Fifty Years of Antibiotic Resistance

Prof. Gary French, Kings College, London

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Infection Prevention Society

50 years of antibiotic resistance

Gary French
Guy's & St Thomas' Hospital
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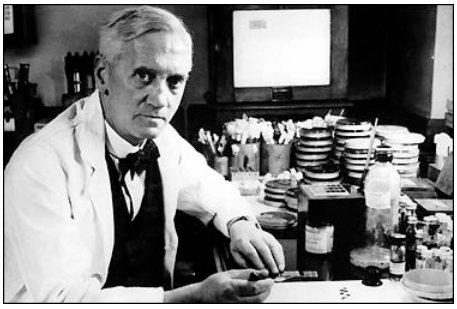
Antibiotics are different

- The only drugs that are:
  - Not directed against the patient
  - Taken at some time by almost everyone in the West
- Every treatment upsets microbial ecology
  - Alteration in the normal bacterial flora of patient and environment
  - Associated with an inevitable evolutionary change to antibiotic resistance



THE BRITISH JOURNAL
OF
EXPERIMENTAL
PATHOLOGY
VOLUME TEN
1929

Reproduced from pages 226–236.

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ*.

ALEXANDER FLEMING, F.R.C.S.
From the Laboratories of the Inoculation Department, St Mary's Hospital, London.

Received for publication May 10th, 1929.

1940–41

- **Penicillin as a chemotherapeutic agent.** *Lancet*, Volume 236, Issue 6104, 24 August 1940, 226-228. E. Chain, H.W. Florey, A.D. Gardner, N.G. Heatley, M.A. Jennings, J. Orr-Ewing, A.G. Sanders.
- **Further observations on penicillin.** *Lancet*, 238, Issue 6155, 16 August 1941, 177-189. E. P. Abraham, E. Chain, C. M. Fletcher, A. D. Gardner, N. G. Heatley, M. A. Jennings, H. W. Florey

Fleming, Penicillin, 1929

Streptococcus pyogenes is also very sensitive. There were small differences in the titre with different strains, but it may be said generally that it is slightly more sensitive than staphylococcus.

Pneumococci are equally sensitive with *Streptococcus pyogenes*.

The green streptococci vary very considerably, a few strains being almost unaffected while others are as sensitive as *S. pyogenes*. Gonococci, meningococci, and some of the Gram-negative cocci found in nasal catarrhal conditions are about as sensitive as are staphylococci. Many of the Gram-negative cocci found in the mouth and throat are, however, quite insensitive.

Certain interesting facts emerge from these Tables. It is clear that penicillin contains bacterio-inhibitory substance which is very active towards some microbes while not affecting others. The members of the coli-typhoid group are unaffected as are other intestinal bacilli such as *B. pyocyaneus*,

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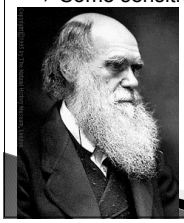
Antimicrobial Resistance

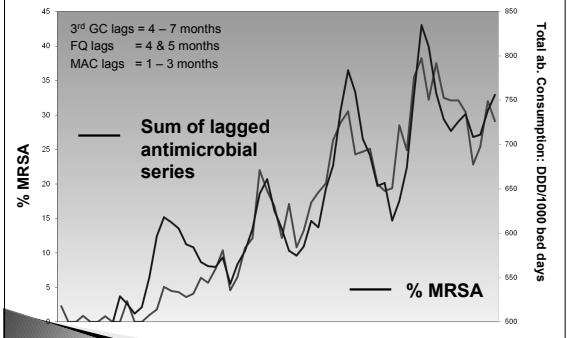
- Some organisms are always sensitive or resistant to a given antibiotic (inherent sensitivity or resistance)
  - Syphilis is always sensitive to penicillin
  - *P. aeruginosa* is always resistant ampicillin
- Some sensitive orgs 'acquire' resistance



Antimicrobial resistance is an inevitable evolutionary response to antimicrobial use

7

Relationship between % MRSA and antibiotic use. (3rd GC, FQ, MAC)



