated. Urine samples were taken from all of them (with consent). Caregivers reported that 75.1% of children had a fever, 65.0% had a cough, and 24.3% had diarrhoea. Sixty-nine percent of caregivers had given their child at least one medication in the 48 hours preceding presentation. Of these, 7.3% of caregivers reported giving a known and named antibiotic and 37.8% of children were given one or more unknown medications. However, the results of the urine tests showed antibiotic activity in 31.7% of samples (against the 7.3% claimed by the caregivers). In addition, 16.3% (40/246) of the urine samples that showed antibiotic activity did so against the MRSA or *S.*

typhi isolates (Emary et al., 2015). The most common source for obtaining medications was a private pharmacy, followed by other health centres and sources such as relatives, mobile 'nurses' or charities.

A similar study was undertaken in the **Philippines**. Between 2 February and 2 July 2015, Saito et al. (2018) investigated 410 febrile patients (age 7-14 years) in the emergency room at San Lazaro Hospital prior to consultation. Urine samples were taken for a bioassay to detect antibiotic activity. A total of 164 patients were found positive for antibiotic activity. Beta lactam antibiotics were reported by caregivers to have been most commonly given. Among bioassay-positive patients, dengue (55%) was the most frequent diagnosis, followed by other viral infections, including measles, rubella and mumps. The authors assert that unnecessary antibiotic use for febrile illnesses before hospital consultation is common in the low-income, highly populated urban community in Manila. Education initiatives targeting this group should be implemented to reduce unnecessary antibiotic use.

In the case of **Taiwan**, a paper introduces another dimension that is suggested to affect the use of antibiotics. It is submitted that an antibiotic prescription is a tangible measurement of quality (Bennett et al., 2015). Patients are interested in quality (as they perceive it) so there is competition between prescribers to deliver 'quality' and so encourage patients to consult their practices. Ho (2005, p. 246) argues that the intensive use of antibiotics also reflects cultural norms: 'The patient's primary purpose in seeing a doctor is to get a prescription. In the Chinese conception, every illness requires some sort of medicine. The idea that some diseases do not require medicine is unacceptable.'

Bennett et al. (2015) explain that Taiwan has a complicated health insurance system that includes a generous drug subsidy that 'incentivizes' patients to see a doctor for mild conditions. Twenty percent of these visits are for upper respiratory tract infections (URTIs), including sore throats and the common cold. Although URTIs are rarely bacterial, patients with these conditions often request antibiotics. Many outpatient visits last only five minutes because the patient's main objective is to obtain medicine.

A study in **Malaysia** (Oh et al., 2011) conducted in the outpatient department pharmacy of a hospital in the state of Penang found nearly 55% of the respondents had a moderate level of knowledge about antibiotics and their role. Three-quarters of respondents were aware that antibiotics are indicated for the treatment of bacterial infections, but 67% thought they were also useful for viral infections. Although nearly 60% were aware of antibiotic resistance in relation to overuse of antibiotics, 38% still believed that taking antibiotics when having cold symptoms could help them to recover faster, and 47.3% expected antibiotics to be prescribed for common cold symptoms. In this study, poor level of knowledge was found in less than one-third of the respondents but more than one-third of the respondents wrongly self-medicated themselves with antibiotics once they had a cold.

The findings in these few studies highlight the importance of Strategic Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.

They also highlight the need for regulatory control of the prescribing and dispensing of antibiotics.

Factors that influence prescribing by medical staff and other providers

In New Delhi, **India**, Kotwani and Holloway (2011) conducted exit interviews between December 2007 and November 2008 with patients after their attendance at private retail pharmacies, public sector facilities and private clinics to determine what prescriptions they had been given. A total of 33,132 patients were interviewed.

Thirty-nine percent of the patients attending private retail pharmacies and public facilities and 43% of patients visiting private clinics were prescribed at least one antibiotic. Consumption patterns of antibiotics were similar at private retail pharmacies and private clinics, where fluoroquinolones, cephalosporins and extended-spectrum penicillins were the three most commonly prescribed groups of antibiotics. At public facilities, there was a more even use of all the major antibiotic groups including penicillins, fluoroquinolones, macrolides, cephalosporins, tetracyclines and cotrimoxazole. Newer members from each class of

antibiotics were prescribed. Not much seasonal variation was seen although slightly higher consumption of some antibiotics in winter and slightly higher consumption of fluoroquinolones during the rainy season were observed. In this study, diagnoses were not requested.

A number of other studies in India by Kotwani, Holloway et al. show the same prescribing patterns for diarrhoea, respiratory infections and others, with excessive use of fluoroquinolones and cephalosporins (Kotwani et al., 2012; Kotwani and Holloway, 2014).

