

**A view from Industry:
Past, present and prospects for
the future**

March 2011

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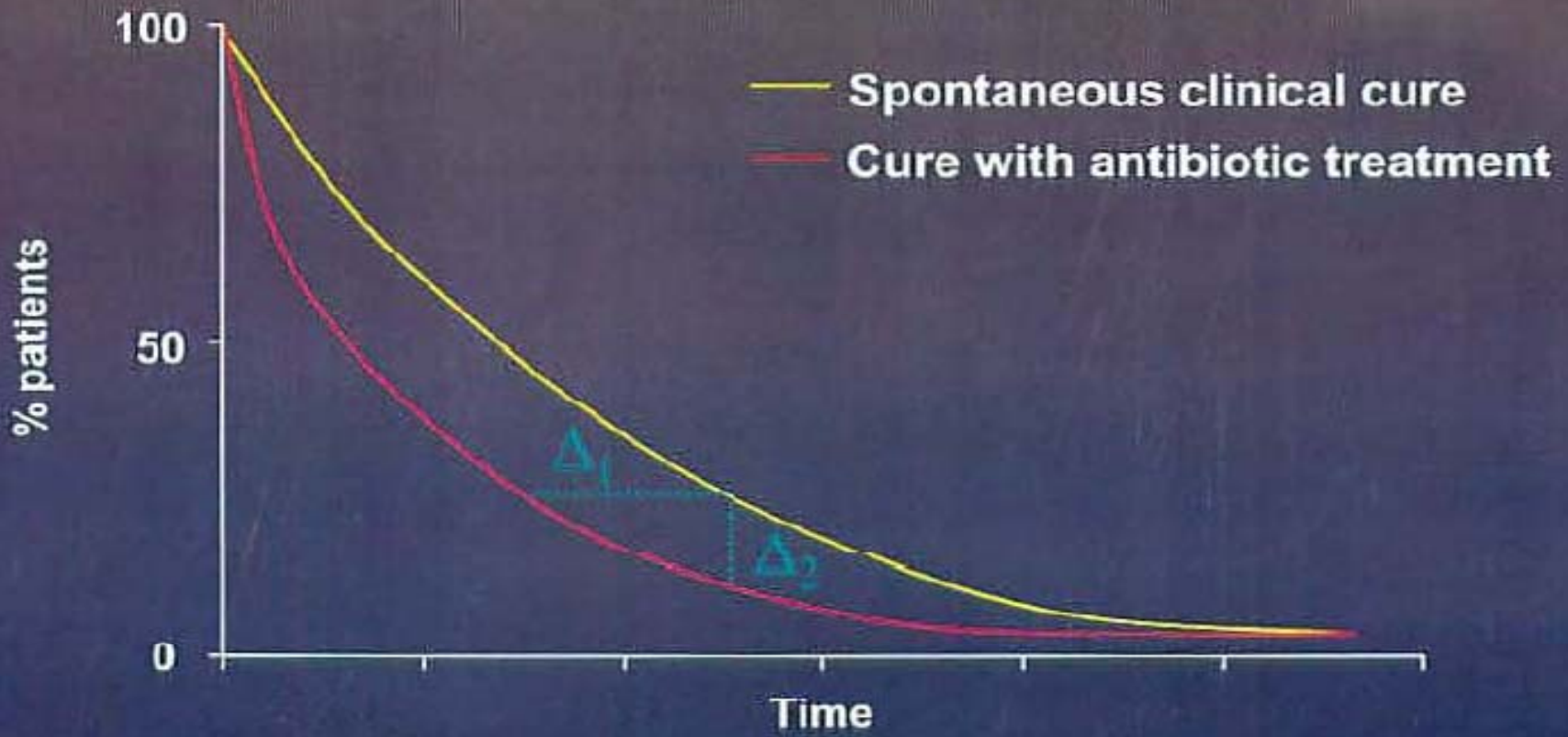
Antibiotics

- Perception of great value
- Increased expectations
- Mature large market with little actual demonstrable differentiation
- 1930s-1980s: Challenge of identifying and developing new antibiotics
- 1990s-more complex definition of most appropriate use and 'omics'
- 2000s-where are the new ones?

