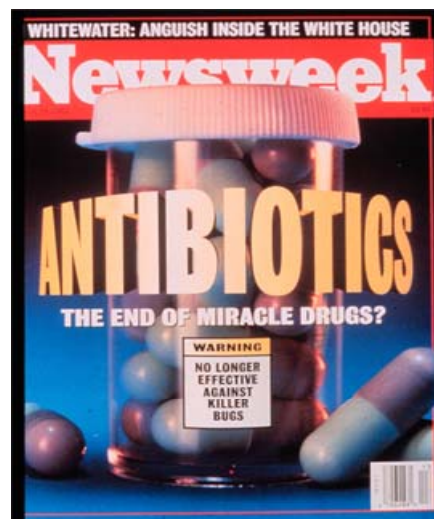
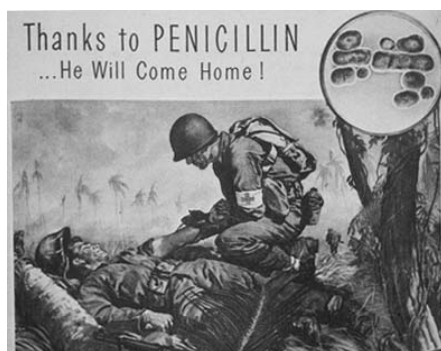


Antimicrobial Resistance The Healthcare Professional Perspective

Professor Didier Pittet

Infection Control Programme
&
WHO Collaborating Center on Patient Safety



NDM1 and Pan-Resistance

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

Karthikeyan K. Kumarasamy, Mark A. Toleman, Timothy R. Walsh, Jay Bhargava, Fajana Blet, Ravikumar Balakrishnan, Umasi Chaudhary, Michel Doumith, Christian G. Giske, Semeefiya, Podina Krishnan, Anil Kumar, Sunil Mohanraj, Shafiq Muzaffar, Tabassum Noor, David L. Paterson, Andrew Pearson, Oksa Perry, Rachel Pike, Bhargava Rao, Ujaywini Ray, Jayanta B. Samra, Madhu Sharma, Elizabeth Shendrik, Manjivani A. Therasarajan, Jane Turner, Srijana Upadhyay, Marwa Warner, William Wajsbort, 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 51 nucleotide 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* (36) and *Klebsiella pneumoniae* (11), 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.

