Bad Bugs Need Drugs

10x'20

Ten new ANTIBIOTICS by 2020

Innovation Dilemma
- the case of antimicrobials -

John Turnidge

The trouble with antibiotics

- **They are designed to be harmless to the host**
  - easy to prescribe "just in case"
- **They select for resistance which is:**
  - only an uncommon problem for the host
  - a major problem for the community
  - doubly contagious (bugs and genes)
- **We made them widely available <u>to all prescribers</u> right at the beginning (the 1940s)**
  - harder to take away a "right to prescribe" than grant it

The trouble with antibiotics

- **We have set the standard as "cheap"**
  - expectation that they stay that way
- **We have introduced some high hurdles**
  - cost-effectiveness for the PBS
    - when the international standard for comparative trials is non-inferiority
  - prediction of resistance selection potential
    - what models are available for estimating this?

Resistance Issues NOW!

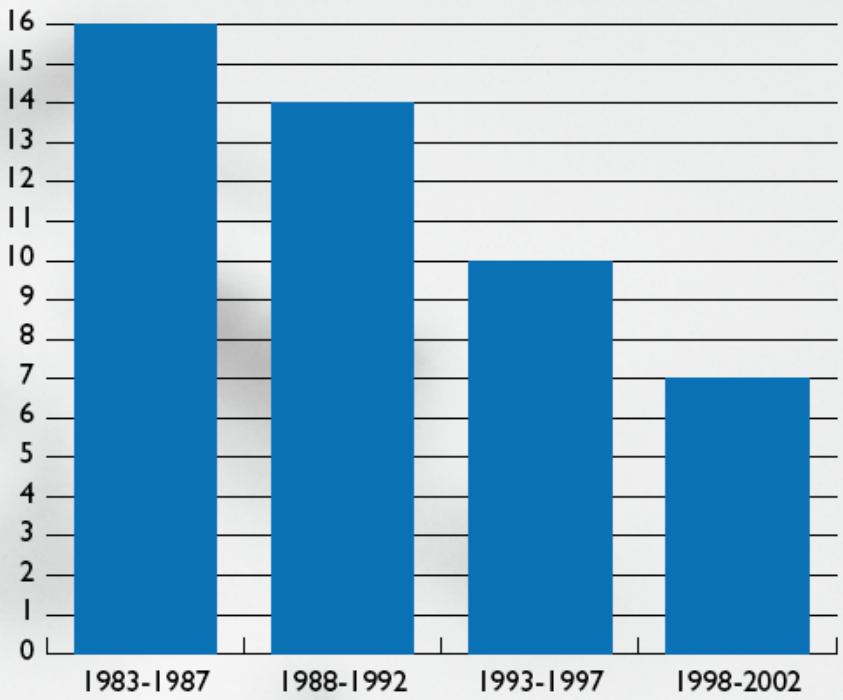
- Methicillin-resistant *Staphylococcus aureus*
- Vancomycin-intermediate *Staphylococcus aureus*
- Vancomycin-resistant *Enterococcus faecium*
- Drug-resistant *Streptococcus pneumoniae*
- Extended-spectrum β-lactamase producing and quinolone resistant *E. coli* and *Klebsiella* spp.
- Carbapenemase-producing Gram-negative bacteria
- Multi-resistant *Pseudomonas aeruginosa*
- Carbapenem-resistant *Acinetobacter baumannii*

Four-letter words!

