# Strategies to control antibiotic resistance

(low- and middle-income countries)

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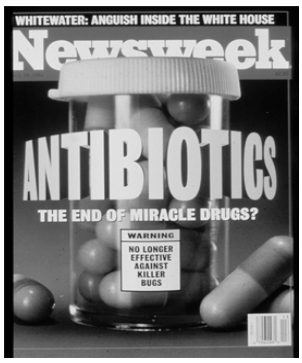
**Hôpitaux Universitaires de Genève**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## NDM1 and Pan-Resistance

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Kanthiveyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fejfhune Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Sarmila Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David C Paterson, Andrew Pearson, Clair Perry, Rachel Pike, Bhargavi Rao, Uj Jayesh Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marios Warner, William Welfare, David M Livermore, Neil Woodford

Summary

Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Methods Enterobacteriaceae isolates were studied from two major centres in India—Chennai (south India), Haryana (north India)—and those referred to the UK's national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene $bla_{NDM-1}$ was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. Plasmids were analysed by S1 nuclease digestion and PCR typing. Case data for UK patients were reviewed for evidence of travel and recent admission to hospitals in India or Pakistan.

Findings We identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among *Escherichia coli* (56) and *Klebsiella pneumoniae* (111), which were highly resistant to all antibiotics except to tigecycline and colistin. *K pneumoniae* isolates from Haryana were clonal but NDM-1 producers from the UK and Chennai were clonally diverse. Most isolates carried the NDM-1 gene on plasmids: those from UK and Chennai were readily transferable whereas those from Haryana were not conjugative. Many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries.

Interpretation The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated international surveillance is needed.

Funding European Union, Wellcome Trust, and Wyeth.

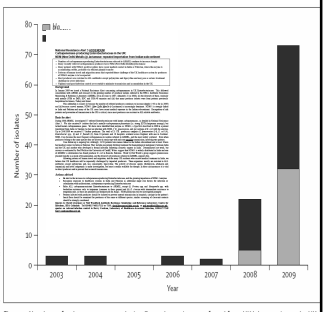


Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009

Harbarth, SPCI-HUG Courtesy: J. Conly, WHO Geneva

## Global Spread NDM1


**Note : recent cases travel related not medical tourism**

Harbarth, SPCI-HUG Courtesy: J. Conly, WHO Geneva

## OUTLINE

- **Hospital setting**
  - Strategic priorities
  - Antibiotic control policies
- **Ambulatory setting**
  - Macro-level determinants
  - Country examples of successful changes

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## Improve antibiotic use

- **Monitor and provide feedback on occurrence of AMR**

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**Control programs for multiresistant *Staphylococcus aureus* (MRSA)**

| | Able to calculate the proportion of MRSA among all *S aureus* isolates |
|---|---|
| **Western Europe** | 25/43 (58%) |
| **Eastern Europe** | 13/27 (48%) |
| **Africa** | 1/6 (17%) |
| **USA** | 1/5 (20%) |
| **South America** | 4/6 (67%) |

Richet et al. Infect Control Hospital Epi 2003; 24: 334-341

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# The important role of sentinel hospitals

- Centralization of available laboratory resources in a few selected centers
- Monitoring and reporting of AB susceptibility data *(WHOnet)*
- Adapt empiric treatment regimens

Archibald LK & Reller LB. *Clinical Microbiology in Developing Countries.* Emerg Infect Dis 2001; 7: 302-305

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# Improve antibiotic use

- **Monitor and provide feedback on occurrence and impact of AMR**
- **Optimize choice and duration of empiric antimicrobial therapy**

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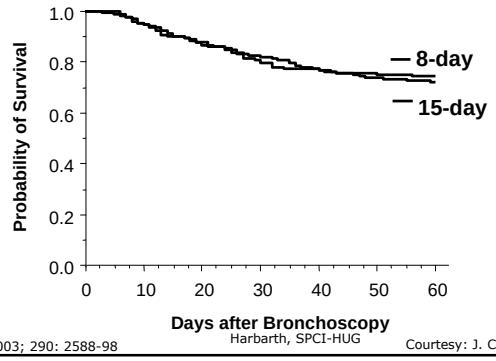
**Survival Among 401 Patients with Nosocomial Pneumonia Assigned to Short (8 d) or Long (15 d) Antimicrobial Treatment**




