Antibiotic Restriction Policies:
Can they hold back the tide?

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Canute, first Viking king of England 1016-1035.

His courtiers flattered him by saying that "He was so great he could command the tides of the sea to go back"

Canute had his throne taken to the waters edge to demonstrate the impossibility of this claim.

Can antibiotic restriction policies hold back the waves of resistant bacteria?

MRSA, ESBL, VRE, VRSA, etc.

Antibiotic use

↓

Resistance to antibiotics

Restriction policies

Antibiotic use ↓

Resistance to antibiotics ↓

Assumptions!

1. Antibiotic use leads to bacterial resistance
2. Antibiotic use has potential for reduction
3. Restriction policies will reduce antibiotic use
4. Reduced use will result in reduced resistance
5. Reduced use will not result in worse patient outcomes
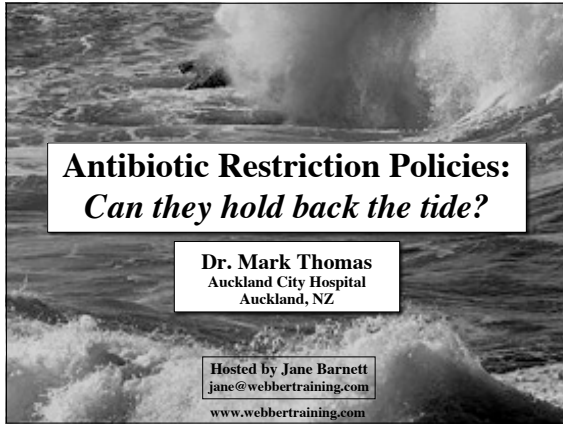6. Reduced use will not cost more

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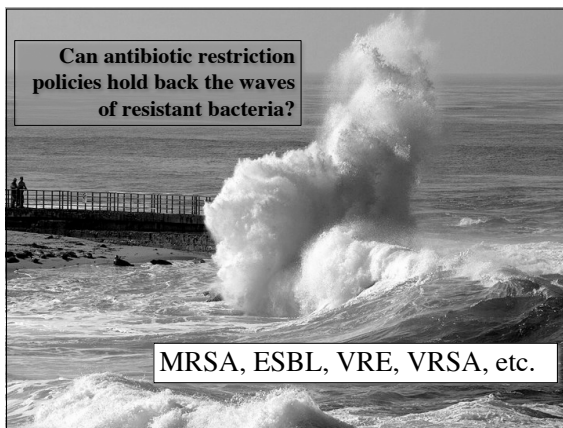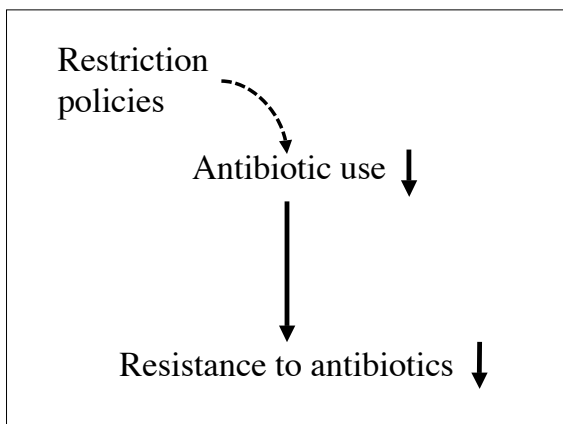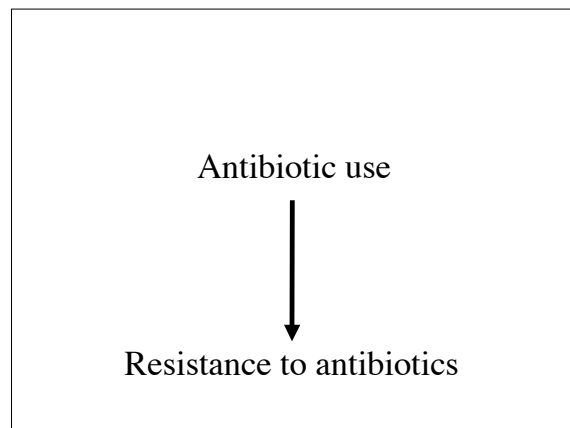## Dr. Mark Thomas, Auckland City Hospital, New Zealand
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Antibiotic use leads to bacterial resistance?

