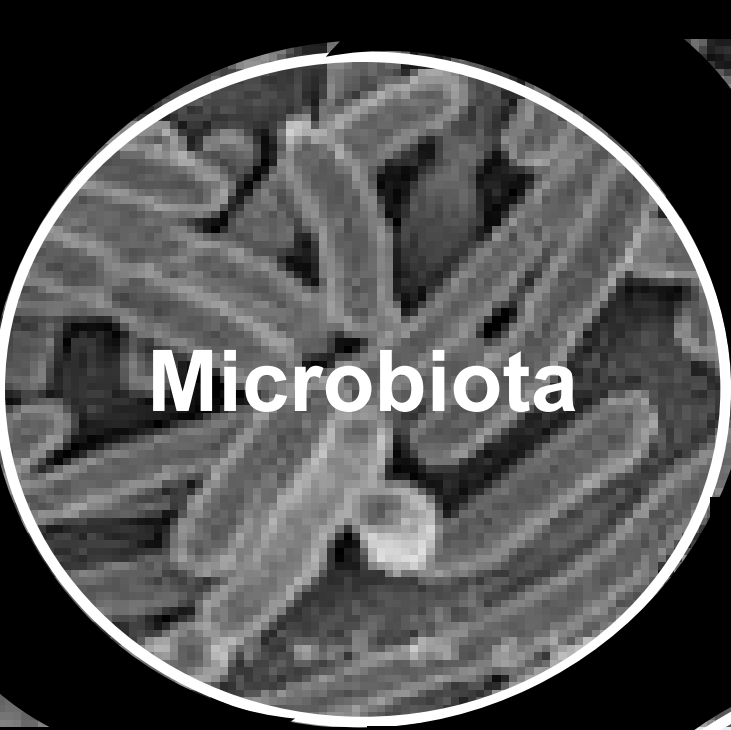


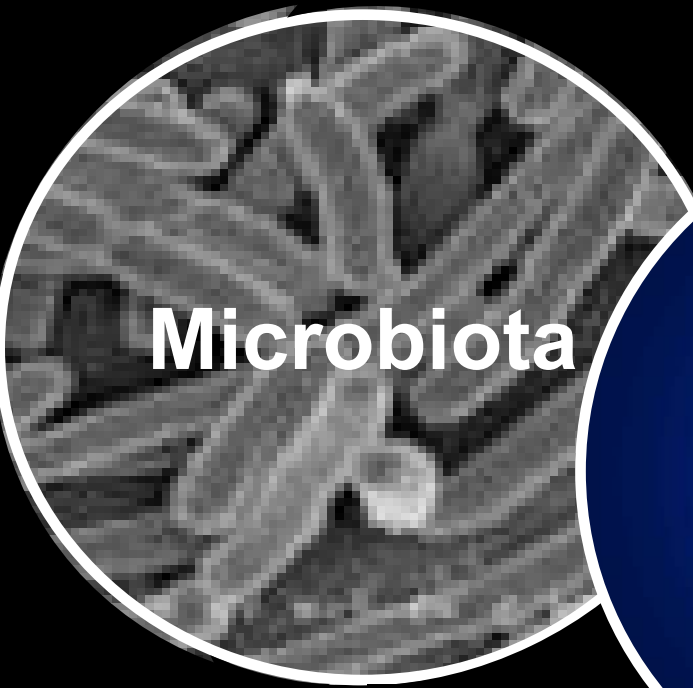
The consequences of antibiotic resistance

Professor Roger Finch

**he City Hospital and University of Nottingham
UK**







Microbiota



**Antibiotic
resistance**



Mankind



Government

A scanning electron micrograph (SEM) showing a dense population of rod-shaped bacteria. The bacteria are elongated, cylindrical structures with varying lengths and orientations. Some appear to have a textured or segmented surface. The background is dark, highlighting the three-dimensional structure of the microorganisms.

ANTIBIOTIC RESISTANCE

Antibiotic resistance

Agent	FDA approval	Resistance first reported
Penicillin	1943	1940
Streptomycin	1947	1947
Tetracycline	1952	1956
Gentamicin	1967	1970
Cefotaxime	1981	1983
Linezolid	2000	1999
Daptomycin	2003	2002