Antibiotic Ages

1935-60	Sulphonamide Penicillin Macrolides Cephalosporins Nalidixic acid	Tetracycline Streptomycin Aminoglycosides Vancomycin Rifamycin
1960-75	New Quinolones Penicillin's	New penicillins Trimethoprim
1975-90	Ciprofloxacin β -lactamase Inhibitors Imipenem	2 nd Generation cephalosporins Azithromycin Clarithromycin
1990-2000	Meropenem	Synercid
2000-2006	Ertipenem Tigacycline Linezolid	Gemifloxacin Daptomycin
2007	?	

Spontaneous cure vs. antibiotic treatment



GSK promise (Merger-2000)

- Higher R&D and marketing costs ✓
- More launches ✗
- More diverse customers, market emphasis on value ✓
- Earlier launches, quicker market penetration ✗
- Shorter period of exclusivity and rapid loss of market share post patent ✓
- More competitive, lower price and lower market share ✓
- Less products break even or make money ✓

Top ten selling anti-infectives 1998

		\$ 1998	% share
Augmentin	SmithKline Beecham	1,593	4.1
Ciproxin	Bayer	1,478	3.8
Biaxin	Abbott	1,160	3.0
Rocephin	Roche	1, 124	2.9
Zithromax	Pfizer	1, 041	2.7

Superbugs and Superdrugs

Small Pharma

Arpida ✗

Ambi ✗

Avi Biopharma ✗

Basilea ✓

Biosearch Italia ✓

Biosyn ✗

Cubist ✓

Elitra ✗

Genome Therapeutics ✗

GPC ✗

Inhibitex ✗

Integrative Proteomics ✗

Intrabiotics ✗

Ligocyte ✗

Millenium ✗

Microcide ✗

Nabi ✗

New Biotics ✓

Nat Immune ✗

Panthecho ✗

Ribotargets ✗

Novozyme ✓

Pantherix ✗

Paratek ✓

Peptide Therapeutics ✗

Quorex ✗

Ribogene ✗

Siga ✗

Versicor ✓

Xoma ✗

Antimicrobial Resistance

- Increasing use of antibiotics
- Increasing resistance
- Across ALL classes of antibiotics
- No totally new classes of antibiotics launched
- Hospital and NOW community
- Magnitude and rate of change and effect on patient outcomes are poorly defined and incompletely understood

Antibiotics active against *Enterobacteriaceae*

Compound	Company	Phase	Notes
Ceftazidime + NXL104	AZ	II	Not MBL's
CXA-101 + tazobactam	Calixa Cubist	II	Not carbapenemases
P2601	Protex Novartis	II	Not carbapenemases
CHN-490	A chaogen	II	<i>Not Protease spp</i>
CXA + tazobactam	Cubist	II	<i>P. aeruginosa</i>
Boron antibiotic	GSK	I	<i>Enterobacteriaceae</i>

Antibiotics active against *Enterobacteriaceae*

Compound	Company	Phase	Notes
BAL 30072	Basilea	I	Not KPC's
Ceftaroline +NXL104	AZ	I	Not MBL producers
AN 3365	Anacor GSK	I	?
Carpenem + ME1071	Meiji	Preclinical	Not MBL carbapenemases
New polymyxins	N antibiotics	Preclinical	Not <i>Serratia spp</i> , <i>Proteus spp</i>
Efflux pump inhibitors	MPEX	Preclinical	<i>Pseudomonas aeruginosa</i>
POL 7080	Polyphor	Preclinical	<i>Pseudomonas aeruginosa</i>

FDA Approvals New Antibiotics 2003 - 2011

Daptomycin	Yes	cSSSi/Endocarditis, bacteraemia
Oritavancin	No	
Telavancin	Yes	cSSSi, not HAP/VAP
Cethromycin	No	
Ceftibiprole	No	
Ceftaroline	Yes	CAP, cSSSi

