PATOLOGIE EMERGENTI E RIEMERGENTI

Globalizzazione, Migrazione, Salute e Vaccini

Giovedì 6 novembre 2008, ore 08.30 – 16.30

CAMERA DEI DEPUTATI
Palazzo Marini - Sala delle Conferenze
Via del Pozzetto, 158 Roma

CARENZA NUOVI ANTIBIOTICI: UN ALLARME MONDIALE

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Le problematiche legate allo sviluppo di un nuovo antibiotico sono molteplici e riguardano sia il tempo (in media 10 anni) che necessità per un'accurata ricerca preclinica (studi in vitro e nei modelli animali di infezioni) e clinica (studi nelle infezioni umane) sia i costi.

La sperimentazione preclinica e clinica è molto impegnativa dal punto di vista.

Le più grosse multinazionali del farmaco hanno cessato di investire un patrimonio ingente nella ricerca di nuovi antibiotici che sono poco remunerativi (trattamenti brevi e abbastanza rari nell'arco della vita umana), spostando i propri interessi verso malattie croniche legate al miglioramento generale della "qualità di vita" della nostra società del benessere (dislipidemie, malattie cardiovascolari, ipertensione, diabete).

Le più importanti società scientifiche internazionali del settore hanno già da 2-3 anni lanciato un allarme mondiale che richiama alla necessità ormai inderogabile della ricerca supportata anche da organi istituzionali (Università e Governi).

Nei prossimi anni assisteremo infatti all'emissione nell'uso clinico di pochi nuovi antibiotici (non più di 4-5 molecole) soprattutto attivi nei confronti di batteri Gram positivi responsabili di gravi infezioni ospedaliere.

Gli antibiotici, farmaci meravigliosi che hanno salvato dagli anni 30 ad oggi milioni di vite umane, stanno inoltre perdendo in parte la loro efficacia nei confronti dei batteri, per l'insorgenza di fenomeni di resistenza.

I batteri cioè hanno imparato a difendersi contro queste "armi letali" con vari meccanismi:

dall'alterazione dei bersagli di azione alla produzione di enzimi inattivanti gli antibiotici fino alla produzione di proteine di membrana responsabili dell'estrusione del farmaco dal proprio citoplasma.

Paradossalmente non avremo nuovi antibiotici per le infezioni da Gram-negativi difficili e quelle acquisite in comunità quali polmoniti, sinusiti, riacutizzazioni di bronchite cronica.

Da questo deriva la necessità di un richiamo a un impiego più corretto degli antibiotici, che devono essere somministrati alle dosi giuste e per periodi di tempo appropriati.

Carenza nuovi antibiotici: un allarme mondiale

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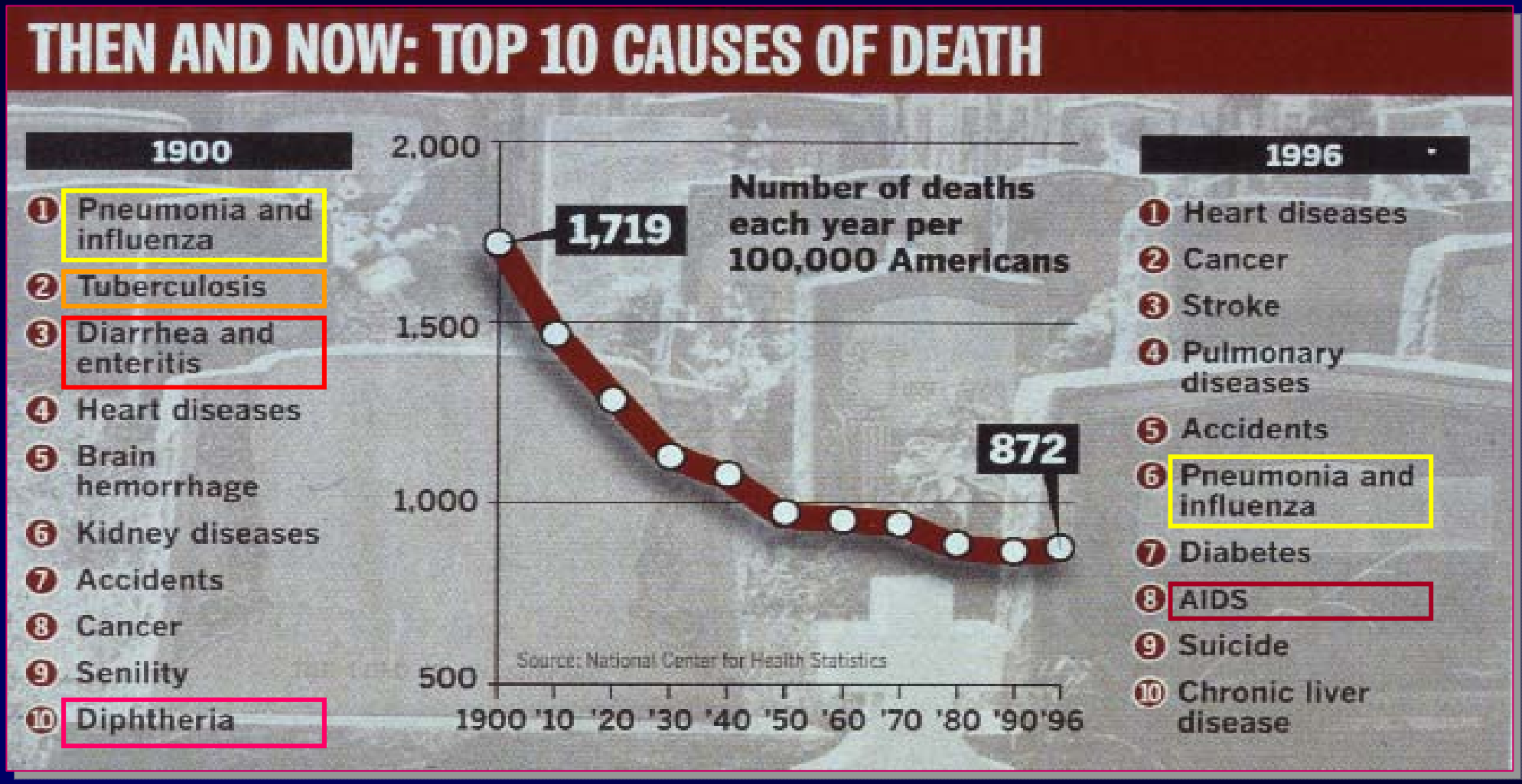
Le dieci principali cause di morte nel secolo XX