In Ujjain in Central India (Hutchinson-Kern, 2017), selected households were surveyed to explore the relationship between health-seeking behaviour determinants (pre-disposing, treatment-related and illness-related factors) and outcomes of both antibiotic use in general and fluoroquinolone/third-generation cephalosporin use. Informal healthcare providers (IP) were consulted for 58% of episodes, and of these, 47.4% prescribed an antibiotic, 34.4% specifically a fluoroquinolone and/or a third-generation cephalosporin. For those with symptoms of pocks or boils, 80% used an antibiotic; while for those with fever and cold, 53.1% used an antibiotic and 48.5% of those specifically received a fluoroquinolone or third-generation cephalosporin.

Kanungo et al. (2015) found that health-seeking behaviour in India is influenced by factors including accessibility, acceptability and costs of healthcare. In the Kroeger (1983) study examined by Hutchinson-Kern, 90% of those seeking care outside the home chose an IP – which is higher than seen in a cross-sectional study of individuals' illness and health-seeking behaviour from a similar setting in India where 53.2% of individuals reporting illness consulted IP, 34% qualified private practitioners and 12.8% public health facilities (Kanungo et al, 2015). This difference could reflect the availability of healthcare providers in the area. Hutchinson-Kern determined that the respondents in her study were mostly within 15 minutes' travel of an IP. She also concluded that diagnostic tests were almost completely absent.

According to Kotwani et al. (2012), 'Important factors identified for antibiotic prescriptions by doctors [prescribers] in India were diagnostic uncertainty, perceived demand and expectation from the patients, practice sustainability and financial considerations, influence from medical representatives and inadequate knowledge.'

A study in **Sri Lanka** of 50 patients with acute respiratory tract infection (ARTI) and five physicians in the outpatient department of a large tertiary hospital (Tillekeratne et al., 2017) was undertaken to assess Sri Lankan patients' and physicians' attitudes towards ARTI diagnosis and treatment. Most patients expected to receive medication prescriptions at their visit, but not specifically an antibiotic prescription. However, more than 70% of patients did receive antibiotic prescriptions. Interviews with physicians revealed that they incorrectly perceived that patients desired antibiotic capsules and cited patient demand as an important cause of antibiotic overuse. They also indicated that the high patient load and fear of bacterial super-infection drove antibiotic overuse.

In this group of Sri Lankan patients, medicines commonly mentioned as used for respiratory infections included paracetamol, the antihistamine chlorpheniramine, amoxycillin, vitamin C, salbutamol bronchodilator and 'capsules'. (In that setting, the term 'capsule' is commonly used for antibiotics.) Only five of the patients said they knew about how antibiotics worked.

In **Australia**, the Aged Care National Antimicrobial Prescribing Survey (acNAPS) was undertaken in 2016.[4] Participating aged care homes conducted a single-day survey between June and September when nurses, pharmacists and infection control practitioners collected data about residents who had signs and symptoms of infection and/or who had been prescribed an antimicrobial. The data were submitted to the National Centre for Antimicrobial Stewardship via an online data entry portal. A total of 251 aged care facilities (mostly in Victoria state, located in inner regional areas and operated by a state government) participated and 13,447 residents were interviewed.

On the survey day, the prevalence of residents with signs and/or symptoms of infection was 3.1% but the prevalence of residents prescribed at least one antimicrobial was 9.7%.

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[4] acNAPS is a collaborative project between the National Centre for Antimicrobial Stewardship (NCAS), the Guidance Group, Victorian Healthcare Associated Infection Surveillance System (VICNISS) Coordinating Centre and the participating aged care homes. It is supported by funding from the Australian Commission on Safety and Quality in Health Care under the Antimicrobial Use and Resistance in Australia (AURA) project.

Respiratory tract (34.5%), skin or soft tissue (29.3%) and urinary tract (14.8%) infections were the three most common indications for prescribing antimicrobials. Cephalexin (21.7%) was the most commonly prescribed antimicrobial.

After that study, issues targeted for quality improvement interventions included:

The prescription of antimicrobials for 'unconfirmed' infections: About one-third (32.4%) of the antimicrobials were prescribed for residents with no signs and/or symptoms of infection in the one week prior to the antimicrobial study date.

For those prescriptions where signs and/or symptoms of infection were recorded, *67.2% of records did not meet the McGeer et al. criteria* (a set of widely referenced, internationally recognized infection definitions that have been specifically developed for use in long-term care facilities).[5]

Prolonged duration of antimicrobial prescriptions: The antimicrobial start date was greater than six months prior to the survey date for 23.3% of prescriptions and administration was continued.

Widespread use of topical antimicrobials: About one-quarter of antimicrobial prescriptions were for topical use. The most commonly prescribed topical antimicrobial was clotrimazole (13.3%).