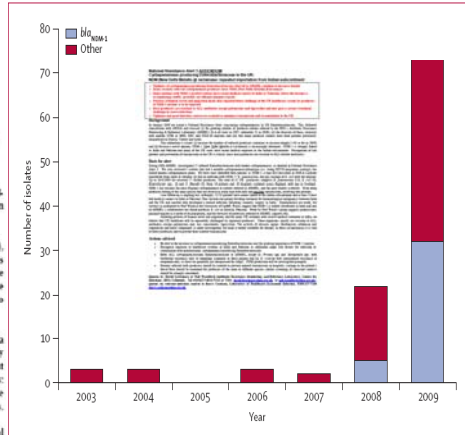


Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009

Courtesy: J. Conly, Geneva

Global Spread NDM1



Note : recent cases travel related not medical tourism

Courtesy: J. Conly, Geneva



**Antimicrobial resistance...
Who is responsible ?**

Globalisation

Dr Z

Patient Y

The bacteria itself

Food processing industry

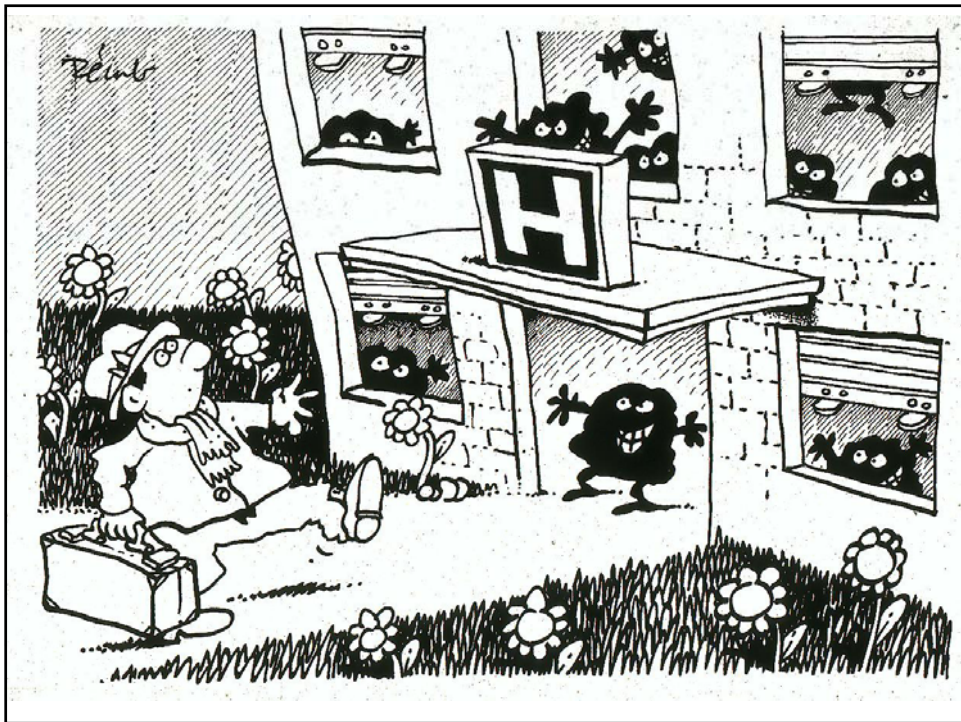
Antibiotic dilemma

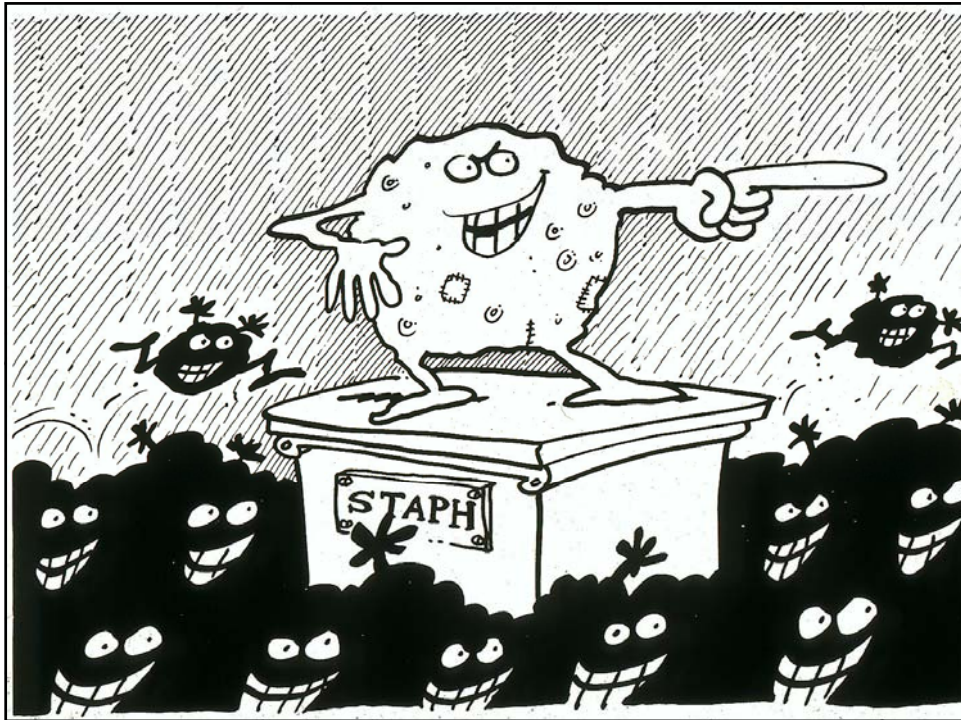
Benefit is individual

Risk is collective

OUTLINE

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





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Après son accident de moto, Guillaume Depardieu a dû subir 17 opérations ■

L'acteur contracte un staphylocoque à la jambe droite. Ne supportant plus la douleur, il choisit l'amputation.

mieux répertoriées, sans oublier que les
CHU accueillent les patients



Le Point
www.lepoint.fr

HÔPITAUX
Le palmarès 2003

700 établissements au banc d'essai, les meilleurs ville par ville pour 24 spécialités

LE POINT

Improve antibiotic use

- Monitor and provide feedback on occurrence of AMR

Control programs for multiresistant *Staphylococcus aureus* (MRSA)

	Able to calculate the proportion of MRSA among all <i>S aureus</i> 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

The important role of sentinel hospitals

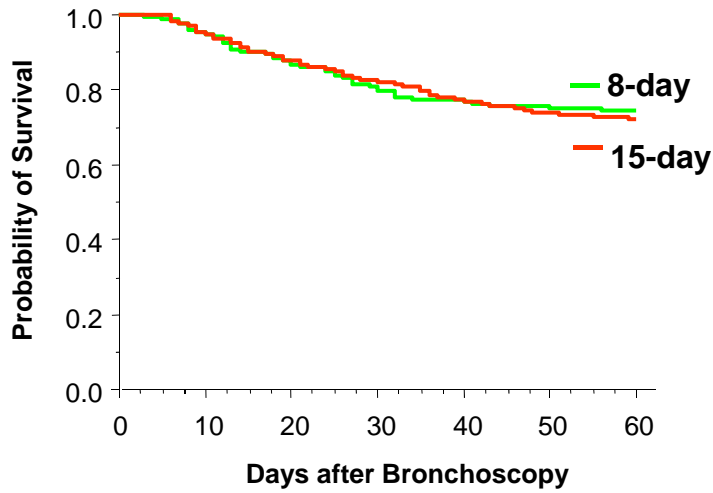
- Centralization of available laboratory resources in a few selected centers
- Monitoring and reporting of AB susceptibility data
- Adapt empiric treatment regimens