Approval rate 50%

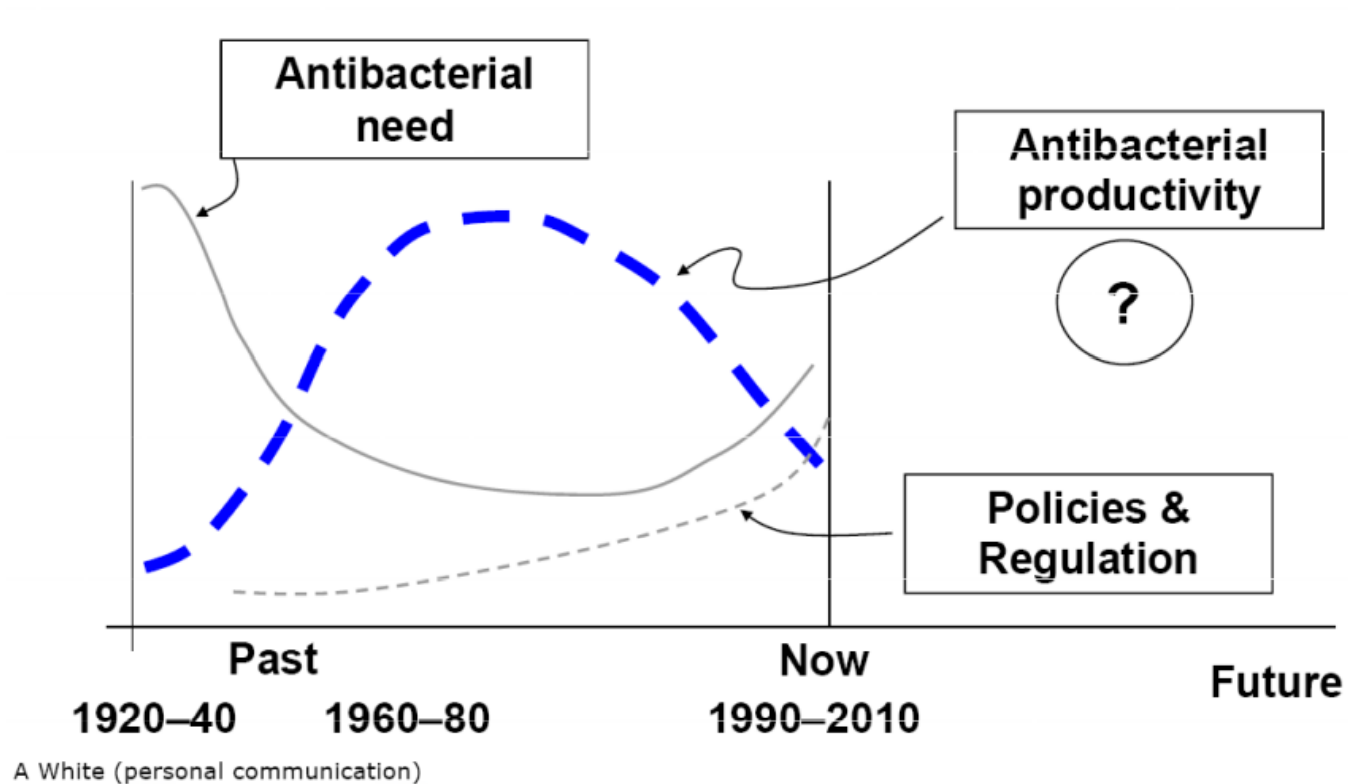
Pharma investing in antibiotic R&D

- GlaxoSmithKline
- AstraZeneca
- Novartis
- Sanofi Aventis
- Merck

Challenges in developing new antibacterial drugs. K.J.Williams, R.P Bax. Curr. Opin Invest Drugs 2009 10 (2) 157

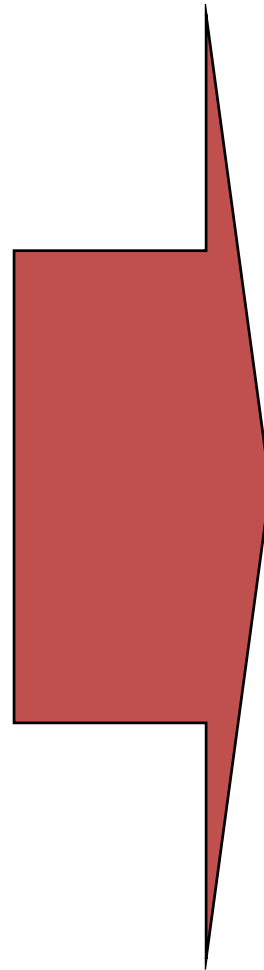
- Regulatory activities have had a major negative impact on the R&D of new antibiotics.
- Pharmaceutical companies have abandoned R&D.
 - Lack of successful R & D on 'gram negative' antibiotics.
 - Easier R & D for 'gram positive' antibiotics.
- Lack of expertise from R & D commercial groups.