Antibiotic Resistance

the Community

Strep. pneumoniae

Haemophilus influenzae

Moraxella catarrhalis

MRSA

ESBLs

M. tuberculosis

HIV

In hospitals

◆ MRSA

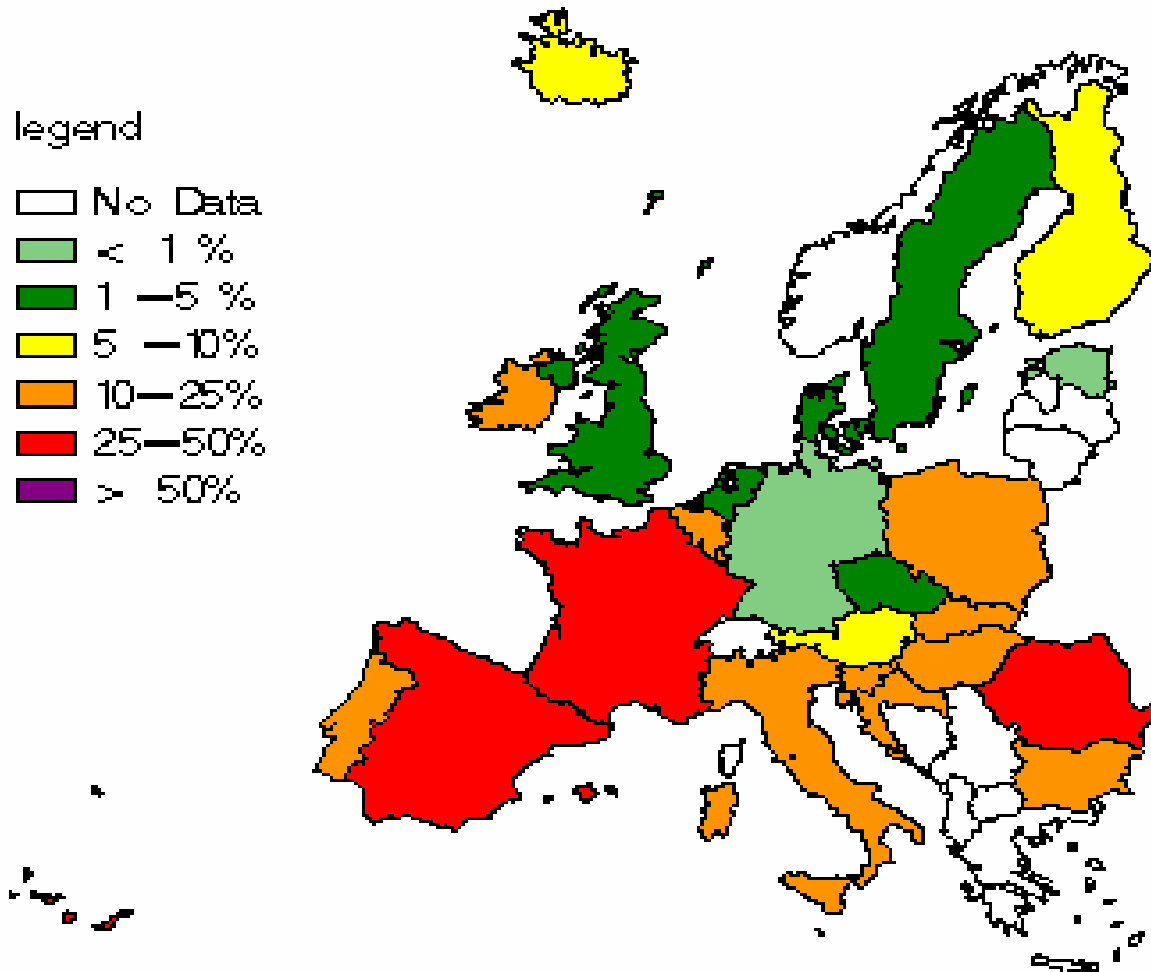
◆ *Candida* spp

◆ *Pseudomonas aeruginos*

◆ *Acinetobacter* spp

◆ ESBLs

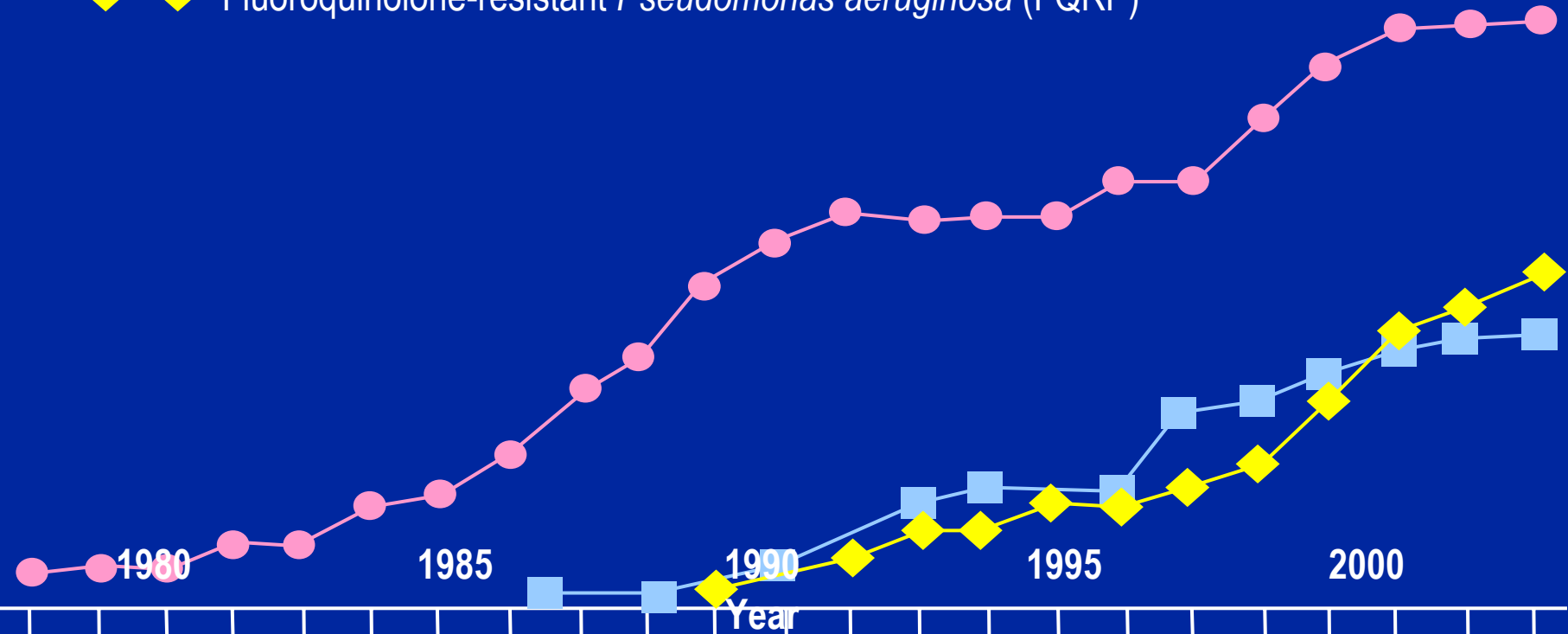
penicillin non-susceptible *S. pneumoniae* - 200



European Antibiotic Resistance Surveillance System)

Hospital acquired infection and antibiotic resistant pathogens (USA)

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci (VRE)
- ◆ Fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP)



VRE: vancomycin-resistant *E. faecium*

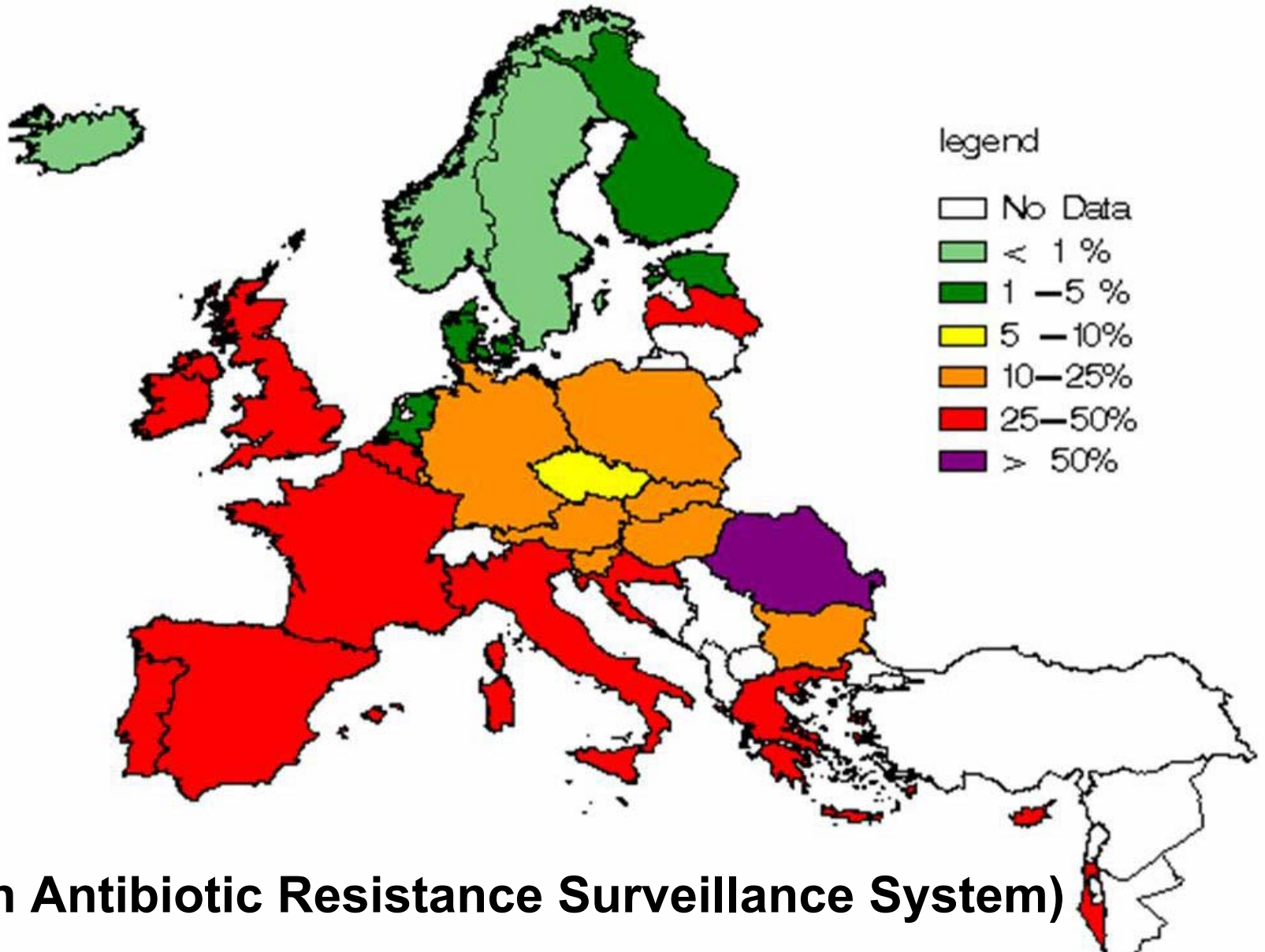
◆ In Europe in 2004:

- ◆ *E. faecalis* – 0.9% of isolates fully resistant; 0.3% showed intermediate resistance¹
- ◆ *E. faecium* – 9% of isolates fully resistant; 0.8% showed intermediate resistance

◆ Rates higher in the US:

- ◆ VRE – 28.5% of isolates resistant to vancomycin in 2003²

MRSA in Europe - 2004



European Antibiotic Resistance Surveillance System)