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

Improve antibiotic use

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

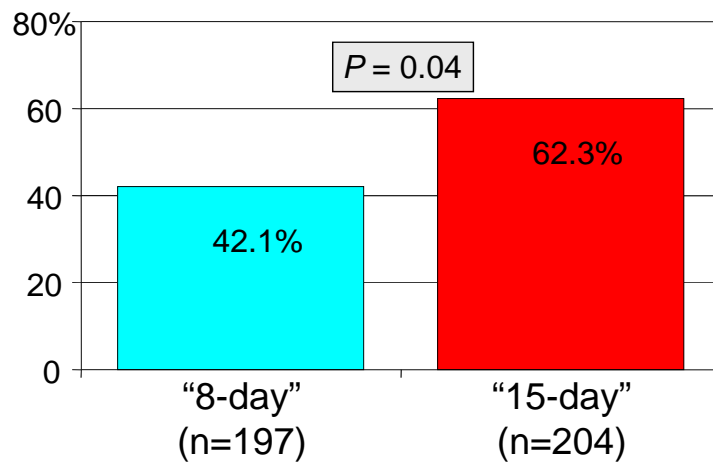
Survival Among 401 Patients with Nosocomial Pneumonia Assigned to Short (8 d) or Long (15 d) Antimicrobial Treatment



JAMA 2003; 290: 2588-98

Courtesy: J. Chastre, Paris

Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence



JAMA 2003; 290: 2588-98

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.328.7493.791

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

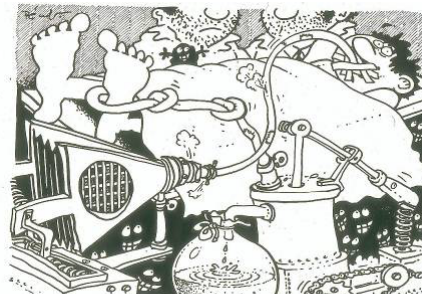
Grant GB et al. Lancet Infect Dis. 2009 Mar;9(3):185-96

Improve antibiotic use

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

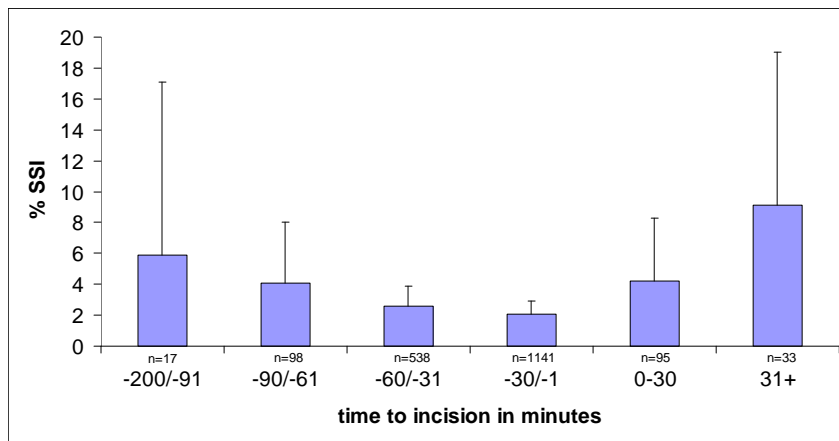
Common Misconceptions in Surgical Prophylaxis

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



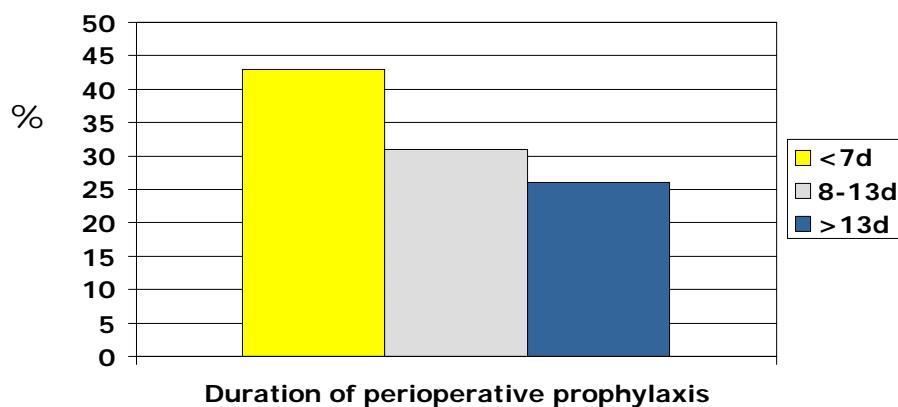
Antibiotic Prophylaxis and the Risk of Surgical Site Infections following Total Hip Arthroplasty: Timely Administration Is the Most Important Factor