JAMA 2003; 290: 2588-98

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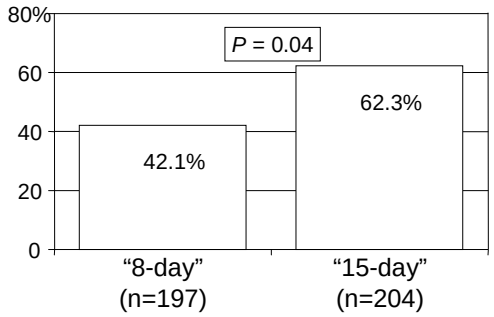
Courtesy: J. Chastre, Paris

**Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence**




JAMA 2003; 290: 2588-98

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Courtesy: J. Chastre, Paris

BMJ Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial

BMJ 2004;328:791-; originally published online 18 Mar 2004; doi:10.1136/bmj.38049.490255.DE

ARTICLES

**Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial**

*Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group**

**Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months (Review)**

Haider BA, Saeed MA, Bhutta ZA

## Non-severe CAP in children - Conclusions of recent review -

- Most episodes of pneumonia can be treated for a short duration
- Ambulatory non-severe pneumonia can be treated with 3 d of oral antibiotics
- Shorter course results in lower prevalence of resistant organisms

Grant GB et al. Lancet Infect Dis. 2009 Mar;9(3):185-96



## Reduced antimicrobial R

**Carriage of cotrimoxazole non-susceptible organisms 2-4 weeks after antibiotic therapy**

- 5 vs 10 days (Schrag et al JAMA 2001) → *S. pneumoniae* 34% vs 44%
- 3 vs 5 days (ISCAP BMJ 2004) → *H. influenzae 57%* vs *61%*; *S. pneumoniae* 67% vs 78%
- 3 vs 5 days (SCC WHO report 2003) → *H. influenzae 54%* vs *62%*; *S. pneumoniae* 62% vs 64%



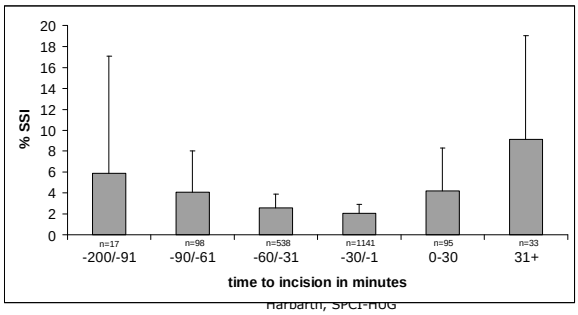
## Improve antibiotic use

- **Monitor and provide feedback on occurrence of AMR**
- **Optimize choice and duration of empiric antimicrobial therapy**
- **Optimize perioperative antimicrobial prophylaxis**



Antibiotic Prophylaxis and the Risk of Surgical Site Infections following Total Hip Arthroplasty: Timely Administration Is the Most Important Factor

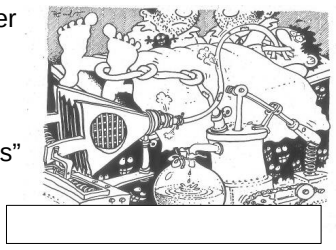
M.E.E. van Kasteren, J. Manniën, A. Ott, B.J. Kullberg, A.S. de Boer, I.C. Gyssens. *Clin Infect Dis* 2007;44(7):921-7






## Common Misconceptions in Surgical Prophylaxis

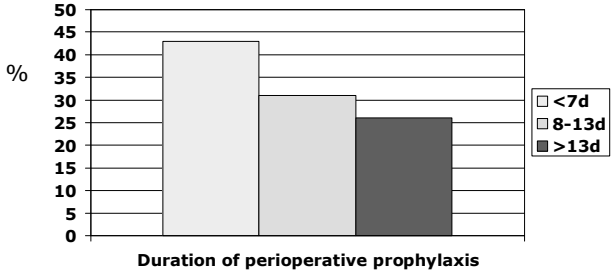
- Broad-spectrum is better
- Longer antibiotic prophylaxis is better
- Prophylaxis should be continued until all “tubes” are out





## Misuse of prophylactic antibiotics in a university hospital, China

80% of prophylactic antibiotics (191/239) were started after the end of the operation