The changing pattern of community MRSA

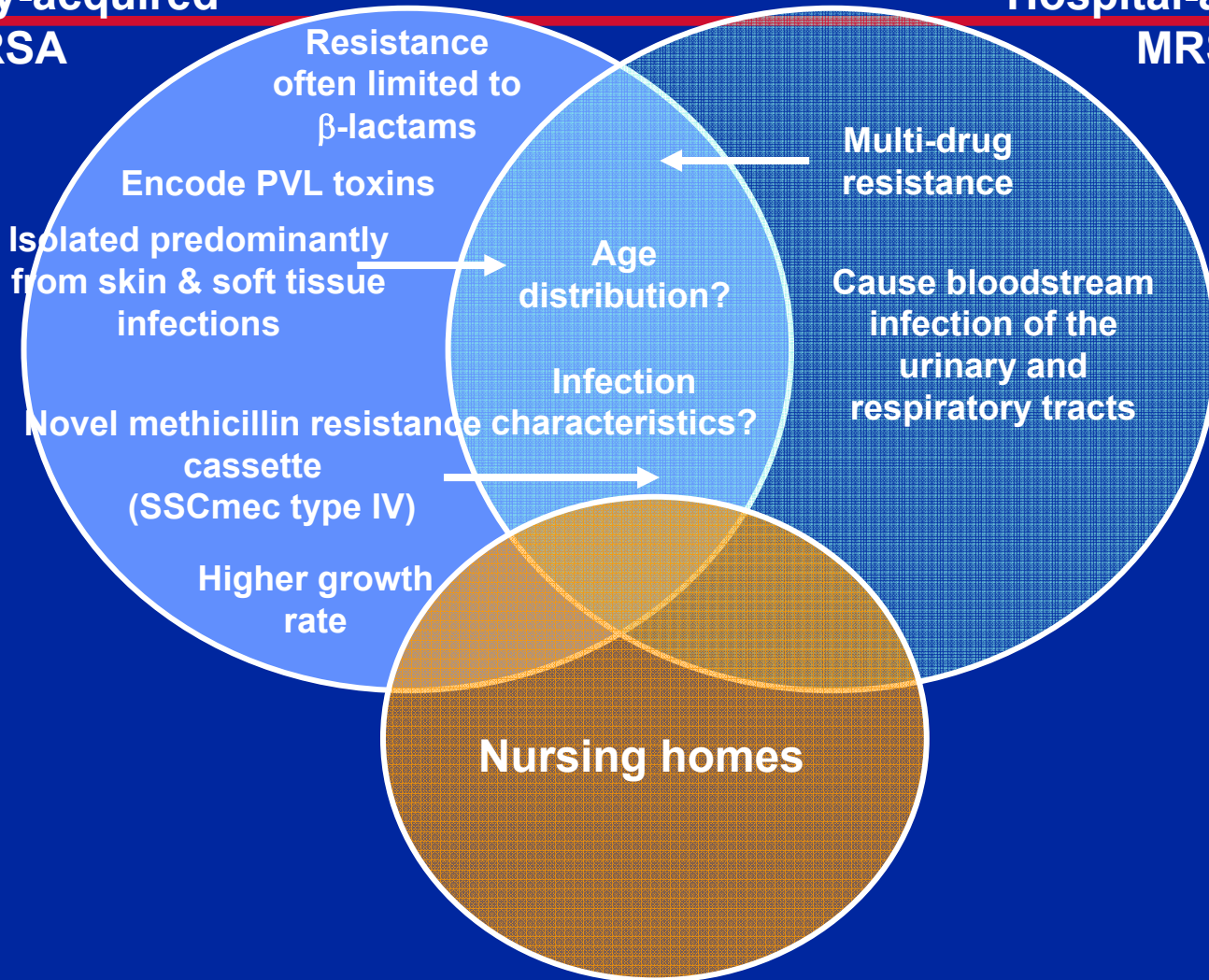
hospital and new community pathogens

Community-acquired

MRSA

Hospital-acquired

MRSA





IMPACT OF RESISTANCE

What is the clinical and economic impact of antibiotic resistance?

- ◆ failure to respond
- ◆ ↑ morbidity/mortality
- ◆ prolonged LOS
- ◆ ↑ complications of disease
- ◆ costs of alternative management
- ◆ time to return to baseline activities

Examples of increased mortality resulting from empirical and inappropriate versus appropriate antibiotic prescribing

Study	Relative mortality %	<i>p</i>	Reference
Gram-negative bacteraemia	37.2% v 19.5%	<0.05	Kreger et al, 1980
P*	24.7% v 16.2%	<0.039	Alvarez-Lima et al,
bacteraemia	34% v 20%	<0.0001	Leiberici et al, 1998
patients	52% v 12%	<0.001	Kolleff et al, 1999
P	91% v 38%	<0.001	Luna et al, 1999
bacteraemia	61.9% v 28.4%	<0.001	Ibrahim et al, 2000