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



Misuse of prophylactic antibiotics in a university hospital, China

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



Suping Hu et al. *J Infect* 2003; 46:161-63

Duration of surgical prophylaxis and selection of resistance

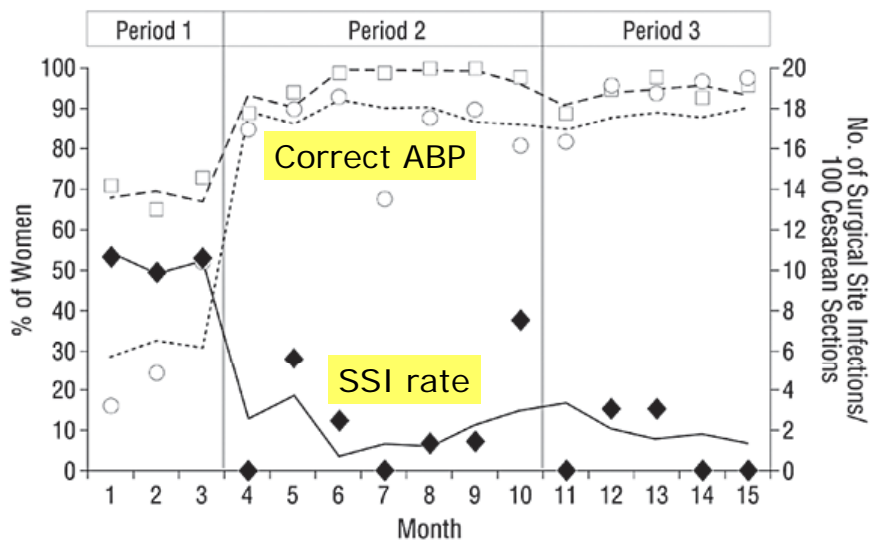
Cardiovascular surgery

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

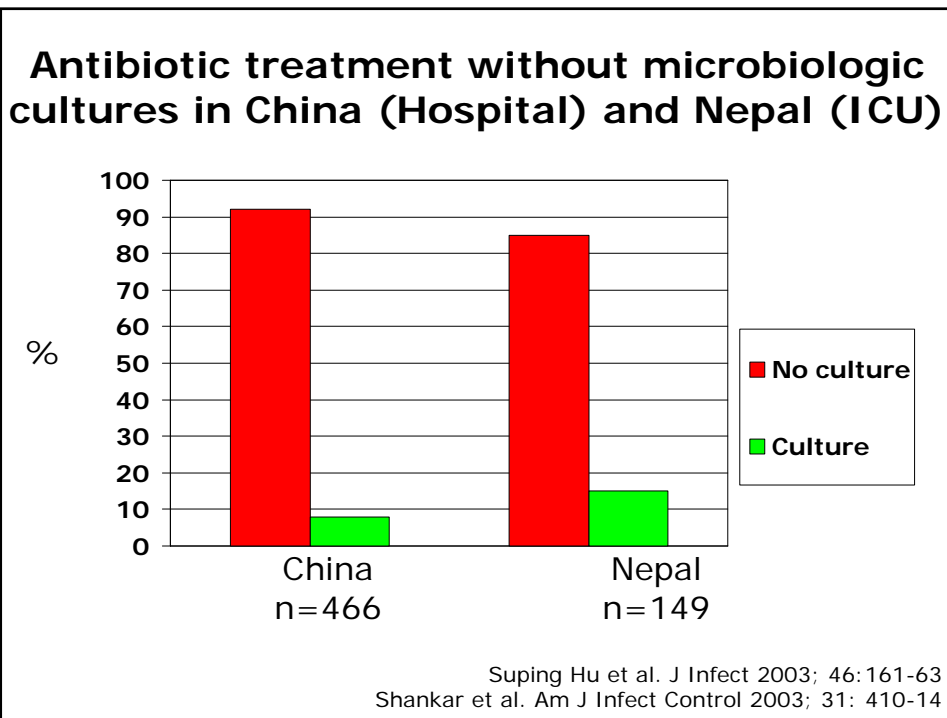
Use and timing of perioperative antibiotics and surgical site infection rates



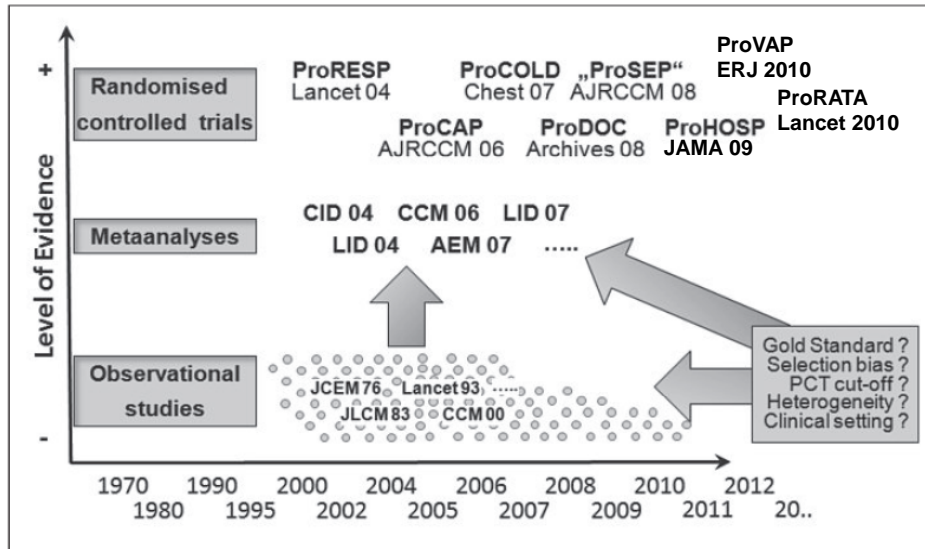
Weinberg et al. *Arch Intern Med* 2001; 161:2357-65