Harbarth S et al. J Infect 2003; 46:161-63

## Overuse of prophylactic antibiotics in a community hospital, Saudi Arabia

*-- representative cases --*

| Procedure | Prophylactic antibiotics administered |
|---|---|
| Delivery | Ampicillin, amikacin, cefotaxime |
| Urinary cath | Amoxycillin, metronidazole |
| C-section | Cephradine, ceftriaxone, gentamicin, metronidazole |
| Appendectomy | Cephradine, cefoxitin, amikacin, metronidazole, TMP-SMX |
| Cystoscopy | Amikacin, tetracycline, ceftazidime, amoxycillin-clav |
| Cholecystectomy | Cephradine, cefuroxime, gentamicin |
| Incision | Ampicillin, amikacin, amoxycillin-clav, cephradine |
| Episiotomy | Amoxycillin, gentamicin, cephradine, metronidazole |
| Delivery | Amoxycillin, gentamicin, cephradine, metronidazole |

Al-Ghamdi S et al. J Hosp Infect 2002; 50:115-21



## Duration of surgical prophylaxis and selection of resistance

**Cardiovascular surgery**
**n= 2'641, multivariate analysis** **< 48 h prophylaxis** **> 48 h prophylaxis**

| | OR (95%CI) > 48 h prophylaxis | P |
|---|---|---|
| SSI | 1.0 (0.8-1.3) | ns |
| Resistant Enterobacteriaceae/enterococci | 1.7 (1.1-2.7) | 0.027 |

Harbarth et al. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. Circulation 2000;101:2916 - 2921



## Improve perioperative antibiotic prophylaxis (ABP)

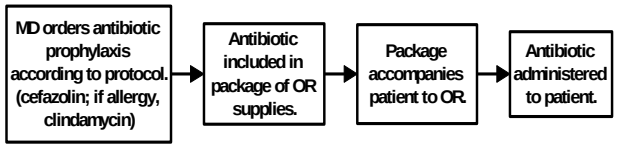
| Process | Problem area | System changes |
|---|---|---|
| ABP choice appropriate | - Suboptimal<br>- Coverage too large | - Guidelines<br>- Adequate supply |
| Duration adequate | Too long (>1 dose) | - Standard order form |
| Timing correct | Too early or too late | - Administer in preoperative area<br>- Designate responsible person |

Huskins et al, Infect Control Hosp Epidemiol 1998;19:125-35



## Prophylactic Antibiotics and Infections after Cesarean Section in Colombia

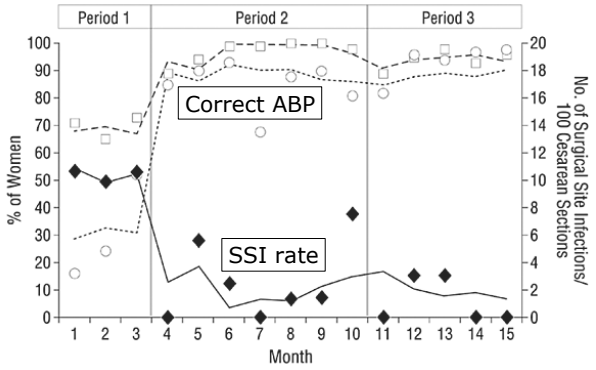
**Antibiotic prophylaxis in C-section**
- Appropriate indication
- Agent, dose, # of doses
- Timing of first dose




Weinberg et al. Arch Intern Med 2001; 161:2357-65



## Use and timing of perioperative antibiotics and surgical site infection rates



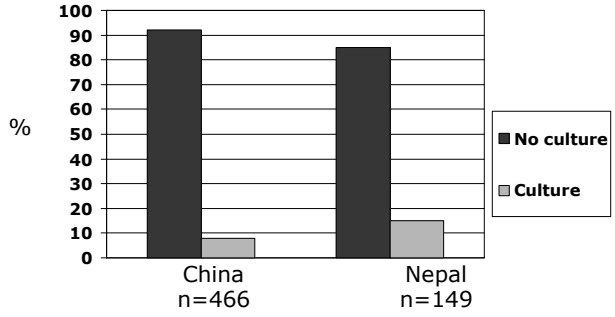

Weinberg et al. Arch Intern Med 2001; 161:2357-65



## Improve antibiotic use (2)

- **Decrease diagnostic uncertainty:**
  - **Improve diagnostic tools**
  - **Promote use of clinical algorithms**