VAP = ventilator associated pneumonia

Impact of resistance on antibiotic prescribing

Infection

Changing regimens

meningitis

sulphamide → trimethoprim → FQ

primary sepsis

chloramphenicol → ceftriaxone → vanc/TGC

gellosis

ampicillin → cephalosporins → FQ

eric fever

tetracycline → co-trimoxazole → FQ

orrhoea

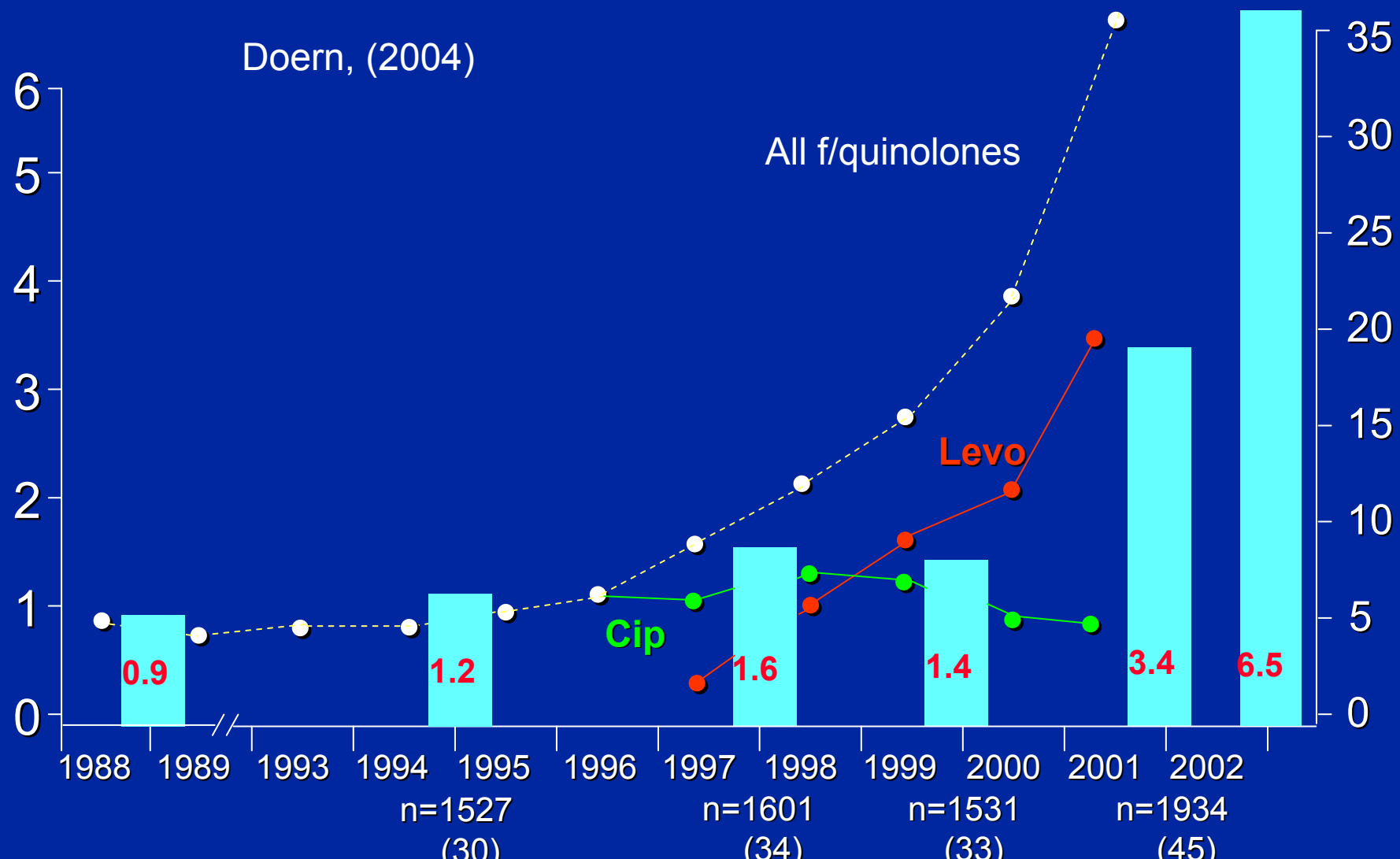
chloramphenicol → ampicillin → FQ

phylococci

penicillin → quinolone → ceftriaxone

penicillin → flucloxacillin → vancomycin

Impact of penicillin resistance and changing quinolone usage on *S. pneumoniae*: (USA)



Clostridium difficile-associated diarrhoea (CDAD) and antibiotic usage

Adjusted hazards ratio (95% CI)

<u>Antibiotic class</u>	<u>≥ 7 days</u>
Fluoroquinolones	4.33 (3.21-5.80)
Third-generation cephalosporins	1.75 (1.08-2.80)
Macrolides	2.09 (1.12-3.90)
Clindamycin	2.38 (1.15-4.90)
Intravenous β -lactam/ β -lactamase inhibitors	1.82 (1.15-2.80)



GOVERNMENT RESPONSE

**SUPERBUG
IS KILLING
OLD FOLK
IN HOMES**

**A voyage of
superbug
discovery**

**Infection teams working with
nursing staff to control MRSA**

Intensive care
**SUPERBUG
CASES
SOAR
AT QMC**

**to stop
spread
of killer
bug...**

MRSA in the UK: political & patient concerns

UK prevalence of MRSA is one of the highest in Europe

Political concerns

- ◆ UK Department of Health Mandatory Bacteraemia Surveillance Scheme
 - ◆ Mandatory for all NHS Acute Trusts in England since 1 October 2005
 - ◆ Data published every six months – latest data February 2006
 - ◆ Target 50% reduction in MRSA bacteraemias by March 2008

Patient concerns

- ◆ Patient action group (MRSA Action UK)

Economic impact of MRSA infection

- ▶ **MRSA more costly to manage than other types of infection^{1–3}**
 - ◆ Prolonged hospitalisation
 - ◆ Screening costs
 - ◆ Increased costs of isolation care
 - ◆ Added cost of second-line therapy
- ▶ **\$3.2–\$4.2 billion: estimated annual cost of MRSA infection to US hospitals⁴**

1. Archer et al. *Emerg Infect Dis.* 1999; 5: 9–17

2. Archer et al. *Infect Control Hosp Epidemiol.* 2001; 22:99–104

3. Archer, Samson & Sexton. *Infect Control Hosp Epidemiol.* 1999; 20: 408–411

4. Archer & Liu. Poster presented at ISPOR, 2005

Political Response to Antibiotic Resistance

House of Lords Select Committee 1998

Specialist Committee on Antimicrobial Resistance (UK) 2001

European CMOs Copenhagen 1998

WHO Global Strategy 2000

National Educational Campaigns

- Belgium 2000, 2001

- UK 1999, 2001, 2006



**Bad Bugs, No
Drugs
As Antibiotic
Discovery
Stagnates . . . A
Public Health
Crisis Brews**

Report: IDSA 2



Ministry of Health
Ministry of Food,
Agriculture and Fisheries
Denmark



The Copenhagen Recommendations

*Report
from the Invitational EU Conference on*

The Microbial Threat

*Copenhagen, Denmark
September 1998*

*Health of the population:
Strategies to prevent and control the emergence and
spread of antimicrobial-resistant micro-organisms*

Copenhagen recommendations: the response to antibiotic resistance

Better microbiological surveillance

Monitor drug utilisation

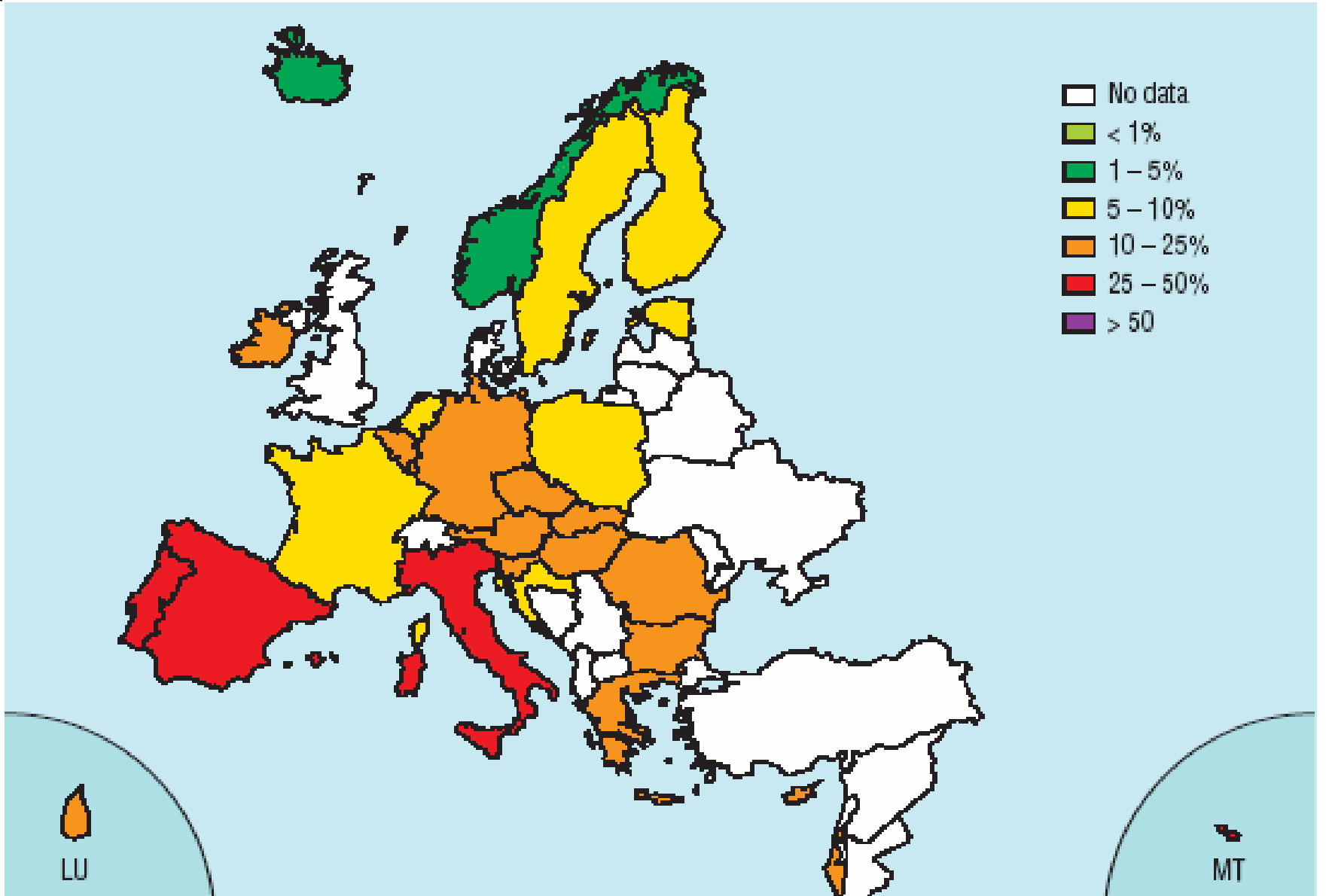
Promote prudent prescribing

Educate professionals & public

Promote infection control and hygiene

Encourage new drug and vaccine development.