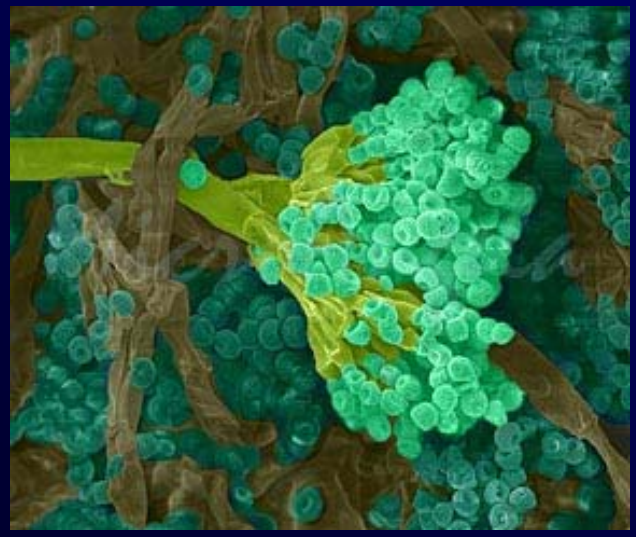


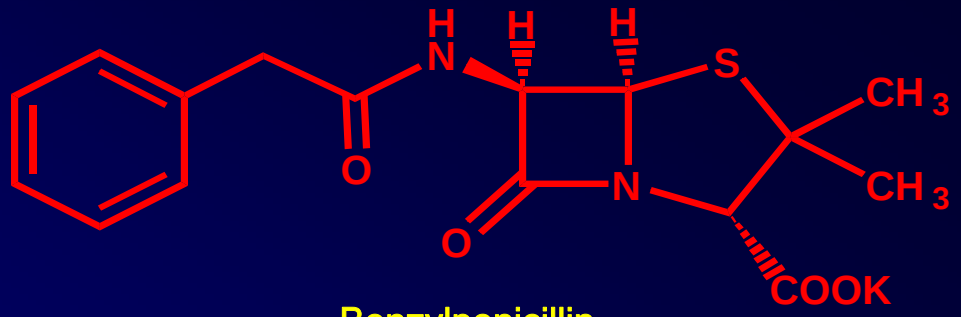
Discovery of penicillin 1928

Alexander Fleming

6 August 1881 – 11 March 1955

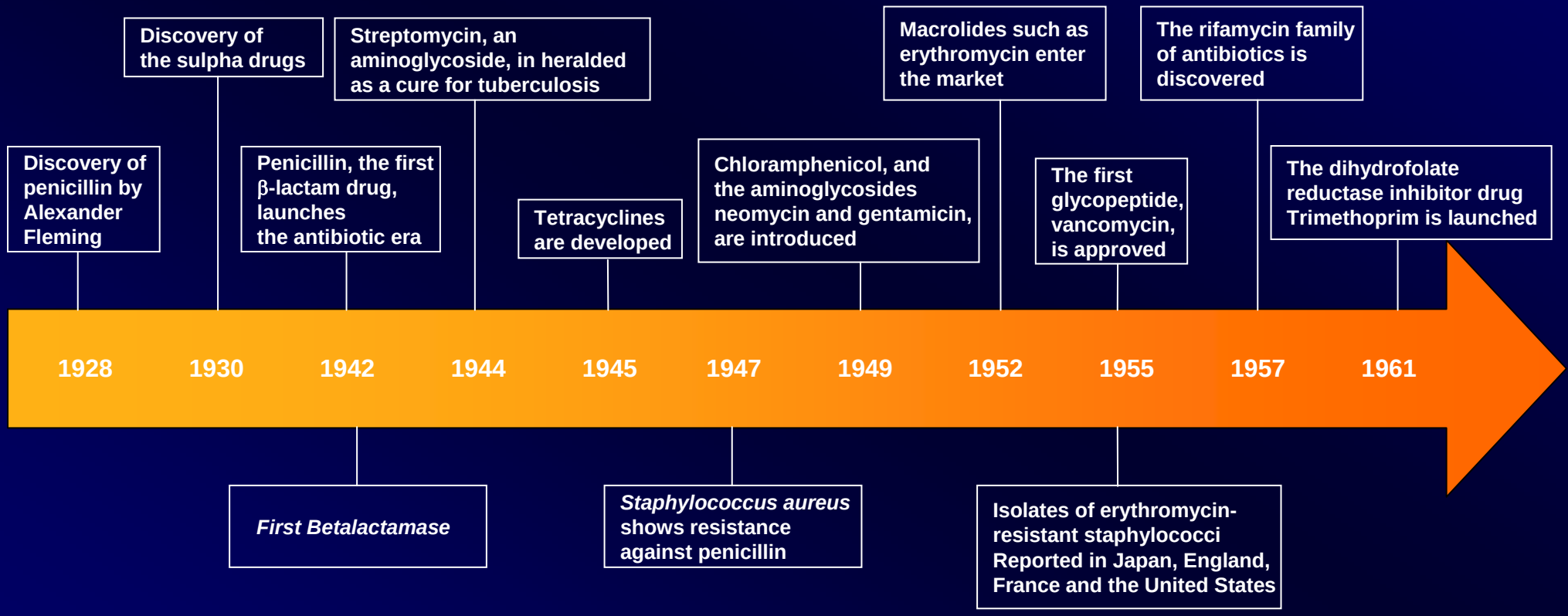