## Antibiotic treatment without microbiologic cultures in China (Hospital) and Nepal (ICU)



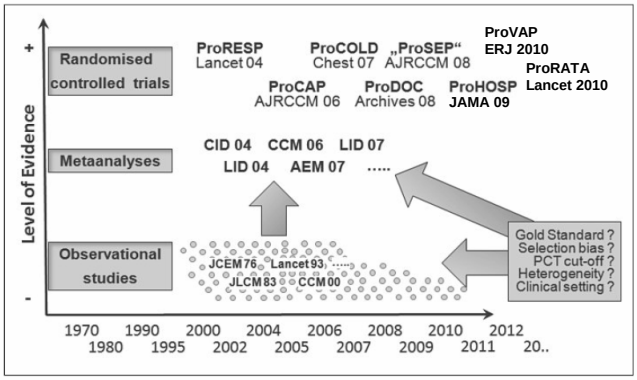

Suping Hu et al. J Infect 2003; 46:161-63
Shankar et al. Am J Infect Control 2003; 31: 410-14

## Use of clinical algorithms

- Prediction of bacteremia & mortality in hospitalized Malawian children
  - Association with lethargy, oral thrush, chronic cough and malnutrition
- The WHO Young Infants Study Group
  - Clinical prediction rule to identify and treat serious bacterial infection

Norton EB et al. Pediatr Infect Dis J 2004; 23: 145-51
WHO study group. Pediatr Infect Dis J 1999; 18: S23-31

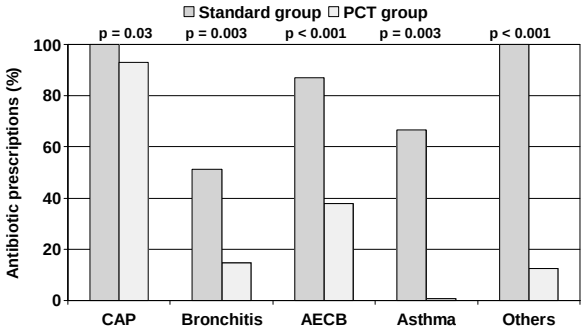
## Procalcitonin: a long & complicated story…




Schuetz P et al. Swiss Med Weekly 2009; 139: 318-26



## Antibiotic prescriptions in lower respiratory tract infection comparing standard group and PCT-guided group

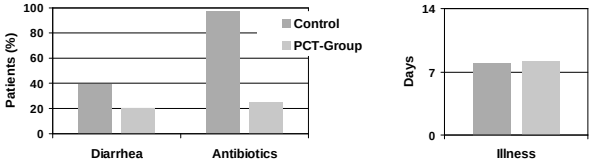



Harbarth, SPCI-HUG Christ-Crain M et al , Lancet 2004

ORIGINAL INVESTIGATION

## Procalcitonin-Guided Antibiotic Use vs a Standard Approach for Acute Respiratory Tract Infections in Primary Care

*Matthias Briel, MD; Philipp Schuetz, MD; Beat Mueller, MD; Jim Young, PhD; Ursula Schild, RN; Charly Nusbaumer, PhD; Pierre Périat, MD; Heiner C. Bucher, MD, MPH; Mirjam Christ-Crain, MD*

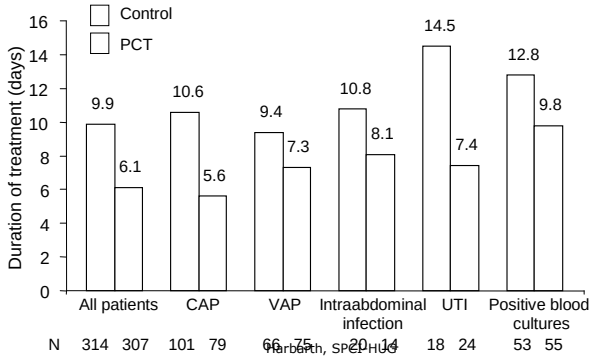



*Arch Intern Med. 2008;168(18):2000-2007*



## Use of Procalcitonin to Shorten Antibiotic Exposure in ICU Patients : The ProRata Trial

*Bouadma et al. Lancet 2010*



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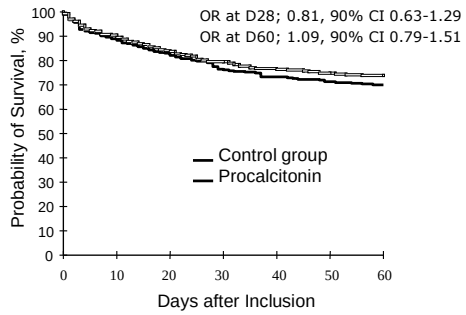