Incomplete documentation of key prescribing elements: The antimicrobial start date was unknown for 3.2% of prescriptions and the indication for antimicrobial use was not documented in 22.1% of cases. The review or stop date was not documented in 50% of prescriptions.

This 2016 acNAPS study confirmed 2015 pilot survey results. Key issues that can promote AMR were identified in the aged care facilities, including poor infection control practices and excessive and inappropriate antimicrobial use. It is not surprising that aged care facilities are included in Australia's National AMR Plan.

[5] http://www.infectioncontrolct.org/uploads/2/6/2/4/26245608/nh-hac_mcgeer criteriarevcomp_2012.pdf

In **Thailand**, a study was conducted to evaluate the impact of education together with an antibiotic-control programme on antibiotic-prescribing practices, antibiotic consumption, antimicrobial resistance, and cost of antibiotics in a tertiary care hospital in Thailand (Apisarnthanarak et al., 2006). Local hospital antibiotic guidelines developed from existing published guidelines were used to measure the appropriateness of antibiotic use. The study was conducted one year before and one year after the educational intervention that was based on principles of good antibiotic use and the recommendations in the hospital antibiotic guidelines.

After the intervention, there was a 24% reduction in antibiotic prescriptions and the incidence of inappropriate prescribing was reduced from 42% to 20%. A sustained reduction in use was observed, with significant reduction in third-generation cephalosporins. However, rates of use of cefazolin and fluoroquinolones increased. There were no significant changes for other antibiotic classes. Significant reductions in the incidence of infections due to methicillin-resistant *Staphylococcus aureus, Escherichia coli,* extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* and third-generation cephalosporin-resistant *Acinetobacter baumanii* were also observed. There were significant total cost savings ($32,231 during the study period). The researchers concluded that education and an antibiotic-control programme constituted an effective and cost-saving strategy to optimize antibiotic use in a tertiary care centre in Thailand.

A more recent study in Thailand (Sumpradit et al., 2012) examined the Antibiotics Smart Use (ASU) programme that was introduced in the country in 2007 as an innovative model to promote the rational use of medicines and counteract antimicrobial resistance. It was piloted in 10 district hospitals and 87 primary health centres in a typical medium-sized province with a population of 0.6 million located in central Thailand, 200 km from Bangkok. Importantly, the provincial health office was willing to participate in this project and able to facilitate ASU implementation and data collection, thus endorsing the ASU programme. A similar neighbouring province was purposively selected as the control group.

On-site training in half-day sessions focused on educating prescribers and making them feel confident enough to not prescribe antibiotics. Educational materials were prepared for health professionals and patients, and for display in waiting rooms and consultation rooms. Prescribers were also given ASU treatment guidelines for URTIs, diarrhoea and simple wounds, posters showing diagnosis and treatment algorithms, and diagnostic tools such as white light illuminators for throat examination. Hospitals received seed money for project implementation and evaluation.

Intervention effectiveness was assessed in terms of four indicators: a reduction in antibiotic prescription rates; improved knowledge and attitudes on the part of prescribers; percentage of patients with the targeted conditions who were not prescribed antibiotics (since they did not need them); and patients' perceived health and satisfaction with the treatment outcome.

With the International Conference on Improving Use of Medicines emphasizing the need to scale up successful interventions, this programme was subsequently scaled up in a second phase to cover 44 hospitals and 621 primary health centres in three provinces (one large, one medium, one small) as well as two hospital networks – a public network in the south of the country and a private one in Bangkok.

To increase the likelihood of sustainability, ASU scale-up was conducted with an emphasis on integrating ASU into routine practice. At the time of publication of the article, the programme was still being evaluated but successes had been documented.

ASU practice was adopted as a Pay for Performance (P4P) criterion by the National Health Security Office (NHSO) and the decentralized network approach promotes local ownership, mutual respect and social recognition. Local partners are given full autonomy in naming their own ASU projects and designing culturally sensitive interventions and media materials. This, in turn, generates a sense of ownership, pride and long-term commitment. Despite limited resources, the interventions implemented at the network and policy levels showed the feasibility of programme scale-up and sustainability. Some local partners applied ASU methods to promote the rational use of medicines other than antibiotics.

The 2011 Thai National Drug Policy on the rational use of medicines, which comprises national strategies for the containment of antimicrobial resistance, as well as other policy movements offer an opportunity to consolidate ASU. Policies, despite not being law, reflect a strong commitment to support the rational use of medicines in Thailand – but can long-term commitment be maintained? The study team recognized that strong political commitment is a crucial element for success. The Thai health system is structurally conducive to the overuse of antibiotics because it allows physicians to dispense drugs, pharmacists to prescribe them and patients to medicate themselves. A strong regulatory framework must be in place, and enforced and accompanied by bottom-up approaches (e.g., community empowerment) along with tools such as treatment guidelines and surveillance mechanisms with strong laboratory support and effective infection prevention and control.