Improve antibiotic use (2)

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

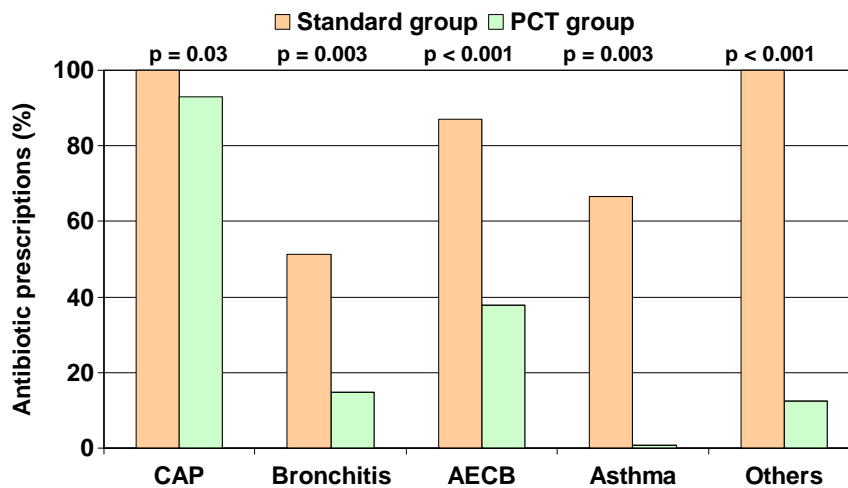


Procalcitonin: a long & complicated story...



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

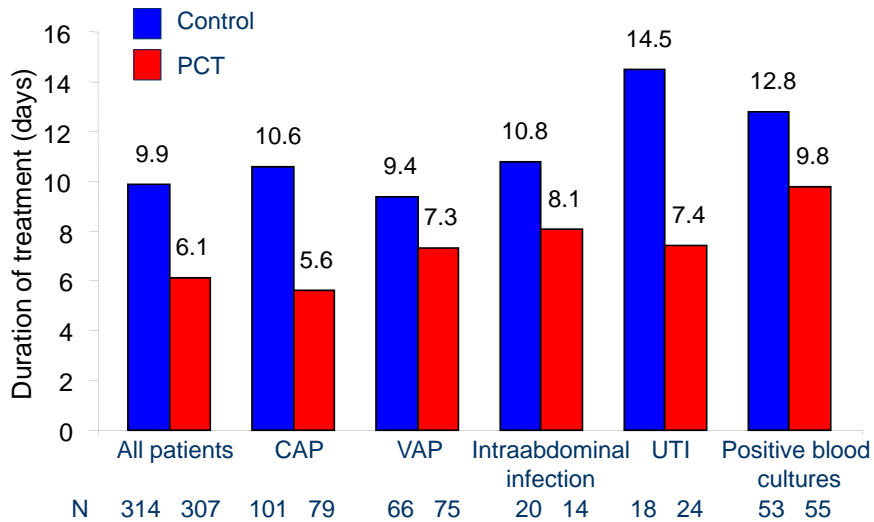
Antibiotic prescriptions in lower respiratory tract infection comparing standard group and PCT-guided group



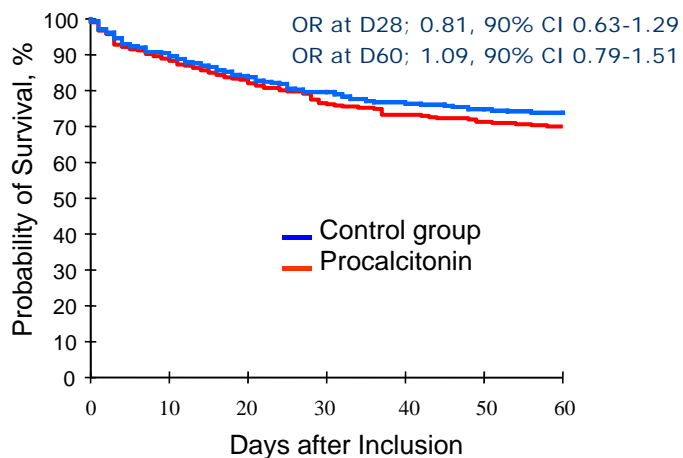
Christ-Crain M et al, Lancet 2004

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

Bouadma et al. Lancet 2010



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



Bouadma et al. Lancet 2010

Improve antibiotic use (2)

