

# **Potential Threats of Community-Acquired Infections in Southeast Asia: Problems and Solutions**

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# Outlines

- Scenario and overview of the problem in developing countries
- Impact of over-the-counter (OTC) antibiotic use
- Relationship of antibiotic resistance to OTC antibiotic use in the community
- Solutions to these challenges

# WORLD

Political Map



# Inappropriate Usage of Antibiotics: Examples in Asia-Pacific Region (vs. USA)

Countries	Results	References
Philippines (OTC purchase)	Manila: 66%	(Lansing et al. J Clin Epidemiol 1990)
China Prescribing for viral infections	<ul style="list-style-type: none"> <li>•Beijing Children's Hospital: 98% of cold</li> <li>•Taiwan: 30% of all "colds" (45% aged ≤ 15 yrs) and "RTIs"</li> </ul>	(Yang et al. PIDJ 1993) (Chang et al. Int J Ant Ag 1999)
Malaysia	53% inappropriate Rx in hospital	(Lim Singapore Med J 1993; 1994)
Hong Kong False diagnostic indicators and attitudes	Older, more senior, private practice = > AB Rx	(Lam. Int J Clin Pract 2001/3)
Thailand	Overall 80% inappropriate prescribing in drug store setting	(Apisarnthanarak et al. ICHE, 2008)
US	<ul style="list-style-type: none"> <li>•Antibiotics for common cold 36%</li> <li>•Antibiotics for acute resp infection 51%</li> </ul>	(Gilberg, J Man Care Pharm 2003) (Huang et al, J Clin Epidem 2005)

# Scenario and Overview of the Problem

# Dispense of Antibiotics from Thai Drug Stores

- Six interns trained as patients with common syndromic ailments presented to all drug stores in Pratumthani from July-December 2006
- Six presentations were simulated



Zinnat<sup>®</sup>  
suspension  
250 mg  
Each 5 ml contains  
50 mg Cefuroxime  
as cefuroxime axetil  
when prepared as  
directed  
Granules for  
50 ml  
GlaxoWellcome

Zinnat<sup>®</sup>  
suspension  
250 mg  
Each 5 ml contains  
250 mg Cefuroxime  
as cefuroxime axetil  
when prepared as  
directed  
Granules for  
50 ml

60 ml No. L950  
**KLACID<sup>®</sup>**  
CLARITHROMYCIN  
Granules  
For oral suspension  
125 mg per 5ml

30 ml  
Fill Weight 7.5g  
**CEDAX<sup>®</sup>**  
Ceftibuten  
Powder for  
Oral Suspension  
30mg/ml

30 ml  
Fill Weight 7.5g  
**CEDAX<sup>®</sup>**  
Ceftibuten  
Powder for  
Oral Suspension  
30mg/ml

Pfizer  
**ZITHROMAX<sup>®</sup>**  
(azithromycin)  
Oral suspension 200mg/5ml  
Powder for 15 ml

**ZITHRO<sup>®</sup>**  
(azithromycin)  
Oral suspension 200mg/5ml  
Powder for 15 ml

ยาปฏิชีวนะ, ยาฆ่าเชื้อ

GlaxoSmithKline  
**Augmentin<sup>®</sup>**  
amoxicillin +  
clavulanate potassium  
Daily Dosing  
mg/5 ml  
syrup  
powder form  
457 mg

GlaxoSmithKline  
**Augmentin<sup>®</sup>**  
amoxicillin +  
clavulanate potassium  
156 mg/5 ml  
60 ml syrup  
in powder form  
457 mg

gsk GlaxoSmithKline  
**Augmentin<sup>®</sup>**  
amoxicillin +  
clavulanate potassium  
156 mg/5 ml  
60 ml syrup  
in powder form  
156 mg

gsk GlaxoSmithKline  
**Augmentin<sup>®</sup>**  
amoxicillin +  
clavulanate potassium  
156 mg/5 ml  
60 ml syrup  
in powder form  
156 mg

**Miotin<sup>®</sup>**  
DRY SYRUP  
5 ml contains:  
Midecarycin Acetate  
200 mg (Potency)  
60 ml  
200 mg

**Miotin<sup>®</sup>**  
DRY SYRUP  
5 ml contains:  
Midecarycin Acetate  
200 mg (Potency)  
60 ml  
200 mg

**BANAN<sup>®</sup>**  
DRY SYRUP  
5 ml  
contains 40 mg  
Cephalexime  
Cephem  
antibiotic  
60 ml syrup  
in powder form  
Manufactured by  
DAI NIPPON PHARMACEUTICAL CO., LTD.  
Saitama, Tokyo, Japan

**BANAN<sup>®</sup>**  
Forte  
DRY SYRUP  
Each 5 ml  
contains 80 mg  
Cephalexime  
Cephem  
antibiotic  
60 ml syrup  
in powder form  
Manufactured by  
DAI NIPPON PHARMACEUTICAL CO., LTD.  
Saitama, Tokyo, Japan

**Amc<sup>®</sup>**  
250 mg

# Presentation and Treatment Guidelines

Presentation	Diagnosis	Treatment
Acute low grade fever and sore throat	Viral pharyngitis	No antibiotic
Acute fever, myalgia, rhinorrhea, cough	Influenza	No antibiotic
Acute fever, tender maxillary sinus with d/c	Viral sinusitis	No antibiotic
Acute watery diarrhea, no abdominal pain	Viral diarrhea	No antibiotic
Skin abrasion without exudate	Non infected wound	No antibiotic
Acute dysuria with suprapubic pain	Urinary tract infection	Quinolones

Slavin RG, et al. *The diagnosis and management of sinusitis. J Allergy Immunology, 2005.*

Bisno AL. *Pharyngitis. In: Principle and Practices in Infectious Diseases, 6<sup>th</sup> ed, 2005.*

Treanor j. *Influenza virus. In: Principle and Practices in Infectious Diseases, 6th ed, 2005.*

Guerrant RL, et al. *Practice guidelines for the management of infectious diarrhea. Clin Infect Dis, 2001*

Stevens DL, et al. *Practice guidelines for the diagnosis and management of SSTI. Clin Infect Dis, 2005*

Gupta K, et al. *Increasing antimicrobial resistance and the management of Uncomplicated CAUTI. Ann Intern Med , 2001*

# Results

- 315 first-class drug stores were identified; 35 were no longer in business
- 280 were surveyed
- Appropriate antibiotic dispensed for all indications at 56 (20%) drug stores

**Table 1. Dispensing of antibiotics by drug stores for six common syndromic ailments**

Clinical Syndrome	No.(%) Drug stores that prescribed antibiotics (N=280)	Antibiotic Dispensed <sup>a</sup> (%)							Other(%)
		Pen V	Amoxi cillin	Amoxi cillin/ Clavulonic acid	Tetra cycline	Erythro mycin	Azithro mycin	Rifam pin	
Acute low-grade fever and sore Throat	207 (74)	18	32	15	8	5	11	-	Cefu(8), Cefd(7)
Acute fever, myalgia, rhinorhea, cough	182 (65)	23	38	25	3	2	4	-	Cefd(5), Cefu(5)
Acute fever, tender maxillary sinus with non-purulent discharge	224 (80)	-	37	35	2	2	16	-	Nor(23), Olf(20)
Acute watery diarrhea without fever or Abdominal pain	213 (76)	-	6	14	12	8	14	-	Cefu(4), Cefd(4)
Skin abrasion without exudates	179 (64)	14	24	18	8	6	4	-	Mupi(8), Fus(6), Cefp(10)
Acute dysuria and suprapubic pain	280(100)	3	14	15	17	-	-	12	Olf(13), Cipro(30), Cefp(6)

# Antibiotic prescription is so easy?

Table 1. Sale of antibiotics according to the clinical case and statement made to obtain the drug.