Picture of *Penicillium notatum*





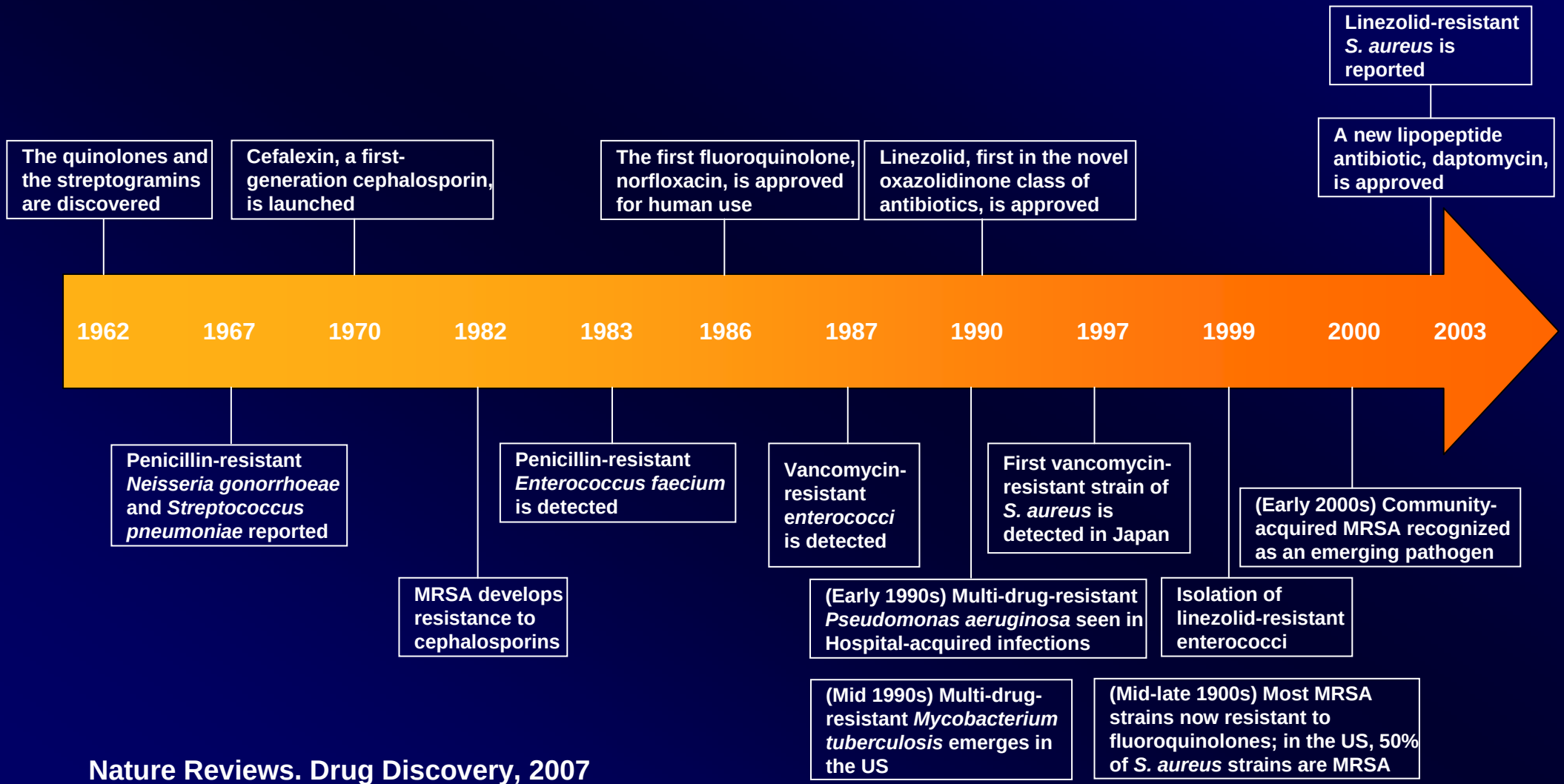
Benzylpenicillin

Race against time: the introduction of new antibiotic classes and the emergence of resistance (I)



