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# ของภาวะเชื้อดื้อยาต้านจุลชีพในประเทศไทย

# Current situation of the Antimicrobial resistance

# in Thailand : a review

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**Content**



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**Research Report**

# Current Situation of Antimicrobial Resistance in Thailand: A Review

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**Abstract:**

The effective control of infectious diseases is seriously threatened by the sustained increase in the number of antimicrobial resistant microorganisms. Once resistance has emerged in a population, it can spread geographically. The problem is particularly severe in developing countries, where patients have inadequate access to or are unable to afford second–line treatments. Because these are typically more expensive, the economic impact of drug resistance in developing countries may be substantial.

Antimicrobial resistance is a global challenge, even not a new phenomenon. It is important for governments to ensure that the effectiveness of our current arsenal of anti–infectives is not depleted too rapidly. Many activities have been implemented in attempts to control the spread of antimicrobial resistance in Thailand, but little evidence of widespread success exists nonetheless. The magnitude and the trend of the problem of the antimicrobial resistance in Thailand were the focus of the study. The past and current attempt to tackle and solve problems on the antimicrobial resistance in Thailand was initially mapped. Then the research areas and the strategies to move forward to control the antimicrobial resistance were summarized.

At the end, the report suggests a range of efforts that can reorganize incentives and lead to increase changes in how patients, doctors, hospitals, and drug companies regard and use antibiotics. There is a possible role for health insurance systems in employing reimbursement methods that do not encourage overuse of antibiotics. There is an important role for physicians and medical associations to adopt standards that would discourage inappropriate antibiotic use. And there is a clear role for government—to promote careful demonstration projects, including providing incentives, to push hospitals to engage in better infection control and pharmaceutical makers to boost antibiotic research. Just as important, public awareness campaigns are needed to educate parents, doctors, clinics, and patients about the threat of drug resistant infections.

**บทคัดย่อ**

อัตราการดื้อยาต้านจุลชีพที่เพิ่มขึ้นอย่างต่อเนื่อง เป็นปัจจัยคุกคามการควบคุมโรคติดเชื้อ เมื่อเชื้อเกิดการดื้อยาขึ้นในกลุ่มประชากรหนึ่ง มันสามารถแพร่ระบาดไปทั่วภูมิภาคได้ ปัญหาเชื้อดื้อยาต้านจุลชีพมีความรุนแรงโดยเฉพาะในประเทศที่กำลังพัฒนา ซึ่งประชาชนไม่สามารถเข้าถึง หรือไม่สามารถรับภาระราคายาที่เพิ่มสูงขึ้นกว่าการรักษาขั้นพื้นฐานเดิม เพราะการเปลี่ยนยาตามความไวของเชื้อมักต้องใช้ยาที่มีราคาสูงขึ้น ดังนั้นจึงส่งผลกระทบอย่างมากต่อภาวะเศรษฐกิจโดยรวม

ภาวะเชื้อดื้อยาต้านจุลชีพเป็นความท้าทายระดับโลก ทั้งไม่ใช่เป็นปัญหาที่เกิดขึ้นใหม่ เป็นปัญหาสำคัญสำหรับรัฐบาลที่จะต้องดำเนินการ เพื่อให้มั่นใจว่ายาต้านจุลชีพที่มีใช้อยู่ในปัจจุบันไม่สูญเสียความไวในการต้านเชื้อรวดเร็วเกินไป ในประเทศไทยมีการนำโครงการและกิจกรรมมากมายมาใช้เพื่อควบคุมสถานการณ์เชื้อดื้อยา แต่มีหลักฐานของความสำเร็จที่เกิดขึ้นเพียงเล็กน้อย การศึกษานี้เพื่อบอกขนาดและแนวโน้มของปัญหาสถานการณ์เชื้อดื้อยาต้านจุลชีพในประเทศไทย ความพยายามในอดีตและปัจจุบันเพื่อแก้ปัญหา รวมทั้งพยายามสรุปองค์ความรู้ที่ยังไม่มีคำตอบ และแนวนโยบายที่พอจะเป็นไปได้

ท้ายที่สุด รายงานฉบับนี้พยายามนำเสนอตัวอย่างของแรงจูงใจอันจะนำไปสู่การเปลี่ยนแปลงเพื่อให้ผู้ป่วย แพทย์ โรงพยาบาล บริษัทยาได้ตระหนักถึงปัญหา และใช้ยาอย่างเหมาะสม มีความเป็นไปได้ของการใช้นโยบายจำกัดการเบิกค่ารักษาพยาบาล เพื่อลดการใช้ยาต้านจุลชีพเกินความจำเป็น ในองค์กรที่เกี่ยวข้องกับการประกันสุขภาพ แพทย์และสมาคมวิชาชีพแพทย์ต่างๆควรยอมรับแนวทางการรักษา ที่ไม่เอื้อต่อการใช้ยาต้านจุลชีพที่ไม่เหมาะสมให้เป็นมาตรฐานเดียวกัน รัฐบาลควรส่งเสริมโครงการต่างๆอย่างชัดเจน เพื่อเพิ่มแรงจูงใจ หรือผลักดันโรงพยาบาลต่างๆให้มีการควบคุมการติดเชื้อดีขึ้น และส่งเสริมผู้ผลิตยาให้มีการวิจัยค้นคว้ายาใหม่ๆ การรณรงค์ในภาคประชาชนให้มีส่วนร่วม รับรู้ปัญหาการติดเชื้อดื้อยาต้านจุลชีพ มีส่วนสำคัญที่จะผลักดันให้เกิดการแก้ปัญหานี้

**Executive summary**

The study of current situation of antimicrobial resistance in Thailand was aimed to review the magnitude and the trend of the problem of the antimicrobial resistance in Thailand, the past and current attempt to tackle and solve problems on the antimicrobial resistance.

The drug consumption as defined daily doses (DDD) showed the increasing trend of oral new generation of antibiotics. Resistance to first line drug of choice in many organisms has been reported two times higher in 2005 than in 1998. In hospital setting, inappropriate antibiotic use was found in general hospitals and regional hospitals about 13.2 – 77.8%. Due to lack of awareness in National Essential Drug lists and prescription of original brand drugs may effect the economical lost especially when the doctors over prescribed.

In term of policy, improved education and hygiene in prevention of resistance such as infection control in hospitals were raised by many studies (1-5). Although this will reduce the development and spreading of resistance, complete intervention is unachievable in general hospitals and not sustainable. For this, financial means and incentives will be an important element in developing a sustainable policy, which would be the available armament to manage the antimicrobial resistance problem (6). The big challenge for public education, unlike a successful example of “tobacco campaign” is to achieve a meaningful reduction in unnecessary antibiotic use without adversely affecting the management of bacterial infections. Carefully designed mass education campaigns could improve antibiotic use nationally and should be considered. However, these campaigns should employ techniques of social marketing and use appropriate outcome measures.

After review, analysis and with additional insights from the interviews and workshop group discussion, the key recommendations emanating from are summarized below under the following heading:

1. Establish a national independent organization to coordinate surveillance network, evaluate and update antibiotic use data, resistance patterns, efficacy and cost, and make recommendations for proper antibiotic use.
2. Improve awareness of antibiotic resistance in the public.
3. Prioritize infection control in all levels of heath facilities as national campaign.
4. More researches about the impact of policies on drug system after Drug Act, 2530 implementation.
5. More researches about the impact of universal coverage scheme (no co-pay) on pattern of self medication and antibiotic prescription behavior.
6. More researches about the impact of disease related groups (DDGs) on pattern of self medication and antibiotic prescription behavior.
7. Develop package of clinical practice guidelines for reimbursement of health insurance system.

**Key Words:** Antimicrobial resistance, Antibiotics,

**คำสำคัญไทย:** เชื้อดื้อยา, เชื้อดื้อยาต้านจุลชีพ, ยาปฏิชีวนะ

"it is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body…"

*—Alexander Fleming, 1945*

## 1. Background

At the beginning of the 21st century, antimicrobial resistance is commonly developed against every class of antimicrobial drug, and the effective control of infectious diseases is seriously threatened by the sustained increase in the number of antimicrobial resistant microorganisms. For more than 5 decades, the problem of how to contain antimicrobial resistance has preoccupied policy makers and members of the academic societies, since antimicrobial resistance has become a public health concern throughout the world (7-9).