Surveillance - example: EARSS map of E. coli showing fluoroquinolone resistance (2004)



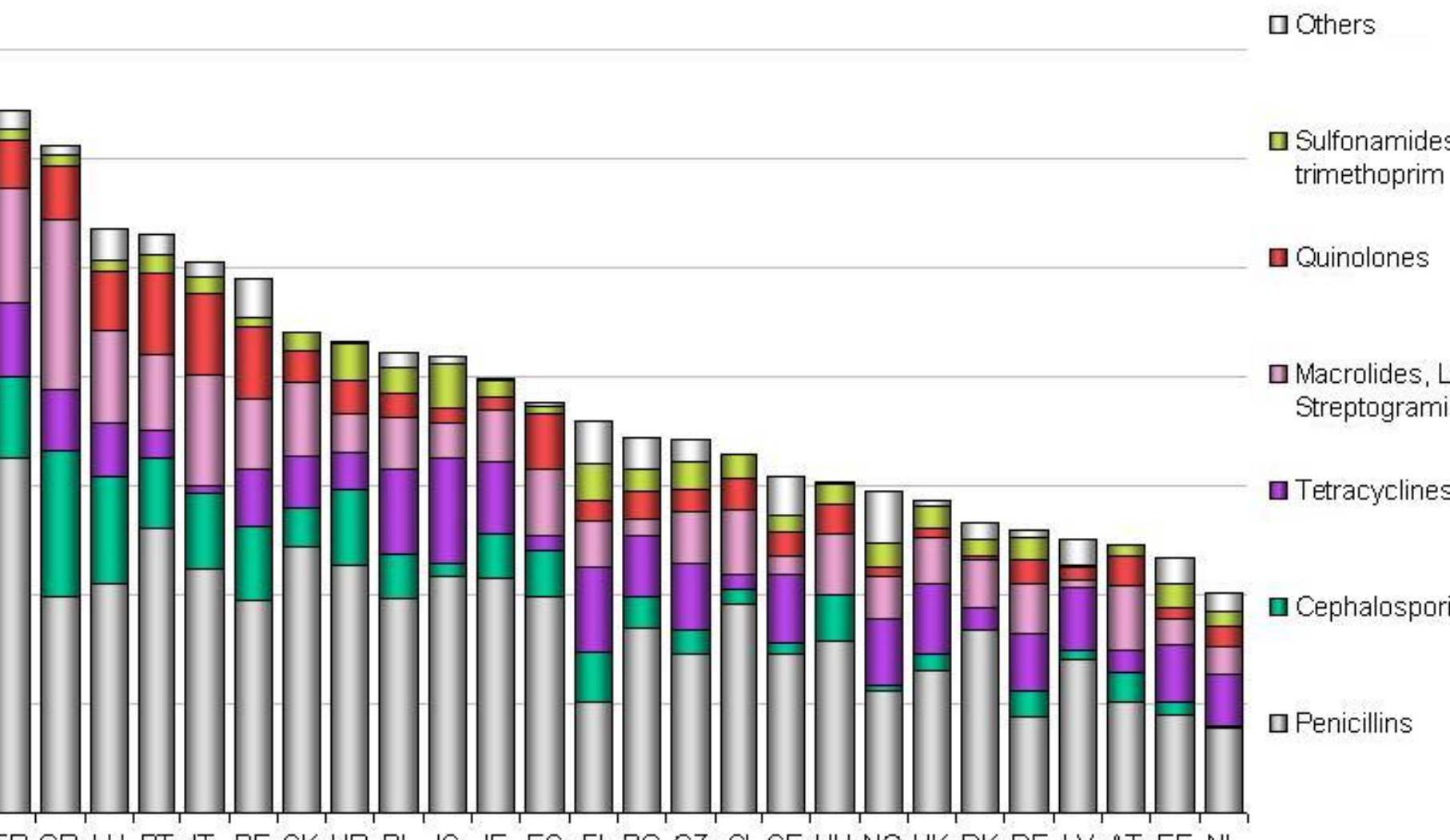
Weaknesses of current surveillance system

in vitro surveillance data

- ◆ not denominator controlled
- ◆ selective sampling
- ◆ not real time
- ◆ not linked to diagnosis
- ◆ not linked to prescribing patterns
- ◆ variable geographic coverage
- ◆ not always sufficiently local
- ◆ links to outcome data remain poor

Monitoring antibiotic Use In 26 European countries (2002)

<http://www.esac.ua>



The main cause of antibiotic resistance inappropriate prescribing practice

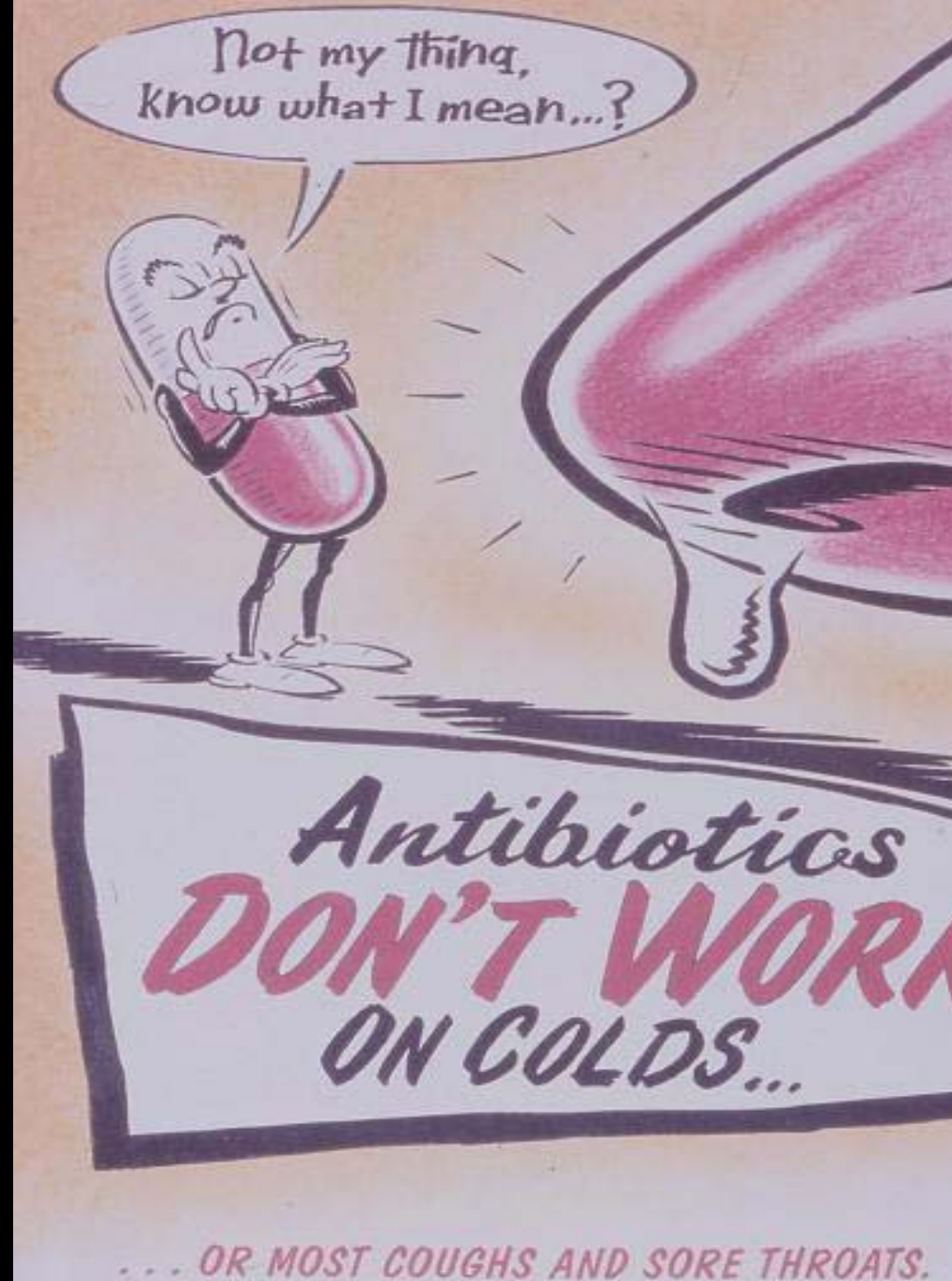
- Prescribing for community viral URTIs**
- Perioperative prophylaxis >24 h**
- Inappropriately prolonged courses of treatment for uncomplicated infections**
- Unnecessary use of multi-drug regimens**
- Under dosing or use of low potency regime**
- Failure to define the microbiological nature the target infection**