- **MRSA**
- **VISA**
- **VREF**
- **DRSP**
- **ESBL**
- **CRAB**
- **MBla**

We are starting to lose our last-line antibiotics

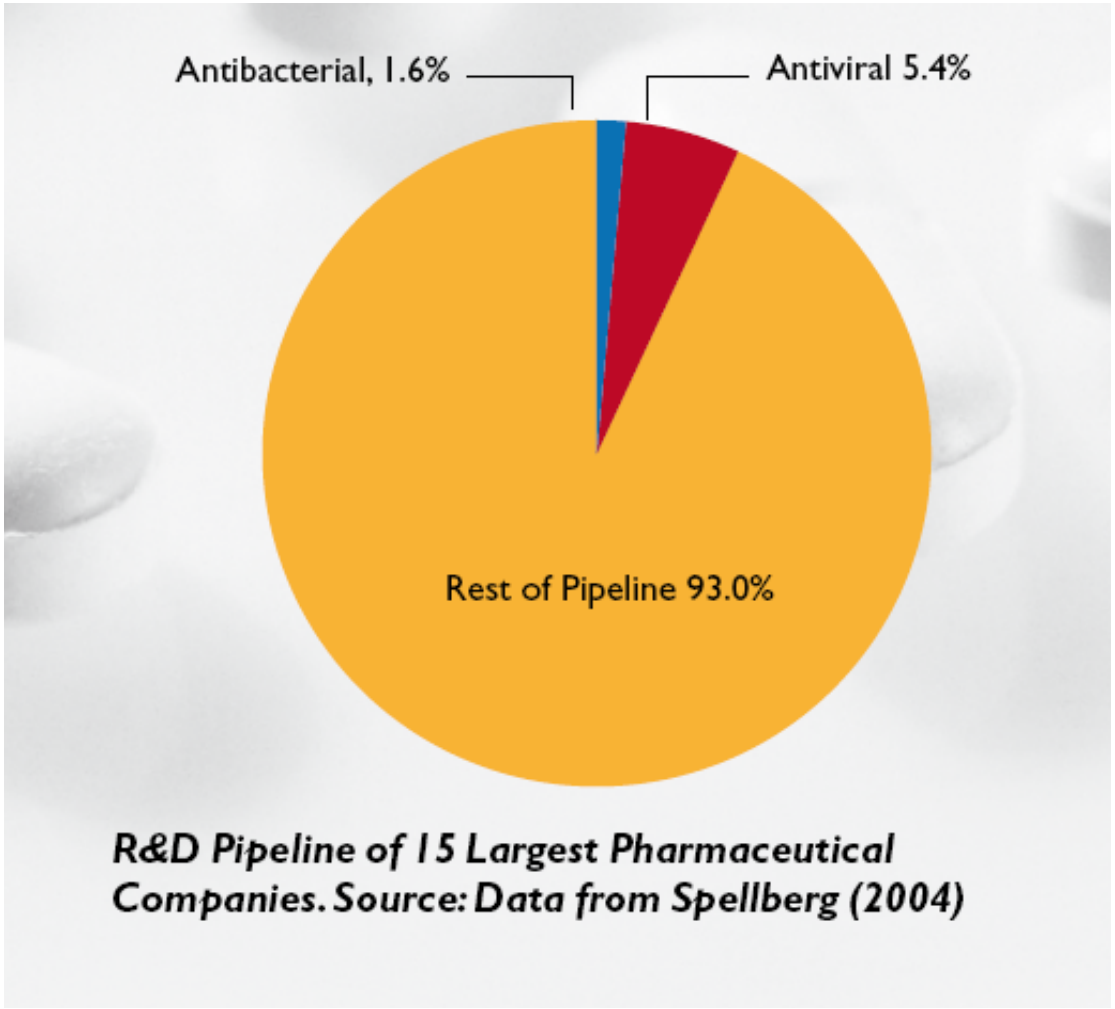
From a flood to a trickle



New antibacterial agents approved in the United States, 1983-2002. Source: Adapted from Spellberg (2004)

Year Introduced	Class of Drug
1935	Sulfonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/ Lincosamides/ Streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidiazoles
1963	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

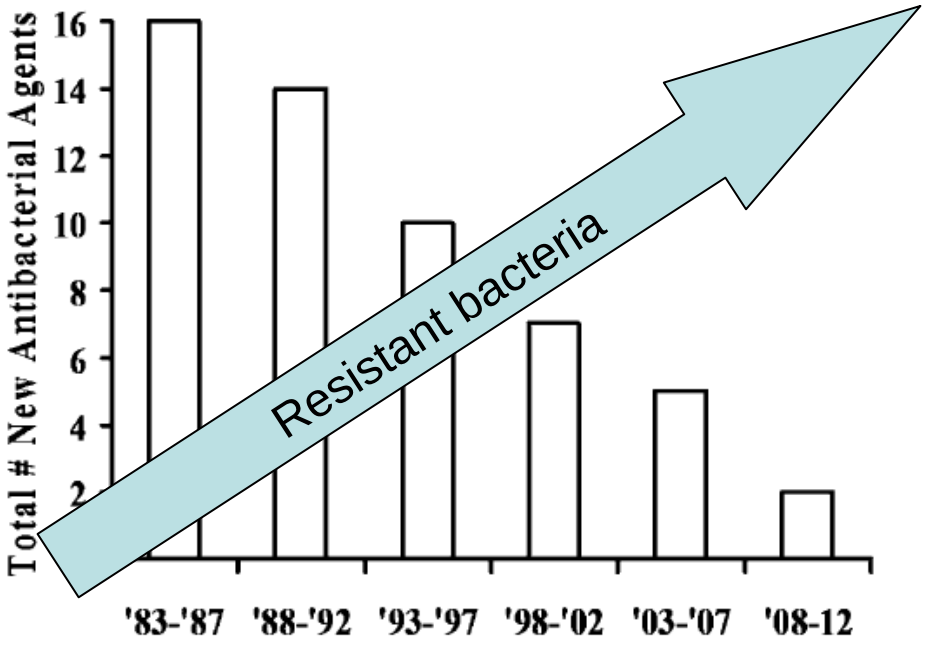
And worse to come?