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

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

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

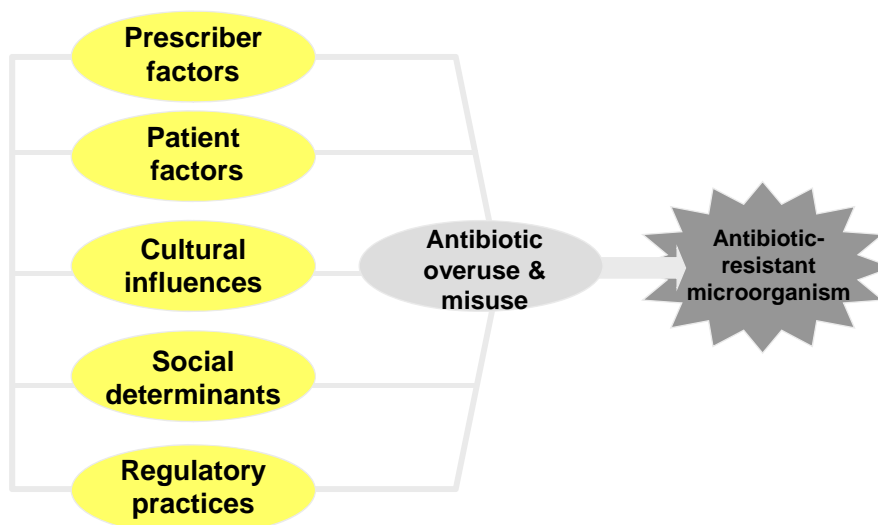
Davey P, et al.Cochrane Database of Systematic Reviews 2005; Issue 4. Art.No CD003543.



Outpatient setting

Macro-level determinants

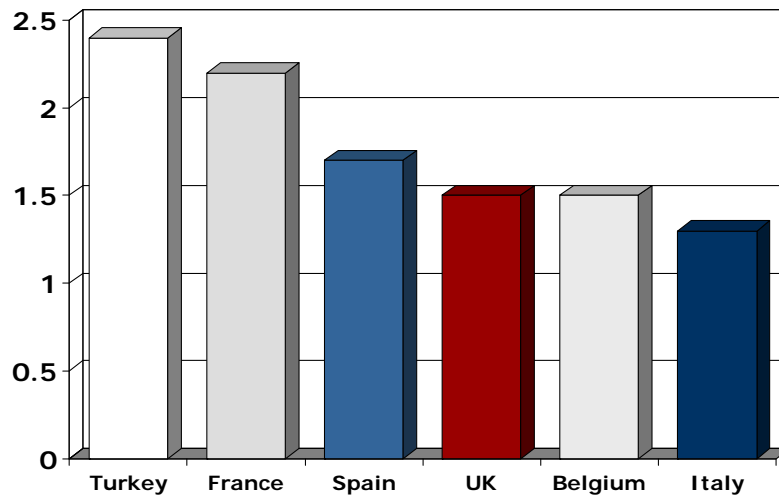
Macro-level determinants influencing antibiotic overuse in the outpatient setting