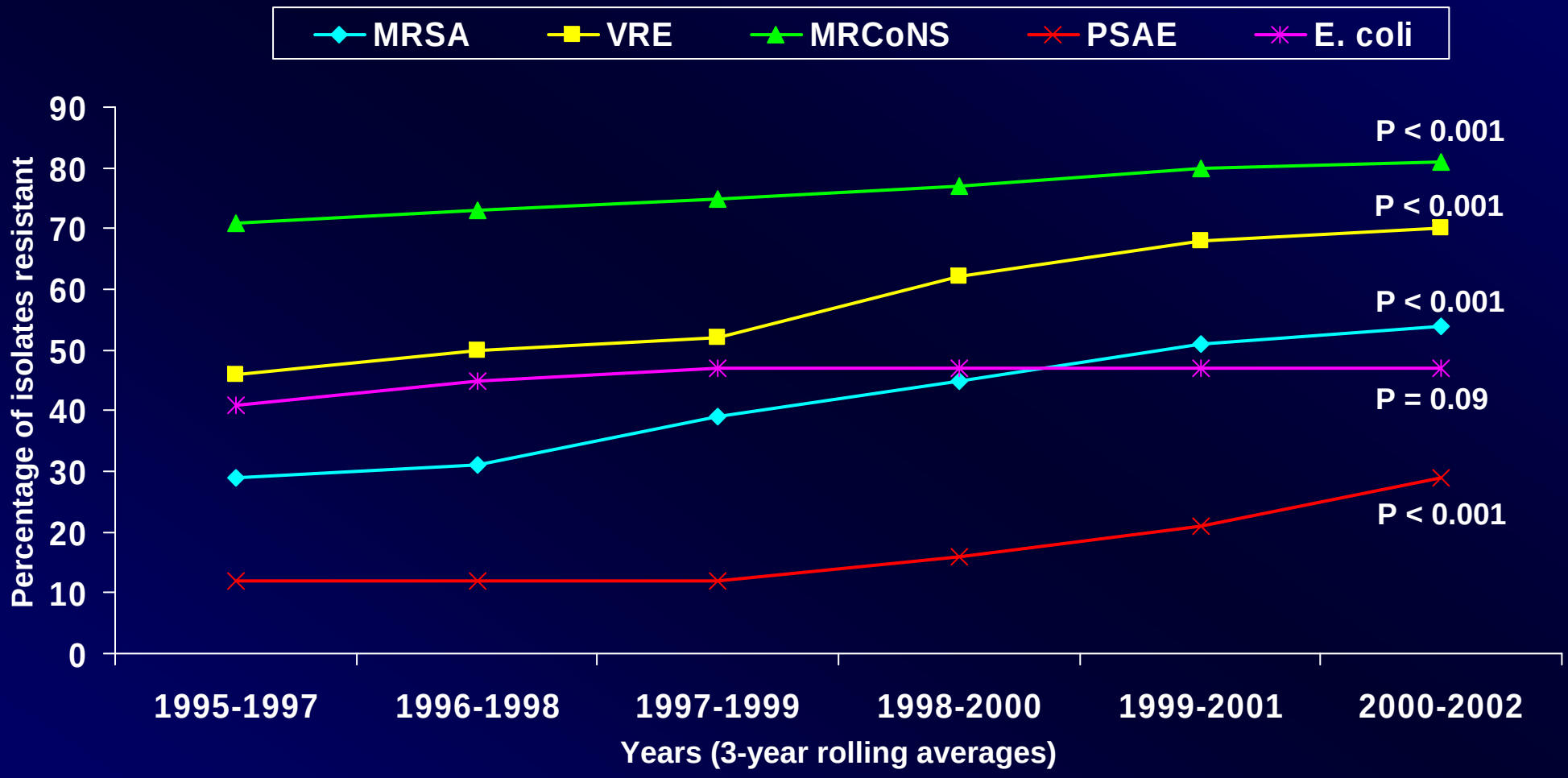
Nature Reviews. Drug Discovery, 2007

Race against time: the introduction of new antibiotic classes and the emergence of resistance (II)



Nature Reviews. Drug Discovery, 2007

Antimicrobial resistance rates overtime in US hospitals



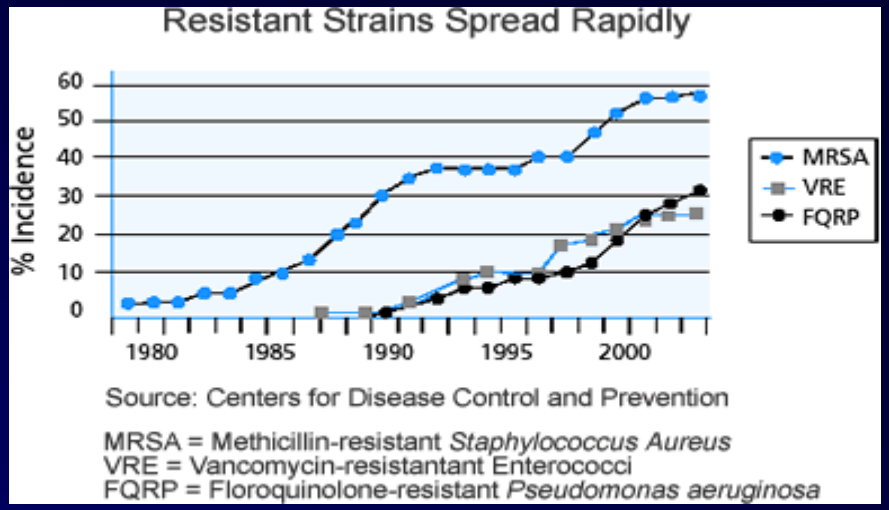
Wisplinghoff H et al., CID, 2004

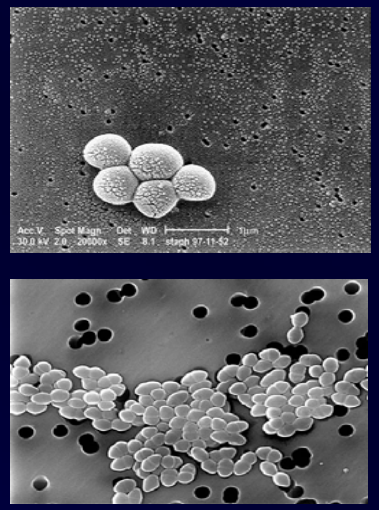
Current Problems of Bacterial Resistance