Bouadma et al. *Lancet 2010*



## Improve antibiotic use (2)

- **Decrease diagnostic uncertainty**
- **Implement formulary restrictions for important types of antimicrobial use**



**Impact of an antibiotic restriction policy on hospital expenditures and bacterial susceptibilities: a lesson from a pediatric institution in a developing country**

| Variable | Pre-intervention period (1995/96) | Intervention period (1997/98) |
|---|---|---|
| Vials (#) | 199,427 | 132,496 |
| Total costs ($) | 699,543 | 347,261 |

**-- Stable or decreasing resistance rates --**

Saez-Llorens et al. Ped Infect Dis J 2000; 19: 200-6

## Does restriction always work?

Formulary restriction at Mass Gen Hosp, Boston (USA) :

" Imipenem, tic/clav, aztreonam, cefta, cipro, pip/tazo require prior approval by infectious diseases "

*Gilbert et al.*
*Am J Med; 1998; 104: 17-27*

The reality at the same hospital ….

35-y old woman with severe sepsis:
" Ampicillin-sulb, clindamycin, penicillin, gentamicin, vancomycin were infused intravenously "

*Case report 28-2002 of the MGH, NEJM Sept 12, 2002, p.831-37*



## Improve antibiotic use (2)

- **Improve diagnostic tools**
- **Implement formulary restrictions for important types of antimicrobial use**
- **Improve antimicrobial prescribing:**
  - **Education (pre- and postgraduate)**
  - **Practice guidelines**
  - **Administrative means (antibiotic order forms)**
  - **Feedback to prescribers**



**Implementing practice guidelines for appropriate AB use: Systematic review**

- 40 studies (in- and outpatient areas)
- Multifaceted implementation methods were most successful
- Most useful implementation methods:
  - Locally adapted guidelines (drug committee)
  - Small-group interactive sessions
  - Academic detailing
  - Participation of opinion leaders
  - Feedback to prescribers

Gross PA et al. Med Care 2001; 39: Suppl 55-69

## Impact of an educational program on antibiotic use in a tertiary care hospital in Thailand

### Appropriate antibiotic use (in-patients, %)

| Variable | Preintervention period ($n$ = 4305) | Postintervention period ($n$ = 2830) | $P$ |
|---|---|---|---|
| Inappropriate antibiotic use | 1808 (42) | 566 (20) | <.001 |
| Reason for inappropriateness[a] | | | |
| Inappropriate surgical prophylaxis[b] | 452 (25) | 115 (20) | **.02** |
| Use of antibiotic without any evidence of infection | 723 (40) | 200 (35) | **.04** |
| Redundant spectrum | 217 (12) | 50 (9) | **.03** |
| Bacterial resistance[c] | 235 (13) | 91 (16) | .07 |
| Narrow spectrum was available[d] | 181 (10) | 41 (7) | **.04** |
| Department[e] | | | |
| Surgery | 633 (35) | 170 (30) | **.01** |
| Obstetrics and gynecology | 452 (25) | 125 (22) | .17 |
| Internal medicine | 416 (23) | 113 (20) | .14 |
| Other[f] | 307 (17) | 113 (20) | .12 |

Apisarnthanarak et al. Clin Infect Dis 2006; 42: 768

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## Impact of an educational program on antibiotic use in a tertiary care hospital in Thailand

### Antibiotic resistance

| Microorganism | Resistance rate, %[a] Preintervention period | Postintervention period |
|---|---|---|
| Methicillin-resistant *Staphylococcus aureus* | 48 | 33.5 |
| … | … | … |
| ESBL-producing *Escherichia coli* | 33 | 21 |
| ESBL-producing *Klebsiella pneumoniae* | 30 | 20 |
| Third-generation cephalosporin–resistant *Acinetobacter baumanii* | 27 | 19 |
| Imipenem-resistant *Pseudomonas aeruginosa* | 5 | 4 |
| Multidrug-resistant *Acinetobacter baumanii* | 4 | 5 |