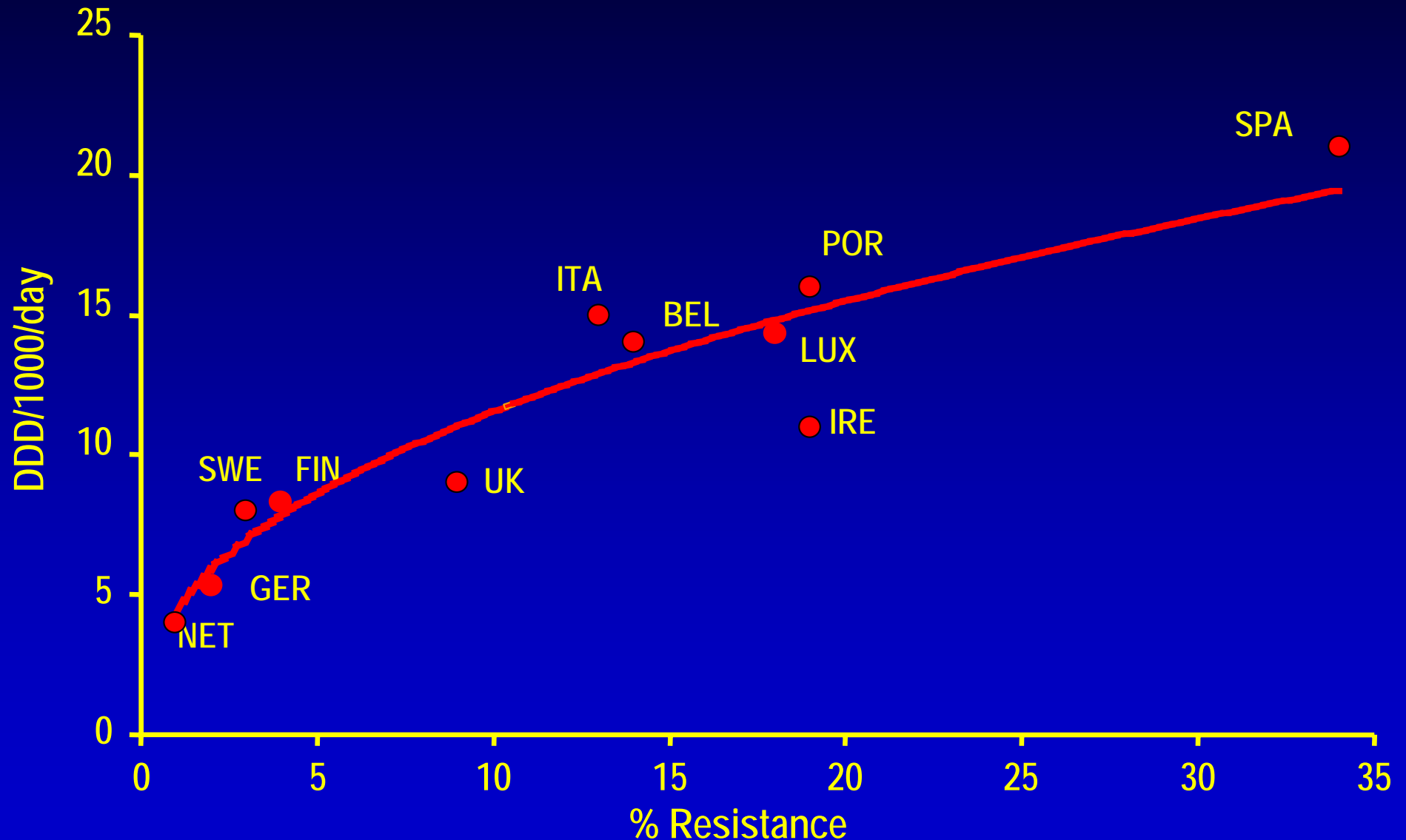
Result and level of demand (statement)	Clinical case presented, no. (%) of pharmacies visited			
	UTI (n=69)	Sore throat (n=69)	Acute bronchitis (n=59)	Total (n=197)
Antibiotic obtained				
1. (Can you give me something to alleviate the symptoms of the infection?)	52 (75.4)	12 (17.4)	1 (1.7)	65 (33.0)
2. (Can't you give me something stronger?)	2 (2.9)	10 (14.5)	5 (8.5)	17 (8.6)
3. (I would like an antibiotic.)	1 (1.4)	2 (2.9)	4 (6.8)	7 (3.6)
All	55 (79.7)	24 (34.8)	10 (16.9)	89 (45.2)
Antibiotic not obtained	14 (20.3)	45 (65.2)	49 (83.1)	108 (54.8)

Table 2. Explanation and questions from the pharmacist to the simulated patient in the pharmacies in which the antibiotic was obtained.

Pharmacist statement	Clinical case presented, no. (%) of pharmacies providing antibiotic			
	UTI (n=55)	Sore throat (n=24)	Acute bronchitis (n=10)	Total (n=89)
Explained how often to take the antibiotic	52 (94.5)	17 (70.8)	5 (50.0)	74 (83.1)
Explained how long the antibiotic should be taken	52 (94.5)	9 (37.5)	1 (10.0)	62 (69.7)
Asked patient about other symptoms	38 (69.1)	17 (70.8)	6 (60.0)	61 (68.5)
Asked patient about possible drug allergies	5 (9.1)	17 (70.8)	6 (60.0)	61 (68.5)
Asked patient whether she might be pregnant	2 (3.6)	...	...	2 (3.6)
Recommended that patient see a physician if there is no improvement	1 (1.8)	3 (12.5)	0 (0)	4 (4.5)