In **Oman**, Al-Maliky et al. (2017) conducted a study to evaluate antibiotic prescribing in the Sultan Qaboos University Hospital (SQUH) by measuring the overall compliance with the local antibiotic prescribing guidelines. Analyses were performed using descriptive statistics, and main outcome measures were antibiotic prescribing compliance with the local guidelines as well as the overall Restricted Antibiotic Policy adherence at the hospital.

They found that diagnosis was documented as required in 89% of the admission episodes. However, compliance with local guidelines was sub-optimal at 63%, and of 211 restricted antibiotics prescribed, the overall adherence to Restricted Antibiotic Policy was inadequate at 46%. The majority of the antibiotics prescribed were broad spectrum at 90%, penicillins 31% and cephalosporins at 17%. It was concluded that the study had provided valuable baseline details of antibiotic prescribing patterns in SQUH, and that additional studies would be required to address the reasons behind the non-compliance with local guidelines.

Atif et al. (2017) in **Pakistan** investigated the prescribing patterns and utilization of antimicrobials in 10 selected wards at Bahawal Victoria Hospital in Bahawalpur, Punjab.

They undertook a descriptive cross-sectional study based on the WHO indicators for antimicrobial use.[6] Data from 1,000 prescription records were collected for the six months January to June 2016.

For the hospital indicators, a formulary list or essential medicines list was available, but standard treatment guidelines (STGs) for infectious diseases were not. The average number of days that key antimicrobials were out of stock was 3.3 days per month. For the prescribing indicators, the percentage of hospitalizations with antimicrobial(s) prescribed was 82.3%. None of the patients who were prescribed antimicrobials received them according to the STGs for pneumonia and cesarean section cases. Drug sensitivity testing was almost non-existent, with only 0.24% prescription records having drug sensitivity tests. Ceftriaxone (39.6%), metronidazole (23.4%) and cefotaxime (23.1%) were the top most frequently prescribed antimicrobials.

In the absence of STGs for infectious diseases, prescribers do not have a standard to follow and they can prescribe antimicrobials freely, and it is difficult to measure whether antimicrobial prescribing is rational or not in the absence of a standard to measure against. Besides the availability of STGs, it is essential that the key antimicrobials should be available all the time at hospitals.

The development and launch in 2015 of antibiotic guidelines in **Solomon Islands** (Solomon Islands Antibiotic Guidelines (SIAG)) was a collaborative effort involving all clinical departments at the National Referral Hospital (NRH) led by local doctors. Hutchinson-Kern et al. (2016) conducted a study to assess whether introduction of the guidelines was enough to change clinical practice. Doctors were surveyed before and after the implementation of the SIAG to assess the impact of antibiotic prescribing guidelines on prescribers' knowledge of rational antibiotic prescribing and antibiotic treatment for common indications. It was intended that the results would inform the design and implementation of more effective antimicrobial stewardship interventions for Solomon Islands.

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[6] World Health Organization. 2012. How to investigate antimicrobial use in hospitals: selected indicators. http://apps.who.int/medicinedocs/documents/s21031en/s21031en.pdf

All doctors, from intern to consultant, working at NRH were invited to participate. All prescribers had been given a copy of the SIAG at the launch of the guidelines in June 2015.

The survey was by administration of a pretested questionnaire covering:

1. Attitudes: confidence in prescribing in various scenarios; sources of information on antibiotic prescribing; attitudes about current and potential interventions to improve antimicrobial stewardship
2. General knowledge: questions to assess knowledge about antimicrobial resistance and rational prescribing of antibiotics
3. Specific knowledge: antibiotic treatment for common indications; antibiotic choice, dose, route and duration classified as 'correct' or 'incorrect' according to the SIAG.

Questionnaires were distributed during the weekly continuing medical education session. Data collection points were baseline, 2 months and 6 months after the launch of the guidelines. Participation was voluntary and results anonymous. No prior warning for the survey was given.

Additional interventions were two continuing medical education sessions for all prescribers, two medical intern education sessions, posters promoting the SIAG and highlighting associated dose changes, and ward treatment chart audits.

It was found that general knowledge did not change significantly over the study period but there was improvement in specific knowledge of antibiotic prescribing, demonstrating that doctors were becoming familiar with the new SIAG recommendations. That was reflected in an antibiotic point prevalence study carried out at NRH during the same period.

The guidelines had introduced a number of significant dosing changes to commonly prescribed antibiotics including cloxacillin, gentamicin, metronidazole and amoxycillin. The survey demonstrated that prescribers continued to require support concerning changes. For example, at 6 months all respondents with the correct antibiotic for community-acquired pneumonia (CAP) in children used the old dosing.