Antibacterial need vs productivity



Successful Therapies – New Problems – Challenge 1

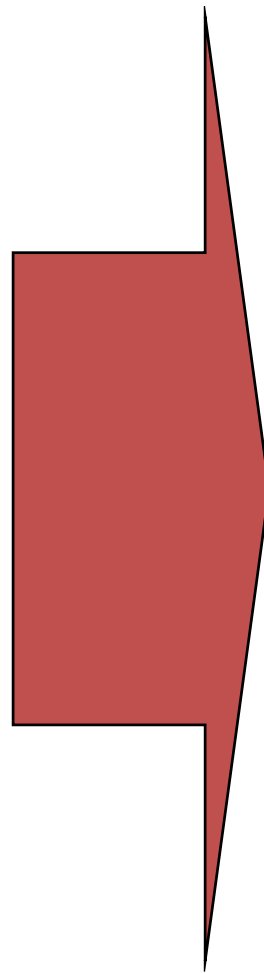
- Infectious disease morbidity and mortality was decreasing
- Progress was, in large part, due to antibiotics
- Due to the large growth in other markets and relative ease of discovering new compounds compared to antibacterials, some companies have halted antibiotic discovery and development



- But new problems are emerging leading to increases in morbidity and mortality
- Demand for and use of antibiotics exceeds rational role
- Proliferate use linked to increased bacterial resistance leads to pressures to reduce antibiotic use

More Rational, But less Intuitive Choices Have Led to More Complex Decisions - Challenge 2

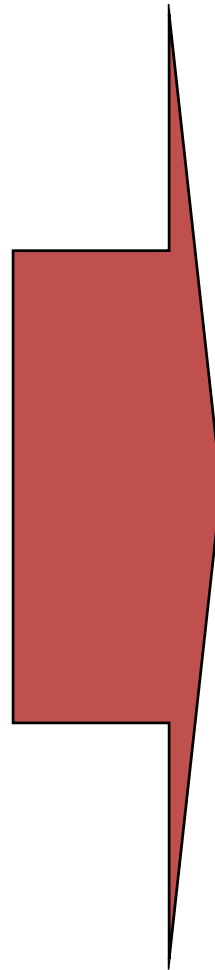
- Many antibiotic classes available with well defined but overlapping antimicrobial effectiveness
- Rationale prescribing difficult except to constantly reduce use



- Questionable link between use of antibiotics and improved patient outcome in some infections
- Most appropriate choice not clear, even in common infections
- Clinical and societal implications of bacterial resistance of concern but implications unclear

More Available Data, Less Useful Knowledge - Challenge 3

- Increased regulatory demands for clinical trials, other data and multiple analysis, interpretation and reporting
- Large and growing research, clinical, and community database
 - Omics
 - Sensitivity/Resistance Patterns
 - Prescribing Patterns
 - Healthcare Utilization
 - Demographics and Clinical Data



- But...
- Market small compared to others
- Data Sources/Databases isolated
- Episodes of Care Unconnected
- Patients Outcomes not documented

Current Antibiotic Situation – 4

Increasing concern on use and spread of bacterial resistance and lack of new antibiotics

- Fears of “andromeda strain” growing
- Many bacteria are promiscuous and have acquired resistance to multiple classes of antibiotics
- Many initiatives to combat antibacterial resistance in developed and developing World

- Significant reduction in antibiotic market especially in profitability
- Very few “new and novel” antibiotics discovered since the 1960’s. In spite of promises of riches in the 90’s, very few new and novel antibiotics in pre-clinical or clinical trials
- Will they come in time?

Antimicrobial Resistance

- Will the development of new products keep pace with the rapid development of bacterial resistance?

