

Antimicrobial Resistance Panel:

Promoting Appropriate Antimicrobial Drug Use in Developing Countries

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- CHINA'S CRACKDOWN ON CORRUPTION

THE INTERNATIO?

Minimum and an and

Month 28, 100 a

THE END OF MIRAGLE DRUGS?

WARNING NO LONGER EFFECTIVE AGAINST KILLER BUGS

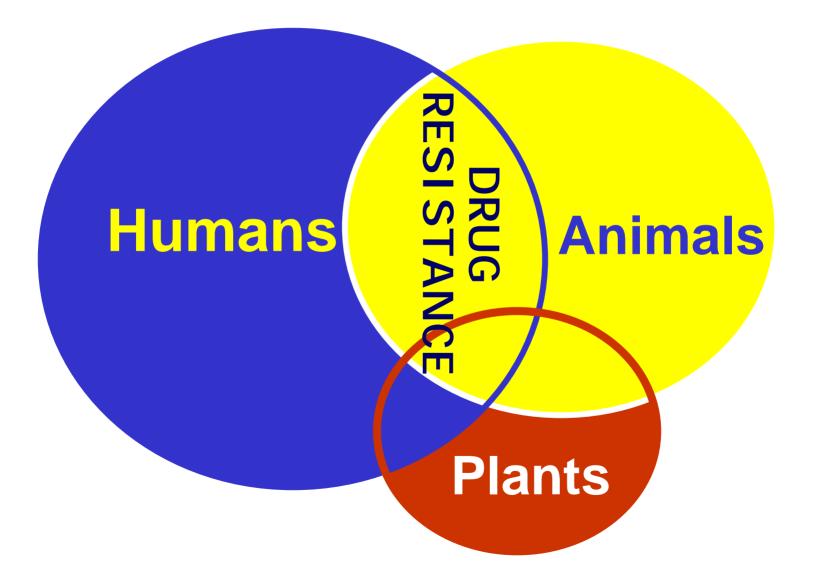
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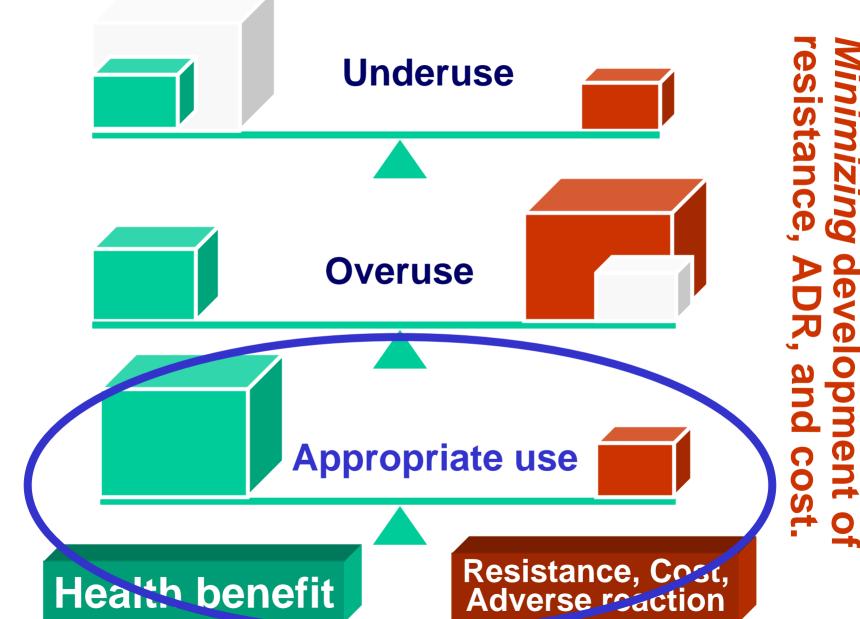
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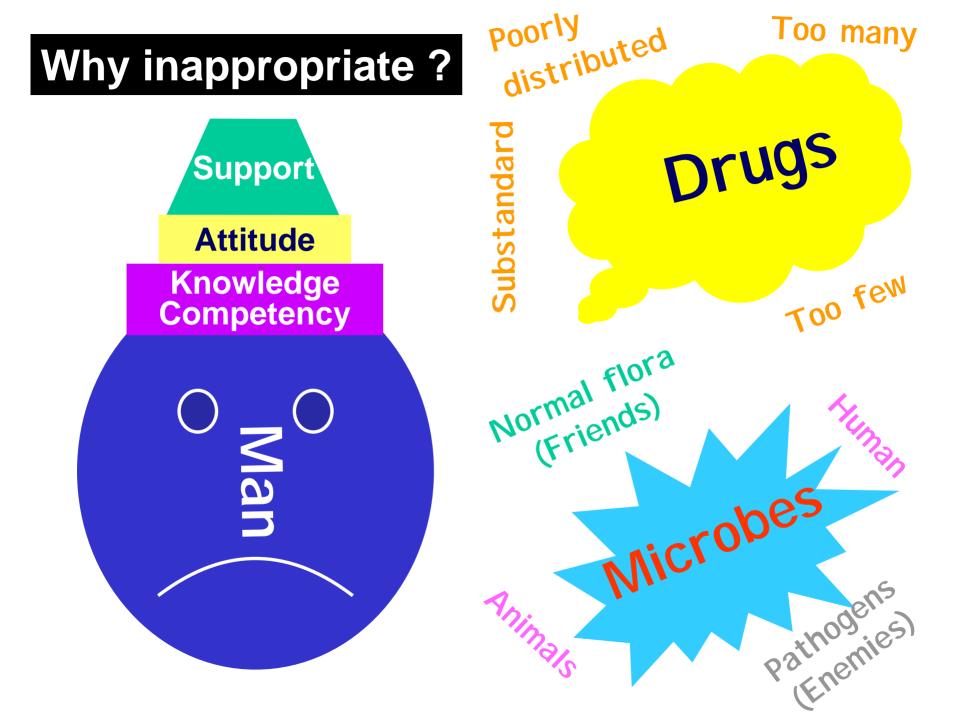
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Where Antimicrobials are Used