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

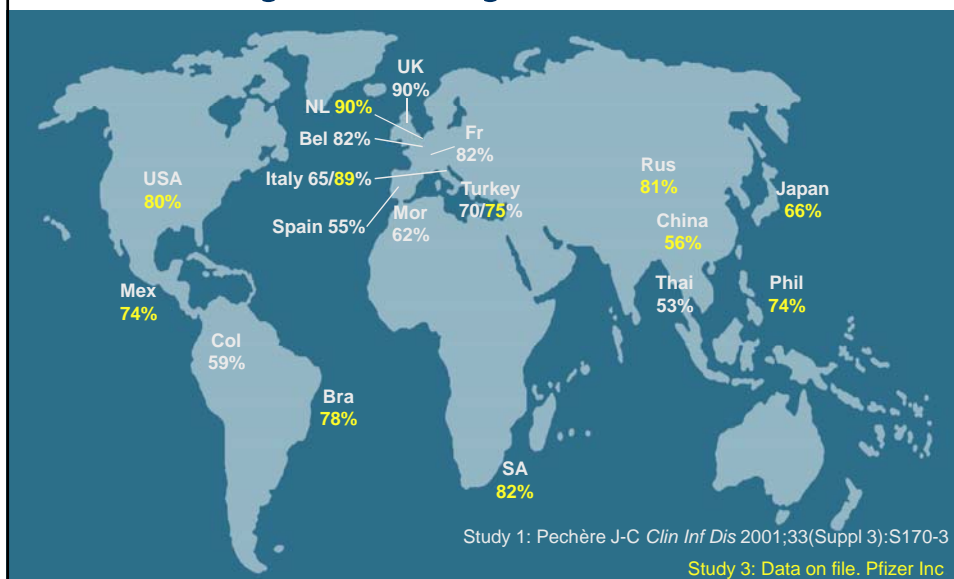
Index of antibiotic demand

- Cumulative proportion of patients expecting antibiotics for RTI --



Branthwaite & Pechere; J Intern Med Research 1996; 24: 229-238

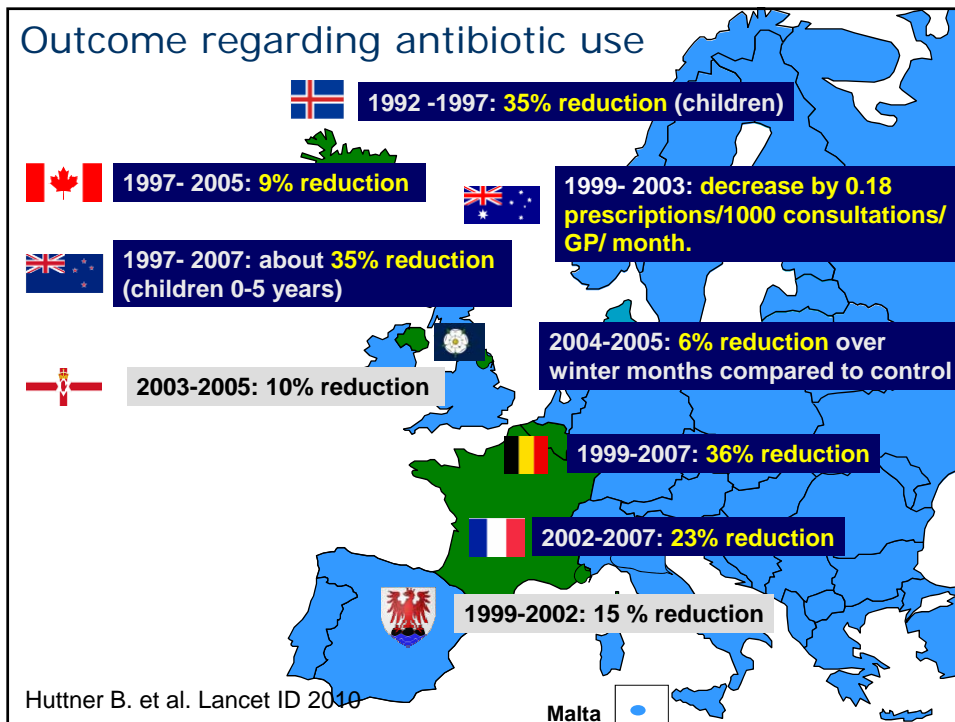
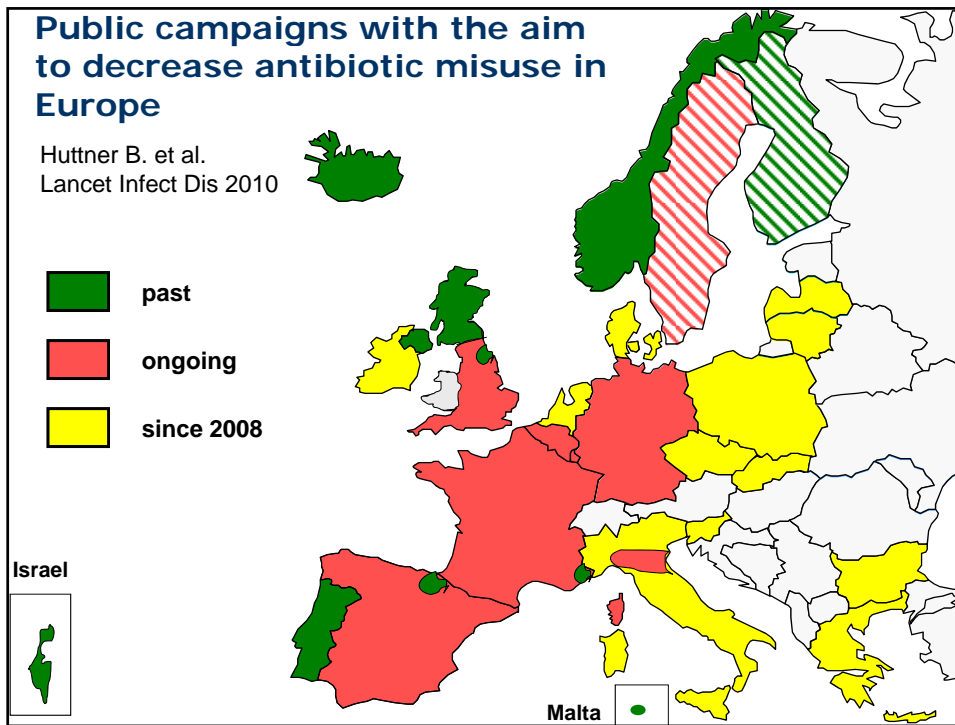
Compliance with antibiotic use varies by country