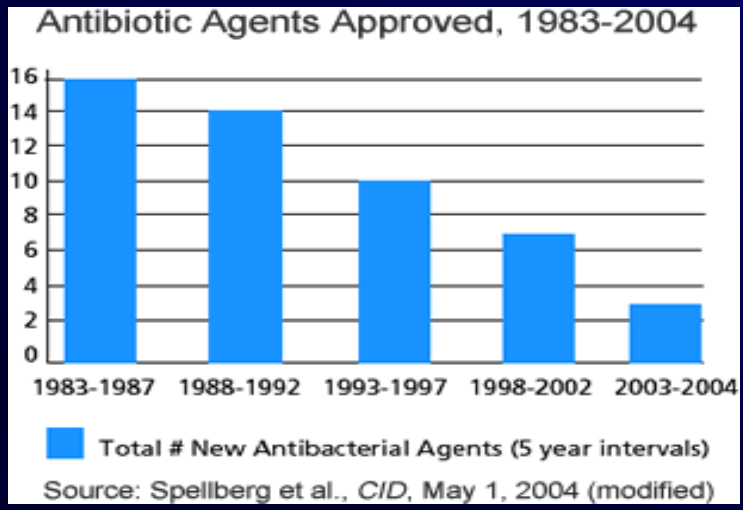
“ Policy & Advocacy of IDSA; July 2004 “

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates … A Public Health Crisis Brews







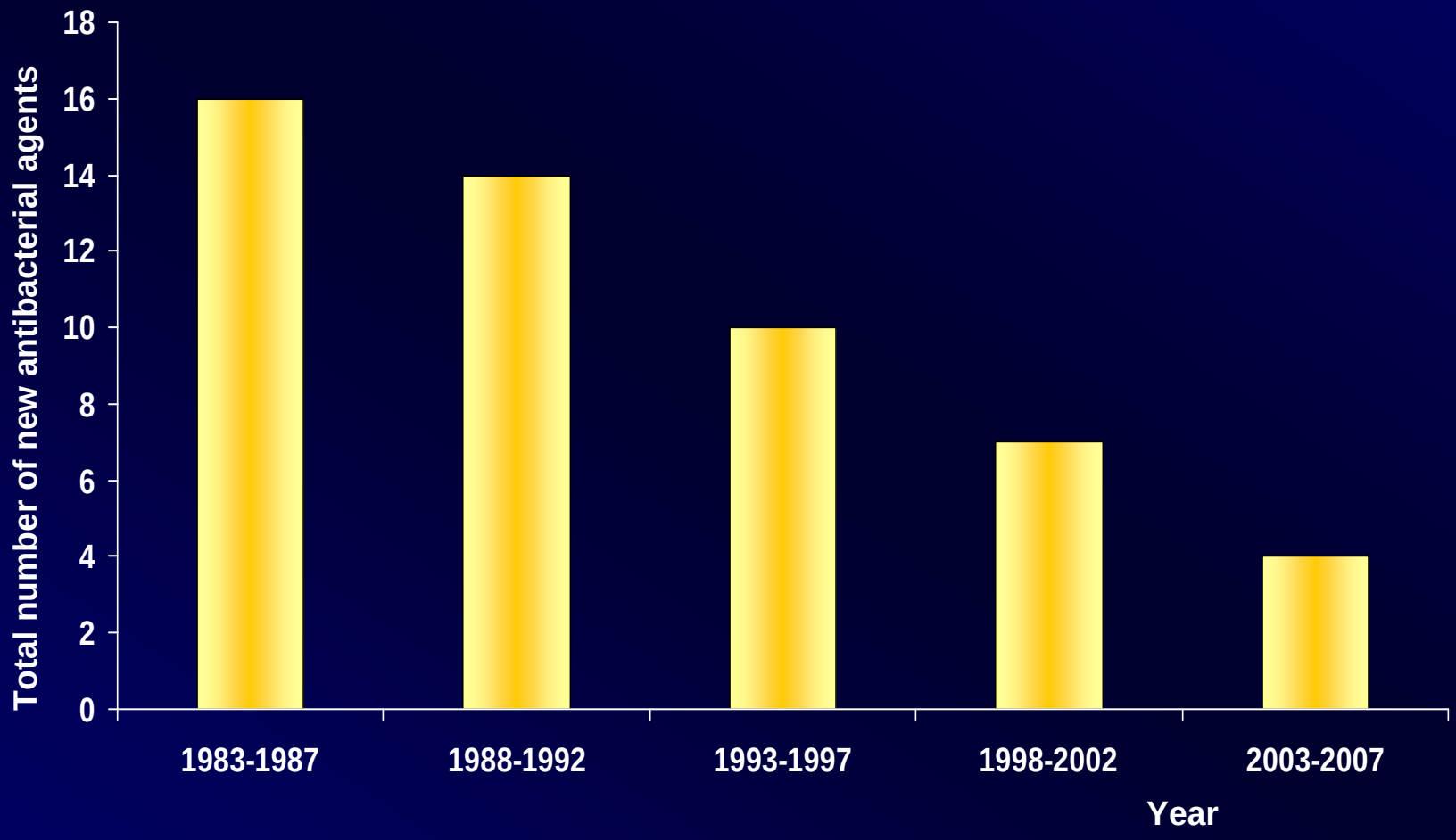
“ Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability “ [Task Force of the Infectious Diseases Society of America]