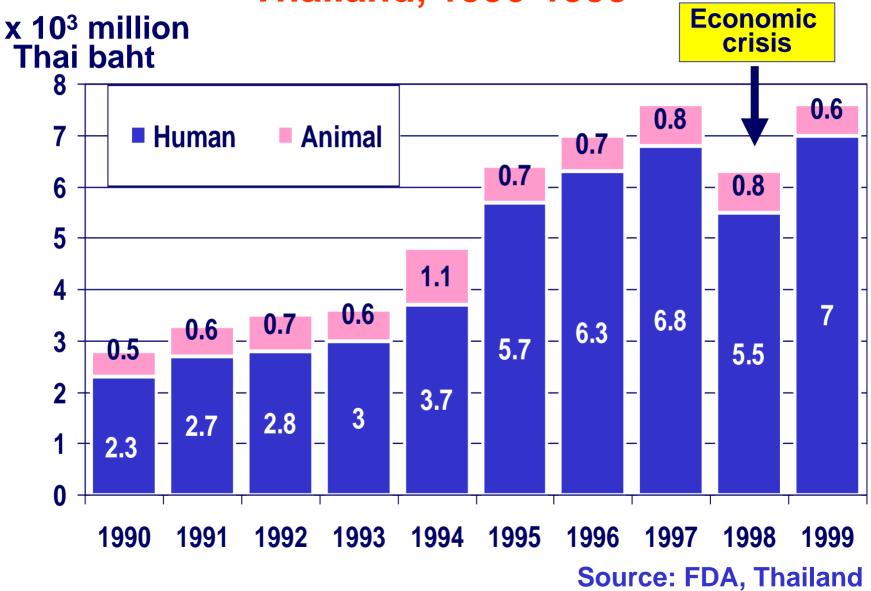


Appropriateness of antimicrobial drug use





Annual Expense on Antimicrobial Agents Thailand, 1990-1999



Licensed Antimicrobial Drugs in Thailand, 1998

Antibacterial Drugs

Amikacin Amoxvcillin Ampicillin **Azithromycin** Azusulfamide **Aztreonam** Bacampicillin Carbenicillin Cefaclor Cefadroxil Cefalexin Cefamandol Cefazolin Cefdinir Cefixime Cefminox Cefodixime Cefoperazone Cefotaxime Cefotiam Cefoxitin Cefpirome Cepodoxime

Cefprozil Cefsulodine Ceftazidime Ceftibuten Cefizoxime Ceftriaxone Cefuroxime Cefpodoxime Chloramphenicol Chlortetracycline Ciprofloxacin Clarithromycin Clindamycin Clioquinol **Cloxacillin** Colistin **Co-trimoxazole** Dibekacin Dicloxacillin Doxycycline **Erythromycin Fleroxacin Flucloxacillin**

Fosfomycin Framvcetin **Furazolidone Fusidic acid** Gentamicin Imipenem Kanamycin Lincomycin Lemefloxacin Mecillinam **Methenamine Methicillin Metronidazole Midecamycin** Minocycline **Mupirocin Nalidixic Acid** Neomvcin Netilmicin Nitrofuroxazide Nitrofurantoin Norfloxacin Ofloxacin