After Ian Gould

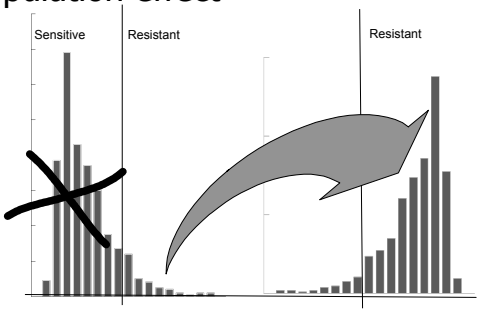
Emerg. Inf. Dis 2004, 1432

Emergence of resistance

- Population effect
  - Antibiotic use kills sensitive members of bacterial population
  - more resistant orgs flourish (Within & between species)

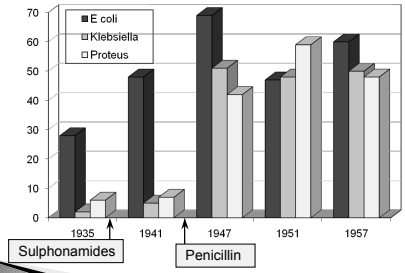
8

Population effect



Occurrence of serious bacterial infections since introduction of antibacterial agents

Finland M, Jones WF. *JAMA* 1959;170:2188-97



Emergence of resistance

- Population effect
  - Antibiotic use kills sensitive members of bacterial population
  - more resistant orgs flourish (Within & between species)
- Emergence of resistant mutants
  - Related to short bacterial generation time
- Infectious resistance
  - Acquisition of new 'resistance genes' (R-factors') by plasmid or transposon transmission
    - 90% *Staph aureus* now resistant to penicillin
    - 60% *E coli* now resistant to ampicillin

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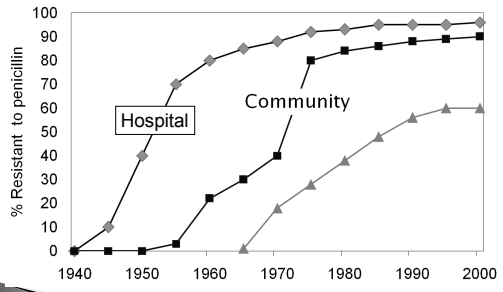
Resistance to penicillin in *S. aureus,* ampicillin in *E.coli*



McDonald, Clin Infect Dis, 2006

Main mechanisms of antimicrobial resistance

- Enzyme inactivation
- Target site alteration
- Reduced permeability/increased extrusion
  - Two or more mechanisms may interact to determine the actual level of resistance

Resistance mechanisms in MRSA

Drug	Mechanism		Chromosome	Plasmid
Penicillin	Enzyme	β-lactamase	(+)	+
β-lactams	Target (PBP)	PBP2a	+	(+)
Aminoglycosides	Enzyme	AME	(+)	+
Erythromycin/ Clindamycin (MLS)	Target (23S rRNA)	Methylation of target	(+)	+
Tetracycline	Efflux (+others)	Tet protein	(+)	+
Chloramphenicol	Enzyme	CATs	(+)	+
Sulphonamide	Target	Mutation dihydropteroate	(+)	+
Trimethoprim		synthetase & dihydrofolate reductase		
Fusidic acid	Target	Mutation elongation factor	+	-
Rifampicin	Target	Mutation RNA polymerase	+	-
Quinolones	Target	Mutation of *gyrA*	+	-
Mupirocin	Target	Mutation isoleucyl -tRNA synthetase	+	+
Glycopeptides	?	?	?	?

Antibiotic 'pressure'

- McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis 1983;5:1033–1048.
- Antibiotic use is concentrated in hospitals
- Resistant bacteria proliferate in the hospital environment and treated patients
- Infection with resistant organisms fails to respond to empirical therapy, increasing the time during which cross-infection may occur
- More and more hospital infections become antibiotic resistant

Antibiotic 'pressure'

- Resistance thus favours hospital infection:
- **Hospital infection is resistant infection**
- At any given time the common nosocomial pathogens are often resistant to the antibiotics in current use
  - *S. aureus* (MRSA)
  - Enterococci (GRE)
  - *Klebsiella/Enterobacter/Serratia*
  - *Ps. Aeruginosa/Acinetobacter etc.*

Which is safer?