G. H. Talbot et al : Clin Infect Dis 42; 657-668, 2006

“ Alarm about FDA’s Delay in Issuing Anti-infective Drug Guidelines ”

[IDSA Statement on September 28, 2006]

Antibacterial agents approved 1983-2007



Spellberg B et al., Clin Infect Dis, 2004; Fox JL, Nature Biotechnology, 2006; Abbanat D et al., Curr Opin Pharmacol, 2008

Antibiotic development at selected major pharmaceutical companies

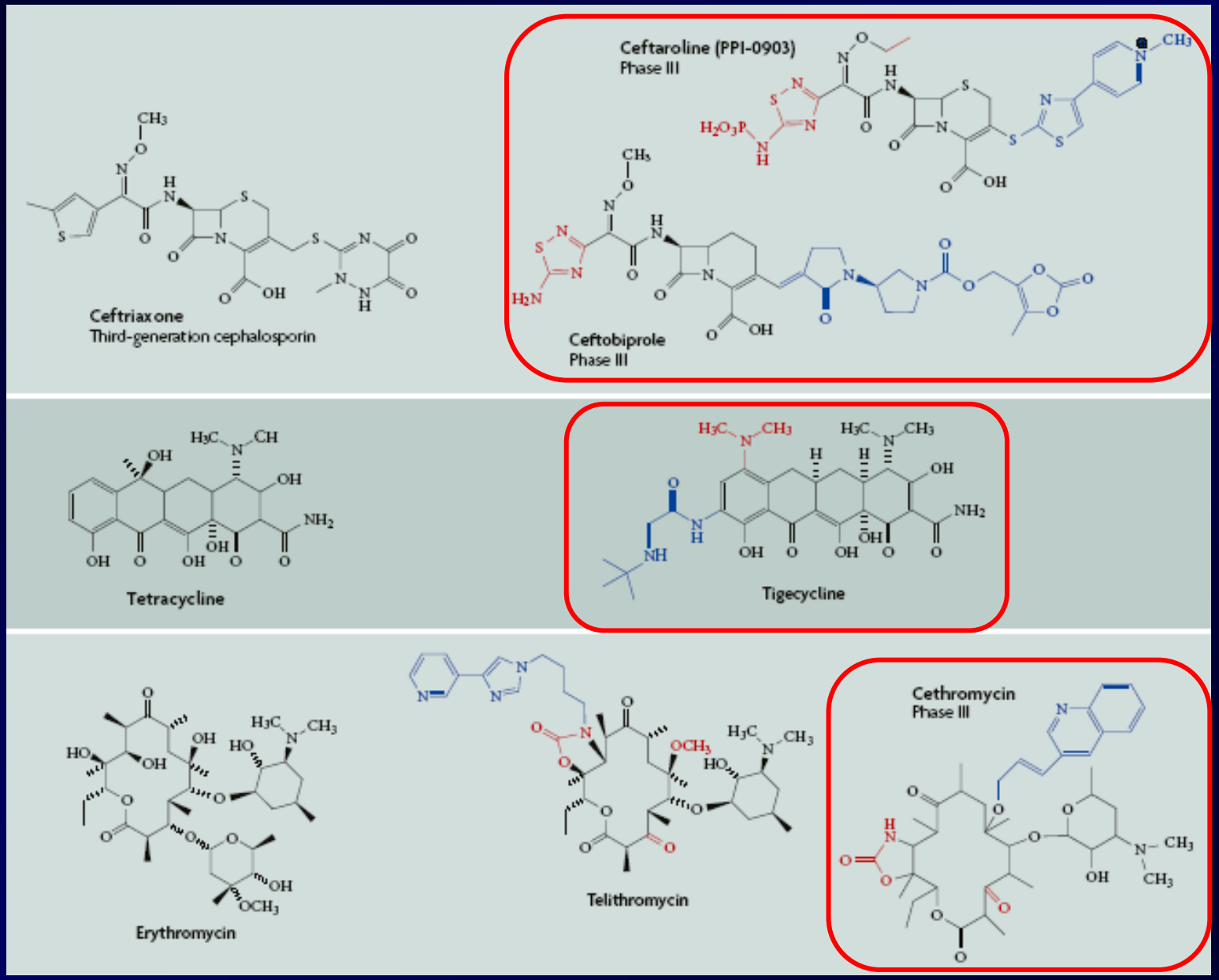
Company	New antibiotics or new used of old antibiotics approved since 1998	New antibiotics approved since 1998	No. of antibiotics in phase 2 trials or beyond	Approximate total no. of drugs in phase 2 trials or beyond
Pfizer	3	2	2	16
Merck & Co.	1	1	1	26
Johnson & Johnson	0	0	1	18
GlaxoSmithKline	0	0	1	34
Wyeth	1	1	0	12
→ AstraZeneca	0	0	0	24
→ Bristol-Meyers Squibb	1	0	0	8
→ Sanofi-Aventis	2	0	0	31
→ Novartis	0	0	0	41
→ F. Hoffmann-La Roche	0	0	0	16
→ Abbott Laboratories	0	0	0	7
→ Eli Lilly & Co.	0	0	0	13
Schering-Plough	1	0	1	13
→ Bayer	0	0	0	4