Ornidazole Oxacillin **Oxytetracycline** Pefloxacin Penicillin G **Penicillin V Phthalvl** sulfathiazole **Pipemidic acid Piperacillin Pivampicillin Pivmecillinam** Spiramycin Sulfacetamide Sulfamethoxazole Rolitetracycline Roxithromycin Silver Sulfadiazine **Spectinomycin** Streptomycin **Sulbenicillin Sulfadiazine** Sulfadimidine

Sulfamethizole Sulfamethoxypyridazine Sulfasalazine Sulfasomidine Sulfathiazole Sultamicillin **Tetracycline** Thiamphenicol Teicoplanin Tinidazole Tobramycin Trimethoprim Vancomycin Amoxycillin + Clavulanic a Ampicillin + **Sulbactam** Ticarcillin + Clavulanic a Cefoperazone + Sulbactam



National Drug List, Thailand, 1999 Antimicrobial selection by using a scoring system

National Committee on National Drug List

Sub-committee on antimicrobial drugs



Evidence-based antimicrobial drug selection

National Drug List, Thailand, 1999 Antimicrobial selection by using a scoring system

National Committee on National Drug List

Sub-committee on antimicrobials

Explicit guideline for drug selection

Develop a "scoring system"

Explicit guideline for selection of antimicrobial drugs

- 1. List of all available antimicrobial drugs licensed in Thailand, provided by FDA
- 2. Exclude the well-known inappropriate drugs e.g. dibekacin, ampicillin+cloxacillin
- 3. Group the competitive drugs according to their clinical and microbiological indications e.g. cloxacillin and oxacillin
- 4. Compare the competitive drugs using a scoring system
- 5. Rational judgement
- 6. Record the reason for choosing or not choosing a drug

"Scoring system" for selection of antimicrobial drugs, National Drug List, Thailand 1999

- Route
- Efficacy
- Safety
- Cost
- Ease of administration
- Bioavailability
- Tolerability
- Availability
- Total score
- Decision
- Comment