In the initial prescriber survey 100% of respondents stated that the availability of national guidelines would be very helpful in improving antibiotic prescribing (*very unhelpful* to *very helpful*). Locally developed, evidence-based guidelines were welcomed at the launch of the SIAG, but at 6 months only 69% of respondents listed the SIAG as an antibiotic prescribing reference. Confidence in prescribing in different scenarios was high at both baseline and 6 months but this was not reflected by accuracy in responses to specific treatment questions particularly for serious but common infections such as severe CAP in adults.

The survey team acknowledged that practice change requires ongoing support and education. A national Antimicrobial Stewardship Committee was planned to provide oversight and input into the ongoing antimicrobial stewardship programme which will help to ensure patients in Solomon Islands receive effective and appropriate antibiotic treatment.

In **China**, research by Zhang and Harvey (2006) adapted Australian best-practice guidelines on the prophylactic use of antibiotics in surgery to a Beijing teaching hospital in 2002-03. The Australian and international guideline materials were amalgamated with the help of Chinese experts and then used as a quality assessment and improvement tool, supplemented by educational interventions. Qualitative data about factors influencing antibiotic use were also obtained.

Antibiotics prescribed for surgical prophylaxis in 60 consecutive patients undergoing clean or clean-contaminated surgery (120 total) were then compared with guideline recommendations in three phases: a pre-intervention period from June to August 2002, an intervention period from June to August 2003, and post-intervention period from September to November 2003. During the intervention phase, feedback about prescriptions not in accord with the guidelines was discussed with around 25 prescribers every two weeks. In addition, local factors influencing antibiotic use were explored with 13 junior surgeons and eight high-level informants.

While agreement was reached on the principles of antibiotic surgical prophylaxis, there was no consensus on detail. Of 180 patients undergoing clean surgery (where prophylaxis is not indicated) throughout all phases of the study, antibiotic prophylaxis was administered to 78%,

compared with 98% of the 180 patients undergoing clean-contaminated surgery. Second- and third-generation cephalosporin antibiotics predominated in both low-risk clean and clean-contaminated operations. The timing of prophylaxis was correct in virtually all patients and the duration of prophylaxis was less than 24 hours in 96% of patients undergoing clean surgery, compared with only 62% of patients undergoing clean-contaminated surgery.

The intervention had produced no improvement in the duration of prophylaxis nor the overuse and inappropriate choice of unnecessary broad-spectrum and expensive drugs. Interviews and focus groups revealed an important explanation for the latter problem – that the Chinese government policy expected hospitals to support themselves, so there was a vested interest in prescribing high-profit medicines. It was concluded that improving antibiotic use in China would require hospital funding reform, more authoritative best-practice guidelines, and hospital authorities embracing quality improvement.

In **Fiji**, a study of colistin use in major hospitals was undertaken (Pickmere et al., 2016). It had been perceived by the procurement department that the use of colistin had escalated alarmingly. Colistin is an expensive 'last-resort' broad-spectrum antibacterial agent that is used to treat multi-resistant *Acinetobacter baumannii (*an opportunistic organism that often causes nosocomial infections) and certain other *spp.* Therefore, colistin use and misuse raises the potential for the development of significant bacterial resistance with profound clinical impact on the Fijian healthcare system.

The study was to determine the extent of the intravenous use of colistin and the rationale and reasons for its use during the time it had been available in Fiji. During the study period, records of treatment were sought and analyzed for patients who had been treated with colistin. Information from physicians was gathered about their use of colistin. Records of treatments were gathered with great difficulty from pharmacy and patient files. Microbiology and infectious diseases teams were interviewed, cost issues were explored and resistance patterns of organisms were examined.

This study produced a range of significant findings:

Patient records: Comprehensive patient records were not routinely maintained and retrievable so drug use evaluation studies (DUEs) could not be undertaken, diagnosis statistics could not be maintained and quantities of medicines needed for treating those diseases/conditions could not be estimated.

Stock-outs: There were stock-outs of medicines in the wards, infection control consumables and equipment, and laboratory supplies. Stock-outs of first-line antimicrobial drugs can lead to the prescription of restricted antimicrobials because the recommended antibiotics are not available.

Patient treatment:

- Many of the patients treated with colistin were suffering from infections that warranted prompt treatment with colistin – inadequate infection prevention and control (IPC) (supposedly due to inadequate supplies) fostered the development of nosocomial multidrug-resistant organisms. There had been a recent outbreak of *Acinetobacter baumannii* in the main referral hospital.
- There was sub-optimal understanding among prescribers of the use of protocols and standard treatment guidelines and these documents were not always readily available, so a detailed guideline for the use of colistin was needed. The third edition of the Antibiotic Guidelines had been published in 2011, almost five years before. Revision of that edition was urgently needed.