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Increasing resistance and multi-resistance with time

- HOSPITAL
  - Penicillin, methicillin, ciprofloxacin in *S. aureus*
  - Glycopeptides in enterococci
  - Ampicillin, gentamicin, ESBLs in *E. coli*
  - Aminolycosides in *Ps aeruginosa*
- COMMUNITY
  - Penicillin etc in pneumococcus
  - MDR in Haemophilus
  - Penicillin, methicillin in *S. aureus*
  - Glycopeptides in enterococci
  - Ampicillin, ESBLs in *E. coli*
  - Ampicillin, ciprofloxacin in salmonellas
  - MDR in *M tuberculosis*

Increasing resistance and multi-resistance with time

- The gradual worldwide emergence of multidrug and 'pan-resistance'
- Associated with antimicrobial use & abuse and falling standards of hygienic practice

Health Protection Agency. Antimicrobial Resistance and Prescribing in England, Wales and Northern Ireland, 2008.

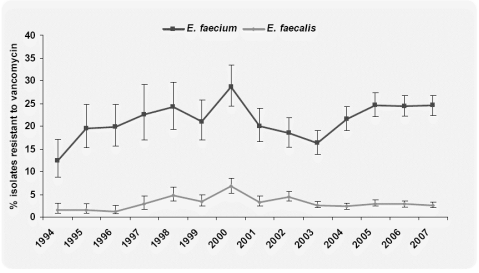
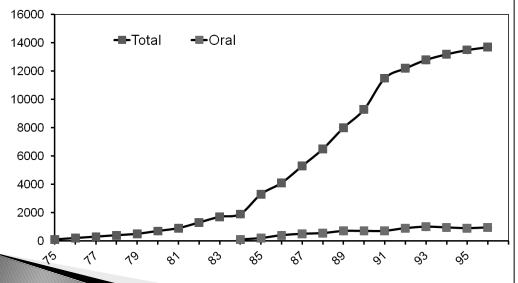


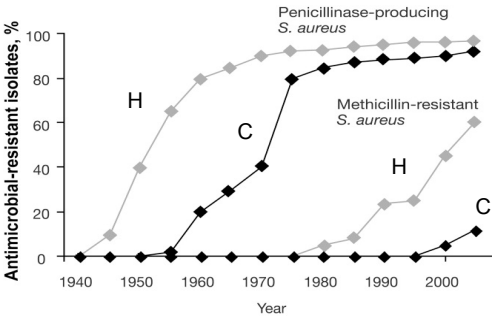
Figure 10: Resistance to vancomycin in *E. faeclum* and *E. faecalis* from bacteraemia, England, Wales and Northern Ireland, 1994-2007 (voluntary laboratory reporting)

Yearly vancomycin usage (Kg)

USA, France, Italy, Germany, UK, Netherlands

Kurst HA et al, AAC 1998;42:1303-4.





McDonald, Clin Infect Dis, 2006

MRSA Hospital Prevalence Rates* in Europe, 2001-2005

	2001	2005		2001	2005
Austria	8	13%	Denmark	0.8	2.0%
Belgium	22	31%	Finland	0.4	3.0%
Cyprus	n/a	56%	Sweden	0.9	1.0%
France	33	27%	Norway	n/a	< 1%
Germany	18	21%	Netherlands	0.5	< 1%
Greece	39	42%			
Ireland	42	42%			
Italy	41	37%			
Portugal	32	47%			
Romania	n/a	61%			
Spain	23	27%			
UK	45	44%			

*% of SA isolates that are MRSA.

European Antimicrobial Resistance Surveillance System (EARSS) Annual Report, 2001. EARSS Annual Report, 2005 (1-2). Interactive database results: www.rivm.nl/earss/result/Monitoring_reports/.

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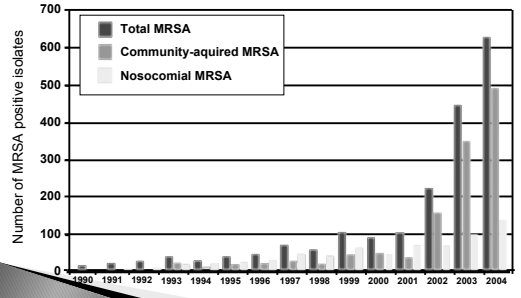
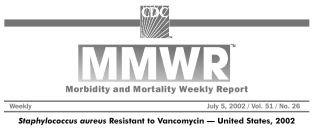
Number of MRSA isolates, Naval Medical Center San Diego, Ca.