Conclusion

- The rise of MDR pathogens has now outstripped the available antibiotics
- The introduction of new antibiotics will lag behind the need for new antibiotics to treat these infections
- Large pharma has decreased activity in Europe and the US and is increasing activities in the developing world
- Narrow spectrum agents used in combinations will be the norm.

“The difference between a sick organism and a healthy organism constitutes the difference between success or failure. If we are to extend the problem into modern pharmacology then we have no option than to learn to shoot better.”

Paul Erlich 1908

Backup slides



TOP 20 MOST IMPORTANT MEDICAL DEVELOPMENTS OF THE LAST 50 YEARS
As voted by Fellows and Members of the Royal College of Physicians of Edinburgh, November 2010*

2. Imaging
3. Anti-TB therapy
4. Tobacco control
5. Angioplasty
6. Randomised controlled trials
7. Anti-viral therapy for HIV
8. Statins
9. Kidney dialysis

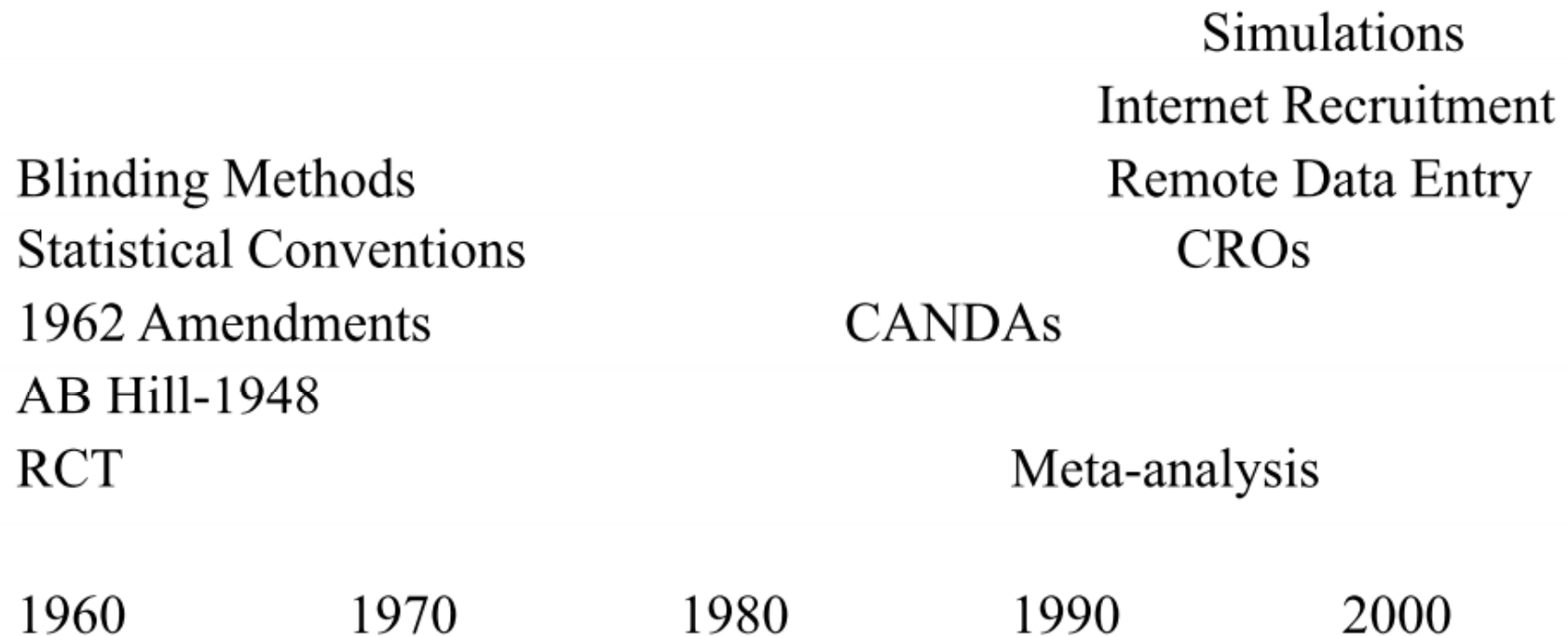
Late Preclinical Companies at ICAAC 2005