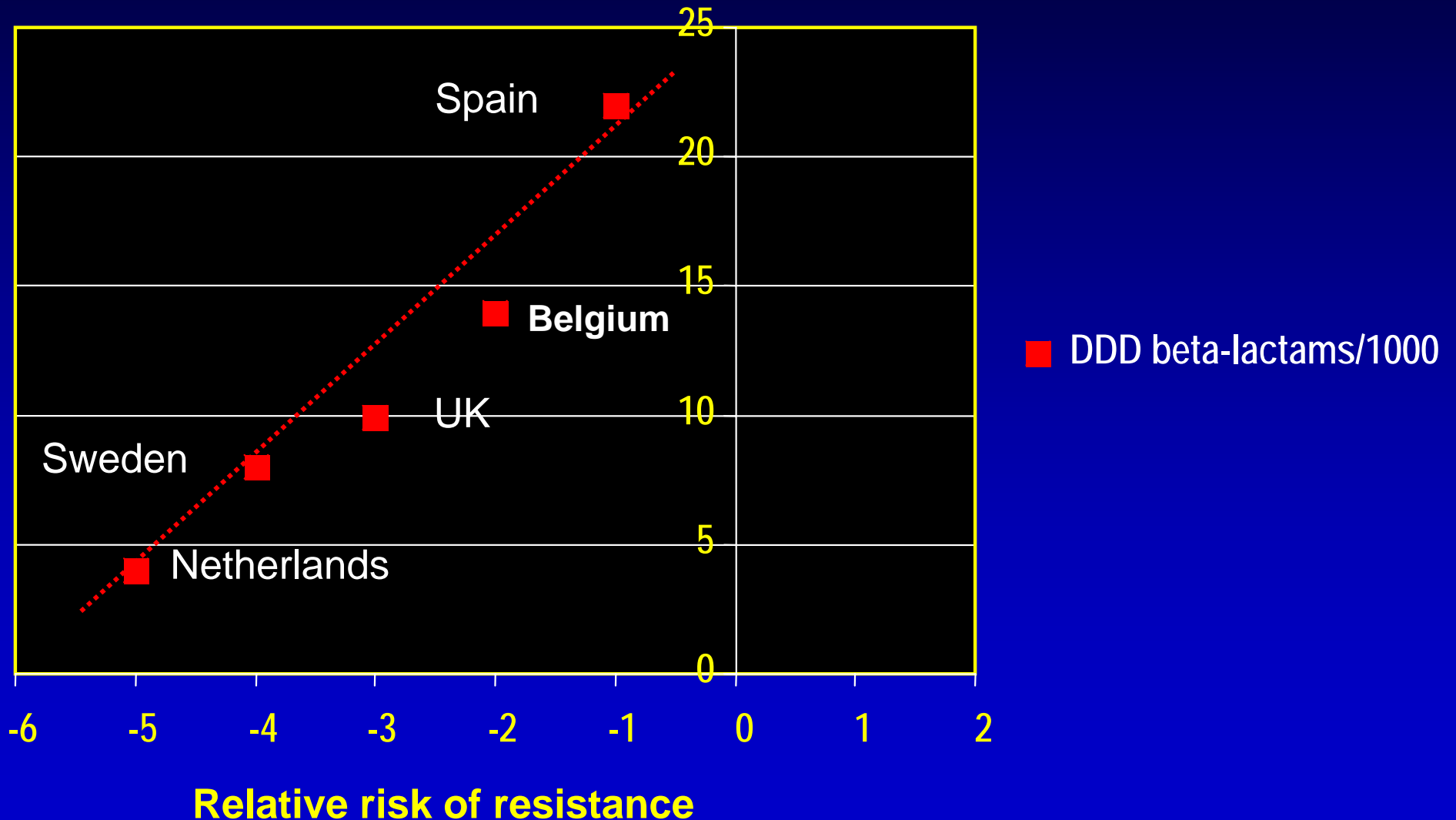
# **Impact of Antibiotic Use Over the Counter (OTC)**

# Relationship between Pneumococcal Resistance and Beta-lactam Usage

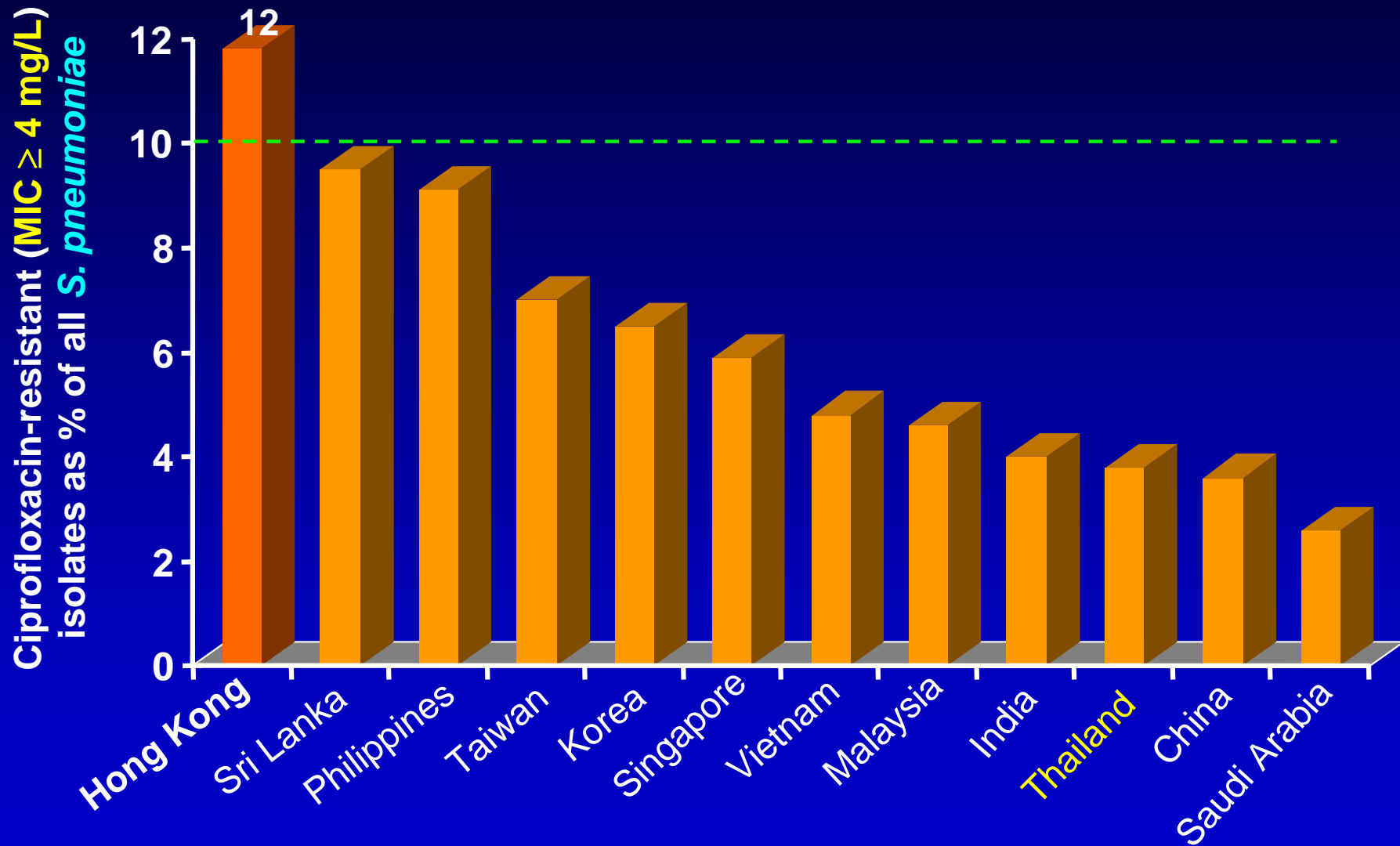


Adapted from Bronzwaer *et al.* Emerg Infect Dis 2002; 8:278-282

# Relationship between Pneumococcal Resistance and (inappropriate) Beta-lactam Usage



# Fluoroquinolone Resistance in Asia



685 invasive isolates from 11 Asian countries

## Correlation between Bacterial Resistance and Antibiotic Consumption in the Community around Pratumthani (central Thailand) from 2000 - 2006