Apisarnthanarak et al. Clin Infect Dis 2006; 42: 768

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## Interventions to improve quality of antibiotic prescribing for hospital inpatients (review)

Davey P, Brown E, Fenelon L, et al.
*Cochrane Database of Systematic Reviews 2005; Issue 4. Art.No CD003543.*

- 51/66 studies showed a significant improvement in at least one outcome
  - Reduction of costs, AMR or HCAI
- Interventions to improve antibiotic prescribing in inpatients likely to be successful
- Absence of good evidence which interventions are most cost-effective in reducing AMR

*Davey P, et al.Cochrane Database of Syst Rev 2005; Issue 4. Art.No CD003543.*

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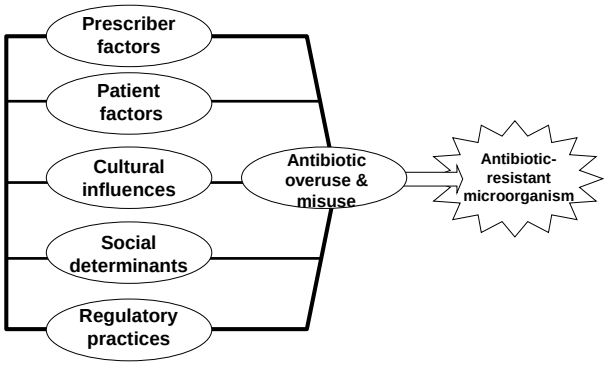
# Outpatient setting

Macro-level determinants

## Macro-level determinants influencing antibiotic overuse in the outpatient setting




Harbarth et al. Emerg Infect Dis 2002; 8: 1460-1467

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PERGAMON

Social Science & Medicine 57 (2003) 733–744

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

## Improving antibiotic use in low-income countries: an overview of evidence on determinants

Aryanti Radyowijati, Hilbrand Haak*

*Consultants for Health and Development, Sleedoorntuin 7, 2317 MV Leiden, The Netherlands*

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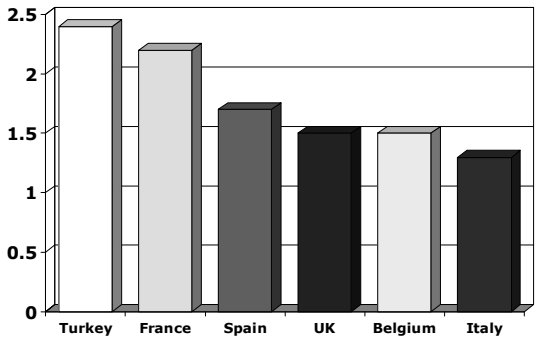
## Index of antibiotic demand

- Cumulative proportion of patients expecting antibiotics for RTI --

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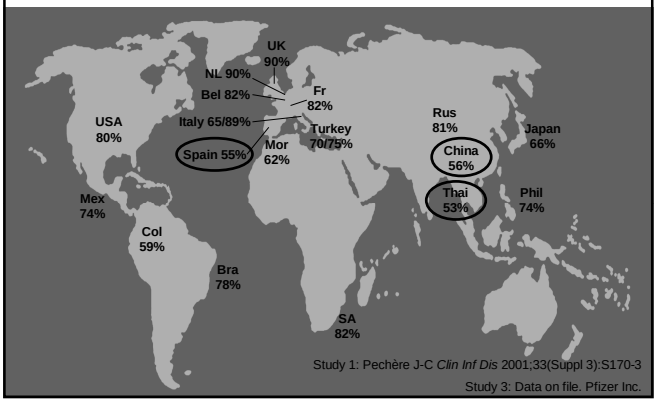
*Branthwaite & Pechère, J Intern Med Research 1996; 24: 229-238*

## Compliance Varies by Country




Study 1: Pechère J-C *Clin Inf Dis* 2001;33(Suppl 3):S170-3

Study 3: Data on file. Pfizer Inc.