Laboratory services: The laboratory was short-staffed and capacity needed to be strengthened. Records of laboratory tests were not kept, meaning there was no way to study resistance patterns.

Infection prevention and control: IPC was very poor, supposedly due to staff shortages and stock-outs of consumables needed for IPC.

Cost implications: The cost of purchasing colistin urgently from Australia (due to stock-outs) for treating infected patients was unnecessarily high.

Antimicrobial stewardship was urgently needed in all three hospitals to monitor all aspects of infection control, laboratory services and antimicrobial use according to STGs and protocols.

To address the identified issues, it was recommended that quantification of medicines and other stock needs be based on comprehensive patient records of treatment according to STGs. A reliable supply of stock of all medicines needs to be maintained so first-line antibiotics are always available when needed. Similarly appropriate quantities of laboratory and infection control stock are necessary and those services should be strengthened.

Physicians' possession and ownership of up-to-date STGs and revised medicine-use protocols will facilitate prompt initiation of treatment where necessary to overcome delays that can be caused through waiting for laboratory results or signatures.

The establishment of an antimicrobial stewardship team in all hospitals will make a significant contribution to all aspects of management of the use of antimicrobial medicines.

Australia: NPS study

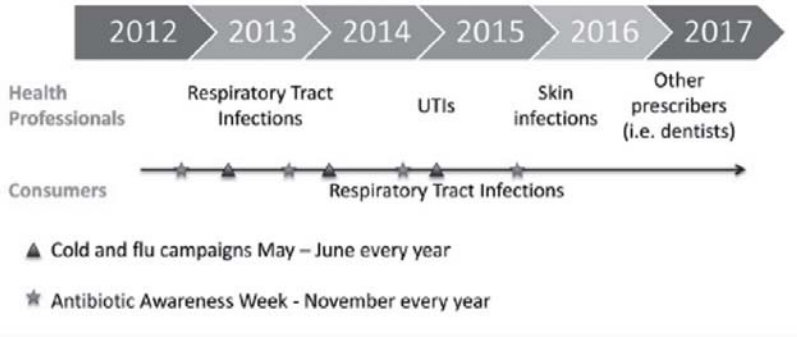
In an attempt to reduce inappropriate use of antibiotics for URTIs and, in particular, to modify patient misconceptions about the effectiveness of antibiotics for URTIs, Wutzke et al. (2007) and Australia's National Prescribing Service Ltd (NPS) undertook a comprehensive, multistrategic programme for health professionals and the community. Targeted strategies for the community, via the NPS common colds community campaign, commenced in 2000 and were repeated annually during the winter months. Community strategies were closely integrated using the same tagline, key messages and visual images, and were delivered in numerous settings including general practice, community pharmacy, childcare centres and community groups. Strategies included written information via newsletters and brochures, mass media activity using billboards, television, radio and magazines, and small grants to promote local community education. Interventions also targeted health professionals including prescribers at all levels. The evaluation used multiple methods and data sources to measure process, impact and outcomes.

Consistent with intervention messages, the integrated nationwide prescriber and consumer programme was associated with modest but consistent positive changes in consumer awareness, beliefs, attitudes and behaviour regarding the appropriate use of antibiotics for URTIs. These positive changes within the community were corroborated by a national decline in total antibiotic prescriptions dispensed in the community (from 23.08 million prescriptions in 1998-99 to 21.44 million in 2001-02) and, specifically, by a decline in use among the nine antibiotics commonly used for URTIs.

After the rollout of the first health professional educational programme – when the median number of original antibiotic prescriptions for the nine antibiotics commonly used for URTIs was decreasing – it was concluded that the NPS common colds community campaign, in synergy with interventions for health professionals, communicated clear, consistent, positive and persuasive messages via multifaceted media and strong branding repeated over five years.

A further five-year campaign directed at the community and health professionals was conducted between 2012 and 2017 (see Figure 1) (Dartnell and Heaney, 2017). Analysis of that campaign is currently being undertaken.

Figure 1: NPS programme timeline



Source: NPS

Chapter 3

Discussion

THE studies presented here demonstrate clearly the need for education of the community and health professionals as a basis for improving the understanding and use of antimicrobial medicines and controlling the development of AMR. Clear principles of appropriate antimicrobial prescribing are available and the WHO AMR Plan template includes wide-ranging strategies to support improved understanding and use of antimicrobials.

It has been demonstrated that standard treatment guidelines must be in place but they alone do not have a sustainable impact on prescribing. Ownership of the guidelines is important, and involving users in their preparation can assist ownership. Promotion of the guidelines needs to be supported by other ongoing interventions, and the guidelines must be kept updated by regular review. It has been shown that the impact of promotional messages 'wears off'.