YES!!

Penicillin   S. aureus 90%

NO!! (not yet)

Penicillin   S. pyogenes 0%

T. pallidum 0%

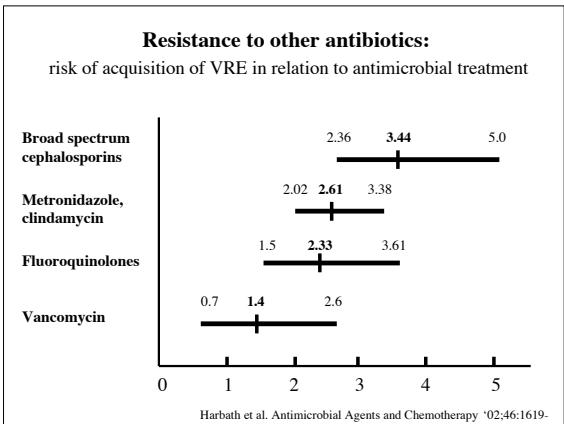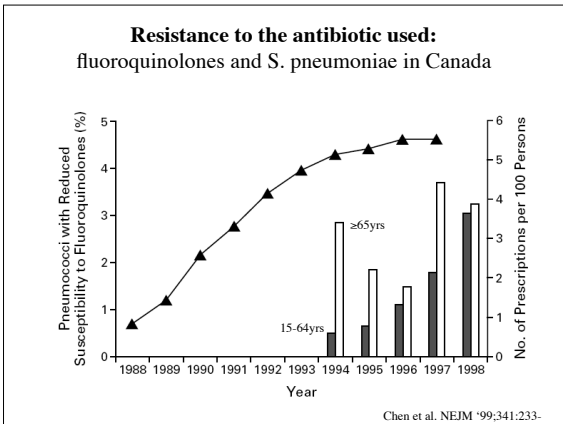**Antibiotic use leads to bacterial resistance**

1. Resistance to the antibiotic used

2. Resistance to other antibiotics

Resistance to the antibiotic used:

VRSA in a patient treated with vancomycin

June 2002, Michigan USA

49 yr old diabetic, PVD, renal failure

MRSA bacteraemia – infected A-V graft

Treated with vancomycin and rifampicin

VRSA infection temporary dialysis catheter

VRE and Klebsiella oxytoca in foot ulcer
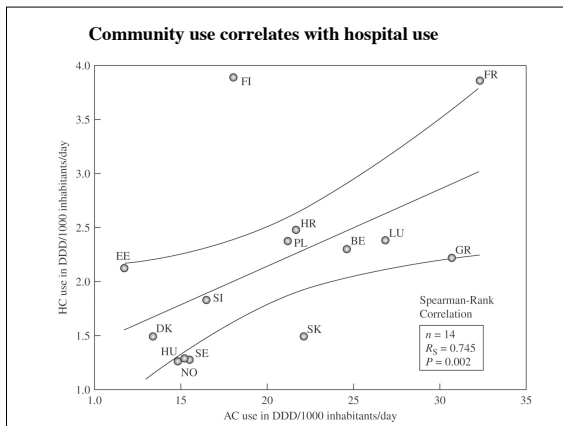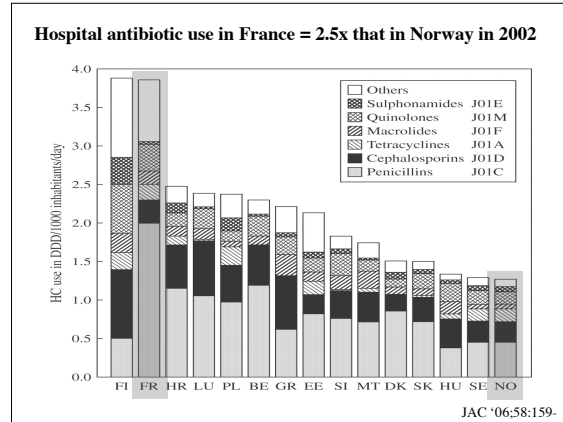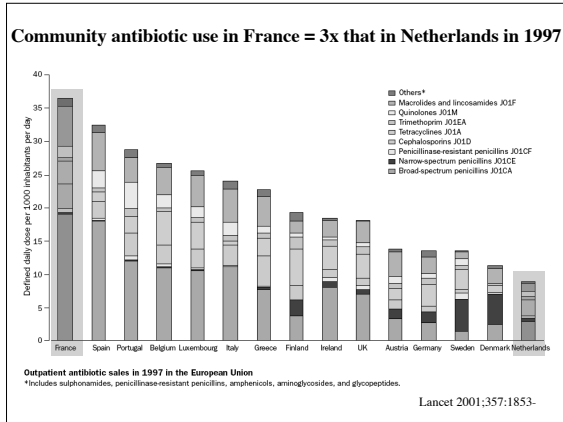
MMWR July 5, 2002; 51:565-7.

Resistance to the antibiotic used:
fluoroquinolones and S. pneumoniae in Canada

Chen et al. NEJM '99;341:233-

Resistance to other antibiotics:
risk of acquisition of VRE in relation to antimicrobial treatment

Broad spectrum cephalosporins	2.36	**3.44**	5.0
Metronidazole, clindamycin	2.02	**2.61**	3.38
Fluoroquinolones	1.5	**2.33**	3.61
Vancomycin	0.7	**1.4**	2.6

Harbath et al. Antimicrobial Agents and Chemotherapy '02;46:1619-

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Antibiotic use:
does have potential for reduction!

Human	80% community	20-50%
	20% hospital	unnecessary
Agricultural	80% prophylactic	40-80%
	20% treatment	highly questionable

BMJ '98;317:609-

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2

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Community antibiotic use in France = 3x that in Netherlands in 1997

Outpatient antibiotic sales in 1997 in the European Union
*Includes sulphonamides, penicillinase-resistant penicillins, amphenicols, aminoglycosides, and glycopeptides.

Lancet 2001;357:1853-

Hospital antibiotic use in France = 2.5x that in Norway in 2002

JAC '06;58:159-

Community use correlates with hospital use

Spearman-Rank Correlation
$n = 14$
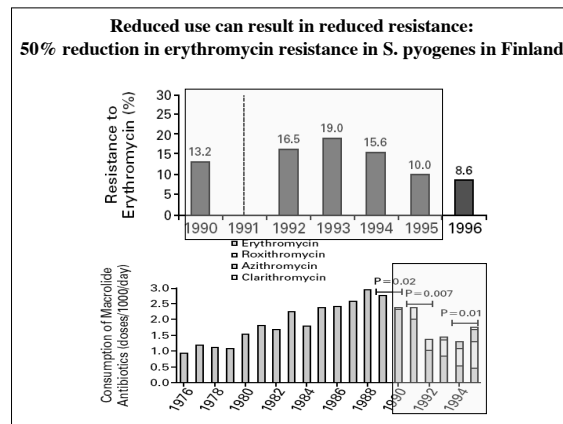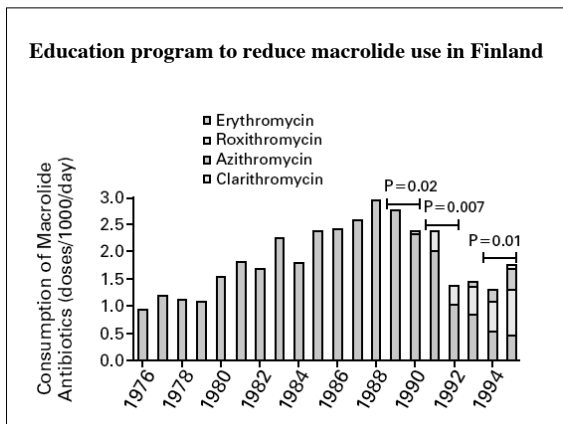$R_S = 0.745$
$P = 0.002$