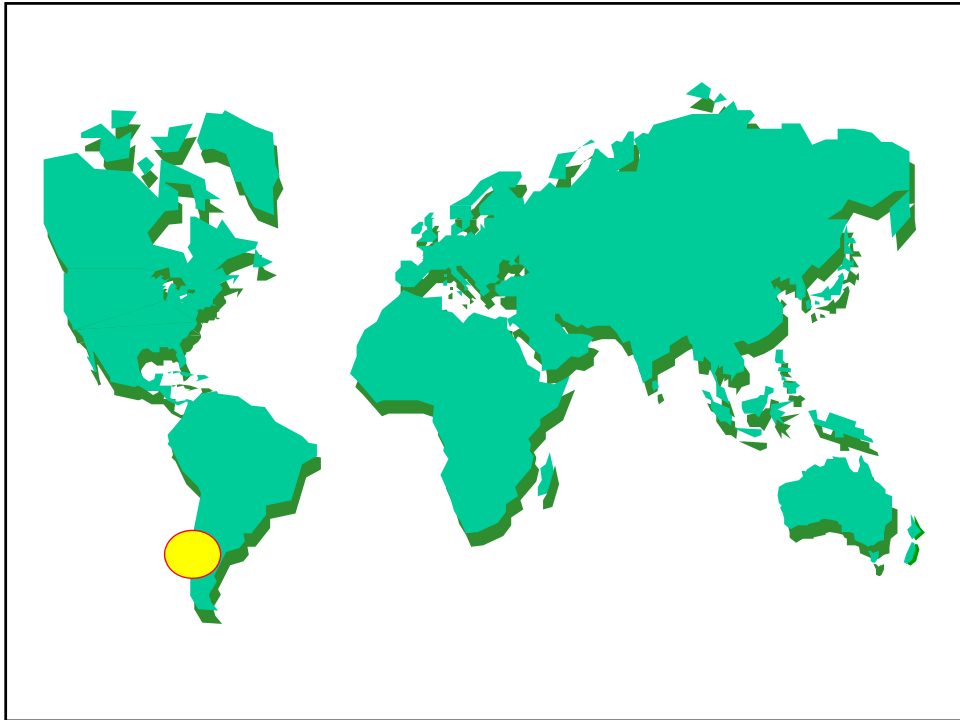


**Available in a pharmacy in Delhi –
over-the-counter without prescription!**



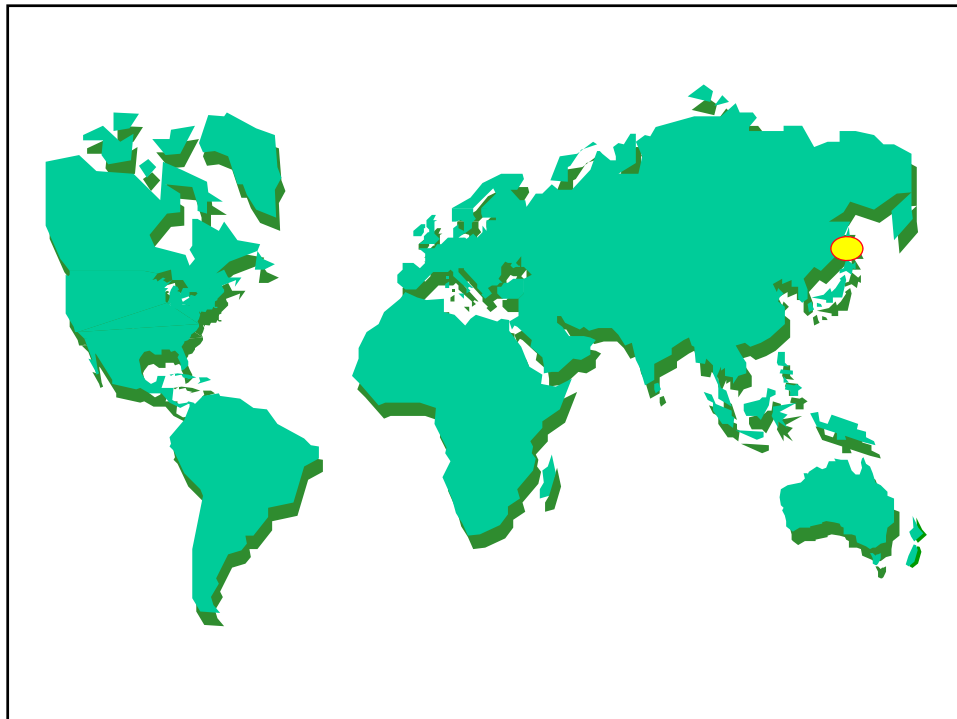
**Country examples:
Possible interventions**





Action plan

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

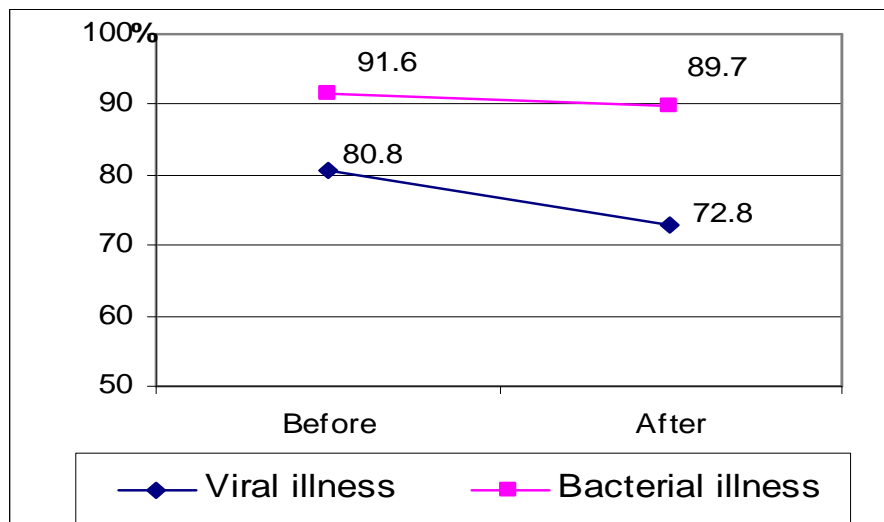


Korea- Government Policy

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



South Korea: Impact of the Policy on Prescribing



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

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

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

Policy priorities: AB use

International level

- Support national and international initiatives
- Coordinate initiatives
- Develop public-private partnerships
- Monitor use and resistance, feedback, act, and regulate

“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