Katz M et al., Nature Biotechnology, 2006

Lack of new compounds in development

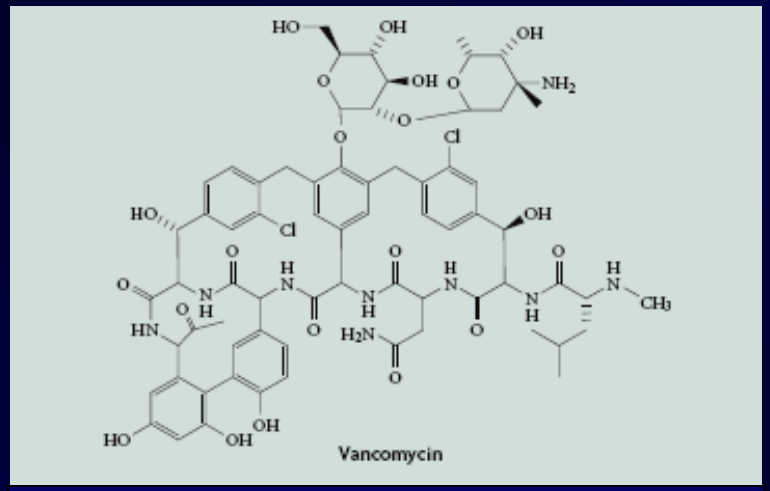
- Part of the problem is simple economics
- Most antibiotic generate only ~$ 200-300 milion annually
- They cure, rather than treat, patients in a few days and do not have to be prescribed for a lifetime, making them less attractive for investment
- Patent lifetimes and clinical “misuse” leading to resistance combine to restrict a drug’s commercial life to 8-10 years
- Antibiotics for use against resistant bacteria are often reserved as drugs of last resort, further limiting sales

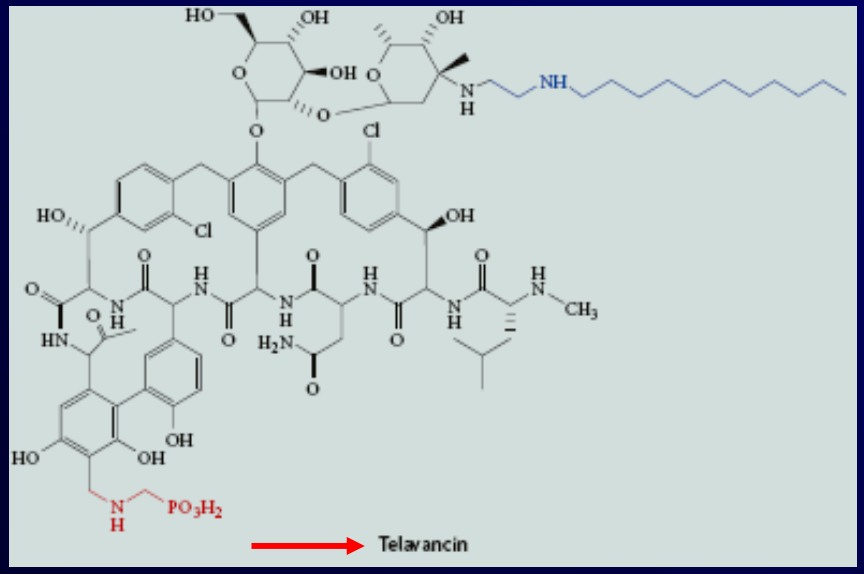
Next-generation compounds overcoming resistance (I)