Restriction policies can reduce use:
Erythromycin and S. pyogenes in Finland.

3X increase in macrolide antibiotic use during 1980s

Erythromycin resistance in S. pyogenes:
  1988, 1989 = 5%
  1990 = 13%

High use regions had high resistance rates.

NEJM '97;337:441-

Education program to reduce macrolide use in Finland

- Erythromycin
- Roxithromycin
- Azithromycin
- Clarithromycin

$P = 0.02$
$P = 0.007$
$P = 0.01$

Reduced use can result in reduced resistance:
50% reduction in erythromycin resistance in S. pyogenes in Finland

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Methods to reduce antibiotic use (in hospitals)

Education and Guideline Formulation

Formulary and Restriction Strategies

Pharmacist, Physician or Computer administered

Persuasive   or   Restrictive

Survey of 88 US hospitals

2/3 used a formulary to restrict antimicrobial choices

28% required ID approval for dispensing of restricted antimicrobials

21% required pharmacist approval for dispensing of restricted antimicrobials

Am J Health Syst. Pharm. '96;53;2054-

A computer-based restriction program in an Australian Hospital

Royal Melbourne Hospital – 1999 - excessive use of cefotaxime and ceftriaxone

Web-based approval system
  - prescriber login code
    patient identifiers
    select indication from drop-down list
    (or seek approval from ID registrar)
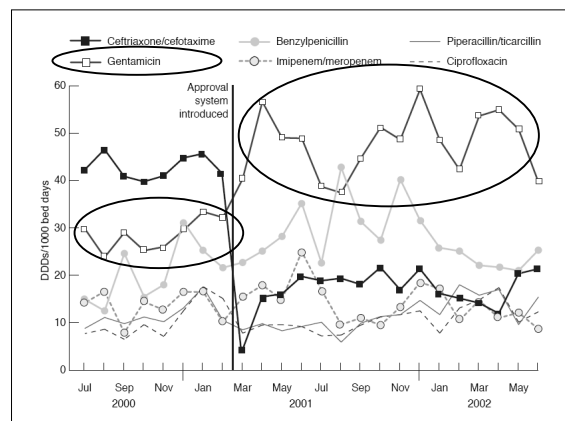   no dispensing without approval number

MJA '03;178:386-
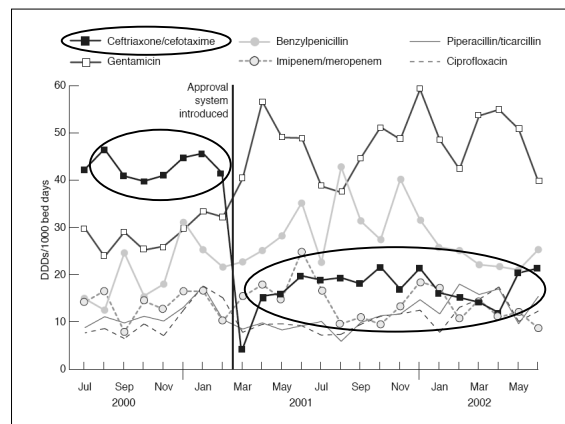
Conclusion:

A computer based restriction policy can dramatically reduce prescribing of targeted antimicrobials.