## Available in a pharmacy in Delhi – over-the-counter without prescription!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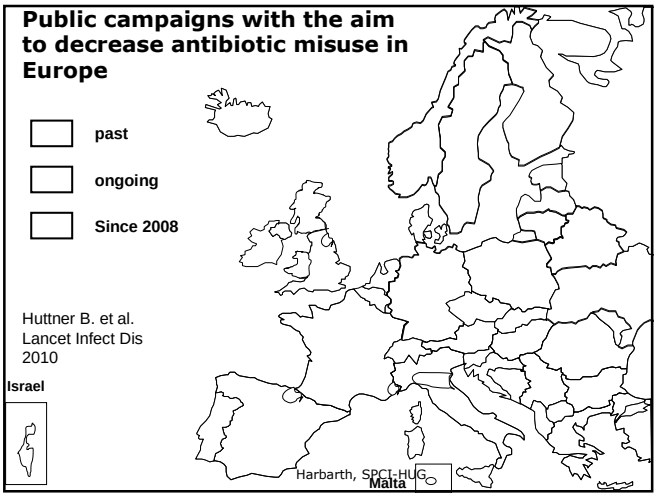
## Country examples: Possible interventions

## Public campaigns with the aim to decrease antibiotic misuse in Europe

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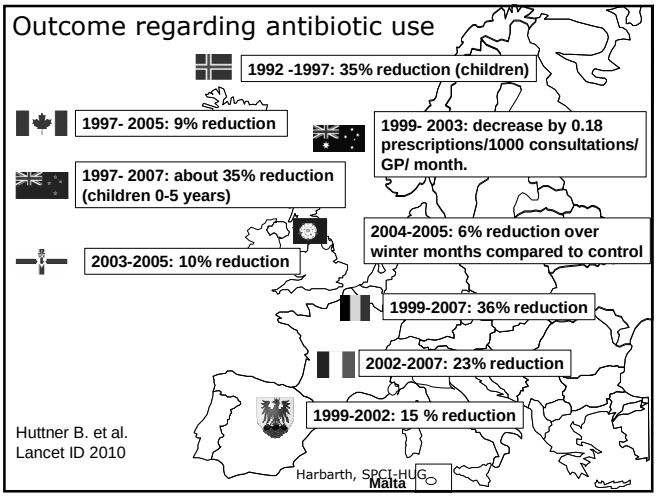
## Outcome regarding antibiotic use

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## Action plan

- In 1999, Chile decided an intervention to:
  - educate physicians & public
  - regulate the consumption of antibiotics
  - restrict over-the-counter antibiotic sales

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mil muertos deja en Turquía Pág. 14

Los empleos que ofrece el plan del Gobierno Pág. 5

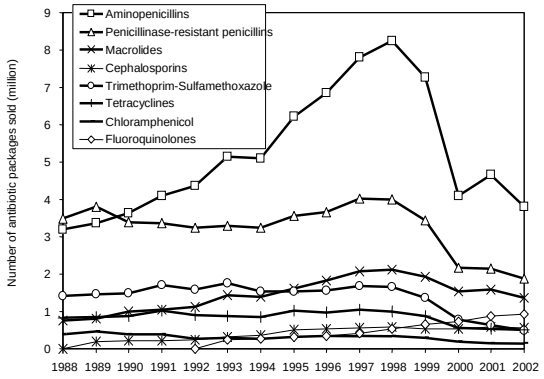
EXIJA HOY "Grandes Hechos Históricos de la Humanidad"

Las Últimas Noticias

MEDIDA SE APLICARÁ A PARTIR DE SEPTIEMBRE

Exigirán receta para comprar antibióticos

Afecta, entre otros, a la amoxicilina y a la eritromicina Pág. 8

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Harbarth et al. Emerg Infect Dis 2005

## Sales of oral antibiotics in US$ (Million)

| Year | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 |
|---|---|---|---|---|---|---|---|
| USD | 37,6 | 45,8 | 45,8 | 38,9 | 32,1 | 29,4 | 26,1 |
| | | | | - 15% | - 30% | - 36% | - 43% |

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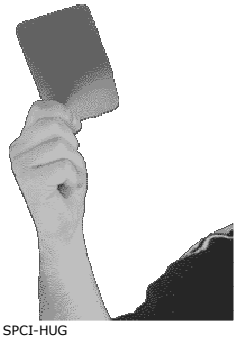
# Korea- Government Policy

- A new Korean government policy announced in 2000 prohibited doctors from dispensing and pharmacists from prescribing drugs by law.