Bacterial resistance began to accumulate since penicillin and sulphonamide antimicrobials entered clinical use in the 1930s and 1940s. After that, resistance has emerged to every antibiotic class and analogue that has been marketed. Resistance has led to the abandonment of many previously effective therapies (for example, the use of penicillin for staphylococcal infections or cotrimoxazole for the treatment of salmonella diarrhea), and is associated with increased mortality and treatment failure rates in severe infections (10). Antimicrobial resistance is a naturally occurring biological phenomenon and once occurred, can rapidly give rise to vast numbers of resistant progeny (11). Genes encoding resistance had likely been present for thousands of years and incorporation of these genes by human commensal and pathogenic flora rapidly followed (12). The impressive reproductive rate of most microorganisms, the tremendous selective pressure that antimicrobial agents apply to these populations and the huge number of unculturable organisms in the environment may be serving as reservoirs of antimicrobial resistance genes. The mass production of antimicrobials gave a temporary advantage in the defeat with microorganisms; however, if the current rate of increase in resistance to

antimicrobial agents is sustained, it is possible we may enter into what some termed the 'postantibiotic era' in which common infections are frequently untreatable (13). The consequences of resistance in some bacteria, such as *Staphylococcus aureus* can be measured as increases in the term and magnitude of morbidity, higher rates of mortality, and greater costs of hospitalization for patients infected with resistant bacteria relative to those infected with sensitive strains (14). The higher cost difference does not reflect MRSA's greater virulence; rather, it reflects the increased cost of vancomycin use and isolation procedures (if used).

The process of antimicrobial resistance commonly originates from inadequate treatment, inappropriate use of antimicrobials (overuse of antimicrobials and is amplified by misuse of antimicrobials) (15). Antibiotic use is being increasingly recognised as the main selective pressure driving this resistance. Outpatient use of antibiotics in Europe was proved to be associated with resistance as the consumption was determined by the prescription rate of defined daily doses (DDD) (16). In the United States and other developed countries, the over-prescription by physicians of antimicrobials, particularly antibiotics, even in the absence of appropriate indications is the main culprit. Such inappropriate practices are often encouraged by diagnostic uncertainty, lack of opportunity for patient follow-up, lack of prescriber knowledge regarding optimal treatments, and patient or parental demand (17, 18). In many developing countries, problems typically arise because antimicrobial agents are readily available and can be purchased as a commodity without the advice or prescription of a physician or other well-trained health care provider.

Although many activities have been implemented in containment of spreading of antimicrobial resistance in Thailand, only small success exists. A national guideline for antimicrobial therapy was developed since 1994 and revised in 1996 (19). More recently, the National Antimicrobial Resistance Surveillance Center Thailand (NARST) was established in 1996 to collect the data of susceptibility of microorganisms from the university hospital and general hospitals in Thailand and the Center for Antimicrobial Resistance Monitoring in Food-borne Pathogens (in cooperation with WHO) Faculty of

Veterinary Science, Chulalongkorn University was developed to monitor in food and animals. There are also several strategies implemented for improvement of the prevention and treatment of infectious diseases in hospitals and the community. In 2000, the National Committee on Revising the Essential Drug List has tried to restrict the availability of nonessential new agents by minimizing the antimicrobial items in a National Drug List with classification of restriction levels.

Interventions to address the scope of drug resistance are often the same as those that reduce the burden of disease. Reducing disease diminishes the need for drug treatment, which lowers the likelihood that resistant strains will emerge. In addition, the appropriate choice of drug treatment is an important step in delaying the evolution of drug resistance. Education, professional accountability, and improved communication between patients and providers are necessary.

This project is belonging to HSRI as a part of Drug System Research Project and aims to address stage of the arts for the current situation of the antimicrobial resistance in Thailand

**Objective of the review**

1. to identify the magnitude and the trend of the problem of the antimicrobial resistance in Thailand
2. to map the past and current attempt to tackle and solve problems on the antimicrobial resistance in Thailand.
3. to identify the research areas and the strategies to move forward to control the antimicrobial resistance

**Methodology**

The study was a qualitative research including three data collection methods;

1. Document analysis by reviewing the literatures in Thailand from secondary sources (other review papers including the reports from Infectious Diseases Network by National Research Council of Thailand) mainly focusing in human.
2. Interview with relevant key informants from the responsible agencies (including Department of Medical Science, MOPH).
3. Group discussion among academics and health experts to fill the gaps of information and identify the research area and opportunities to move forward.

**Review literatures**

By using the keywords “antimicrobial” or “antibiotic” or “antiviral” or “antifungal” or “anti-infective” and “resistance” and/or “prescription”, “containment”, “control” or “strategy”, the documents were retrieved from many resources eg.

1. Thai index medicus
2. PubMed Database
3. Research library at office of the National Research Council of Thailand
4. Health Technical Office, Ministry of Public Health
5. Health Research Information Center,
6. Digital Library at Food and Drug Administration, Ministry of Public Health
7. National Antimicrobial Resistance Surveillance Center Thailand (NARST), National Institute of Health, Ministry of Public Health.
8. Institute for Population and Social Research, Mahidol University

**Results**

## 2. Magnitude and trend of the antimicrobial resistance in Thailand

The infectious diseases are the leading of top ten causes of deaths in Thailand in 2002 as the Figure 1 (Source: Death and DALY estimates by causes, 2002 http://www.who.int/entity/healthinfo/statistics/bodgbddeathdalyestimates.xls)

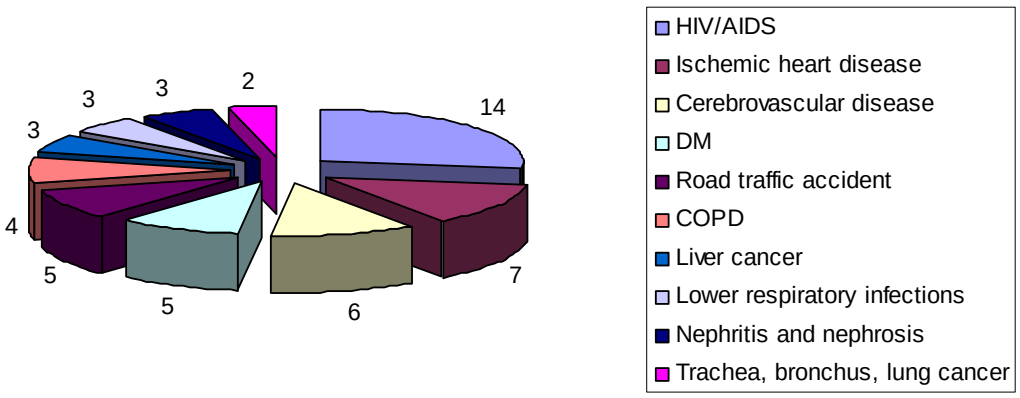


**Figure 2.1 Top ten causes of death for all ages in Thailand, 2002**

Causes of death for all ages in Thailand were described as percentage of total number of death. HIV/AIDS will lead to any causes of opportunistic infection.

In 2004, Bureau of Epidemiology, Department of Disease Control (DDC), Ministry of Public Health reported of 2.1 million infectious cases e.g. infectious diarrhea, fever of unknown origin, pneumonia. By estimation, there are 50,000 deaths per year and the most common cause of death is pneumonia. Additionally, there are the emerging and reemerging infectious diseases, including the antimicrobial resistance organisms. The

trend of nosocomial infection was not decrease from 1992 (7.3%) to 2001 (7.4%). The economical lost from nosocomial infection was estimated about 1,560 million baht per year (20).

Resistance to ampicillin of *Escherichia coli*, a major culprit in urinary infections, was reportedly rated at 50, 43, 40 and 20 percent in United Kingdom, U.S.A, Germany, and Finland respectively. Similarly in those areas, the resistant of that micro-organism to cotrimoxazole was found to be 20, 25, 30 and 20 percent (21-24). On the same front, Thailand fared worse when the success rates of the two antimicrobial drugs were only 21 and 25 percent (25) for the ailment. These micro-organisms also tend to resist to quinolones (resist to norfloxacin, 37% and ciprofloxacin, 40%). At this rate the former two drugs appeared almost useless in coping with the particular bacterial infection in this country and would have to depend on other drugs such as imipenem and ceftriaxone (26). Resistance of one of the leading causative agents for acute respiratory infection pneumonia, *S. pneumonia* to penicillin jumped two fold within four years or 8.3 % in 1993 to 16.6 % in 1997 (27).

MDR-TB (multi drug resistance TB), defined when tuberculosis resisted to both isoniazid and rifampicin, had also devastated Thailand. A survey of drug resistance patterns in Thailand was conducted during 1997-1998 in 59 diagnostic centres throughout the country. The results of newly diagnosed smear positive pulmonary tuberculosis without prior treatment showed 25.4% resistance to one or more drugs, yet MDR-TB was found to be 2% (28). Moreover, the data for acquired drug resistance in the central region of Thailand showed 53.6% resistance to any drug and MDR-TB was found to be 25% (29).

Data from Thai Drug Control Division, Food and Drug Administration in Thailand in 1998-2003 shows the increasing trend of oral new generation antibiotics calculated as Defined Daily Doses (DDD) by Miss Chutima Akaleephan (Figure 1.2). Over several years, there was a trend to increase in consumption of new generation of antibiotics dramatically as Figure 2.2.