Microorganism	Year (%)							Associated Antibiotic (R)	P Value
	2000	2001	2002	2003	2004	2005	2006		
Penicillin resistant <i>Streptococcus pneumoniae</i>	37	40	42	45	49	50	54	Beta-lactam (0.84) Macrolides (0.75)	< 0.001 0.01
Erythromycin resistant <i>Streptococcus pneumoniae</i>	26	32	30	33	35	37	39	Macrolides (0.79) Erythromycin (0.71)	0.01 0.007
Ciprofloxacin resistant <i>Salmonella non-typhi</i>	2	1.8	1.5	2.2	2.1	2.2	2.5	Quinolones (0.64) Ciprofloxacin (0.75)	0.04 0.01

# Correlations of Outpatient Antibiotic Use and Drug Resistance

- Inappropriate use of rifampin

*Riantawan P, et al. Resistant of MTB to anti-tuberculosis in Central Thailand. Int J Tuberc Lung Dis, 1999 (primary rifampin resistance approached 15%)*

- Inappropriate use of 2<sup>nd</sup> & 3<sup>rd</sup> cephalosporins

*Apisarnthanarak A, et al. Clinical and molecular epidemiology of CO-ESBL E. coli in Thailand. Am J Infect Control 2008*

# This is a global issue!

- Tangden T, et al. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum {beta}-lactamases. AAC 2010
- Leverstein-van Hall MA. Carbapenem resistant *K. pneumoniae* following foreign travel. Ned Tijdschr Geneesk. 2010
- Emergence of new antibiotic resistant mechanism in India, Pakistan and the UK. Lancet Infect Dis 2010
- Rolain JM, et al. New Delhi metallo-beta-lactamase (NDM-1): towards a new pandemic? CMI 2010