Promoting prudent prescribing

Definition:

The use of antimicrobials in the most appropriate way for the treatment or prevention of human infectious diseases, having regard to the diagnosis (or presumed diagnosis), evidence of clinical effectiveness, likely benefits, safety, cost (in comparison with alternative choices), and propensity for the emergence of resistance. The most appropriate way implies that the choice, route, dose, frequency and duration of administration have been rigorously determined.'

educational campaigns



Non-prescription pad



These 'non-prescriptions' can be given where appropriate to patients who do not need a prescription for antibiotics.

Diagnosis: Sore throat Ear Ache
Cold or Flu Catarrh
Dry Cough Other:
Chesty Cough

NO ANTIBIOTIC PRESCRIPTION NEEDED

The reason why . . .

- Your doctor has explained that antibiotics are not needed today to help you get better
- You probably have a virus infection
- Antibiotics don't work against viruses
- Your infection should start to clear up within a few days

Here are some things you can do to make you feel better:

Stay at home and rest if you have a temperature (feel feverish)

Drink plenty of water or soft drinks

Take paracetamol, according to the instructions on the packet, to bring down your temperature or if you are in any discomfort

Speak to your local pharmacist about other remedies you can safely take for your symptoms

Phone or visit the surgery for further advice if you are not getting better within a few days, or at any time if you are concerned about your symptoms

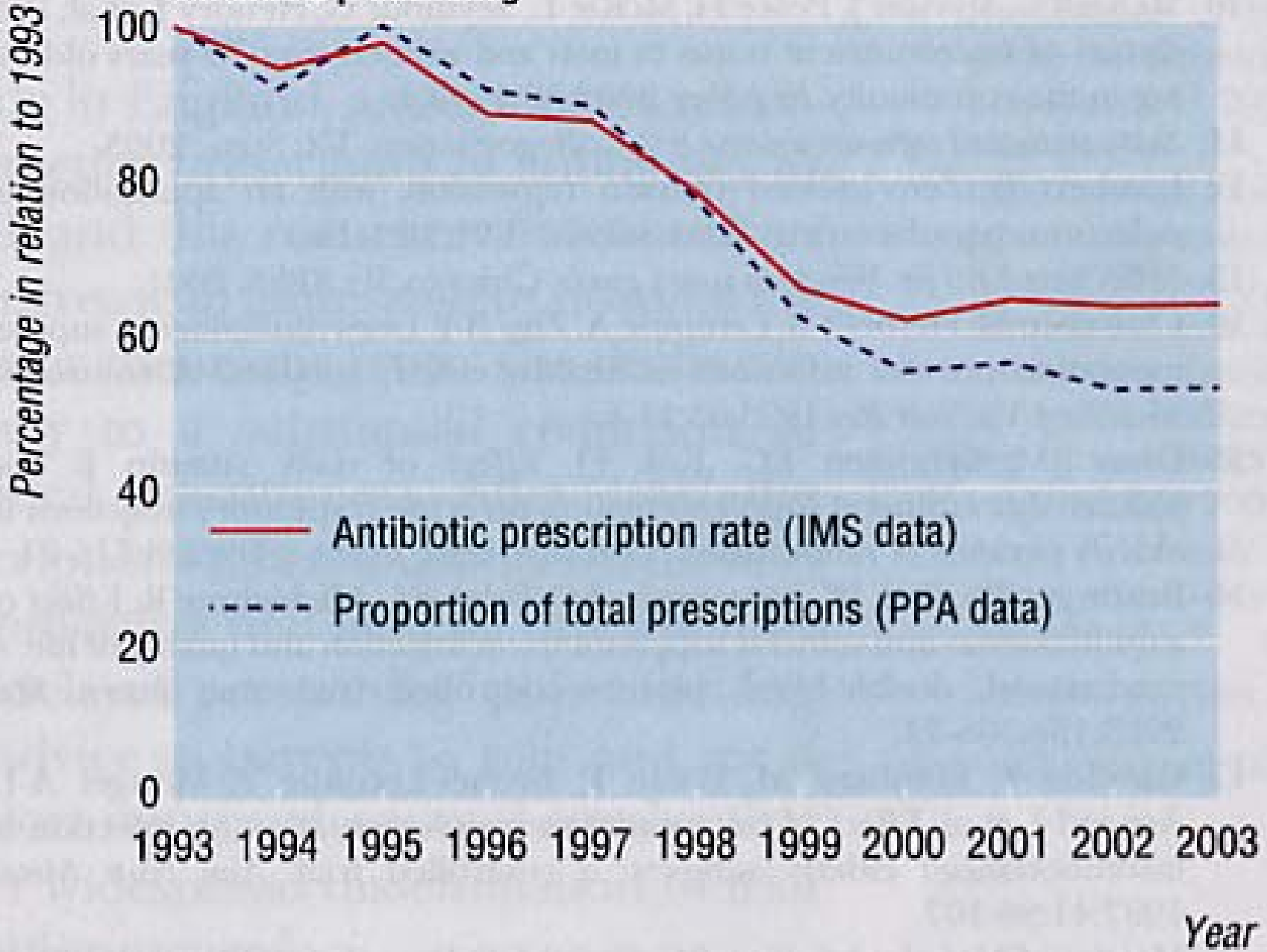
To order further pads quote NP PAD and:

- Fax 01623 724 524
- or write to PO Box 777, London, SE1 6XH

NHS

NHS

Antibiotic prescribing



Promoting hygiene & infection control

The path of least resistance – SMAC report 1998

Getting ahead of the curve: a strategy for combating infectious disease (2003)

www.doh.gov.uk/cmo/idstrategy/index.htm

Winning ways: working together to reduce HCAI (2003)

www.doh.gov.uk/cmo

National resource for infection control (2005)

www.nric.org.uk

Saving lives: a programme to reduce HCAI including MRSA (2005)

www.dh.gov.uk/reducingmrsa

Department of Health (2005): The delivery program to reduce HCAI including MRSA/Productivity Tool

Name **Nottingham City Hospital NHS Trust**
 Cost Reduction by 2008 **60%**

	2003/04	2004/05	2005/06	2006/07	2007/08
MRSA Bacteraemias	51	52	41	31	27
Cost- MRSA	£ 218,416	£ 222,698	£ 177,588	£ 132,477	£ 87,000
Additional Bed Days- MRSA	576	588	469	350	280
Potential Saving- MRSA	-	-	£ 45,111	£ 90,221	£ 135,332
Potential Bed Day Saving- MRSA	-	-	119	238	189
Total Bed Days Saved- MRSA	-	-	0.0%	0.1%	0.1%
All HCAIs	2,121	2,162	1,724	1,286	1,000
Cost- All HCAI	£ 9,082,988	£ 9,261,086	£ 7,385,123	£ 5,509,159	£ 3,633,000
Additional Bed Days- All HCAI	23,966	24,436	19,486	14,536	9,000
Potential Saving- All HCAI	-	-	£ 1,875,964	£ 3,751,927	£ 5,627,850
Potential Bed Day Saving- All HCAI	-	-	4,950	9,900	14,850
Total Bed Days Saved- All HCAI	-	-	1.7%	3.4%	3.4%

Strategies to contain the emergence of antimicrobial resistance (Cochrane Review)

systematic review (1960-2000) - 21 studies

- Restricting the use (5)
- Prescriber education, feedback and use of guidelines (6)
- Combination therapies (7)
- Vaccination (3)

Conclusion: overall, there is an absence of good evidence concerning what is effective in reducing the emergence of antimicrobial resistance.