- Arpida spin off from Roche, Iclaprim IV Phase III, PO Phase I
- Basilea spin-off from Roche, Ceftobiprole licenced to J&J
- Blanca, BP-102 carbacephem
- Cerexa PP1-0903, TAK-599
- Meij Seika carbapenem ME1036, CP5609
- Nereus Pharma, 4-oxazolidinones
- Novexel, Betalactamase inhibitor, oral streptogramin, S.aureus topoisomerase inhibitor
- Optimer, PAR 101 for C. difficile diarrhoea
- Rib-X, designer oxazolidinones
- Romark, nitazoxanide, tizoxanide for C. difficile associated diarrhoea
- Theravance, Televancin linked to Astellas
- Replidyne, faropenem
- GSK, Topical pleuromutalin

Bad Bugs No Drugs

- 15 major Pharma and 7 major biotech companies previously in antibiotics
- Only a few new antibiotics being developed but 67 new drugs for cancer

Systems View of Medical Innovation Clinical Development



Whitley Park – May `98 – RCT's

Concept	Scientifically accepted	Over emphasis on outcome as truth – EBM inhibits development of alternatives
	Equivalence	Is equivalence needed?
Conduct	Capable of rigour	Costly, complex, difficult practically
	Long and Short term	Short term only
Interpretation	Internally valid	Externally less valid
		Poorly predictive for individual prescribing decision

Whitley Park – May `98 – RCT's (Cont'd)

Application		
Industry	Good for registration and marketing	No demonstration of superiority
Physicians	Efficacy and safety known versus standard antibiotics	Mean results only extrapolation to real patients difficult
Microbiologists	Confirmation of S category	No confirmation of I or R category
Society	Some benefits and costs clarified	No long term epidemiology
	Development of resistance in few and selected patients	No data on spread of sensitive/resistant organisms
		True costs and outcomes seldom determined

Development Response

- The paradigm for clinical development has not changed over the past three decades
- In general we do more of the same and have invested little in new methodologies

Academic Critiques

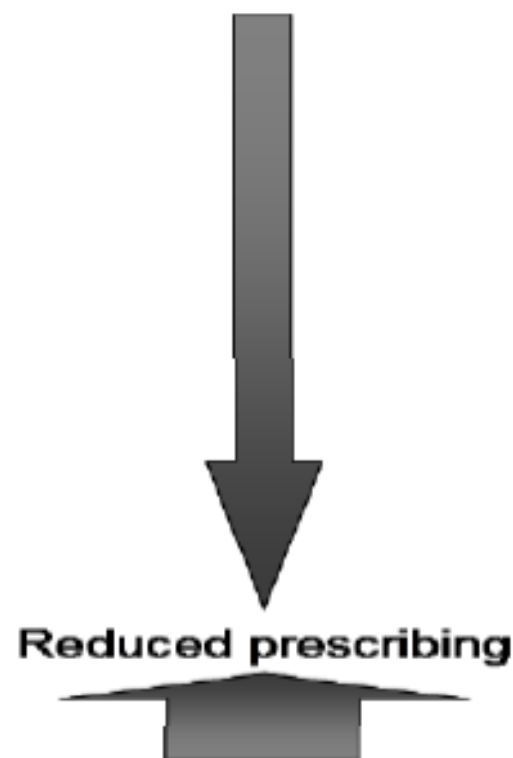
“Clinical research in general, and drug trials in particular, are suffering from an intellectual illness of an irrelevant analysis, a great waste of time and an excessive conservatism.”

Lewis Shiner, MD

1991 Presidential Address

92 Annual Meeting of the American Society for
Clinical Pharmacology and Therapeutics

Antibiotic prescribing restrictions



Antibiotic restrictions:

- **Licensing**
- **Reimbursement authorities**
- **National review bodies/guidelines/formularies**
- **Regional targets/guidelines**
- **Local formulary committees**
- **Practice budgets**
(impacted by incentives/penalties set nationally)
- **Physician**
- **Patient**
(through antibiotic consumption/patient education campaigns)

T>MIC for Augmentin 500 & 875mg BID

Fig. 1 Theoretical free drug serum concentration time curve for amoxicillin/clavulanate 500mg TID and 875mg BD