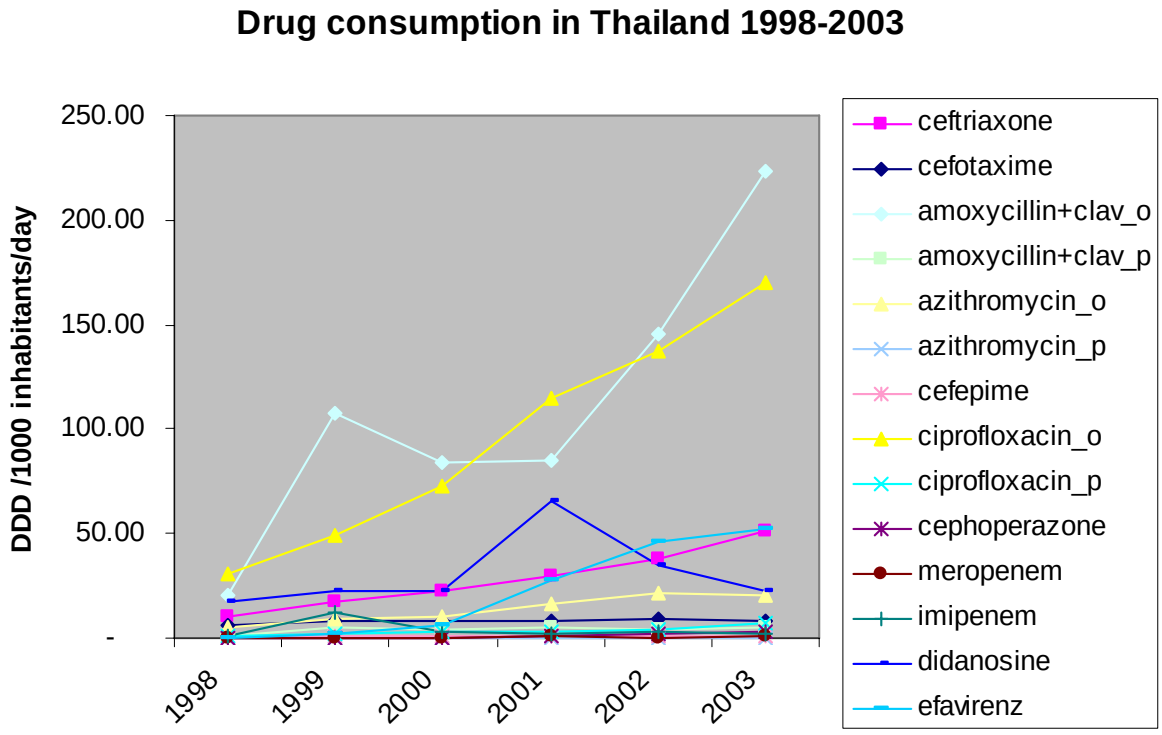


**Figure 2.2 Drug consumption in Thailand, 1998-2003**

Oral amoxicillin+clavulonic acid and ciprofloxacin were significantly consumed in an increasing trend. Ceftriaxone and oral azithromycin also showed the steady increasing trend over 6 years.

From a review of Hospital-Based Drug Use Evaluation, the hospital utilization of antibiotics (ceftazidime, ceftriaxone and imipenem) was grossly deemed inappropriate in a large based on most DUE criteria. The rational for ceftazidime and imipenem use is indicated for empirical therapy 80-90% (30). The inappropriate use of antibiotics is the problem found in all levels of health facilities in Thailand around 28.2-47.8% especially in the children less than 5 years (31).

In Thailand, problems typically arise because antimicrobial agents are readily available and can be purchased as a commodity without the advice or prescription of a physician or other well-trained health care provider. Some common human behaviors also play a role

in promoting resistance. Of particular importance, for example, are patient self-medication and noncompliance with recommended treatments. Noncompliance occurs when individuals forget to take medication, prematurely discontinue the medication as they begin to feel better, or cannot afford a full course of therapy. Self-medication almost always involves unnecessary, inadequate, "left over" from previous course and ill-timed dosing.

Once resistance has emerged in a population, it can spread geographically. Resistant infections lead to increased morbidity and prolonged hospital stays, as well as to prolonged periods during which individuals are infectious and can spread their infections to other individuals (14, 32). Furthermore, the presence of exacerbating factors, such as poor hygiene, unreliable water supplies, civil conflicts, and increased numbers of immunocompromised patients attributable to the ongoing HIV epidemic, can further increase the burden of antimicrobial resistance by facilitating the spread of resistant pathogens. In this chapter, we discuss the current situation of drug use in hospital setting and outside hospital.

**Current Situation of drug use in hospital setting**

Various practices common in hospitals contribute to the resistance problem as well. Indeed, hospitals are especially fertile grounds for breeding resistant microbes. They deal regularly with large numbers of patients (many with suppressed immune systems) in relatively close proximity to each other, and they frequently treat their patients with intensive and prolonged antimicrobial therapy. Large hospitals and teaching hospitals generally experience more problems with drug-resistant microbes, probably because they treat greater numbers of the sickest patients and those at highest risk of becoming infected. Transmission of drug-resistant organisms among patients may be airborne, from a point source (such as contaminated equipment), or by direct or indirect contact with a contaminated environment or the contaminated hands of staff. Failure of health care workers to practice simple control measures (e.g., hand washing and changing gloves

after examining a patient) is a leading contributor to the spread of infection in hospitals (สมหวัง).

Hospitals typically rely on two major forms of intervention to minimize resistance problems. One approach involves limiting antimicrobial use as much as possible; the other involves implementing intensive infection-control programs. Important components of these programs include surveillance; outbreak investigation and control; sterilization and disinfection of equipment; and implementation of such patient-care practices as hand-washing, isolation, and barriers between infected patients. While the intense selective pressure of antimicrobial drug use has been an important factor in the emergence of resistance, the inconsistent application of infection control guidelines by hospital personnel largely accounts for the dissemination of resistance in the healthcare setting.

The incidence and patterns of and factors associated with inappropriate antibiotic use were studied in the tertiary care university hospitals in Thailand (3, 5, 33, 34). The incidence of inappropriate antibiotic use was ranged from 24.8% - 91% as Table 1. Admission to the surgical department and to the obstetrics and gynecology department were associated with inappropriate antibiotic use, whereas consultation with an infectious diseases specialist was protective against inappropriate antibiotic use.

**Table 1 Incidence and patterns of inappropriate antibiotic use (IAU) in tertiary care university hospitals in Thailand**

| Reference | Type of study | No. of patients | Patients receiving antibiotics, % | Incidence of IAU, % | Reasons of IAU |
|---|---|---|---|---|---|
| Udomthavornsuk et al., 1990 at Srinagarind Hospital | Incidence [a] | 400 | NA | 52.3 | Inappropriate surgical prophylaxis,[b] no indication of use, or redundant antibiotic spectrum |
| Aswapokee et al., 1990 at Siriraj Hospital | Prevalence | 690 | 44 | 91 | No indication of use, inappropriate choice of antibiotic, or inappropriate dose, interval and duration |
| Thamlikitkul et al.,1998 at Siriraj Hospital | Prevalence | 29,929 | 41 [c] and 19 [d] | 50 | Inappropriate surgical prophylaxis,[b] inappropriate antibiotics for normal labor, inappropriate antibiotics for cataract surgery, inappropriate antibiotics for acute diarrhea, or inappropriate antibiotics for respiratory tract infections |
| Apisarnthanarak et al., 2006 at Thammasart University Hospital | Prevalence | 502 | 63.5 | 24.8 | No indication of use, inappropriate surgical prophylaxis, [b] inappropriate antibiotics for resistant microorganisms, use of broad-spectrum antibiotics where narrow spectrum antibiotic is still available and effective, or other reasons [e] |

Note: NA = not applicable

[a] This was a prospective study to evaluate all antibiotic prescriptions written for 1 month.

[b] For inpatients.

[c] For outpatients.

[d] Includes choices of antibiotics, dose, interval, and duration.

[e] Includes inappropriate choices of antibiotics, administration of antibiotics with redundant spectrum, and inappropriate dose, interval, duration, and administration of antibiotics to colonized patients.

Moreover, the problem of inappropriate antibiotic use without indication was found in all health facilities (community, general and regional hospitals) as in Table 2.