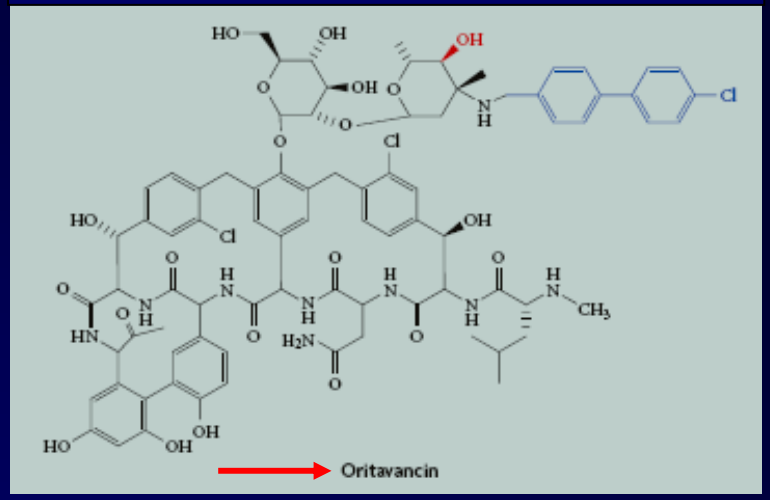


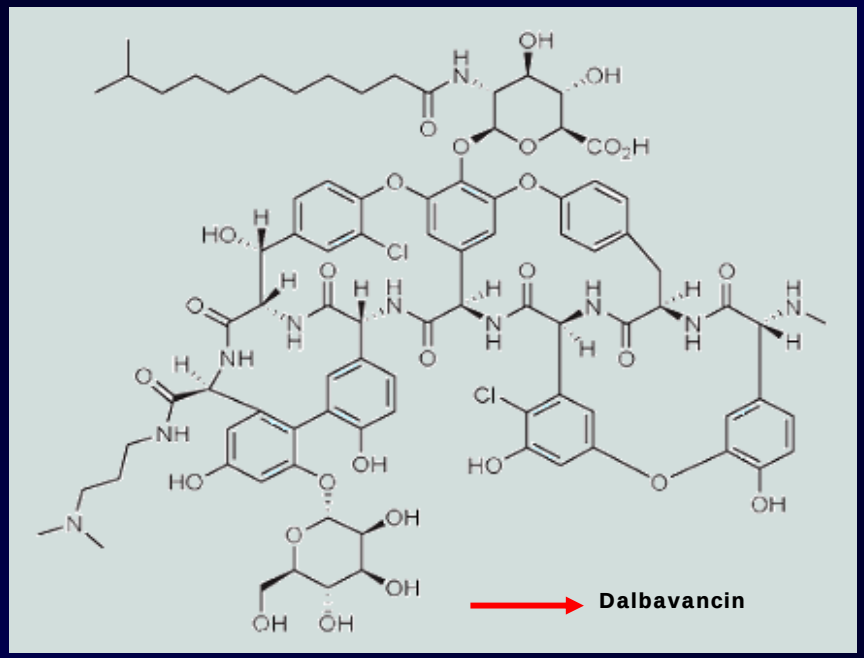
Silver LL, Nature Reviews. Drug discovery, 2007; Abbanat D et al., Curr Opin Pharmacol, 2008

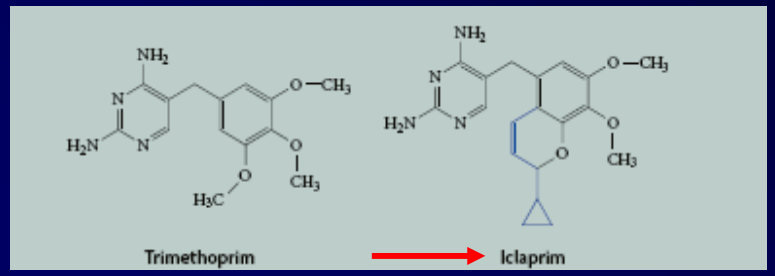
Next-generation compounds overcoming resistance (II)











Silver LL, Nature Reviews. Drug discovery, 2007; Abbanat D et al., Curr Opin Pharmacol, 2008

Newly approved or late-stage antibacterial drugs in development

Compound	Class	Company	Indication
Doripenem	Carbapenem	Peninsula/Johnson&Johnson	HAP/VAP, cUTIs, cIAIs
Dalbavancin	Glycopeptide	Vicuron/Pfizer	cSSSIs
Ceftobiprole (BAL5788)	Cephalosporin	Basilea/Johnson&Johnson	cSSSIs/HAP
Cethromycin	Ketolide	Advanced Life Sciences	CAP, other RTIs
Telavancin	Glycopeptide	Theravance/Astellas	cSSSIs/HAP
Iclaprim	DHFR inhibitor	Arpida	cSSSIs

Kresse H et al., Nature Reviews. Drug Discovery, 2007; Abbanat D et al., Curr Opin Pharmacol, 2008

New antibacterial agents for treating infections caused by multi-drug resistant Gram-negative bacteria

- Paucity of novel agents with potential utility against MDR Gram-negatives described at the 2006, 2007 and 2008 annual Interscience Conferences on Antimicrobial Agents and Chemotherapy (ICAAC), traditionally one of the preminent forums for description of investigational antibacterial agents

- A robust pipeline of preclinical candidates will be essential for successful drug development, as the natural level of attrition will require approximately 20 candidate antibacterials to enter clinical trials to achieve the eventual launch of a single successful agent

Chopra I et al., Lancet Infect Dis, 2008; Proceedings of the 46th ICAAC, San Francisco, CA, 27-30 Sept 2006; Proceedings of the 47th ICAAC, Chicago, IL, 17-20 Sept 2007; Proceedings of the 48th ICAAC, Washington, DC, 25-28 Oct, 2008

New antibacterial agents for treating infections caused by multi-drug resistant Gram-negative bacteria

Compound	Class	Phase	Company
Faropenem	Penem	III	Replidyne
PF-3709270	Penem	I	Pfizer
FR264205	Cephalosporin	Preclinical	Astellas
NXL104	Non β-lactam + β-lactamase inhibitor	I	Novexel
Sitafloxacin	Fluoroquinolone	Under application in Japan	Daiichi Sankyo
----	Novel topoisomerase IV inhibitor	Preclinical	Biovertis
NXL101	Novel topoisomerase IV inhibitor	Preclinical	Novexel
SB-006	Peptide	Preclinical	Spider Biothec

AJ O'Neill, Expert Opin Investig Drugs, 2008; Black MT et al., Antimicrob Agents Chemother, 2008

New antibacterial agents for treating infections caused by multi-drug resistant Gram-negative bacteria

AJ O'Neill

Expert Opin Investig Drugs, 2008, 17(3): 297-302

Results/conclusions

None of the antibacterial agents currently in clinical trials that encompass Gram-negative bacteria in their spectrum of activity possess sufficiently novel modes of action to circumvent extant antibiotic resistance mechanisms. Furthermore, although some interesting anti-Gram-negative drug candidates are nearing the beginning of clinical trials, they are limited in number and, even in the best-case scenario, many years away from the clinic

Correct use of antibiotics

Main parameters

- **Microbiological aspects (susceptibility, resistance)**
- **Pharmacological aspects (pharmacodynamics, pharmacokinetics, patients)**
- **Therapeutics index (efficacy/toxicity)**

Industry, governement and research will have to address four critical challenges for the discovery and development of antibacterial agents to keep infectious diseases in check

The four Horsemen of the Apocalipse

(Albrecht Dürer, ca. 1497-1498)

- Methods for antibiotic discovery
- Antibiotic usage
- Drug development and regulation
- Financial and business

Fernandes P, Nature Biotechnology, 2006