But be aware of potential for increased prescribing of other agents!


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4

Another restriction policy that reduced antibiotic use

Carney Hospital, Boston, 1988-1998

Full-time pharmacist + ¼ time ID physician

Formulary

Review of all prescriptions for:

3^0 cephalosporins, aztreonam

IV quinolones, imipenem

7 day stop orders for all antibiotics

Exclusion of pharmaceutical company staff

Infect Control Hosp Epi'03;24:699-

IV antibiotic use 1991-1998
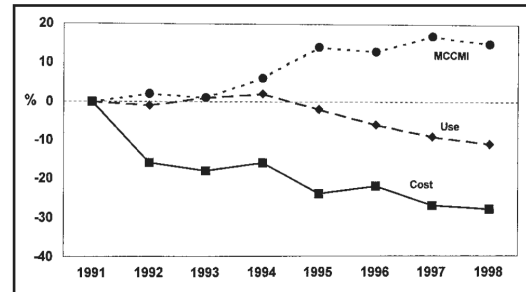
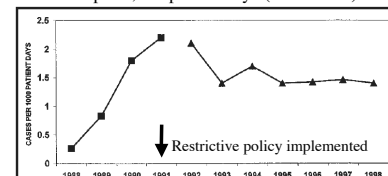MCCMI = Medicare Case Mix Index

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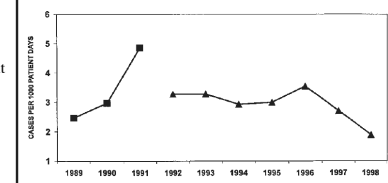### Do reductions in antibiotic use result in reductions in bacterial resistance?

Yes, and No.

YES!

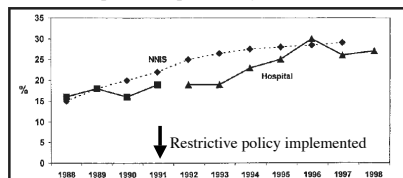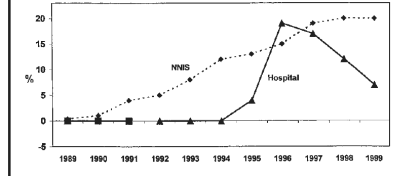Cases per 1,000 patient days (1988-1998)

C. difficile

Restrictive policy implemented

ceftazidime resistant Enterobacteriaceae

NO!

Cases per 1,000 patient days (1988-1998)

MRSA

Restrictive policy implemented

VRE

Do reductions in antibiotic use result in reductions in bacterial resistance?

Restriction of cephalosporin use to control cephalosporin resistant Klebsiella in Queens NY.

Increase in ESBL +ve Klebsiella during 90s

Cephalosporin use severely restricted in 1996

JAMA '98; 280: 1233-

"Squeezing the balloon"

	1995	1996
Cephalosporin consumption	5.6kg	1.1kg
Pts with ESBL Klebsiella	150	84
Imipenem consumption	0.2kg	0.47kg
Pts with I res Pseudomonas	67	113

Cochrane Review!

Interventions to improve antibiotic prescribing practices for hospital inpatients. July 2005

66 acceptable studies
42 USA, 24 elsewhere
29 educational, 27 restrictive, 7 mixed
57 1 hospital only, 9 2 or more hospitals
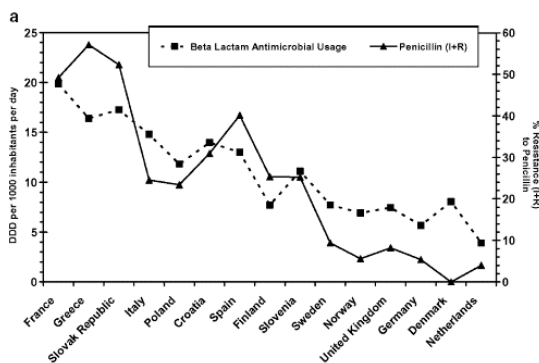22 pharmacist, 17 ID physician, 11 team