Crum MF et al. *Am J Med.* 2006;119:943-951.



Vancomycin resistance
High level resistance due to *vanA*

Noble WC et al. Co-transfer of vancomycin and other resistance genes from *E. faecalis* NCTC 12201 to *Staph aureus*. FEMS Microbiol Lett 1992;93:195–8.



Vancomycin MIC >128 mg/L, teicoplanin 32 mg/L. Isolate contained *vanA* and *mecA*

Gentamicin
1994–2007
England, Wales, N Ireland

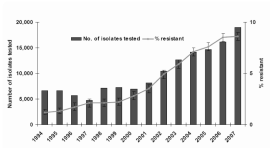


Figure 21: Resistance to gentamicin in *E. coli* from bacteraemia, England, Wales and Northern Ireland, 1994-2007

Health Protection Agency. Antimicrobial Resistance and Prescribing in England, Wales and Northern Ireland, 2008.

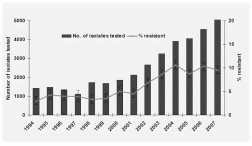


Figure 31: Resistance to gentamicin in *Klebsiella* spp. from bacteraemia, England, Wales, and Northern Ireland, 1994-2007

Ciprofloxacin
1994–2007
England, Wales, N Ireland

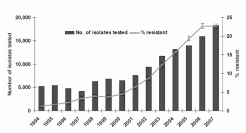


Figure 18: Resistance to ciprofloxacin in *E. coli* from bacteraemia, England, Wales and Northern Ireland, 1994-2007

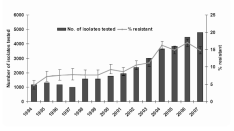


Figure 28: Resistance to ciprofloxacin in *Klebsiella* spp. from bacteraemia, England, Wales, and Northern Ireland, 1994-2007

Ceftazidime
1994–2007
England, Wales, N Ireland

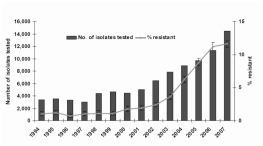


Figure 14: Resistance to ceftazidime in *E. coli* from bacteraemia, England, Wales and Northern Ireland, 1994-2007

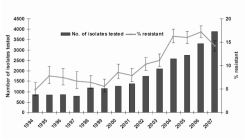


Figure 24: Resistance to ceftazidime in *Klebsiella* spp. from bacteraemia, England, Wales, and Northern Ireland, 1994-2007

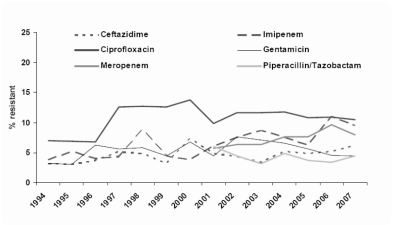


Figure 45: Trends in resistance of *P. aeruginosa* from bacteraemia to a range of anti-pseudomonal agents, 1994-2007

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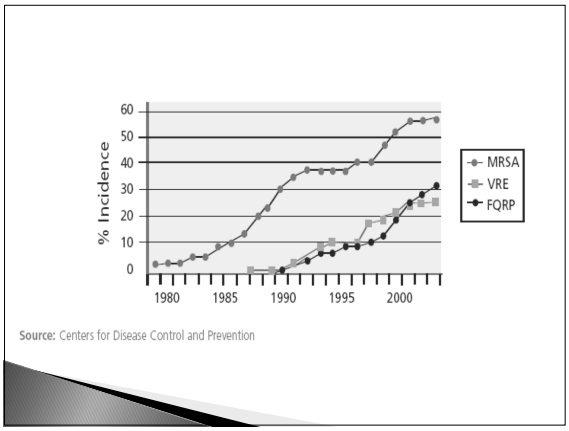