A strong regulatory framework is needed to ensure that sale and distribution of antibiotics is on prescription only and restricted to authorized health professionals. The law needs to be enforced with penalties for non-compliance.

Political support and leadership are also very important. Clear lines of authority need to be in place so there can be no misunderstanding about how decisions are made or confusion about who may authorize activities. The WHO AMR Plan template emphasizes the importance of governance. As in other areas, the support of key opinion leaders would be very helpful and guidance from a well-functioning Medicines and Therapeutics Committee very valuable.

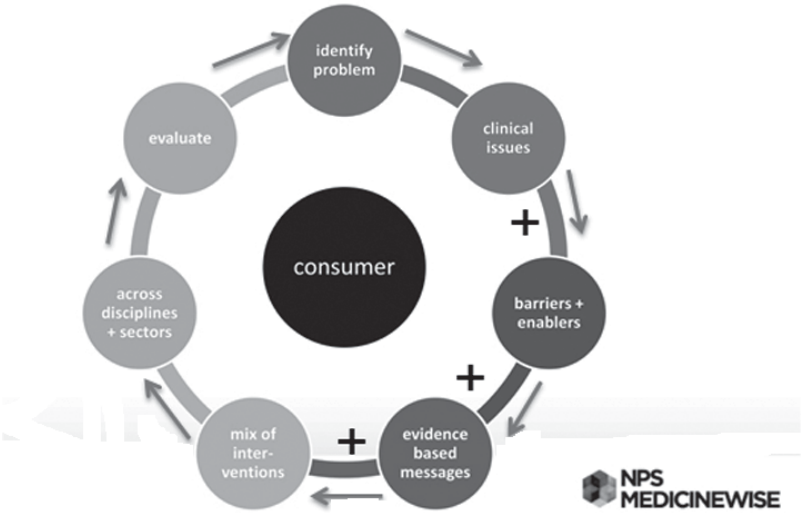
However, even with political will, an appropriate legal framework, sound governance and clear, up-to-date STGs against which to measure use, improved use of antimicrobials cannot occur when other structures such as financial incentives for prescribing expensive medicines are part of the system for funding health services. Another important factor that has an impact on the prescribing and use of antimicrobials is appropriate stock management.

As shown in the Fiji study of colistin use, comprehensive records of prescriptions, including diagnoses, must be kept, as must all laboratory and microbiology records. Without records, there can be no monitoring and evaluation and no surveillance. Without records, there can be no antimicrobial stewardship.

Good antibiotic prescribing depends on more than just compliance with the principles of good antibiotic prescribing. Structures such as efficient laboratory services for diagnosis and surveillance together with effective infection prevention and control also need to be in place.

Where studies have been undertaken and have identified issues that obstruct appropriate use of antimicrobial medicines, recommendations to address the identified issues should be implemented promptly, the impact of the intervention measured promptly and evaluated, and further recommendations made and implemented. The process is a continuing cycle (see Figure 2). The Australian NPS programme is a good example of this process (Dartnell and Heaney, 2017). Improved practices are more likely when there is such a cyclic process.

Figure 2: The cycle of addressing obstacles to appropriate antimicrobial use



Source: NPS

The same process would need to be applied to all the other areas having an impact on the use of antimicrobial medicines, e.g., stock management, laboratory management and IPC. Maintenance of records is crucial, not only for monitoring and surveillance purposes. Quantification of medicines and other stock needs must be based on comprehensive patient records of treatment according to STGs, and records of use of IPC consumables, laboratory use of reagents and consumables. A reliable supply of stock of all medicines must be maintained so that first-line antibiotics are always available when needed. IPC supplies need to be guaranteed in order for meticulous IPC to be in place throughout health facilities, and laboratory supplies need to be guaranteed to facilitate efficient and prompt delivery of laboratory results.

Up-to-date STGs and revised medicine-use protocols need to be in the possession of all prescribers, and prescribers should be involved in their preparation. Protocols and guidelines for use facilitate prompt initiation of treatment to overcome delays that can be caused through waiting for laboratory results or signatures.

National AMR Plans need to include elements to cover all these factors, and an antimicrobial stewardship team should be developed in hospitals as a priority. Resistance patterns of organisms should be studied routinely so that prompt responses can be implemented when needed.