“Magic bullet”

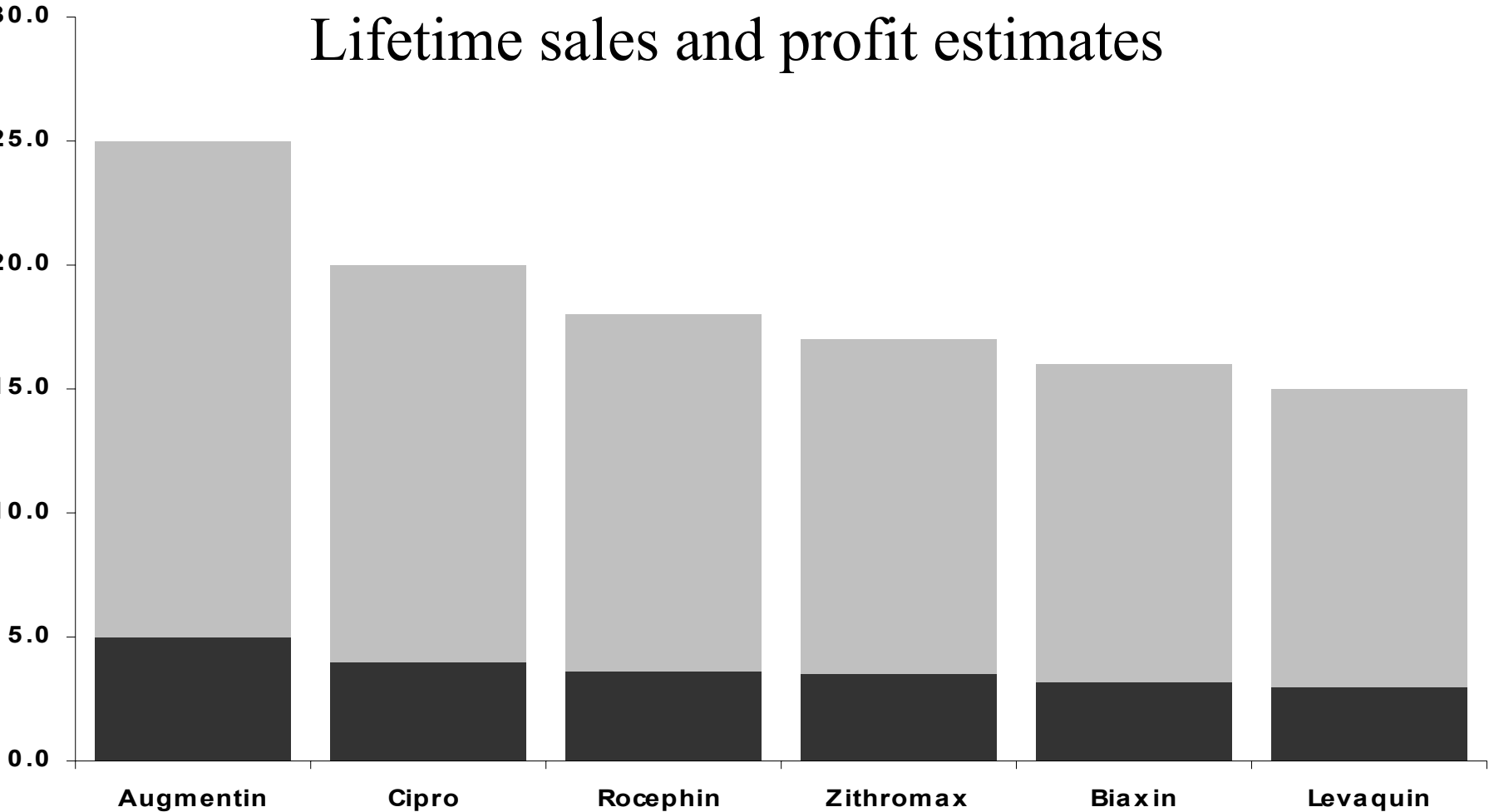


new drugs - the industrial drivers of innovation

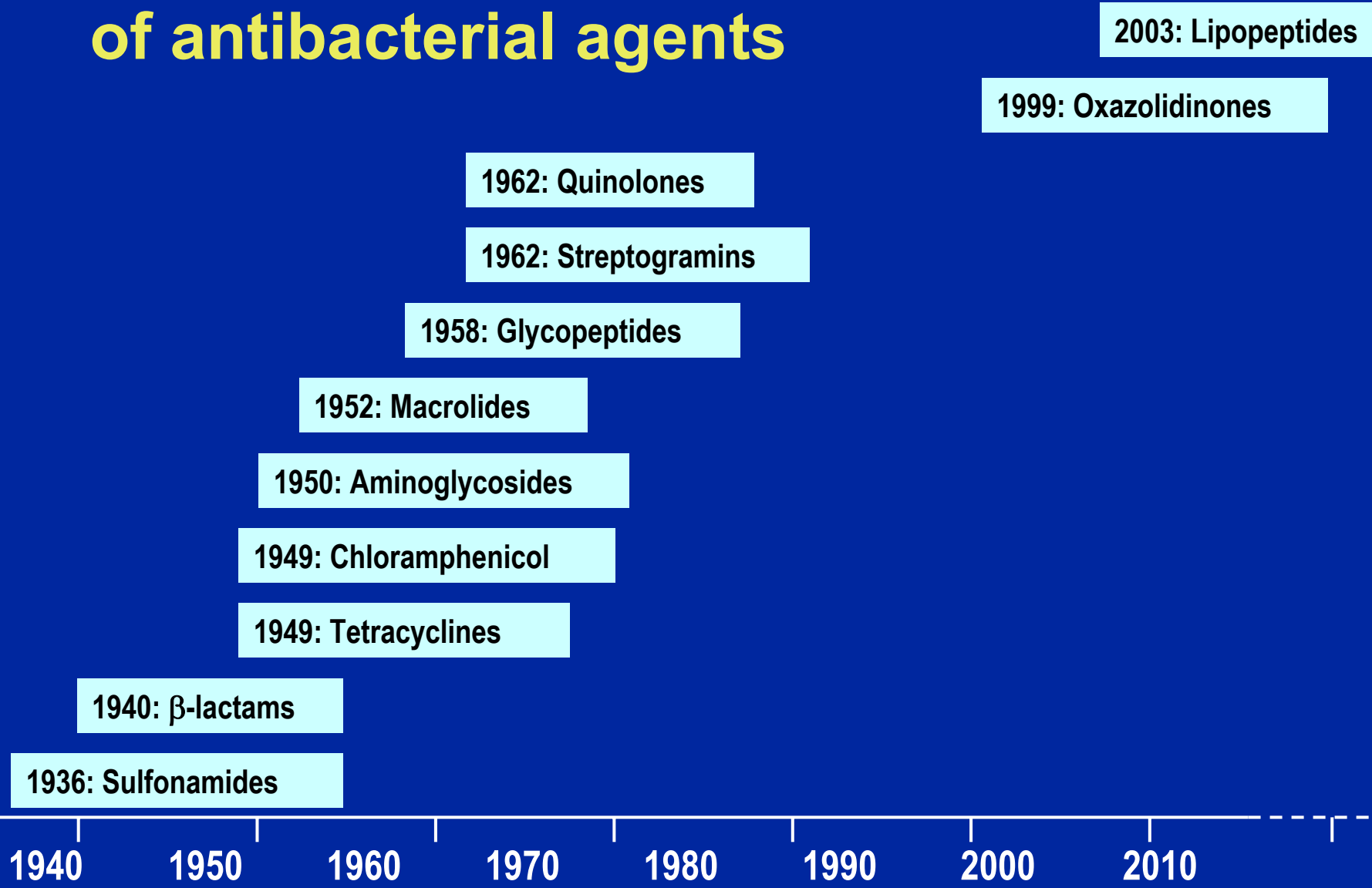
- ◆ **New diseases and new targets**
- ◆ **Enhanced microbiological activity**
- ◆ **Antibiotic resistant pathogens**
- ◆ **Improved pharmacokinetics**
- ◆ **More convenient regimens**
- ◆ **Improved safety**