					000000																	
	Ro	eff	sf	inf	ESI	mg	original	local	G/day	B/day	fre	food	toler	Comp	O/L	difOL	Distri	Avail	Factor	Score	Decis	class
Beta-lactams																						
Penicillin G, benzyl	1						6.84	6.84	0.75						1	0.8					+	1
Penicillin G,	I					1.2 mu	40.8	34.95	0.75						1.167	0.8					+	1
benzathine	1					1.2 mu	40.0	34.33	0.75						1.107	0.0					т	'
Penicillin G,	I					4 mu	20	20	0.5						1	0.8					+	1
procaine	1					4 mu	20	20	0.5							0.8					Ŧ	1
Penicillin V	0					250	0.72	0.72	2						1	0.8					+	1
Cloxacillin	I	1	1	1	1	1000	22	17.04	6	132	0.7	1	1	0.7	1.291	0.8	1	0.8	0.56	236	+	1
Oxacillin	I	1	1	1	1	1000			6		0.7	1	1	0.7		хх						
Flucloxacillin	I	1	1	0.9	0.9	1000			6		0.7	1	1	0.7		хх						
Lincomycin	I	0.9	1	1	0.9	600	64.23	18.12	1.8	192.69	0.8	1	1	1	3.545	0.9	1	0.9	0.81	238	+	1
Clindamycin	1	1	0.9	1	0.9	600	379.17	379.17	1.2	758.34	0.8	1	1	1	1	0.8	1		0.72	1053	+	2
	0	1	1	1	1	250	2.37	1.57	2	18.96	0.7	0.9	1	0.63	1.51	0.8	1		0.50	38		1
Oxacillin	0	1	1	1	1	250	4	3	2	32	0.7	0.9	1	0.63	1.333	0.8	0.9	0.72	0.45	71		
	0	1	1	1	1	250	4.13	2.45	1	16.52	0.7	0.9	1	0.63	1.686	0.9	1	0.9	0.57	29		1
	0	1	1	0.9	0.9	250	5.5	5.5	1	22	0.7	0.9	1	0.63	1	0.8	0.9		0.41	54		
Ampicillin	I	1	1	1	1	250	6.67	6.67	4	106.72	0.7	1	0.9	0.63	1	0.8	1	0.8	0.50	212	+	1
	0	1	1	1	1	500			2		0.7	0.9	0.9	0.567	ļ	xx	1				L	ļ
	0	1	1	0.9	0.9	400			0.8		0.9	1	1	0.9	ļ	xx					ļ	L
	0	1	1						2					0	ļ	xx					L	
	0	1	1	0.9	0.9	=			2					0		xx						
	0	1	1	1	1	500	4.81	2.29	0.75	7.215	0.8	1	1	0.8		0.9	1	0.9	0.72	10		1
Cefazolin	1	1	1	1	1	1000	47.75	23.08	3	143.25	0.8	1	1	0.8		0.9	1	0.9	0.72	199		1
Cephalexin	I	1	1	0.7	0.7	1000	74	74	4	296	0.8	1	1	0.8	1	0.8	0.9		0.40	734		-
Clindamycin		1	0.9	1	0.9	600	379.17	379.17	1.2	758.34	0.8	1	1	1	1	0.8	1	0.8	0.72	1053	+	2
•·····	0	1	0.9	0.9	0.81	150	11.72	11.72	1.2	93.76	0.7	0.9	0.9	0.567	1	0.8	1	0.8	0.37	255	+	2
	0 0	1	1	1	1	500	10.52	5.64	2	42.08	0.7	0.9	1	0.63	1.865	0.9	1	0.9	0.57	74		1
	0	1		1		500	23	23	1.5	69 641.4	0.9	0.9	1	0.81		0.8	0.9	-	0.58	118		-
Cefoxitin Cefmetazole	1	0.9	1		0.9	1000	213.8	147	3	041.4	0.8	1	I	0.8	1.454	0.8		0.8	0.58	1114	+	3
Co-amoxiclav	1	0.9	1	0.9	0.81	1200	225.28	225.28	3.6	675.84	0.8	1	1	0.8	1	xx 0.8	0.9	0.72	0.47	1449	+	3
Sultamicillin	י ו	1	1	0.9	0.9	1500	193.33	193.33	4.5	579.99	0.8	1		0.0		0.8	0.9	<u>8</u>	J	1119		3
Cefuroxime	1	1	1	0.5	1	750	187.06	109.2	2.2	548.7093	0.8	1	1	0.0		0.0	0.0	1		762	?	?
Cefamandole		. 1	1		. 1	1000	212.85	186		851.4	0.7	1	1	0.0	1.144	0.8	. 1	0.8	0.56	1520		
				0.7					4				1					1			<u> </u>	
Cefotiam	і О	1	1	0.7	0.7	1000	324	324	4	1296	0.7	0.9	1	0.7		0.8	0.9	0	2	9	<u> </u>	2
	0	0.9	1	1	<u>R</u>	250	19.09	19.09	0.75	57.27	0.8		1			0.8	1	1	R	-		2
		1	· · · ·	0.9	0.9	250	31.25	31.25	0.5	62.5	0.9	8	1	0.81	1	0.8	0.9		§	119		
	0 0	1	1 1	1	1	250 375	27.43 22.32	27.43 11.79	0.5	54.86 66.96	0.9 0.8	0.9	0.9	0.81	1.893	0.8	0.9	0.72	Į	94 103		2
	0	1	1	0.9	0.9	375	22.32	23.83	1.125	71.49	0.8	1		0.72		0.9	0.9		l	103	+	2
Cefotaxime*		1	1	0.9	0.9	1000	192.93	85.12	1.125)	0.8			0.72		0.8	0.9		8	§	+	3
Ceftriaxone*	·	1	1	1	1	1000	431.63	132.42	4		0.9	1		0.81		0.9	1			1059		3
Ceftizoxime		1	1	0.8	0.8	1000	220	220	3		0.8	8	ļ	0.9		0.9	0.9	<u>.</u>	§	1591	-	5
Cefodizime		1	1	0.8	0.8	1000	434	434	2		0.8			1		0.8	0.9		5	1860		
	0	1	1	0.9	0.9	1000	36	36	0.4	144	0.9	1	0.9	0.81	1	0.8	0.9	1		274		3
Cefpodoxime*	0	1	1	0.9	0.9	100	28.79	28.79	0.4	115.16	0.9	0.9	0.9	0.729	1	0.8	0.9	0.72	0.47	244	+	3
	0	1	1	0.9	0.9	400	138.73			138.73	0.3	1	0.9	B				A		h	4	3
	0	. 1		0.9	0.9	100	28.21	28.21	0.4	112.84		-				0.8			<u>K</u>	8		3
Cefsulodin	1	0.9	1	0.9	0.81	1000	298	298		1294.98				0.7		0.8		1	1	3172		
Cefoperazone		1	1	1	1	1000	363	363						0.9		0.8				<u> </u>	<u> </u>	
Ceftazidime		1	1	1	1	1000	195.03	160					1		1.219	0.8		*			1	3
Piperacillin	I	0.9		1	0.9	2000	215.83			1294.98		1		0.0		0.0	012000000000000000000000000000000000000	8				5
-																						-
Sulfoperazone	1	1	1	0.9	0.9	1000	472.88	472.88		1891.52	0.9			0.9		0.8	0.9				-I	3
Cefpirome	1	1	1	0.9	0.9	1000	461	461	4	1844	0.9		Louis position and a second	0.9			0.9		l			3
Cefepime	1	1	1	0.9	0.9	1000	457.5			1830				0.9			0.9	0.72	0.58	3137.86	+	3
Ticarcillin	1	0.9	1	1	0.9	3000			18-24		0.7	1	1	0.7		XX						