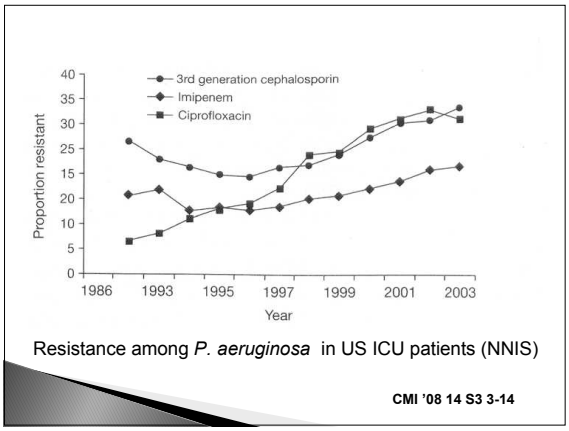

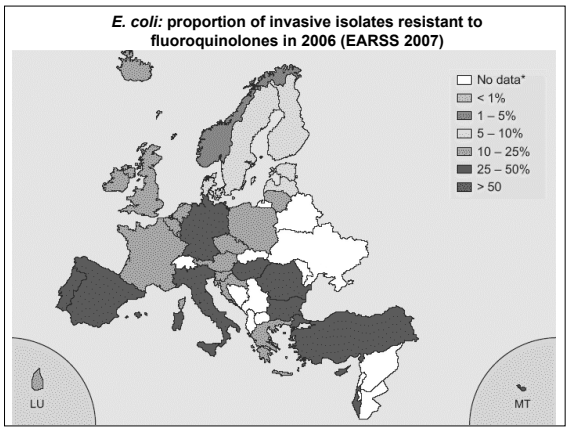

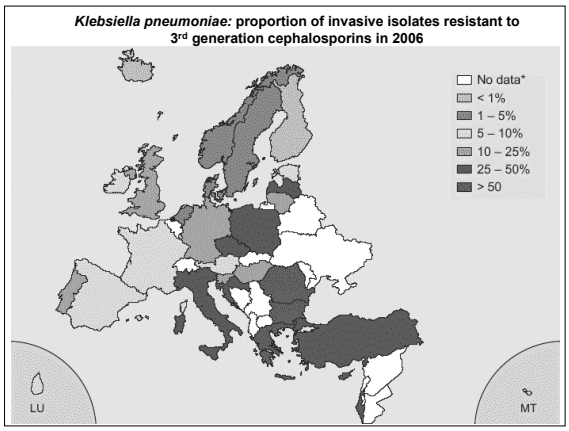

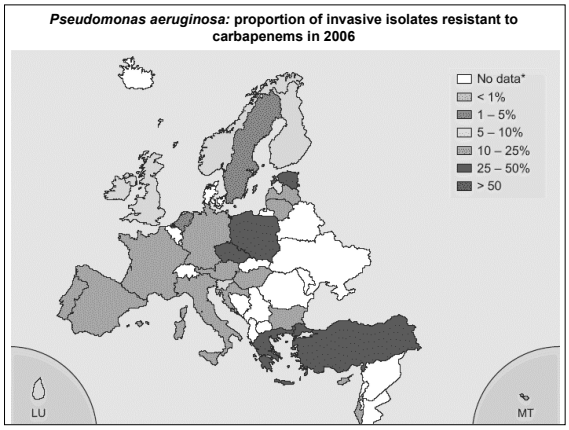

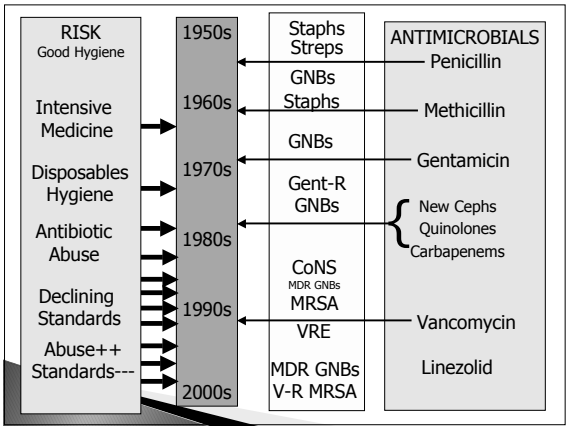

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Impact of Antibiotic Resistance

- **When adjusted for other risks:**
- Mortality rates, likelihood of hospital-ization and length of hospital stay, are generally at least twice as great for patients infected with resistant bacteria as for those infected with susceptible strains of the same species

Niederman MS. Crit Care Med 2001;29(4 Suppl):N114-20.
Cosgrove SE & Carmeli Y. Clin Infect Dis 2003;36:1433-7.
McGowan JE. Emerg Infect Dis 2001;7:296-292.
Singer ME et al. AAC 2003;51:1269–1282