The Australian setting

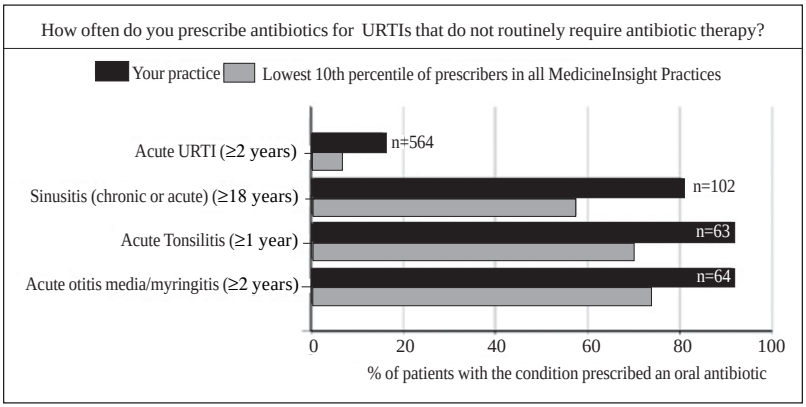
Australia provides an example where all the elements needed for sustaining a good programme for control of antimicrobial resistance in humans are in place:

- **Legislative framework:** Strict regulation controls health professional practitioners through registration and in the possession, prescribing and dispensing of antimicrobial medicines. The regulations are enforced and penalties apply for non-compliance.
- **Continuing Professional Development** (CPD) is mandatory for maintaining annual registration, with the number of points needed per year specified.
- **Prescribing is controlled** by the computer-driven Pharmaceutical Benefits Scheme (PBS) that determines how prescriptions are written and also provides control of restricted antimicrobials. Prescribers need to apply for an authority to prescribe certain antimicrobial medicines.
- **Major hospital policies are directed by therapeutic committees** and they are strong with extra protocols covering antimicrobial use in that setting.
- **Authoritative, up-to-date treatment guidelines** are available and widely used.
- **Independent ongoing education** is available for all health professionals. Industry-sponsored education is also available but all links to industry must be stated.
- **Records of all antibiotic prescriptions** are available through the PBS.
- **Laboratory services** are advanced and can provide complete information relating to antimicrobial use, sensitivities and resistance.
- **Surveillance** is established and functioning.
- **Infection control is efficient** and strictly enforced by regular audit.

- **Ongoing education is provided by NPS**,[7] a government-funded body that is totally independent of industry support. NPS is a not-for-profit body 'making Australia more medicinewise' through digital health and data insights, health professional education and reliable health information for consumers. Its activities include the MedicineInsight programme which allows general practitioners (GPs) to reflect on their own patterns of prescribing and patient care, and compare these with other GPs in their practice. The patterns can be benchmarked at local, regional and national levels. Participating practices are offered customized quality improvement activities that support alignment with best practice and identify key areas for improvement. (See Figure 3 for an example of a MedicineInsight feedback report.)

  NPS conducts targeted campaigns for communities and health professionals and conducts surveys of knowledge and behaviour in consumers and health professionals. Because the PBS prescribing data does not include diagnoses, separately organized studies are undertaken by NPS to measure prescribing patterns related to diagnoses. The incentive for participation in these studies is provision

Figure 3: MedicineInsight feedback report (example)



Source: NPS

NPS MEDICINEWISE

[7] https://www.nps.org.au/

of CPD points. According to Dartnell and Heaney (2017 and personal communication), this incentive is valued. NPS maintains an ongoing independent library of up-to-date medicines information and access to authoritative peer-reviewed publications.

- ***Australian Prescriber*** is a free quarterly independent peer-reviewed journal providing critical commentary on drugs and therapeutics for health professionals.[8]

Does all this mean that prescribing and use of antimicrobial medicines in Australia is perfect? Absolutely not! The studies covered here show clearly that there is significant sub-optimal prescribing and use and plenty of room for improvement.

Doctors in Australia still feel multiple pressures to prescribe antibiotics when they may not be necessary (Dartnell and Heaney, 2017). They cite patient expectations, time pressure, diagnostic uncertainty and medical liability. They still believe their individual prescribing doesn't make a difference in view of other antibiotic use in hospitals and in the veterinary and agricultural sectors.

However, Australia is fortunate to have an environment that makes improvement possible.

[8] https://www.nps.org.au/australian-prescriber

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Factors That Get in the Way of Appropriate Use of Antimicrobial Medicines in Humans

IN light of established principles and strategies for appropriate use of antimicrobial medicines, this paper examines studies on antimicrobial use trends across several countries in the Asia and Pacific regions. The author draws upon the outcomes of these studies, which look at prescribing patterns and consumer perceptions regarding antimicrobials, to identify key factors that have an impact on antimicrobial use. It is found that proper antimicrobial use — which is integral to controlling the development of antimicrobial resistance — hinges crucially on, among other factors, education of prescribers and consumers, up-to-date standard treatment guidelines, and a strong regulatory framework governing the prescribing, sale and distribution of antimicrobials.

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