**Table 2 Inappropriate antibiotic use in other hospital setting**

| Drug groups | Reference | Pattern of use | Inappropriate rates (%) |
|---|---|---|---|
| Ceftriaxone | (35), 1997 | unnecessary indicated for the cause of infection | 77.8 |
| Parenteral antibiotic[a] | (36), 1998 | Not suitable | 39.4 |
| Ciprofloxacin | (37), 1997 | Not as standard guideline of drug use | 50 |
| Parenteral antibiotic[a] | (38), 1996 | Not as standard guideline of drug use | 44.7 |
| Ceftazidime | (39), 2000 | Not as drug's indication | 60.4 |
| Ceftazidime | (40), 1997 | Not as drug's indication | 40 |
| Cephalosporins[b] | (41), 1992 | Unknown indication | 13.2-15.3 |
| Ceftazidime | (42), 1998 | Not appropriate with culture result | 25 |
| Ceftazidime | (43), 2001 | Without evidence of culture | 37.5 |
| Ceftriaxone | (44), 1997 | Without evidence of culture | 41 |
| Cephalosporins[c] | (45), 1997 | Without laboratory support | 70.2 |

Modified from (46)

Note:

[a] : aminopenicillin, 2nd & 3rd generation cephalosporins, new beta-lactam, quinolones

[b]: cefazolin, cefamandol, cefotaxime, ceftazidime, ceftriaxone

[c]: cefotaxime, ceftizoxime, ceftriaxone

Although much is known about how hospitals can minimize the spread of infection, research is still needed to fill some important gaps in knowledge. One need is for development of rapid, reliable diagnostic methods for identifying the presence of infection, the specific infecting organism, and the susceptibility of the microbe to various

therapeutic agents. Diagnostic precision is the key to effectively modifying the current approach of widespread empiric antimicrobial use in ill patients with suspected infections. A further need is to develop materials for use in medical devices, such as catheters, that are resistant to colonization by microorganisms. In addition, continuing development of new antimicrobial agents remains a priority.

**Current Situation of drug use outside hospital**

Patients may buy over the counter only a few tablets of an antibiotic because of inadequate health care facilities and limited money. Some patients may begin an antimicrobial regimen and stop it when they feel better before finishing the regimen, saving the remaining tablets for use at another time.

With the minimal illness, 30% of patients lived in municipality and 22% of patients outside bought the drug from store (47). After economical crisis in 1997, the proportion of drug dispensing in the drug store in community is increasing and people favor self-medication (46). In Bangkok, half of the consumers specified the symptoms when they bought the drug store and only 1.8% of the consumers bought with prescription. Majority (81%) of the consumers bought with the specified brand name of drug because of the previous good impression of responses (26.5%). Antibiotics are in the first three rank of most common dispensing drugs (antipyretics 12.3%, cold remedies 11% and antibiotics 8.7%)

No clear information showed the causal link between the self-medication and antimicrobial resistance in the community.

## 3. Prescribing and the reduction of antimicrobial resistance pattern

There is a direct relationship between antimicrobial prescribing and the development and spread of resistance (48). The antimicrobial prescribing could be measured by the volume

of consumption of antimicrobial agents. To investigate the correlation between non-hospital antimicrobial consumption and resistance, the information on the non-hospital sales of antimicrobials from 14 European countries in 1997 and 2000 was compared with the antimicrobial resistance profiles of *Escherichia coli* isolated from women with community-acquired urinary tract infection in the same countries in 1999/2000 (23). This study showed that the degree of antimicrobial consumption was significantly correlated to the incidence of multidrug-resistant *E. coli*.

Appropriate measures taken to improve antibiotic prescribing can have a great impact on the development and spread of resistance. Although it is not clear that by reducing our use of these drugs alone we will be able to reverse the growing tide of resistance (49-52), we can certainly slow the accumulation of the new resistance and maybe even stop that tide. But how do we reduce antibiotic use? Although many antibiotic-prescribing decisions in human medicine may be black or white (clearly medically necessary or clearly not indicated), there is a large gray area in which they could provide a small but possible significant clinical benefit to the individual (for example, more rapid cure of acute otitis media) or psychological benefit to the patient (for example, a placebo effect) and/or the physician (for example, to facilitate the closure of a consultation). These gray-area applications of antibiotics must be weighed against the incremental harm to the population as a whole caused by the additional selective pressure for antimicrobial resistance. In such contexts, determining what is an appropriate use of an antibiotic is a judgment call in which cultural, social, psychological, and economic factors play at least as great a role as clinical and epidemiological considerations.

**Current situation**

The Thai health care system was structurally vulnerable to the over-prescribing and inappropriate selling of drugs in several respects. First of all, both physicians and pharmacists were allowed to provide diagnosis and drugs for outpatients. This was partly because Thai people have long been familiar with the traditional system of one-stop service medicine, wherein doctors offered a full spectrum of care, including the

pharmacist's function of dispensing drugs. Combining prescribing and dispensing creates incentives for physicians to increase drug prescriptions and is hypothesized to be a major cause of high drug expenditure and widespread prescription of antibiotics in Asia (53). In addition, as there was a shortage of physicians, especially in rural areas, pharmacists or drug dispensers would be able to sell the drugs over-counter without prescriptions even antibiotics.

The greatest resource of information of drugs which the physician could access is the leaflets and brochures from the detailer of the drug companies. In a study to access the accountability of this information, the completeness of information is only 12 from 24 items required to be included. Furthermore, there were also incorrectness, misleading, inappropriate illustration and without references (54).

In Thailand, there is an effort to enforce the legislation on "Separation of Prescribing from Dispensing of Drugs" (SPD). The term is taken to mean that the doctor's dual role of disease diagnosis with prescription and drug dispensing is to be separated. The doctor will assume the role of disease diagnosis with prescription only, leaving the role of drug dispensing to an independent person (a pharmacist or a trained dispenser) who will do so according to the direction of the doctor written in a prescription. SPD is practiced in countries like UK and USA where there is a health insurance system for the reimbursement of drug costs.

Among the people interviewed after SPD was implemented in Taiwan, the prescription transparency service they receive is 100% in academic medical centers, 66% in hospitals, and 23% in clinics. Fifty two percent of the interviewees pays strong attention to drug information, 31.8% pays attention, 11.4% pays little attention, 2.8% pays very little attention and 1.7% do not pay attention at all (55). The separation policy could be effective in reducing drug expenditure and affecting prescription behaviour, but is less certain as a policy for reducing total health expenditure. The policy has practically no effect on clinics that have on-site pharmacists (56).

**Intervention of antibiotic use control in various hospital setting**

In a recent study of intervention including education, introduction of an antibiogram, use of antibiotic prescription forms and prescribing controls, there was a 24% reduction in the rate of antibiotic prescription (640 vs. 400 prescriptions/1000 admissions; $P < 0.001$) (1). The incidence of inappropriate antibiotic use was also significantly reduced (42% vs. 20%; $P < .001$). Third-generation cephalosporins were significantly reduced, whereas, the rates of use of cefazolin and fluoroquinolones significantly increased. There were no significant changes for other antibiotic classes. Significant reductions in the incidence of infections due to methicillin-resistant *Staphylococcus aureus* (48% vs. 33.5%; P<.001), extended-spectrum beta -lactamase-producing *Escherichia coli* (33% vs. 21%; P<.001), extended-spectrum beta -lactamase-producing *Klebsiella pneumoniae* (30% vs. 20%; P<.001), and third-generation cephalosporin-resistant *Acinetobacter baumanii* (27% vs. 19%; P<.001) were also observed. Total costs saving were about 1.5 million baht (US$ 32,231) during the study period. The reduction of antibiotic prescription and inappropriate use is similar to previous studies in Siriraj hospital (3, 4). But there is no available data about resistant patterns of organisms pre- and post intervention in Thamlikitkul's studies.

**Table 3 Intervention for antibiotic control program in Thailand**

| Reference | Intervention | Pre-Post intervention antibiotic prescription rates | Pre-Post intervention inappropriate antibiotic use |
|---|---|---|---|
| Sirinavin et al., 1998 at Ramathibodi hospital | using an antimicrobial order form to assist rational usage of expensive antimicrobial agents: imipenem, vancomycin, injectable ciprofloxacin (in 1992), netilmicin and ceftazidime (in 1995) | • The adjusted expenditures per year of the first 3 restricted antibiotics were 1.41-1.87 million baht less (22-29%) in 1992-1994 than the pre-intervention year 1991 but did not work for ceftazidime | NA |
| Thamlikitkul et al., 1998 at Siriraj hospital | education comprising information feedback and providing guidelines | • prevalence of antibiotic use and the cost of antibiotics during post-intervention period was significantly decreased by 20%<br>• the use of antibiotic prophylaxis for obstetrics and patients undergoing cataract surgery decreased significantly<br>• there was a shift from $2^{nd}$ or $3^{rd}$ generation cephalosporins to cefazolin<br>• mortality, median length of hospital stay, and nosocomial infection rate among the patients who received antibiotics during the post-intervention period were not significantly different | • the duration of perioperative antibiotic prophylaxis was reduced to < 2 days<br>• there was a shift from netilmicin or amikacin to gentamicin for the treatment of community acquired infection |
| Ayuthya et al., 2003 at Ramathibodi hospital | use of an antibiotic order form (AOF), restricted antibiotic formularies and provision of educational information. | | • No data of pre-intervention<br>• Post-intervention inappropriate antibiotic use was 26% |
| Thamlikitkul et al., 2004 at Siriraj hospital | implementing clinical practice guidelines (CPG) on adults with upper respiratory infection (URI) | • Antibiotic use fell from 74.0% to 44.1% ($P$ <0.001)<br>• Fewer prescriptions for amoxicillin, roxithromycin, co-trimoxazole and doxycycline, and more for penicillin V ($P$ <0.05) | |

| Reference | Intervention | Pre-Post intervention antibiotic prescription rates | Pre-Post intervention inappropriate antibiotic use |
|---|---|---|---|
| Apisarnthanarak et al., 2006 at Thammasart university hospital | education and an antibiotic-control program on inpatient antibiotic prescriptions | • 24% reduction in the rate of antibiotic prescription (640 vs. 400 prescriptions/1000 admissions; $P < 0.001$)<br>• Reduction in prescription for 3rd generation cephalosporins and more for cefazolin and fluoroquinolones | • incidence of inappropriate antibiotic use was significantly reduced (42% vs. 20%; P<.001) |

## 4. Infection control in hospital

The emergence, persistence, and intra- and interhospital spread of multidrug-resistant organisms have all been facilitated by inadequate infection control practices. Furthermore, the emergence and spread of drug-resistant nosocomial pathogens from hospitals to the community are also a concern, and a history of hospitalization has been identified as a significant risk factor for the acquisition of a resistant infection in family members (OR 4.5, $p = 0.007$) (57).