Antibiotics have been very successful commercially

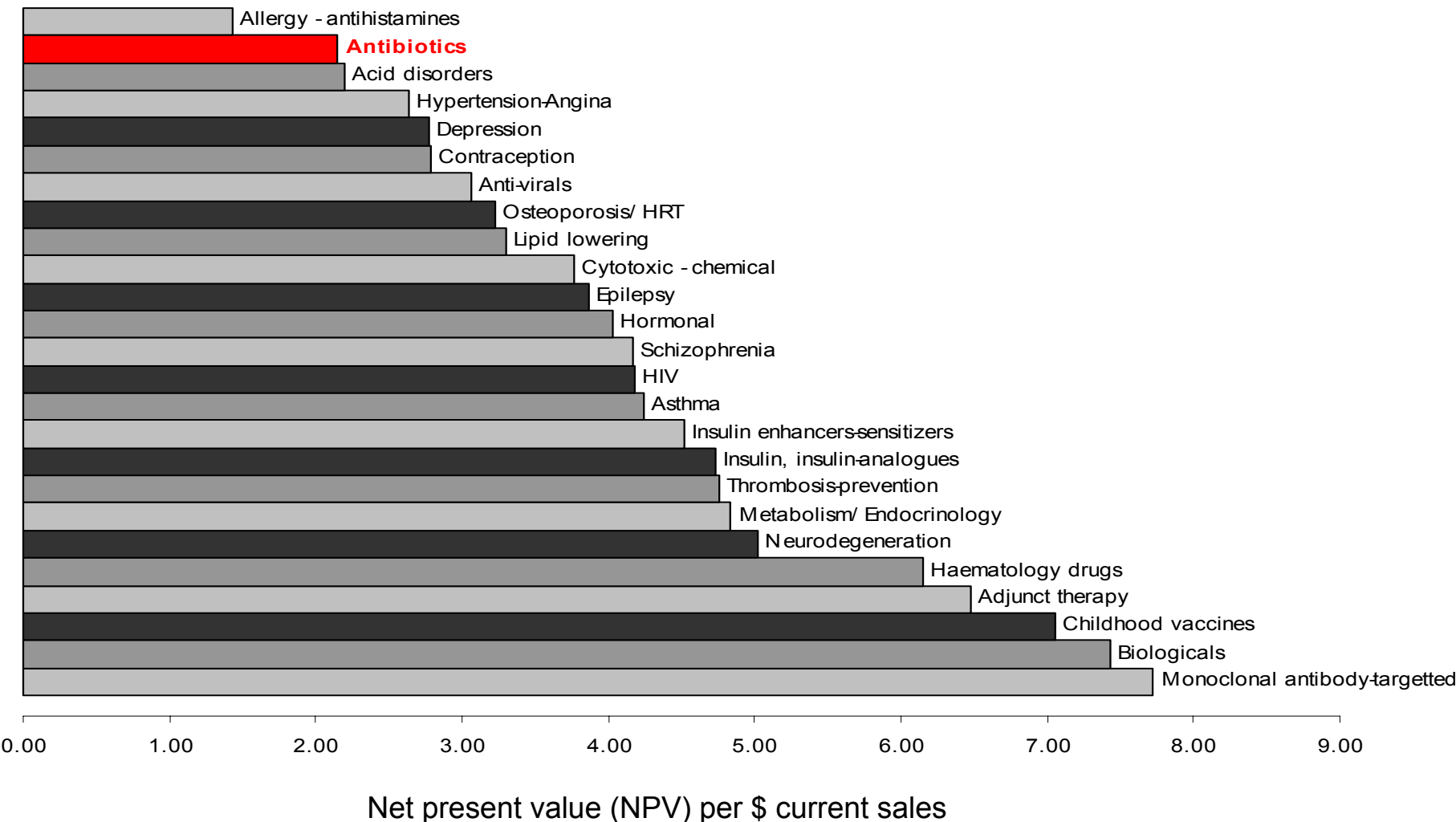
Lifetime sales and profit estimates



Development of new classes of antibacterial agents



Antibiotics show little opportunity compared with other therapeutic categories



Source: Lehman Brothers PharmaPipelines

European Union response to the technology gap

EU Conferences

- ◆ Copenhagen: EU health ministries 1998
- ◆ Rome: Research Solutions 2003
- ◆ Dag Hammarskjold Foundation meeting 2004
- ◆ “Priority medicines for Europe”
(Netherlands/WHO) 2005
- ◆ React Report - ‘Expert Report on a critical need
- ◆ Birmingham: the technology gap 2005

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- ◆ **Birmingham: the technology gap 2005**

FINCH

The Antibiotic Innovation Study:

Expert Voices on A Critical Need

Sophia Tickell, November 2005

Antibiotic innovation study 2005

“Expert Voices on a Critical Need”

- Commissioned by REACT - a joint initiative by the Dag Hammarskjold Foundation, Strama and Division of International Health, Karolinska Institute**
- Summarises in-depth interviews with key leaders in industry, academia, medicine, reimbursement authorities**
- Conclusion - urgent, concerted action to promote new technologies is essential**

EU INTERGOVERNMENTAL CONFERENCE

Antibiotic resistance Action to promote new technologies

(anti-infective drugs, vaccines and diagnostics)



12-13 December 2005

International Conference Centre, Birmingham, UK

PROGRAMME

Organised by:

United Kingdom Specialist Advisory Committee
on Antimicrobial Resistance on behalf of the
Department of Health

Supported by:

British Society for Antimicrobial Chemotherapy

EU INTERGOVERNMENTAL CONFERENCE
**Antibiotic resistance:
Action to promote new technologies**
(anti-infective drugs, vaccines and diagnostics)



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Invited delegate
EU MS representative
EC Directorates
Big Pharma
Biotech companies
Diagnostic companies
Academia
Financial sector
Healthcare managers
EMEA

Press J Antimicrob Chemotherapy

EU conference - Antibiotic resistance

- action to promote new technologies

note presentations

Why action is needed today - *Otto Cars*

clinical perspective: the need for new drugs, vaccines and diagnostics - *Roger Finch*

Why is big pharma reducing investment in antimicrobials - *Andrew Witty*

Can biotech fill the technology gap? - *Gerard Zettlmeissl*

The commercial potential of antibiotics: an investor perspective - *Stewart Adkins*

view from the USA – *Todd Weber (CDC)*

EU conference - Antibiotic resistance

- action to promote new technologies

Workshop 1 - Linking surveillance to identify unmet needs and define the research agenda

Workshop 2 - Obstacles to greater acceptance of new technologies in healthcare

Workshop 3 - The commercial reality of antibiotic innovation - how can the barriers be overcome

Workshop 4 - European regulatory opportunities to encourage new agents

Workshop 5 - Leadership, policy and partnerships to support innovation

Key conclusions

The need for new healthcare technologies is endorsed

New funding models need to be identified, especially for phase I studies

New near-patient diagnostics should be developed to sustain the effectiveness of existing antibiotics

Healthcare systems need to recognise their technology gaps and demonstrate greater acceptance to pay more for innovation

Regulatory processes need to be harmonised, streamlined and supportive of earlier licensing

Leaders, champions and advocates are essential to articulate the need for new technologies to the public and the EU