# Environments Where Antibiotic Resistance Develops and Their Relationships

Nursing Homes



Daycare



Homecare



Tertiary Hospitals



Foreign



Community Hospitals



Community



Feedlots





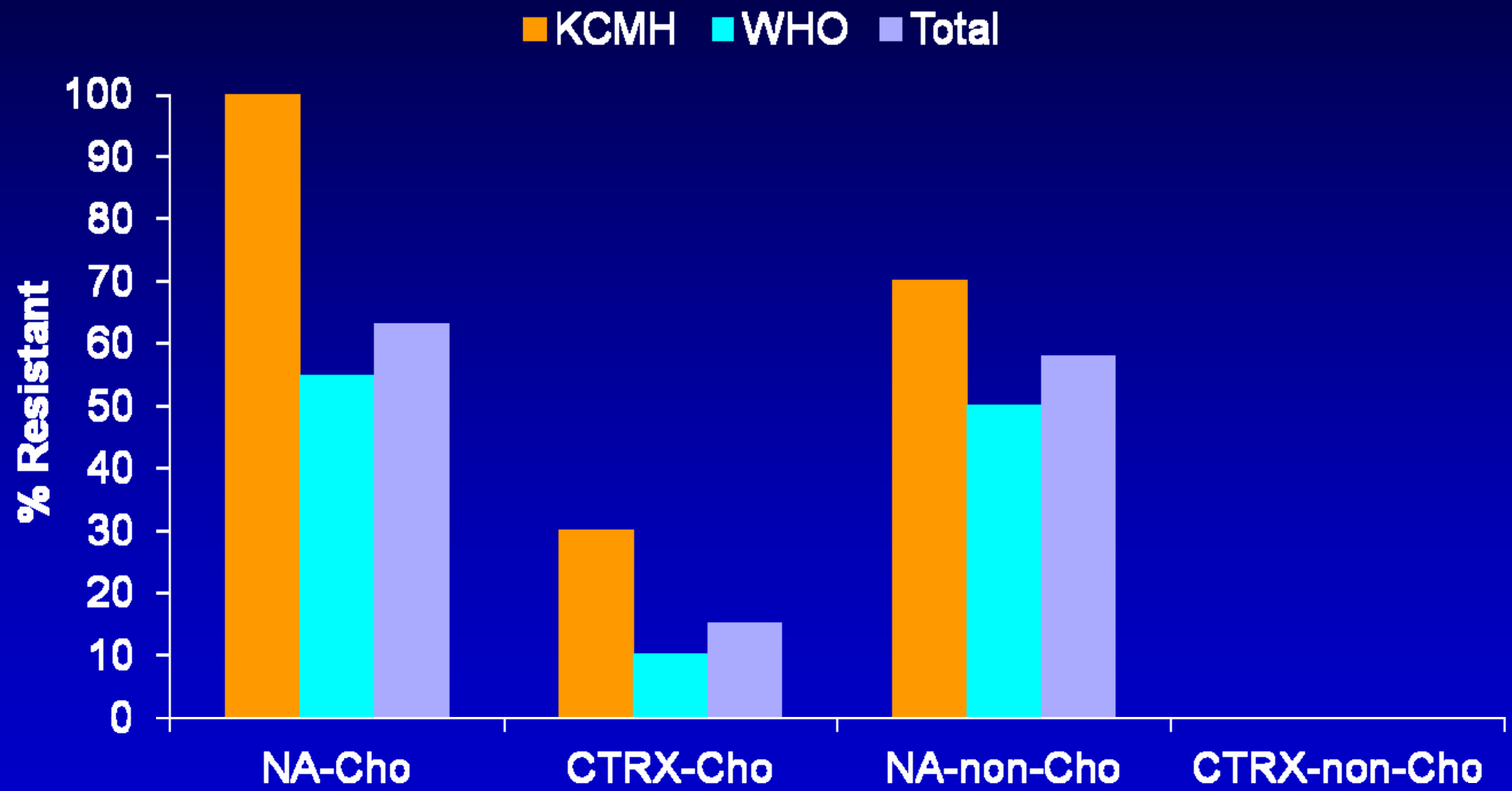
*Salmonella spp.*

*E. coli*

*Clostridium difficile*

*Vancomycin resistant Enterococci*

# Drug Resistant Non-Typhoidal Salmonella Bacteremia in Thailand



# International Spread of Multidrug-resistant *Salmonella Schwarzengrund* in Food Products

Country/ source	No. isolates tested/ total no. isolates	No. isolates resistant to antimicrobial drugs*							
		AMP	CHL	CIP	GEN	NAL	STR	SUL	TET
Denmark									
Humans	14/14	8	3	1	6	8	11	9	8
Pigs on farm	22/22	0	2	0	0	0	4	2	2
Pork	4/4	0	0	0	0	0	0	0	0
Chicken meat of unknown origin	7/7	4	1	0	4	5	5	6	4
Imported chicken	13/13	11	0	0	11	11	12	13	13
Imported turkey	9/9	1	0	0	1	1	4	4	4
Others	0/4	-	-	-	-	-	-	-	-
Thailand									
Humans**	46/57	30	13	10	27	42	45	41	35
Chicken meat	44/48	23	16	2	28	39	39	36	23
Turkey meat	2/4	0	0	0	0	0	0	0	0
United States									
Humans	38/390	13	08	16	4	17	4	20	22
Chicken meat	0/3	-	-	-	-	-	-	-	-
Turkey on farm	0/1	-	-	-	-	-	-	-	-
Pigs on farm	2/2	0	0	0	0	0	0	1	1
Imported food	3/3	1	2	1	2	3	2	3	3
Total	204/581	91	45	30	83	126	126	135	115

# **Solutions to the Problems**

# Initiatives in Lower-income Countries: Recognized Problems

- Inadequate healthcare infrastructure and cohesion
  - NB public services, country clinics and private services
- Lack of resources (money, people, diagnostics, surveillance)
- Difficulties with training and education
- Poor regulatory controls
- Geographical / political logistics
- Population dynamics and beliefs
- HIV / AIDS
- Unrecognized problems

# Suggested Priorities for Action in Middle- and Low-income Countries

Government:

- Regulate prescribers (NB private sector)

Health Service and Health Care Organisations:

- INITIATE AND SUPPORT surveillance

Training Institutions:

- PROMOTE preventative medicine + education of dispensers

Professional Societies:

Pharmaceutical Industry:

Consumer Associations:

# Suggested Priorities for Action in Middle- and Low-income Countries

Government:

Health Service and Health Care Organisations:

Training Institutions:

Professional Societies:

Pharmaceutical Industry:

Consumer Associations:

- ASSESS appropriate use,
- PROVIDE principles and guidelines, AUDIT compliance

# Suggested Priorities for Action in Middle- and Low-income Countries

Government:

Health Service and Health Care Organisations:

Training Institutions:

SCHEDULE curriculum time and TEACH appropriate use

Professional Societies:

Pharmaceutical Industry:

Consumer Associations:

# Suggested Priorities for Action in Middle- and Low-income Countries

Government:

Health Service and Health Care Organisations:

Training Institutions:

Professional Societies:

Pharmaceutical Industry:

Consumer Associations:

PROVIDE evidence-based CME

# Suggested Priorities for Action in Middle- and Low-income Countries

Government:

Health Service and Health Care Organisations:

Training Institutions:

Professional Societies:

Pharmaceutical Industry:

CONTROL promotion, INFORM prescribers/consumers as to prudent use

Consumer Associations:

# Suggested Priorities for Action in Middle- and Low-income Countries

Government:

Health Service and Health Care Organisations:

Training Institutions:

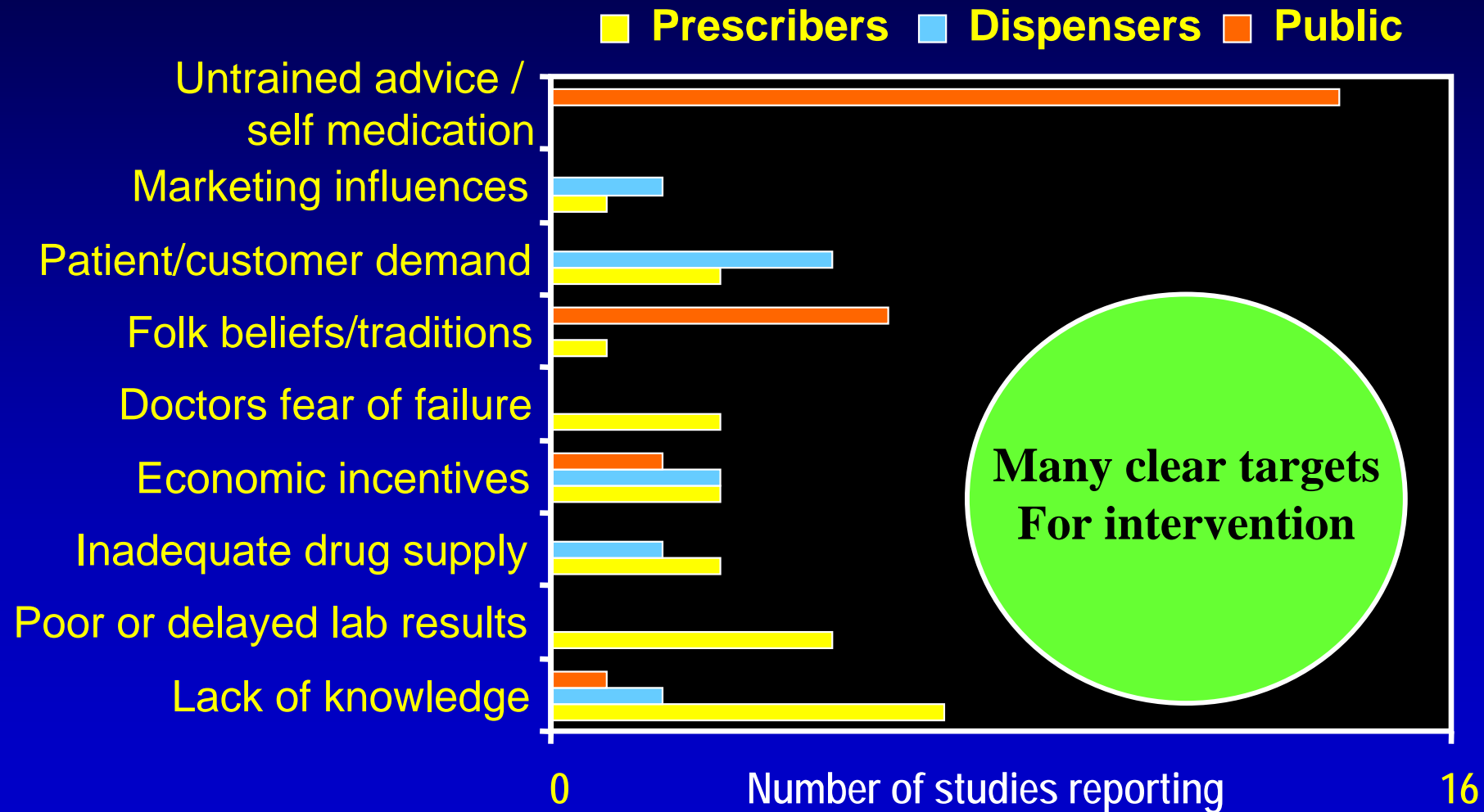
Professional Societies:

Pharmaceutical Industry:

Consumer Associations:

MAKE APPROPRIATE USE A CONSUMER ISSUE

# Determinants of Antibiotic Prescribing in Middle and Low-income Countries (Overview of 37 Studies)



# Who are the TARGETS for intervention?

- Physicians
- Patients
- Pharmacists
- Pharmaceutical Industry
- Policy makers (government)

# Initiative in Thailand Prescriber

รูปที่ 1 แผนผังการดำเนินการโครงการการศึกษาแบบการขยายโครงการ Antibiotics Smart Use

## ระยะที่ 1 เตรียมการ (Preparation phase)

- สรรหาและประสานงานกับจังหวัด (หน่วยงาน) ที่เข้าร่วมโครงการ
- สรรหาและอบรมคณะวิทยากร
- สร้างระบบโครงการ ASU เช่น website โครงการ, ระบบรายงานผล, คู่มือโครงการ, จัดทำสื่อและอุปกรณ์

### หมายเหตุ

- จุดทาบ หมายถึง สำนักโครงการฯ เป็นแกนหลักในการดำเนินงานและในการประสานงานกับผู้ที่เกี่ยวข้อง
- จุดโปร่ง หมายถึง จังหวัดหรือหน่วยงานเป็นแกนหลักในการดำเนินงานและในการประสานงานกับสำนักโครงการฯ และผู้ที่เกี่ยวข้อง

## ระยะที่ 2 สรรหาจังหวัด/หน่วยงานเข้าร่วมโครงการ (Recruitment)

- ประสานงานกับจังหวัด / หน่วยงาน

## ระยะที่ 3 อบรมบุคลากรทางการแพทย์ (Training)

- จัดอบรมบุคลากรทางการแพทย์ โดยเฉพาะผู้ที่มีหน้าที่สั่งใช้ยา
- ถ่ายทอดความรู้ให้แก่ผู้ที่ไม่ได้เข้าร่วมอบรมให้รับทราบโดยทั่วกัน โดยอาจทำในลักษณะของการอบรมภายใน เป็นต้น

**ประเมินตัวชี้วัด 1**  
บุคลากรทางการแพทย์มีความรู้และเข้าใจดีขึ้น มีทัศนคติดีขึ้น มั่นใจมากขึ้น และทนแรงกดดันจากผู้ป่วยดีขึ้น

## ระยะที่ 4 หลังการอบรม (Post-training)

- นำสื่อ/อุปกรณ์ของโครงการฯ ไปใช้เพื่อให้เกิดประโยชน์สูงสุดในสถานพยาบาล
- จัดกิจกรรมรณรงค์นอกสถานพยาบาล (ถ้ามี) เช่น ออกหน่วยให้ความรู้ประชาชน เผยแพร่ความรู้ผ่านสื่อชุมชน จัดหมายข่าว
- รวบรวมข้อมูลปริมาณการใช้ยาปฏิชีวนะ
- โทรศัพท์ติดตามอาการและความพึงพอใจของคนใช้กลุ่มเป้าหมายที่ได้และไม่ได้ยาปฏิชีวนะหลังจากรับการรักษา 7 -10 วัน

**ประเมินตัวชี้วัด 2**  
ปริมาณการใช้ยาปฏิชีวนะในจังหวัด/สถานพยาบาลลดลง

**ประเมินตัวชี้วัด 3**  
คนใช้ที่ไม่ได้ยามีความพึงพอใจและมีภาวะสุขภาพที่ดี

# โครงการ



## ส่งเสริมการใช้ยาอย่างสมเหตุผล



### 3 โรครักษาได้ไม่ต้องใช้ยาปฏิชีวนะ

**Education**



**Management**



**Holistic  
approach**

**Policy**

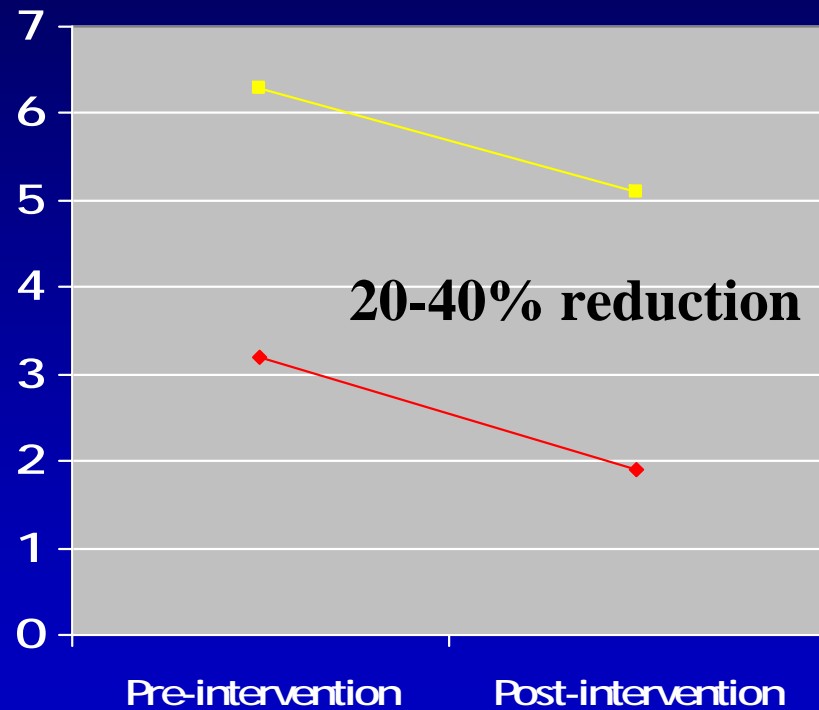


**Incentive**



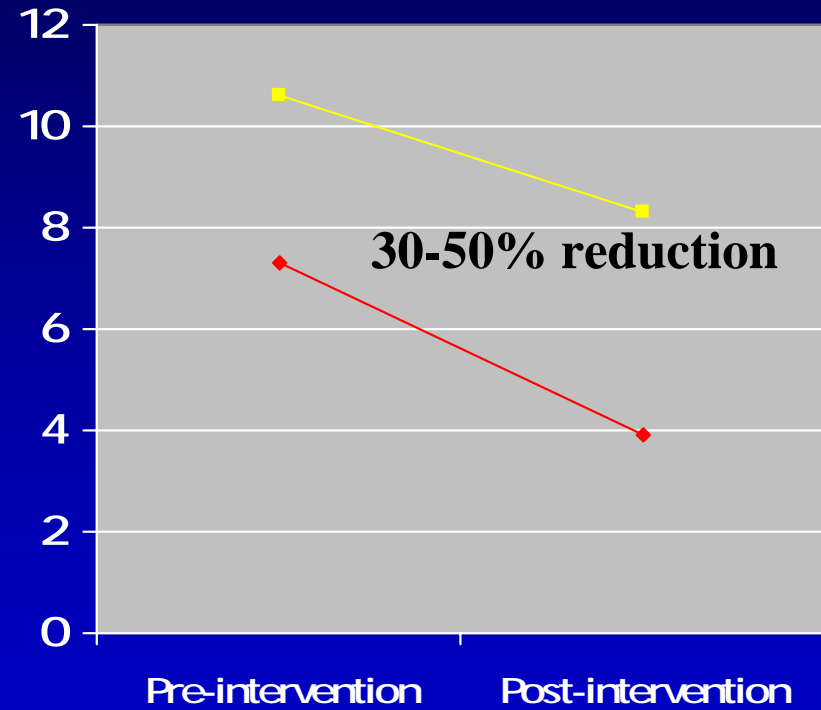
# Impact of Antibiotic Consumption and Cost