National Drug List, Thailand, 1999 Antimicrobial selection by using a scoring system

National Committee on National Drug List

Sub-committee on antimicrobials

Explicit guideline for drug selection

Develop a "scoring system"

Discussion

Decision

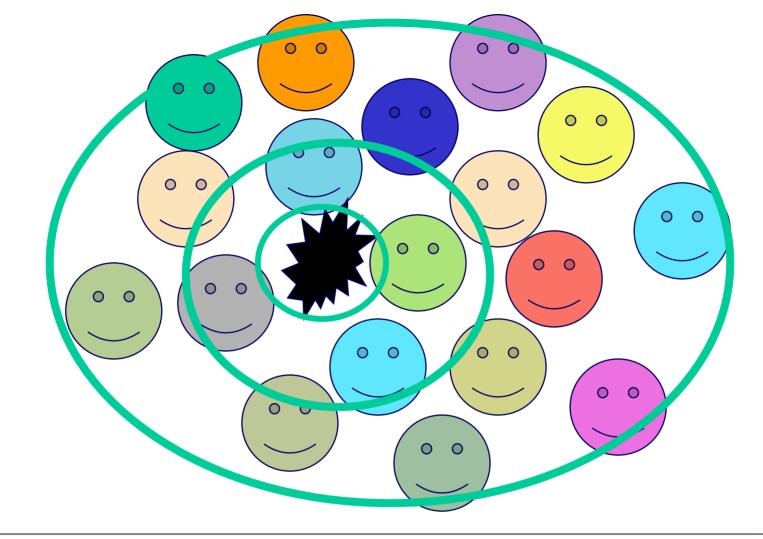
Indication

Grouping by level of restriction

Restriction Policy for Antimicrobial Drugs

- 1. Commonly indicated drugs (Essential Drugs)
 - all MDs should know how to use them well
 - e.g. penicillin G, V, cloxacillin, ampicillin, gentamicin, erythromycin, etc
- 2. Broad-spectrum but commonly indicated (due to local drug-resistance problems)
 - e.g. cefotaxime, ceftriaxone, amikacin, etc.
- **3. Restricted drugs (DUE is required)** (very broad-spectrum and expensive drugs)
 - e.g. imipenem, meropenem, vancomycin, teicoplanin, ciprofloxacin, netilmicin, etc.

Thailand NDL 1999



If the enemy is not identified, how can we use a narrow-spectrum weapon to destroy them without doing harm to the other non-guilty ones.

Infectious Disease Diagnosis

- Anatomic diagnosis

- Etiologic diagnosis

- Pathophysiologic diagnosis

Requirement for accurate diagnosis

1. Diagnostic competency

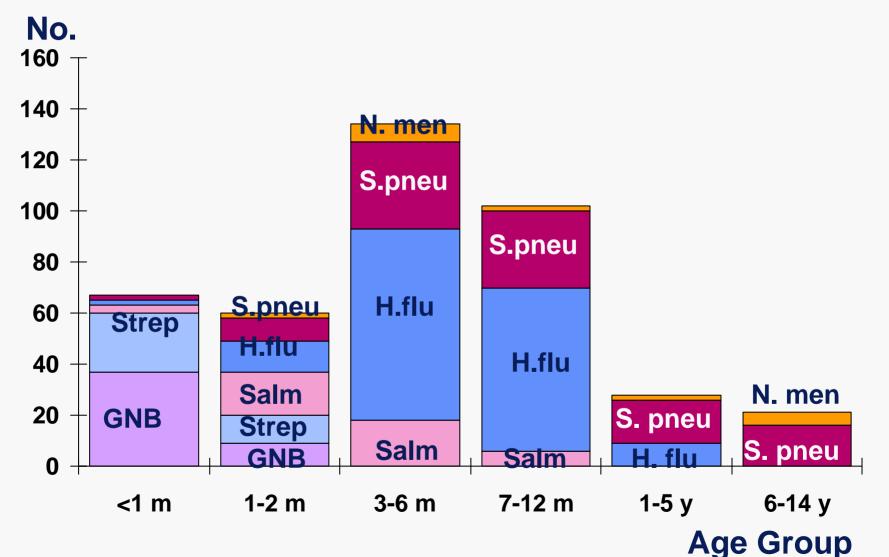
2. Supportive information
- Epidemiology data
- Laboratory data