Infection control measures to limit the spread of antimicrobial resistance are being increasingly well defined. Hand hygiene with alcohol-based hand rubs has been shown to decrease the transmission of resistant organisms (58).

The effect of multifaceted hand hygiene culture-change program on health care worker behaviour, and to reduce the burden of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infections was assessed as a 3 year program of operation clean start (OCS) in a teaching hospital, Australia. Thirty-six months post-intervention, there had been significant reductions in hospital-wide rates of total clinical MRSA isolates (40% reduction; $P < 0.001$), patient-episodes of MRSA bacteraemia (57% reduction; $P = 0.01$), and clinical isolates of ESBL-producing *E. coli* and *Klebsiella spp* (90% reduction; $P < 0.001$) (59).

In Thailand, the report from the Association of Nosocomial Infection showed that infection control program could reduce the nosocromial infection from 11.7 % to 7.3 and hospital cost can be saved about 888 million baht (20).

## 5. Health insurance system in Thailand

The Civil Servant Medical Benefit Scheme (CSMBS) is a package of welfare and health care benefits for active and retired government employees and public sector workers, as well as their dependents including spouse, parents and children. Expenditure per beneficiary is estimated to be as high as 3,800 baht (60). The rapid escalation of health expenditure is the result of problems with cost-containment, especially incentives for providers to over-prescribe due to the use of the "fee for service" payment method. However, a first step in cost containment was taken in April 2002 with the introduction of the Diagnosis Related Groups (DRGs) system within a global budget for the payment of inpatient services. The system was, nevertheless, revoked after four months due to the proof of objection to the enactment of the CSMBS's financing. This year 2007, the Diagnosis Related Groups (DRGs) system will be reintroduced again and the impact should be evaluated in term of medical practice and antimicrobial situation.

Universal coverage scheme under 30 baht co-payment has been implemented since 2001. A retrospective study was done to investigate the antibiotic prescription rates for upper respiratory tract infections in 4 regions (2 provinces in each region), sampling including 30 community hospitals, 4 general hospitals, 2 regional hospitals, 3 private hospitals and 1 university hospital (61). The antibiotic prescription rates for non-specific acute respiratory infection in universal coverage scheme (no co-payment) was less than the other scheme siginificantly as Table 3. Most common antibiotic prescription is decided for pharyngitis 85.1% and followed by laryngitis 69.4%. The antibiotic prescription rates were found significantly less in the primary care units (PCU) outside the hospitals than inside the hospitals.

**Table 4 Antibiotic prescription rates for acute nonspecific respiratory infection according to schemes of health insurance**

| Health Insurance | Number of cases | Percentage of antibiotic prescription |
|---|---|---|
| No health insurance (self-payment) | 946 | 54.9 |
| Universal coverage scheme (no co-payment) | 2,750 | 37.1 |
| Universal coverage scheme (30 baht co-payment) | 833 | 54.4 |
| Social security scheme | 188 | 51.1 |
| Civil servant medical benefit scheme | 414 | 50.0 |
| Private health insurance/insurance by employer | 19 | 57.9 |

* *P-value* < 0.05, Source: (61).

## 6. Other issues in concern

Another factor that is widely believed to contribute to resistance problems is the use of various antimicrobial agents in animals raised commercially for food, such as poultry, pigs, and cows. Participants debated just what contribution such agricultural use makes to the spread of antimicrobial resistance among human pathogens. While some participants maintained that the problem is minimal and being effectively managed by various public and private programs, others described a greater level of risk. They expressed concern that use of antimicrobials in animals, either for therapeutic use or to promote growth, can lead to the development of drug-resistant microbes (largely bacteria, such as salmonella and campylobacter) that subsequently are transmitted to humans, usually through food products.

It is reasonable to assume that physicians and veterinarians prescribing practices are affected by the same incentives. In order to prevent overuse of antimicrobials in food animals and pets, veterinarians should not profit when dispensing drugs, or even better, to completely separate veterinary drug prescribing and dispensing. We believe that the practicing veterinarians should generate their income from fees on the consultancy service, and independent of the volumes of medicines prescribed and or dispensed to the client.

## 7. Priority research topics

Understanding all the issues associated with antimicrobial resistance is probably impossible, but it is clear that there are a number of research keys about which we need more information. The most important current knowledge gaps needs to be defined to guide the direction of future research efforts and to improve future containment initiatives. A summary of some important issues are described below:

### 7.1. Patients and the General Community

- What factors influence patients' expectations from antimicrobials, including marketing directed at the general public?
- In what circumstances do large and small group campaigns designed to reduce antimicrobial use lead to behavioural change?
- Can health educators employ better marketing techniques?
- What patient educational materials and other supportive tools impact optimally on patient behaviour with respect to antimicrobial use?
- What is the effect of patient adherence to prescribed therapy on emergence of resistance?
- What is the impact of interventions that are designed to change antimicrobial use on patient outcome? For example: How do symptom scores and patient satisfaction compare when respiratory infections (e.g. purulent rhinitis/common cold or cough/bronchitis) are treated with symptomatic therapy, antimicrobials or

placebo? What is the impact of deferring antimicrobial therapy for acute otitis media? (since up to 80% of infections will resolve within 2-3 days without antimicrobial therapy)?

- What is the extent of self medication (antibiotics accessed over the counter, drug sellers, "left over" from previous course) and what impact does it exactly have on antimicrobial resistance?
- How reliable is syndromic self-diagnosis by an individual or parent in the community settings?

### 7.2 Prescribers and Dispensers

- How can policies be translated into practice in a sustained manner to improve:
    a) clinical diagnosis and disease management;
    b) prescribing practices (antimicrobial use patterns);
    c) patient care practices (handwashing, catheter insertion, etc.);
    d) adverse effects monitoring and reduction.
- What are the most appropriate and cost-effective training strategies to achieve the above? Do these practices result in improved antimicrobial use and infection control and in reduction in the emergence and spread of antimicrobial resistance?
- What is the reliability and utility of point-of-use diagnostic strategies for common infectious diseases in clinical practice? Can more widespread use of these decrease antimicrobial use and resistance?
- What are the key interventions for a cost-effective outcome (reduced use & resistance etc)
    a) Improved diagnosis
    b) Practice/prudent use guidelines (use of evidence-based medicine to produce guidelines; how to communicate to prescribers; how to audit adherence, effect on antimicrobial use, resistance and health outcome)
    c) Practice profiling and feedback
    d) Education programs (small group, peer run, use of opinion leaders, different materials - printed, web based etc)

e) Use of decision support systems (computer assisted stratified for patient risk and linked to prudent use guidelines)
f) Delayed prescriptions

### 7.3 Hospitals

- What impact does the introduction of a DRGs policy have on prescribing?
- What are the links and interactions between antimicrobial resistance in hospitals and the community?
- What are the most cost-effective methods to limit transmission in hospitals with limited resources?
- In a facility which already has a high level of resistance in a particular organism, what are the benefits of intensification of infection control precautions in decreasing morbidity and mortality associated with the resistant organism?
- What infection control interventions provide the best cost benefit in facilities in Thailand?
- What is the most effective utilization of microbiology resources for diagnosis of infectious diseases in resource-poor countries and facilities?
- What role do different prescribing strategies have, such as restricted use, class restriction, antibiotic cycling?

### 7.4 Use of antimicrobials in food-producing animals

- Clinical trials to optimise dose, dose interval and duration of antimicrobial treatment in animals to improve prescription use of antimicrobials;
- What are the best means to prevent and control foodborne and zoonotic diseases at the animal production level to reduce the risk of transmission of resistant bacteria to humans?
- Non-antimicrobial alternatives for the control of infectious diseases and syndromes in animals, particularly multifactorial diseases in young animals.
- Development of more rapid diagnostic methods for bacterial infections to reduce need for empirical treatment.