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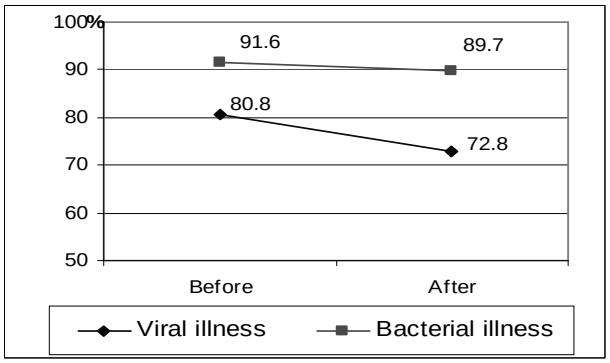
South Korea: Impact of the Policy on Prescribing




Harbarth, SPCI-HUG Park et al, Health Policy Plan. 2005; 20:302-9

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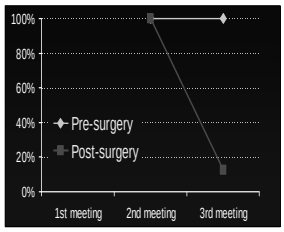
Second International Conference on Improving Use of Medicines

Result 1:

## MTP at General Teaching Hospitals

Problem: Pre- and post surgery ABs in elective hernia surgery
Indicator: % patients receiving antibiotics




Sardjito Teaching Hospital

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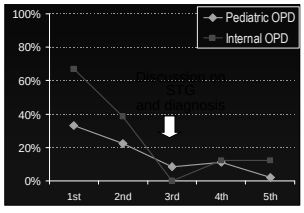
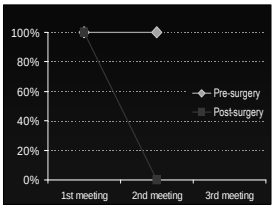
Result 2:

## MTP at Public Hospitals

Problem: - Overuse of AB in acute diarrhea (Sleman)
- Pre- and post-surgery ABs in Caesarian surgery (Yogya)
Indicator: - % patients receiving antibiotics

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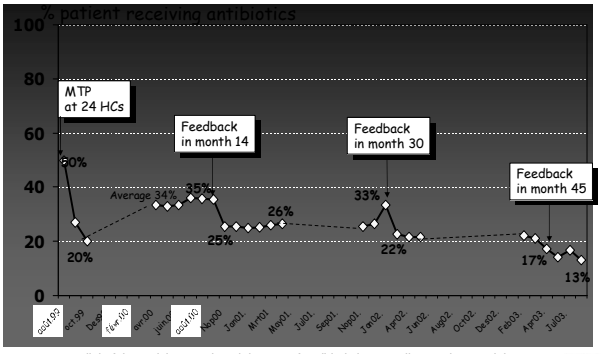
## ANTIBIOTIC USE OVER TIME




Notes: In parallel of the activity to reduced the use of antibiotic in ARI, all HCs also used the MTP approach to address the other problems in medicine use.

## Policy priorities: AB use

**Local level**

- Improve perioperative prophylaxis
- Promote short-course, high-dose AB therapy
- Decrease diagnostic uncertainty by any type of diagnostic tools or decision support
- Promote local guidelines and drug committees

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## Policy priorities: AB use

**National level**

- Create sentinel laboratories for surveillance of antibiotic resistance
- Change consumer expectations
- Implement healthcare regulation for the prudent use of antibiotics
- Control marketing activities of industry

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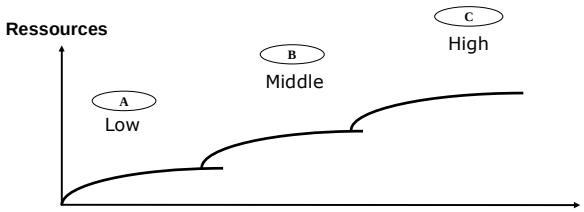
## Summary of Measures




**Measures**

- **Improve antibiotic prophylaxis**
- **Clinical algorithms**
- **Surveillance**
- **Microbiologic support**
- **Restriction & education**
- **Decision support systems**
- **New diagnostic markers**
- **Academic detailing**

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"The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy."

***Dennis Maki 1998***

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