Etiologic Epidemiology Data in developing countries

Usually

- Deficient
- Poorly gathered
- Mostly tertiary-care hospital-based
- Insufficient demographic and clinical data
- Not integrated into practice

Age-specific Etiology of Bacterial Meningitis in Thai Children (National Study Group on Etiology of Bacterial Meningitis)



Microbiology Lab Facilities to support appropriate use of antimicrobials

- **1. Appropriate clinical specimens**
- 2. Reliable isolation and identification
- 3. Appropriate susceptibility test : drugs and discs
- 4. Rapid reports
- 5. Selective and educational report
- 6. Appropriate interpretation and implementation
- 7. Appropriate accumulative review



He may have some kind of infection. This antibiotic may make him better and he will be satisfied. It is safe. He can afford it and I will get some money.

Requirement for appropriate use of antimicrobial agents

Diagnosis

Accurate diagnosis: - clinical diagnosis - causative diagnosis



Cost-effective regimens



Good-quality drug Accurate dispensing



Requirement for cost-effective prescription

1. Competency of prescribers

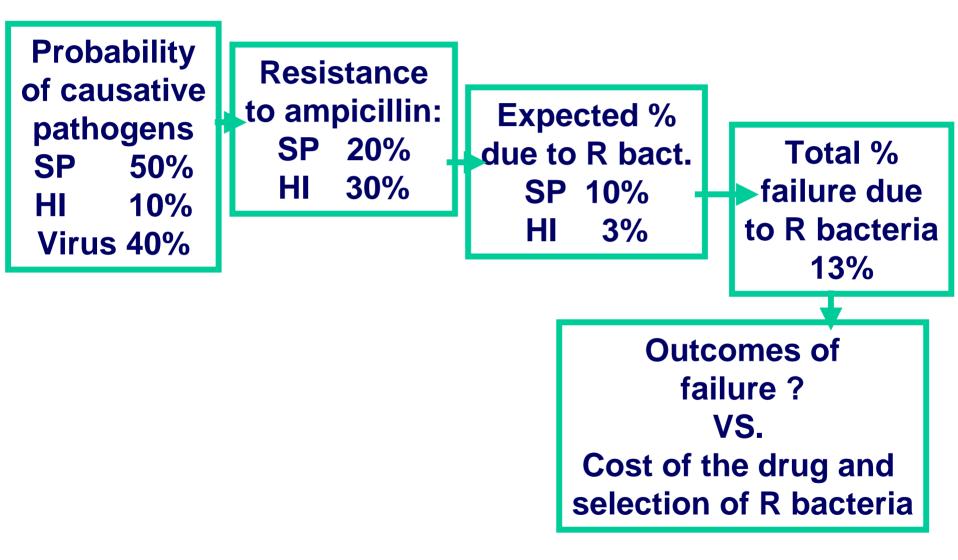
Infectious disease diagnosis
Clinical decision making

2. Accurate diagnosis

- 3. Availability of good data for decision making
- 4. Availability of drugs

5. Patient & society - centered (NOT prescriber - centered)

Evidence-Based Clinical Decision Making: e.g. treatment of pneumonia with ampicillin



Minimise selection pressure, maximise treatment effectiveness.

Constraints in developing countries

- Deficiency of epidemiology data and laboratory support for etiologic diagnosis
- Deficiency of probability data input for decision making

Getting evidence to support clinical decision

Antibiotics for treating salmonella gut infection Sirinavin S, Garner P Cochrane Database Systematic Review 2000;2:CD001167 **Does antimicrobial therapy improve outcomes of salmonella gut infection?**

- **1. Duration of illnesses**
- 2. Duration of diarrhea
- 3. Duration of fever
- 4. Systemic complication
- 5. Duration of salmonella excretion
- 6. Emergence of resistance bacteria
- 7. Adverse effects of therapy

Search Strategy

- Any comparative studies on antibiotic therapy for non-typhoidal salmonella
- From:
 - The Cochrane Controlled trials Registers MEDLINE 1980-1997
 - ExtraMed

Reference lists of all potential trials

Selection criteria

• All trials (RCT) comparing antibiotic therapy with placebo / no antibiotic

Reviewed trials

 15 clinical trials -14 published in 1972-1996 - from Europe & Scandinavia 6, **North America 4** Australia 1, Colombia 1, Egypt 1 Internatinal multicentered 2 - on 857 participants (43% were infants and children) 7.2% were asymptomatic 92.8 % had diarrhea

Outcomes

Any antibiotics VS. placebo / no antibiotic

Clinical outcome	Pooled WMD	95% CI
Duration of illness (days	s) - 0.07	- 0.55, 0.40
Duration of diarrhea (day	vs) - 0.03	- 0.53, 0.48
Duration of fever (days)	- 0.45	- 0.98, 0.08