- Effect of cessation of use of specific antimicrobials on the prevalence and persistence of resistant bacterial in food-producing animals and their immediate environment;
- Information on the stability of important antimicrobials and their metabolites in the environment;
- Impact of the use of antimicrobials in domestic pets and birds on the development and persistence of resistance bacteria in the farm environment;
- Alternative approaches for growth promotion that do not require antimicrobials;

### 7.5 National Governments and Health Systems

- What would be the impact on antimicrobial resistance of enforcement of existing laws and regulations?
- What are the effects of health sector reform and health care policy with respect to antimicrobial use and antimicrobial resistance?
- Do economic and regulatory strategies have an impact on changing prescribers' behavior?
- What are the effects of reimbursement, patient charges, and health insurance on antimicrobial resistance? For example:
    a) Do these have an impact on inappropriate antimicrobial use?
    b) To what extent does a patient's economic situation lead to misuse of antimicrobials?
    c) Do cost control policies have an impact on inappropriate antimicrobial prescribing?
- What are the essential quality assurance procedures required to ensure meaningful antimicrobial resistance data?
- What is the role and cost-effectiveness of laboratory diagnostic results, including culture and antimicrobial susceptibility testing, in specific patient care circumstances, including managed care settings?
- What is the minimum effective surveillance, including data elements and case finding for antimicrobial resistance at a national level, to support a national strategy for antimicrobial resistance?

### 7.6 Drug & Vaccine Development

- Can clinical trial protocols be designed so that the role of resistance in determining clinical and microbiological outcome can be assessed?
- How can clinical trials be developed and funded to promote preservation of current antimicrobial agents, rather than promoting development and use of new agents?

### 7.7 Pharmaceutical promotion

- What are the effects (positive and negative) of medical representatives of drug companies and industry incentives in general (advertising, seminars, travel, free lunches, etc) on the problem of antimicrobial resistance?

### 7.8 Microbiology of Resistance

- What are the effects of combination antimicrobial therapy on resistance and on efficacy?
- Why do some antimicrobials have a greater tendency to select for resistance than others (both within and between antimicrobial classes)?
- What are the clinical implications of resistance detected in vitro?
- What is the impact of vaccines on the problem of antimicrobial resistance in general and on the carriage of resistant strains (including specific stereotypes)?
- What adaptive mechanisms do organisms have to allow persistence of resistance, e.g. increased colonization proficiency, acquisition or mutation to of virulence genes etc?
- Does the reversal of resistance, which can occur upon termination of antibiotic use, relate to the loss of the resistance determinants or the replacement of resistant bacteria with susceptible bacteria of the same species in the environment?

## 8. Summary of reviewed policy options

| Policy | Description | Actors | Pros | Cons |
|---|---|---|---|---|
| **CONTROLING ANTIBIOTIC USE IN HOSPITALS OUTPATIENT SETTINGS** | | | | |
| **Increase cost-sharing for prescriptions** | • Increase copayments<br>• Restrict prescribing through formularies<br>• Impose delay for fulfillment of some prescriptions for certain infections | • Insurance companies<br>• Pharmacies<br>• Governments | • Patients will use fewer antibiotics | • May not distinguish between "appropriate" and "inappropriate" use |
| **Use public information campaigns** | • Educate physicians and patients to discourage inappropriate prescribing | • Doctors (professional societies)<br>• Patient and consumer groups<br>• Government | • Is inexpensive and simple to implement | • May not yield sufficiently large or sustainable reductions in use |
| **Restrict prescribing** | • Require preapproval for some or all antibiotics<br>• Restrict ability of physicians to prescribe antibiotics | • Doctors and hospitals<br>• Governments | • Circumvents current lack of incentives to reduce inappropriate prescribing | • May inhibit patient-physician relationship<br>• May discourage appropriate antibiotic use |
| **Change prescribing patterns in hospital and outpatient settings** | • Monitor and present feedback of prescribing patterns compared with peers<br>• Use pay-for-performance measures | • Professional medical associations<br>• Hospitals | • Creates incentives, since physicians care about their reputation and performance | • May discourage all antibiotic use unless feedback distinguishes between appropriate and inappropriate use |
| | • Conserve new and powerful antibiotics for cases where first-line drugs do not work | • Professional medical associations<br>• DDC<br>• NARST, DMSc<br>• Hospitals | • Maintains viability of new antibiotics longer | • Increases resistance to first-line drugs<br>• Is inefficient from ecological standpoint because diversity of antibiotics may be helpful |
| | • Switch from broad spectrum to narrow-spectrum antibiotics | • Doctors | • Reduces opportunities for resistance to arise | • Few rapid tests to determine pathogen are available<br>• Doctors have few incentives to use narrow-spectrum drugs<br>• Is difficult to switch from broad to narrow-spectrum antibiotics once therapy has started |

| Policy | Description | Actors | Pros | Cons |
|---|---|---|---|---|
| **Change prescribing patterns in hospital and outpatient settings (continued)** | • Cycle or rotate drugs | • Doctors and hospitals | • Ecological models suggest this may reduce risks of resistance | • Has not yet been validated in limited trials<br>• Could be costly to implement<br>• Resistance may reemerge rapidly when drug is reintroduced<br>• There may not be enough antibiotics for rotation in each case |
| | • Increase dose while shortening length of therapy | • Doctors | • May reduce risks of resistance | • Still leaves long tail for recrudescence |
| **Provide substitutes** | • Promote antibiotic substitutes (e.g., cold packs) in cases where antibiotics are not necessary (e.g., flu) | • Insurance companies<br>• Governments | • Simple, does not require major changes, lets physicians reduce antibiotic use without reducing patient satisfaction | • Substitutes lack effectiveness<br>• Impact on antibiotic use has not been widely studied |
| **Impose tax, quota, or permit** | • Tax antibiotic use either generally or selectively | • Governments | • Creates strong incentive to reduce use | • Does not differentiate between appropriate and inappropriate use<br>• Insurance shield intended targets from tax burden |
| **Improve diagnostic accuracy** | • Improve diagnostic tests<br>• Improve decision guidelines on when to use antibiotics | • Doctors (professional societies)<br>• Hospitals<br>• Medical schools<br>• Governments | • Delays drug therapy until need for antibiotics is certain<br>• Encourages use narrow-spectrum drugs when appropriate<br>• Decision guidelines are inexpensive and can easily be incorporated into clinical therapy | • Decision guidelines lack specificity<br>• Some diagnostic tests are expensive and invasive |

| Policy | Description | Actors | Pros | Cons |
|---|---|---|---|---|
| **HOSPITAL INFECTION CONTROL** | | | | |
| **Employ surveillance and patient isolation** | • Screen all patients on admission (active surveillance) and isolate patients who test positive | • Hospitals | • Reduces likelihood of antibiotic-resistant pathogens entering hospital<br>• Reduces chances of transmission | • Is costly and time consuming<br>• Stigmatizes infected patients<br>• Dose not completely eliminate possibility of transmission |
| | • Screen only patients at risk (selective active surveillance): those who were recently hospitalized or had previous resistant infections | • Hospitals | • Reduces likelihood of antibiotic-resistant pathogens entering hospital<br>• Is less costly than screening everyone | • Is costly and time consuming<br>• Requires electronic medical records |
| **Reduce transmission by health care workers** | • Reduce patient cohorting (number of patients seen by each nurse) | • Hospitals<br>• Health care workers<br>• Doctors | • Could reduce transmission | • Is costly and difficult of implement and enforce |
| | • Improve hygiene through education (on hand washing, gloves, gowns) | • Hospitals | • Could reduce transmission | • May require installation of hand-washing stations<br>• Incentives to follow guidelines are lacking<br>• Long-term impact of interventions is unclear |
| | • Improve hygiene through pay-for-performance measures (such as for achieving certain target rates for hand washing) | • Hospitals | • Could change incentives for heath care workers and doctors | • May required installation of hand-washing stations<br>• Effect of changing incentives may wear off |
| **Reduce transmission by patients and visitors** | • Improve cleaning of visitors' and patients' rooms | • Hospitals | • Removes pathogens, reducing likelihood of transmission<br>• Does not affect clinical practice | • Is expensive but may be cost-effective if carried out in many or all health care institutions |
| **Promote regional cooperation** | • Enforce regional cooperation and information sharing to improve hospital infection control at regional level | • Hospitals<br>• Governments | • Ensures coordinated infection control<br>• Reduces free-riding by individual facilities | • Hospitals may not cooperate<br>• May be difficult and costly to ensure cooperation |