ATB consumption (/100,000 tablets)



◆ 44 Primary Care Clinic  
■ 8 Primary Care Hospital

Cost (per 100,000 baht)



◆ 44 Primary Care Clinic  
■ 8 Primary Care Hospital

# But if we educate prescribers – considerable changes are possible!

Diagnosis	Message	Potential reduction (%)
Otitis media	No antibiotic for OME	30
Pharyngitis	No antibiotic unless Strep+	50
Bronchitis	No antibiotic unless specific infection or lung disease	80
Sinusitis	No antibiotic prolonges / severe	50
Common cold	No antibiotic	100

Similar campaign highly effective in HK: Seto, 2003

# Where do patients get information (Taiwan)?

Who should provide education about antibiotics? (% total response)

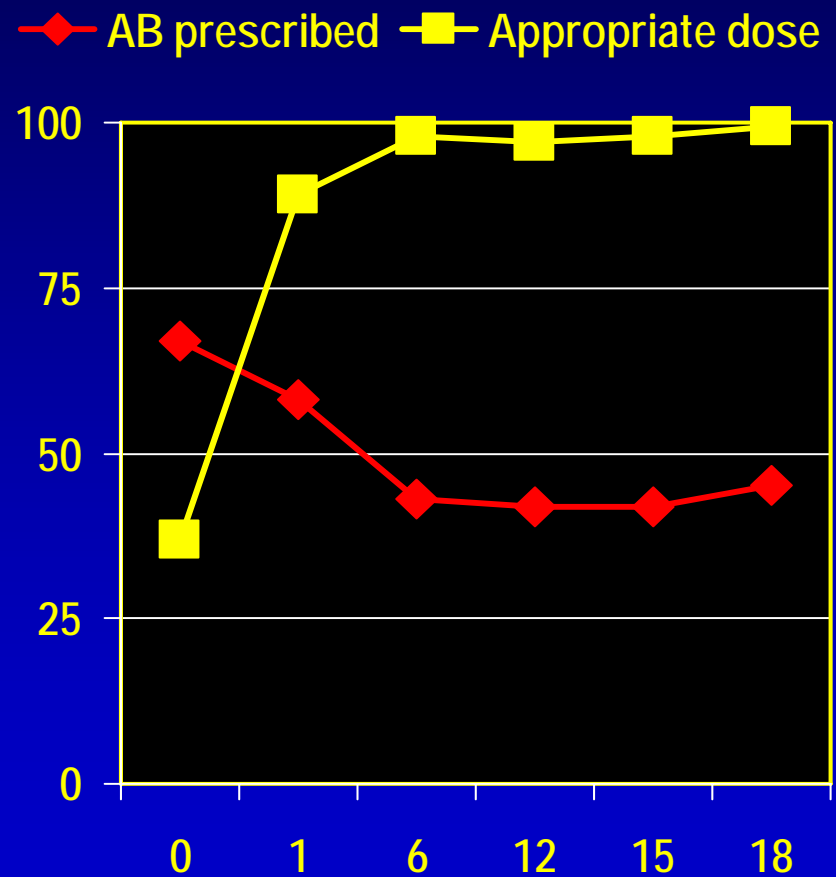
- Physicians 70
- Pharmacists 54.5
- Public health officers 50
- Nurses 35
- Teachers 35
- Mass media 62

45-50% thought antibiotics = anti-inflammatory / antipyretic agents

92% thought taking less than the full course was more healthy

# Improved Prescribing in Viet Nam (Hai Phong)

- Community health station studies: \$\$ grant for drugs
- Outcome: % receiving AB and % receiving adequate dosage after retraining and incentives
- NB continued evaluation and supervision
- Chalker, WHO Bulletin 2001; 79:313-320