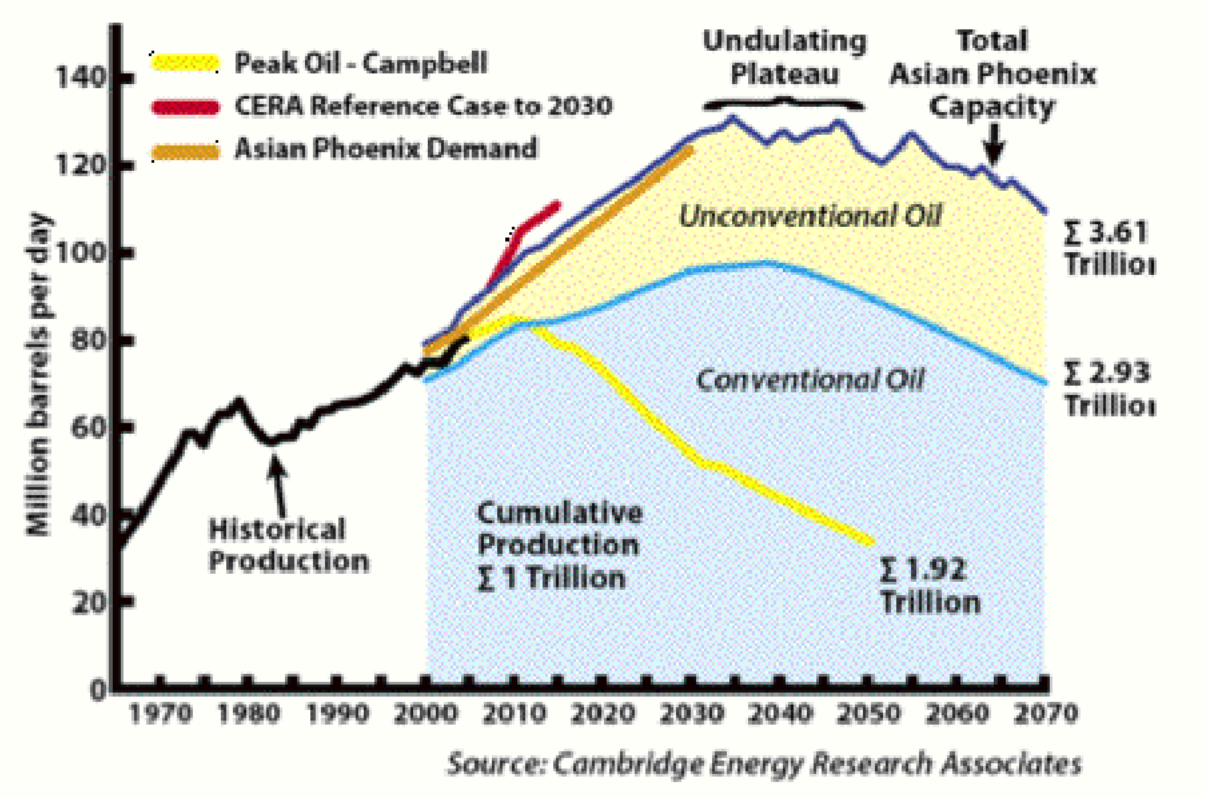
R&D Pipeline of 15 Largest Pharmaceutical Companies. Source: Data from Spellberg (2004)

Why are we losing antibiotics?

- **The bugs are becoming resistant faster than we can make new ones**



Peak Antibiotics?



In the last decade in Australia...

- **New antibacterials that have come and stayed**
  - Moxifloxacin
  - Tigecycline
  - Daptomycin
  - Doripenem
  - Quinupristin-dalfopristin
  - Ertapenem
- **New antibacterials that have come and gone**
  - Gatifloxacin

In the last decade in Australia...