Adverse drug reaction OR 1.67 (95%CI 1.05, 2.67)

Bacteriologic outcome more in antibiotic group

- Bacteriologic relapse
- Salmonella in stool after 3 weeks

Efficacy of norfloxacin or azithromycin in treating non-typhoidal Salmonella carriers

- **Setting** : a province in Thailand
- Study population : asymptomatic food handlers Method : double-blinded RCT
- **Study regimens :**
 - 1. Norfloxacin 400 mg PO bid x 5 days
 - 2. Azithromycin 500 mg PO bid x 5 days
 - 3. Placebo PO bid x 5 days

(Department of Communicable Dis, MOPH, Thailand, 2001)

Total screening numbe	rs : 3205
Positive culture	: 317 (10%)
Inclusion to study	: 284

RSC	% positive salmonella							
	D7	D30	D60	D90				
Same sertypes								
Norflox	1.1	2.3	2.4	1.4				
Azithro	0	1.1	0	3.8				
Placebo	1.1	2.4	3.6	3.7				

(Preliminary data)

Recommendation:

- No antimicrobial drugs for uncomplicated non-typhoidal *Salmonella* gut infection in normal hosts.

- Antimicrobial drugs must be given to patients suspected or proved of extra-intestinal *Salmonella* infection.

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สำนักงานคณะกรรมการมายารและมา สำนักงามปลัดกระทรรงสาธารณสุข International Network for Rational Use of Drugs (Thailand)

นรรณาอิการ สขมพร ศิรินาวิน, ศรีเพ็ญ ต้นติเวลส, ศิวพร จิตตรรณ

Pocket book on antimicrobial therapy

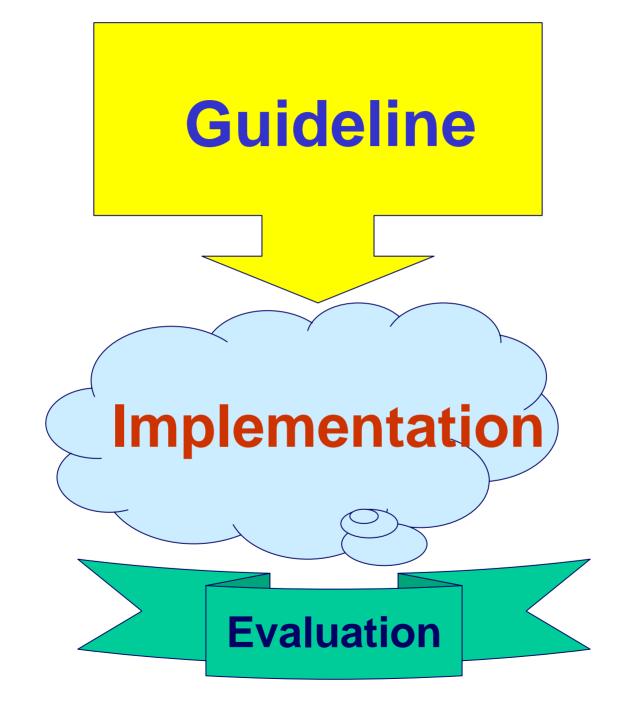
สมะทั่วงานจัดส่างสัตการใช้ตาด้านจุลจิต

การใช้

Guideline for hospital management to promote appropriate use of antimicrobial drugs 1995 (supported by Thai FDA & INRUD) Hospital management to promote appropriate use of antimicrobial drugs

- **1. Drug selection**
- 2. Restrict drugs
- 3. Bacteriology laboratory facility
- 4. Antimicrobial guideline
- **5. Surgical prophylaxis policy**
- 6. Education program
- 7. Monitoring of drug use
- 8. Hospital infection control

(National Workshop 1995 by FDA Thailand & INRUD)



Antibiotic Order Form (AOF)

AOF as a strategy to control use of restricted antibiotics in admitted patients when immediate consultation is not possible.