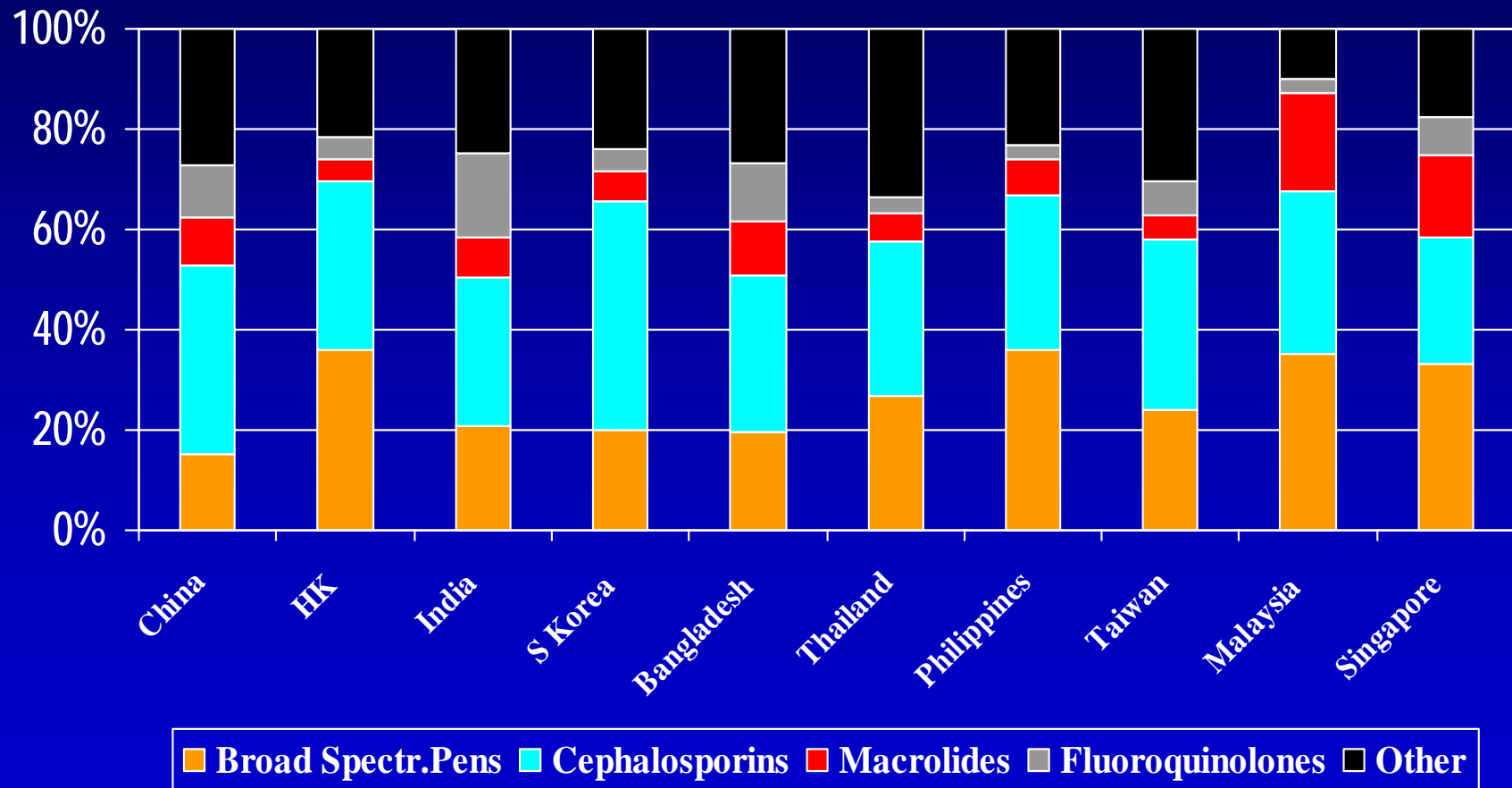


# Impact of a Public Campaign for More Rational Use of Antibiotics in Belgium, Nov 2000 to March 2001

- **Expect antibiotic for flu:**  
49% (before) vs. 30% (after)
- **Expect antibiotic for sore throat:**  
32% (before) vs. 18% (after)
- **Less antibiotic to avoid resistance:**  
64% (before) vs. 75% (after)
- **Antibiotics must be protected:**  
13% (before) vs. 25% (after)
- **Total antibiotic sales decreased by approximately 10%**

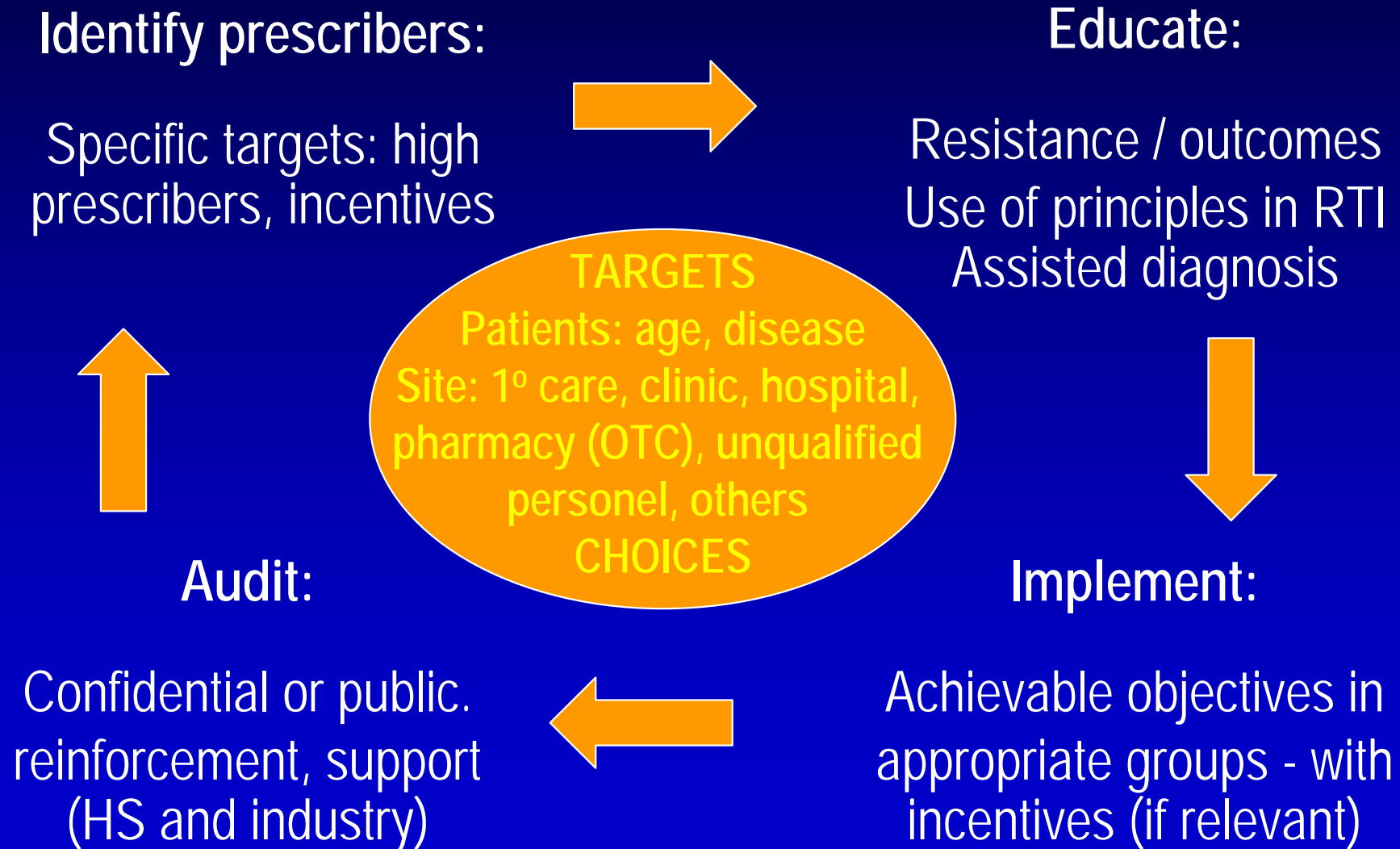


# Targets May Vary between Countries: Relative Consumption Data China & Asia Pacific



IMS- total units (packs) split by main therapeutic classes- 2004

# Implementation process: continued education, audit and feedback



# Summary

- Most unwarranted use of antibiotics OTC targets outpatients with uncomplicated infections that do not need antibiotics
- Educational interventions that targeted various groups of providers have shown to be effective in reducing antibiotic use OTC in developing countries
- Additional studies that combine data on pattern of antibiotic use OTC with methods to explore determinants associated with inappropriate antibiotic use OTC would provide more insight into the solutions of this problem

# Acknowledgement

- Pharmacist at Thammasat University Hospital
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- Thomas C. Bailey, M.D.
- Linda M. Mundy, M.D., PhD
- Piyaporn Apisarnthanarak, M.D.

Thank you very much for  
your attention

***“Kob-Koon-Krub”***

***ขอบคุณครับ***