- **Old antibacterials that have gone**
  - Piperacillin (alone)
  - Cefotetan
  - Cefpodoxime-axetil
  - Cefpirome
  - Netilmicin
  - Enoxacin
  - Nalidixic acid
  - Ofloxacin oral
  - Spectinomycin

In the last decade in Australia...

- **New antifungals that have come and stayed**
  - Voriconazole
  - Posaconazole
  - Caspofungin
  - Anidulafungin
- **Old antifungals that have gone**
  - Conventional Amphotericin B
  - Flucytosine

In the last decade in Australia...

- **New antivirals that have come and stayed**
  - valganciclovir
  - oseltamivir
  - entricitabine
  - atazanivir
  - darunavir
  - fosamprenavir
  - lipinavir with ritonavir
  - tipranivir
  - efuvirtide
  - maraviroc
  - ralegravir
  - tenofover

In the last decade in Australia...

- **Antivirals that have gone**
  - zalcitabine
  - nefinavir

So let's just go and find some new antibiotics...

- **Find new antibiotic**
  - modify older one (common strategy)
  - totally new class (better but harder)
- **Make sure is covers emerging resistances**
  - likely to be broad spectrum
- **Develop new antibiotic (phase I, II, II)**
  - Cost = USD 500 million to 1 billion
- **Determine market size and acquisition cost**
  - Typically ~$200 per day for new parenteral antibiotic
- **Promote**
  - likely to be restricted!! (reserved for last line)

What the ID Community is looking for...

- **Novel classes = novel mechanisms of action**
  - higher development risk (safety issue)
- **Narrower spectrum drugs**
  - less collateral damage
  - smaller market
- **Shorter courses**
  - less collateral damage
  - less use, higher unit price
- **New oral agents for the community**
  - only worthwhile if usage likely to be "high"

New Industry Model

- **SMEs – small biotech companies**
  - venture capital funded
- **In-license molecule for overseas (Japan, Korea) or design new agent**
- **Do all preclinical-phase I work (sometimes phase II)**
- **Sell out to a big multinational to do phase III (they are the only ones with the resources)**
- **Get FDA and EMA clearance ± Australia**

New Industry Model

- **"Successful" examples: DORIPENEM**
  - Peninsula Pharmaceuticals (small Californian biotech)
  - In-licensed doripenem from Shionogi (Japan)
  - Took it through phase I and II to FDA standards
  - Sold out to Johnson and Johnson who undertook phase III and filed the NDA
  - J&J and subsidiaries marketed worldwide
  - In Australia: fails to take significant market share from meropenem (so far)

New Industry Model

- **"Successful" examples: DAPTOMYCIN**
  - Eli Lilly and company drug discovery program in the 1980s finds novel class (lipopeptides)
  - Takes lead molecule to Phase II and encounters toxicity problem (myositis)
  - Enthusiastic ID physician in the US convinces a range of people to obtain the license and resurrect agent
  - New biotech formed: Cubist Pharmaceuticals
  - Toxicity minimised by changing dosing to once-daily
  - Developed and marketed by Cubist in the US
  - Out-licensed to Novartis for ROW
  - Novartis markets in Oz but sales are slow and may be looking for another company to market

Innovations we don't need!

- **Extending the use of reserve agents/classes to areas where benefits are marginal**
  - topical fluoroquinolones!
    - from sight-threatening eye infections to gooey ears
- **Extension of indications to undesirable patterns of use: low-dose, long-term**
  - azithromycin in CF
    - Pseudomonas colonised ⇨ all CF ⇨ all COPD
  - doxycycline for "syphylaxis" trial
- **"Stealing" antibiotic classes from the veterinary sector**
  - retapamulin (pleuromutilin)

Solutions?

- **Pigovian tax (http://en.wikipedia.org/wiki/Pigovian_tax)**
- **New business models**
  - **http://www.reactgroup.org/resources/react-publications/innovation-of-antibacterials.html**

New Business Models?

- **Push mechanisms**
  - Public compound libraries
  - Patent pooling
- **Pull mechanisms**
  - Advanced market commitments
  - Prize funds
- **Product development partnerships**
  - e.g. Global Alliance for TB Drug Development. Medicines for Malaria initiative

Lingering Issues

- **Regulatory hurdles for safety getting higher**
- **No blockbusters**
- **Reserve status for most new agents for resistant organisms**

- **We must be prepared to pay**