10/14 studies that aimed to reduce consumption showed a significant effect (8-69% reduction in consumption)

4/5 studies showed a reduction in C. difficile diarrhoea
6/10 studies showed a reduction in antibiotic resistant GNB
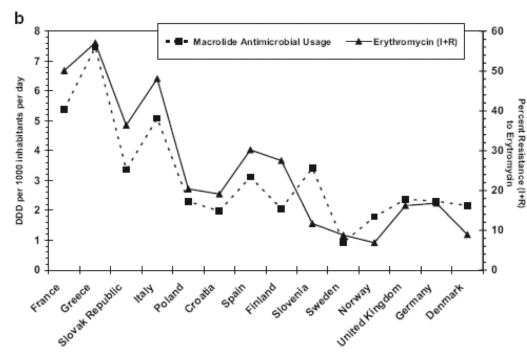2/4 studies showed a reduction in VRE or MRSA

5 studies monitored mortality
3 monitored readmission rates
with no consistent conclusions

While there are relatively few studies
of the effect of restriction policies
on the rates of antibiotic resistance
(or other clinical outcomes)
there is a large amount of data
showing antibiotic use
correlates with resistance rates.

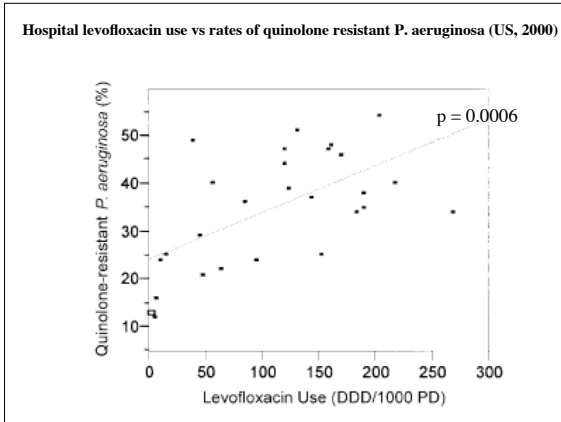Beta-lactam antimicrobial use and penicillin resistance in S. pneumoniae

Macrolide antimicrobial use and macrolide resistance in S. pneumoniae

Hospital levofloxacin use vs rates of quinolone resistant P. aeruginosa (US, 2000)

$p = 0.0006$

Quinolone-resistant *P. aeruginosa* (%)

Levofloxacin Use (DDD/1000 PD)

Overview

1. Antimicrobial use selects for colonisation and disease due to resistant organisms
2. Patients' outcomes are worse when infected with resistant organisms
3. Cautious antimicrobial prescribing can reduce the selection of resistant organisms
4. There is some evidence that restriction policies are effective in slowing the evolution of resistance
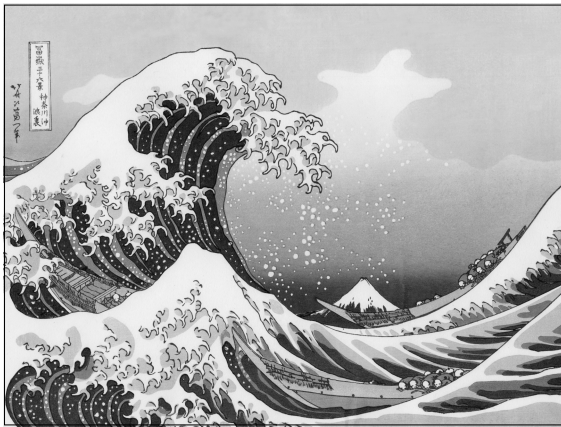
A useful review

MacDougall C, Polk RE.
Antimicrobial stewardship programs in health care systems.
Clinical Microbiology Reviews 2005;18:638-56.

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New Zealand**
Topic & speaker to be determined

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