| Policy | Description | Actors | Pros | Cons |
|---|---|---|---|---|
| **Require hospital infection and resistance reporting** | • Require hospitals to report levels of hospital-acquired infections and resistance | • Hospitals<br>• Governments | • Increases transparency<br>• Creates incentive to reduce levels of infection | • Creates disincentive to monitoring among hospitals with high levels of infection<br>• Creates incentive to cherry-pick patients<br>• May encourage lawsuits by patients with hospital-acquired infections<br>• Is difficult to enforce |
| **Change hospital incentives** | • Link hospital reimbursement to levels of infection | • Hospitals<br>• Insurance companies | • Creates incentive to reduce levels of infection to get full reimbursement | • Is difficult to implement<br>• Creates incentive to cherry-pick patients |
| | • Consider impact of infections on hospital budgets and organizational structure | • Hospitals<br>• Medical research institutions<br>• Government agencies | • Multidisciplinary research could identity organizational issues that reduce hospital incentives to conduct surveillance | • Actors are nonspecific<br>• Mandate is unclear |
| | • Include infection control in hospital accreditation and health care quality ratings | • Hospitals<br>• Institute for HA, HSRI | • Coverage would be comprehensive<br>• Quality indicators are increasingly important in health care purchasing decisions | • Current process is designed to catch egregious violators of medical practice<br>• Infections are only one consideration in determining quality of heath care facility |
| **ROLE OF GOVERNMENT** | | | | |
| **Make government steward of antibiotic effectiveness** | • Create separate agency to handle antibiotic effectiveness | • FDA<br>• DMSc<br>• NHCO<br>• NHSO<br>• HSRI | • Empowers to better control antibiotics<br>• Provides greater financial support for federal antibiotic stewardship | • May require authorization |
| | • Facilitate innovation by conducting field experiments | • HSRI<br>• DMSc | • Creates significant societal benefits through large-scale experiments to slow evolution of resistance | • Is expensive<br>• Mandate to do this is unclear |
| | • Require broad infection control programs as condition of participation | • NHCO<br>• DMSc<br>• NHSO<br>• DDC | • Benefits all patients | • May deny coverage to segment of population |

| Policy | Description | Actors | Pros | Cons |
|---|---|---|---|---|
| | • Create codes (hospitals' diagnosis-related group: DRGs and physicians' common procedure terminology) to track resistant infections and prescribing patterns | • NHSO<br>• Hospitals<br>• Governments | • Creates transparency<br>• Provides more data on problem | • Is difficult to change codes<br>• Hospitals may engage in "creative" coding |

**Note**
**DDC** = Department of Disease Control
**NARST** = National Antimicrobial Resistance Surveillance Center Thailand
**DMSc** = Department of Medical Science
**HA** = Hospital Accreditation
**HSRI** = Health System Research Institute
**FDA** = Food and Drug Administration
**NHCO** = National Health Commission Office
**NHSO** = National Health Security Office

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**Appendix A:**

**ข้อคิดเห็นสำคัญจากบทสัมภาษณ์ ที่1**

ผู้อนุญาตให้สัมภาษณ์: ศาสตราจารย์แพทย์หญิงนลินี อัศวโภคี

หมายเหตุ ได้คัดลอกมาเฉพาะที่สำคัญ

“การใช้ rational drug use ไม่ work ในบ้านเรา ทั้งๆที่มีการฝึกอบรมตลอดเวลา ทั้งนี้เพราะว่าแพทย์มีการเปลี่ยนรุ่นตลอด”

“ทั้งนี้ไม่ได้อยู่ที่คนสอน แต่อยู่ที่ผู้เรียนว่ามี **awareness** หรือไม่”

“แพทย์มีการใช้ยาต้านจุลชีพอย่างเหมาะสม มีข้อบ่งชี้ (appropriate use เช่นให้ยาถูกต้อง ขนาดและระยะเวลาถูกต้อง) เพียง 20% ที่เหลือใช้โดยไม่ตรงตามข้อบ่งชี้ (inappropriate use) ในจำนวนนี้ 60-70% เป็นการใช้เกินความจำเป็น (overuse) อีกประมาณ 30% เป็นการใช้ยาต้านจุลชีพที่ผิด หรือไม่ถูกต้อง (misuse)”

“ดูว่าอะไรคือสาเหตุของ overuse และจะหยุดมันได้อย่างไร มีการใช้เครื่องมืออันหนึ่งที่เรียกว่า AOS (antibiotic order sheet) ในชีทนี้ ส่วนประกอบที่สำคัญคือ indications ในการใช้ยา โดยพี่มีการแตกให้หมดเลยเป็น 5 ข้อ ถ้าเค้าติ๊กได้ข้อใดข้อหนึ่งแสดงว่าไม่ overuse ปรากฏว่าผลที่ออกมาoveruse ไม่หยุด ถามว่าทำไมถึงไม่หยุด ก็พบว่าที่เค้าติ๊กว่าใช่ นี่เป็นการติ๊กส่งเดช เพราะว่าไม่มี rewarding and punishment”

“ได้ปรึกษาอาจารย์อรทัย รวยอาจิณ เพื่อดูทางด้าน social science โดยให้นักศึกษา คุณเพชรศิริ ถวิลหวัง (62) ทำการศึกษา pathway ที่ประกอบด้วย variables ต่างๆ เกือบ 80 ตัว ตั้งแต่ จุดตั้งต้นการใช้ยา อะไรเป็นตัวสั่งให้ใช้ยา เช่น ตัวคนไข้ ลักษณะโรค severity ของโรค diagnosis จนกระทั่งถึง external influences เช่นการอ่านวารสาร journal อะไร ตัวอาจารย์แพทย์ บริษัทยา awareness of cost เค้ารู้มั้ยว่ายาราคาแพง ผลเสีย consequence ของยามีอะไร ส่วน outcome ก็มี overuse หรือ non-overuse ใช้โดยมี indication หรือไม่มี แล้วนำไปเข้า stepwise logistic regression model ผลออกมามีแค่ 2 ตัวที่สำคัญ คือ journal วารสารที่อ่าน และ severity ของโรค”

“เพราะว่าโรคติดเชื้อเป็นอะไรที่วินิจฉัยยากในเบื้องต้น เพราะฉะนั้น แพทย์คิดว่าการให้ antibiotic ในคนไข้ที่มีอาการรุนแรงนั้นให้ response rates ที่ค่อนข้างสูง ก็เลยให้ไว้ก่อนดีกว่า เป็นสาเหตุของ overuse”

“ปัญหาเรื่องเชื้อดื้อยา หรือ infection control มักถูกเพิกเฉยจากผู้คุมนโยบาย ไม่ใช่แค่เฉพาะระดับชาติ แม้แต่ระดับโรงพยาบาลก็ตาม มักไม่ค่อยถูกสนับสนุน”

“การใช้ antibiotic use control หรือการ restrict use เป็นเพียงส่วนเดียวของการแก้ปัญหาเชื้อดื้อยา ซึ่งไม่ใช่วิธีการที่ได้ผลยั่งยืน”

“เหตุการณ์ของการใช้ยา antibiotic เค้าเรียก antibiotic paradox นั่นก็คือเมื่อไหร่ที่ใช้ยาในการรักษา ก็จะมีการดื้อยาเกิดขึ้น ทำอย่างไรจะให้แขนข้างหนึ่งยาว แขนข้างหนึ่งสั้น เพราะถ้าแขนอีกข้างยาวเกิน ก็จะเกิดภาวะที่เข้าสู่ post-antibiotic era”

“step ต่อไปที่ควรทำเมื่อเราไม่สามารถหยุดใช้ยา และการวินิจฉัยก็ค่อนข้างยาก ก็คือการทำ infection control ที่ดี แต่ในระดับโรงพยาบาล ส่วนใหญ่เห็นมีแต่พยาบาลที่ลุยทำนั่นทำนี่ หมอไม่สนใจเลย ล้างมือยังไม่ล้างกันเลย เป็นสิ่งที่ทำกันได้ง่ายแต่แก้ปัญหาได้”

“ซึ่งมีตัวอย่างให้เห็นว่าที่โรงพยาบาลกรุงเทพ การรณรงค์ล้างมืออย่างเดียวสามารถลด MRSA ได้ถึง 70 เปอร์เซ็นต์”

“คงต้องมีการ set priority ว่าจะควบคุมโรคอะไร ยกตัวอย่างเช่น *Streptococcus pneumoniae* เป็นการยากที่จะบอกได้ว่าเด็กที่มาด้วยอาการเจ็บคอรายไหนเกิดจากเชื้อนี้ ซึ่งจำเป็นต้องใช้ยา และการใช้วัคซีน ซึ่งจะลดปัญหา DRSP ได้ซึ่งประเทศในกลุ่มสแกนฯ ทำได้ แต่บ้านเราคงยาก”

**ข้อคิดเห็นสำคัญจากบทสัมภาษณ์ ที่2**

ผู้อนุญาตให้สัมภาษณ์: นายแพทย์ปฐม สวรรค์ปัญญาเลิศ

“แนวนโยบายหลักแห่งชาติเกี่ยวกับโรคติดเชื้อดื้อยาต้านจุลชีพ ยังไม่เป็นตัวบทชัดเจน เพราะว่ามักเปลี่ยนไปตามนโยบายหลักในแต่ละยุคสมัย เพราะที่กรมวิทย์ฯทำก็จะเน้นเรื่องของการเฝ้าระวัง ก็เป็นข้อมูลในระดับโรงพยาบาล ซึ่งเมื่อเสร็จแล้วก็แล้วแต่นโยบายของแต่ละโรงพยาบาลว่าจะเอาข้อมูลเหล่านี้ไปใช้แค่ไหน ซึ่งจะเห็นว่ามีแต่ในโรงพยาบาลระดับมหาวิทยาลัย และโรงพยาบาลใหญ่ๆ อาจต้องไป survey ดูในระดับโรงพยาบาลชุมชน”