Impact of Antibiotic Resistance

Patient	Hospital	Society/Other Patients
• Slower response to therapy/risk of infection • Extra investigations and treatment • Increased morbidity/mortality • Longer length of hospital stay • More absence from work	• Use of more expensive therapies • Control of infection • Use of "broad spectrum" antimicrobials—increased cost and potential adverse reactions	• Risk of spread of infection—in hospital and community • Exposure to greater adverse reactions

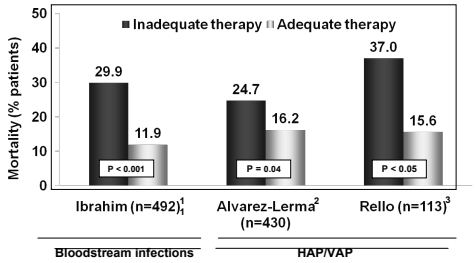
Adapted from Livermore D. *Clin Infect Dis.* 2003;36:S11-S23.

Meta-analyses show that MRSA infections have worse outcomes than MSSA

- MRSA bacteraemias had twice the mortality of those with MSSA
  - (OR, 1.93; 95% CI, 1.54–2.42)
- MRSA surgical site infections had significantly greater 90 day mortality, length of hospitalization and hospital charges

Cosgrove SE et al. *Clin Infect Dis* 2003;36:36:53–9.
Engemann JJ et al. *Clin Infect Dis.* 2003;36:592-598.

Inadequate Antimicrobial Therapy Associated With Higher Mortality



Ibrahim EH, et al. *Chest.* 2000;118:146-155. Alvarez-Lerma F. *Intensive Care Med.* 1996;22:387-394. Rello J, et al. *Am J Respir Crit Care Med.* 1997;156:196-200.

The crisis in antibiotic resistance

Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–1072.
Kunin CM. Resistance to antimicrobial drugs - A worldwide calamity. *Annal Int Med* 1993;118:557-66.
Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. Science 1992;257:1050–1055.

Concern over lack of antibiotics

- Infectious Diseases Society of America 2004. *BAD BUGS, NO DRUGS: As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews'*
- Norrby SR, Carl Erik Nord CE, Finch R, for the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Lack of development of new antimicrobial drugs: a potential serious threat to public health. *Lancet Infect Dis* 2005; 5: 115–19.
- European Academies Science Advisory Council (EASAC). *Tackling antibacterial resistance in Europe*. The Royal Society, London 2007.

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Prevention and control of MDR infections : Two main elements

- **The control of antimicrobial use** (ANTIBIOTIC STEWARDSHIP)
  - Appropriate, prompt therapy based on surveillance, combined with step-down
  - Reduction/elimination of all unnecessary antibiotic usage
- **The control of hospital cross-infection**

Antibiotics are different

- The only drugs that are:
  - Not directed against the patient
  - Taken at some time by almost everyone in the West
- Every treatment upsets microbial ecology
  - Alteration in the normal bacterial flora of patient and environment
  - Associated with an inevitable evolutionary change to antibiotic resistance

Antibiotic use & resistance

- "Consensus rarely exists on topics in infectious disease. Yet, authors of virtually all of the papers reviewed here [68 references] agree on the need for careful, discriminating use of antibiotics as being the keystone of our attempts to control resistant bacteria in the hospital"
- McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis 1983;5:1033–1048.

Value antibiotics

- Standing Medical Advisory Committee of the Department of Health (SMAC) '*The path of least resistance*' 1997:
  - '*prescription of an antibiotic should be seen as a serious step, similar to the prescription of steroids or any other potentially hazardous medicament*'
  - *'we should regard antimicrobial agents as a valuable and non-renewable resource, to be treasured and protected in their own, and everyone else's, interest*'

MRSA Bacteraemia Episodes: England, 2001–2008 (HPA website)

April-March	MRSA Bacteraemia Episodes	Rate per 10,000 OBDs
2001-2	7291	1.71
2002-3	7426	1.78
2003-4	7700	1.83
2004-5	7233	1.76
2005-6	7096	1.78
2006-7	6383	1.67
2007-8	4448	1.16
Fall since 2003	- 2978 - 40.1%	- 0.62 - 34.8%

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