Sirinavin S, Suvanakoot P, Satapathayavongs B, Malatham K. Effect of antibiotic order form guiding rational use of expensive drugs. Southeast Asian J Trop Med Public Health 1998

Antibiotic Order Form

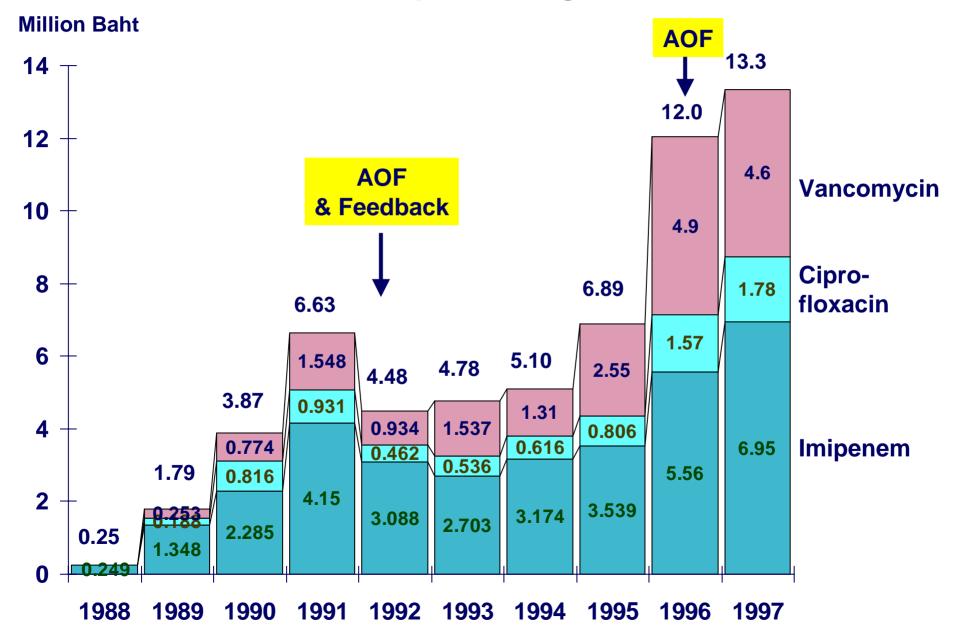
Objectives: 1. Education 2. Audit 3. Surveillance

Antibiotic Order Form (AOF) for restricted drugs (Ramathibodi Hospital, Bangkok)

Information needed to be filled in AOF before the restricted antibiotics were dispensed from hospital pharmacy

- Patient's profile
- Site of infection
- Suspected causative organism
- Microbiology investigation
- Reasons for using the restricted drug

Annual Expense on Restricted Antibacterial Drugs Ramathibodi Hospital, Bangkok, 1988-1997



Lesson learned : AOF is helpful for busy ID consultants. It does not work without auditing and feedback.

It did not prohibit physician's prescription therefore it did not compromise patient care.



Consumers have high expectations in the power of pharmaceuticals and demand them from health practitioners.

Consumers' demand for medicines benefit prescribers, dispensers, and manufacturers.

Decreased patients' demand are likely to make them unpopular with the population, reduce the numbers of clients, and reduce their income.

Homedes N, Ugaldeb A. Soc Sci Med 2001;52:99

Health professionals are trained to cure with pills, and consultation time is shortened by prescribing medicines rather than explaining alternative behavioral therapies.

Homedes N, Ugaldeb A. Soc Sci Med 2001;52:99

Promoting appropriate use of antimicrobial drugs in Specific Disease Management

- Acute respiratory tract infection
- Acute diarrhea
- Sexually transmitted disease

Some of activities to promote appropriate antimicrobial use in Thailand

- 1995 : Pilot project for improving antibiotic use in hospitals, MOPH
- **1995 : National antibiotic guideline**
- 1995 : Workshop for the MOPH hospitals on strategies for improving antibiotic use in hospitals

(supported by Thai FDA and INRUD)

- 1995 : Committee on development of practice guideline for the Pharmacy and Therapeutic Committee, MOPH
- 1997 : Committee on quality improvement of microbiology laboratory, MOPH

Some of activities to promote appropriate antimicrobial use in Thailand

- 1998 : National program on controlling non-typhoidal Salmonella
- 1999 : National program for surveillance on antimicrobial resistance in humans
- **1999 : Center for Antimicrobial Resistance Monitoring of Foodborne Pathogens**
- 2001: National Program for Antimicrobial Resistance Monitoring in Food-borne pathogens
- 2001: National program for promoting prudent use of antimicrobial drugs in food animals
- 2001 : Evidence-based clinical practice guideline for prevention and treatment of communicable disease

More interdisciplinary collaboration in promoting appropriate antimicrobial use

- Medical doctors
- Verterinarians
- Pharmacists (ID pharmacists)
- Drug sellers
- Microbiologists
- Consumers (e.g. AIDS / HIV)
- Ministry of public health and medical schools

Summary

Some activities to promote appropriate use of antimicrobial drugs in a developing country are presented, including:

- Drug selection into National Drug List
- Support for etiologic diagnosis
- National antimicrobial guideline
- Control of restricted broad-spectrum antimicrobials
- Infra-structure development

Summary

Success in improving antimicrobial use and prevention of drug resistance problem is still not achievable. Strong and long-termed policy and support are needed.