“แนวนโยบายเกี่ยวกับการใช้ยาส่วนใหญ่จะขึ้น กับ พ.ร.บ. ยา และ อย. ซึ่งคงต้องเป็นผู้ดูแลโดยตรง”

“ปัญหาที่ต้องดูอาจต้องเกี่ยวข้องกับชมรมร้านขายยา อย่างตัวอย่างตอนเกิดไข้หวัดนกและมี Ryes’ syndrome ที่เราสามารถเชิญเขามาร่วมประชุมให้ความรู้เรื่องนี้ทำให้ลดการเกิดปัญหาไปได้”

“การให้ความรู้แก่ประชาชนทางสื่อโฆษณาโทรทัศน์อาจไม่ได้ผล เพราะว่ากว้างเกินไป และไกลตัว ต้องเป็นเรื่องที่เขาให้ความสนใจ ถ้ายังไม่ป่วย ก็ไม่ค่อยให้ความสนใจเท่าไหร่ เพราะว่ายังไม่ต้องใช้ยา”

“อาจต้องดูผลกระทบของ 30 บาทที่มีต่อพฤติกรรมการซื้อยาทานเองว่าเปลี่ยนแปลงอย่างไร และมีผลอย่างไรต่อการสั่งยาของโรงพยาบาลเปลี่ยนแปลงไปอย่างไร เพราะถ้าผู้ป่วยหันมาใช้บริการของสถานพยาบาลของรัฐมากขึ้นอาจต้องเน้นนโยบายไปที่โรงพยาบาลเป็นส่วนใหญ่”

“ข้อมูลของศูนย์เฝ้าระวังมักจะล่าช้าเกินกว่าความเป็นจริง เพราะว่าต้องรอข้อมูลจากโรงพยาบาลในเครือข่ายให้ครบก่อน เพราะว่าเป็นที่โปรแกรมเก็บข้อมูลเป็นแบบนั้น ทำให้ได้ข้อมูลที่ไม่ทันสมัย”

“น่าจะต้องมีการศึกษาวิจัย โดยควรต้องดูว่าข้อมูลที่ออกจากศูนย์เฝ้าระวังฯ มีคนเข้าถึงแค่ไหน นำไปใช้ประโยชน์แค่ไหน”

**ข้อคิดเห็นสำคัญจากบทสัมภาษณ์ ที่3**

ผู้อนุญาตให้สัมภาษณ์: ศาสตราจารย์นายแพทย์สมหวัง ด่านชัยวิจิตร

เป็นผู้ริเริ่มก่อตั้งคณะกรรมการป้องกันและควบคุมโรคติดเชื้อแห่งชาติ เน้นว่าระบบในการป้องกันและควบคุมการเชื้อที่ทำอยู่ขณะนี้เน้นในเรื่องการฝึกอบรม ส่วนเรื่องการเฝ้าระวังโรคติดเชื้อนั้นเน้นทางด้านการพัฒนาระบบข้อมูลเทคโนโลยี่สารสนเทศ ซึ่งทางคณะกรรมการกำลังดำเนินการพัฒนาอยู่ โดยมีวัตถุประสงค์ เพื่อเชื่อมโยงข้อมูลการเฝ้าระวังโรคติดเชื้อในโรงพยาบาลในประเทศไทย และมีการกำหนดดัชนีคุณภาพ (Quality indicators) แล้ว แต่ระบบนี้ยังขาดการนำไปใช้โดยกระทรวงสาธารณสุขอย่างเป็นรูปธรรม ซึ่งโรคติดเชื้อน่าจะได้รับการดูแลโดยตรงจากกรมควบคุมโรคโดยเน้นเรื่องการควบคุมโรคไม่ว่าจะเป็นในโรงพยาบาลหรือนอกโรงพยาบาล

**Appendix B: Summary Report from Group Discussion on 30th November 2006**

รายชื่อผู้เข้าร่วมประชุม

ประชุมระดมสมอง เรื่อง Current situation of the antimicrobial resistance in Thailand

วันพฤหัสบดีที่ 30 พฤศจิกายน 2549 เวลา 8.30-13.30 น.

ณ ห้องประชุม 1-2 สวรส.

| รายชื่อ | หน่วยงาน |
|---|---|
| 1. นพ. สุวิทย์ วิบุลผลประเสริฐ | สำนักงานปลัดกระทรวง |
| 2. นพ. ปฐม สวรรค์ปัญญาเลิศ | กรมวิทยาศาสตร์การแพทย์ |
| 3. นางสุรางค์ เดชศิริเลิศ | กรมวิทยาศาสตร์การแพทย์ |
| 4. รศ.พญ. สยมพร ศิรินาวิน | ภาควิชากุมารเวชศาสตร์และแพทย์ศาสตร์โรงพยาบาล |
| 5. นพ. วินัย รัตนสุวรรณ | สมาคมโรคติดเชื้อแห่งประเทศไทย |
| 6. คุณศศิวรรณ ปริญญาณ์ | มูลนิธิเพื่อผู้บริโภค |
| 7. ผู้แทนศูนย์สารสนเทศและวิจัยระบบยา | ศูนย์สารสนเทศและวิจัยระบบยา |
| 8. ผศ.ดร. ปรีชา มนทกานติกุล | สภาเภสัชกรรมโรงพยาบาล |
| 9. ภญ. กุลธิดา สุขนิวัฒน์ชัย | สมาคมเภสัชกรรมชุมชน |
| 10. นพ. สมสิทธิ์ ตันสุภสวัสดิกุล | สถาบันบำราศนราดูร |
| 11. ทพญ. ศิริวรรณ พิทยรังสฤษฎ์ | IHPP |
| 12. พญ. วัชรี โชคจินดาชัย | คณะเวชศาสตร์เขตร้อน ม. มหิดล |
| 13. น.ส. นงนุช ทองศรี | สถาบันวิจัยระบบสาธารณสุข |
| 14. นางอรอนงค์ เฮงเจริญ | กลุ่มยาสัตว์และเภสัชเวชภัณฑ์กองควบคุมยา อย. |
| 15. ภญ.พรพิศ ศิลขวุธท์ | สถาบันวิจัยระบบสาธารณสุข |

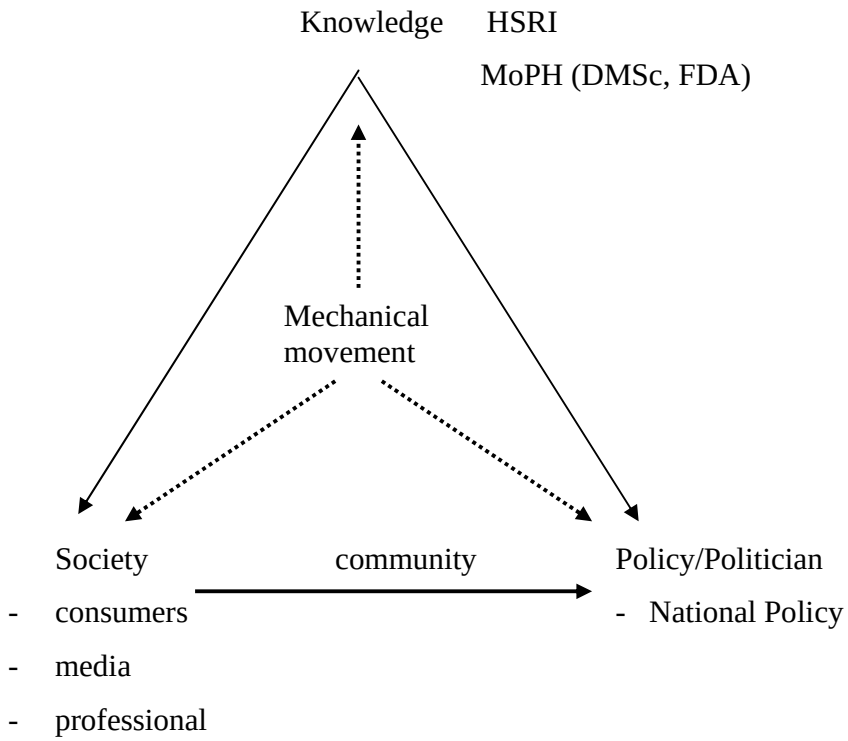
**Prof. Otto Cars**

He has demonstrated global concern of antimicrobial resistance problem and his experience in the successful intervention in Scandinavia

**Problems**

1. Sustained political and policy commitment
2. Successful implementation

**How?**




Mechanical movement by a group of coordinator who should be

1. Senior with respectful manner
2. Good connector
3. Independent
4. Under certain flexible and multi-stakeholder organization: NHCO, NHSO etc.
5. With young committed team

Set of Policies/ Strategies

1. Education
2. Research
3. Economic
4. Enforcement
5. Advocacy

etc.