The search for new tools: the R&D challenge

John H. Rex, MD
Vice President Clinical Infection
AstraZeneca, Boston, USA

1

Background

- Well-known (and often lamented) that the pharma industry has significantly reduced antibiotic R&D
- Reasons include:
  - Difficult to find novel activity compounds
  - Older drugs (often generic) have very broad labels
  - Therapy is brief, not chronic
  - New agents are held in reserve
- All true, but this misses the core problem
  - We (society) fundamentally undervalue antibiotics
  - Let me explain…

2

Five Lessons

3

Lesson One

(Effective) Antibiotics do Amazing Things

"Pneumonia is captain of the men of death"

(Sir William Osler)

4

(Effective) V Antibiotics do amazing things

- Simple infections: Often fatal in pre-antibiotic era
- Mortality benefit of antibiotics for pneumonia[1]
  - You are aged < 30: 12% → 1%: 11% benefit
  - You are aged 30–59: 32% → 5%: 27% benefit
  - You are aged ≥ 60: 62% → 17%: 45% benefit
  - For all ages: A brief course of therapy is curative
- Contrast: aspirin + streptokinase in acute MI
  - 5% decrease in 5-week mortality (13% → 8%)[2]
  - You still have heart disease

1) Spellberg et al. Clin Infect Dis 2008;47:S249–65
2) Baigent et al. BMJ 1998;316:1337–43 and Lancet 1988;ii:349–60 (ISIS-2 studies).

5

Modern care requires antibiotics

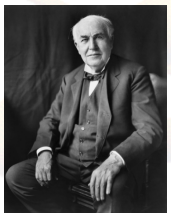
- Without reliable antibiotics, you can't:
  - Have heart surgery
  - Take care of premature infants
  - Replace a joint
  - Treat cancer
- In serious infections, must get it right at the start
  - Delays to effective therapy of as little as a few hours measurably increase morbidity and mortality
  - Diagnostics helpful but unlikely to have adequate speed or sensitivity to eliminate fully the role of reliable broad-spectrum empirical therapy

6

Lesson Two

Discovery of Antibiotics is Hard

"Genius is 1% inspiration and 99% perspiration"



(Thomas Edison)

7

Discovery of antibiotics is hard

- Easy to find: Targets
  - Multiple bacterial genomes are fully sequenced
- Easy to find: Things that kill bacteria
  - Bleach works quite well, as do steam and fire
- Hard to find: Kills bacteria, is drug-like/relatively safe
  - Failures: physical properties, pharmacology or safety
    - Site/organism penetration require high levels → high doses
      - Typical lipid-lowering agent: 5-20 mg/day
      - Typical antibiotic: 100-2000 mg/day
    - Those high levels really stretch the safety margin
- To succeed? Be patient & be persistent

Payne et al. Nat Rev Drug Discov 2007;6:29–40

8

Lesson Three

Discovery & Development is Iterative

"The lesson of history is that we need a pipeline"

(John Bartlett)

9

Discovery of antibiotics is iterative

- The hierarchy of microbiology: A brief lesson
  - Gram-positive (*S. aureus*, MRSA): one cell membrane
  - Fermentative Gram-negatives (*E. coli*): two cell membranes
  - Non-fermentative Gram-negatives (*P. aeruginosa*): more genomic complexity
- Resistance mechanisms follow this hierarchy
  - Gram-positives have a limited range of resistance mechanisms
  - Non-fermentative Gram-negatives can have many mechanisms
- Discovery programmes must follow this ladder
  - This explains the current paucity of novel Gram-negative agents
  - You must walk before you run
  - Supporting early steps leads to later opportunities

10

Development is also iterative

- The first drug in a class
  - Platform for further development in a class
  - Penicillin G → oxacillin → piperacillin
- Insights about a given drug grow with time
  - Ciprofloxacin: Urinary tract infection → anthrax
  - Azithromycin: CAP → *Mycobacterium avium* (AIDS), malaria and GI infection (*Campylobacter*)
- Simple gateway indications provide entry vehicle
  - A path to CAP (Community-Acquired Pneumonia)…
  - … makes possible much more than just CAP

11

Lesson Four

The Paradox of Resistance

"You can't always get what you want"

(The Rolling Stones)

12

The paradox of resistance

- Bacterial resistance drives need
  - New drugs are needed for bad bugs
- But, consider methicillin-resistant *S. aureus* (MRSA)
  - And, imagine Drug X: novel & active *in vitro* for MRSA
- What is the one study I must not do in man?
  - Drug X vs. methicillin
  - Also cannot do a placebo-controlled superiority study
- Rather, must use non-inferiority design vs. active agent
  - This confuses and has driven huge anxiety
    - Non-inferiority is more difficult to implement than superiority designs
    - New drug only seen as 'non-inferior' rather than superior
  - Real value (activity when other drugs not active) is not visible
  - **We have to get past this confusion:** We must not let the perfect be the enemy of the good

13

Lesson Five

The Paradoxes of Antibiotic Value

"Our heads are round so that thoughts can change direction"

(Francis Picabia)

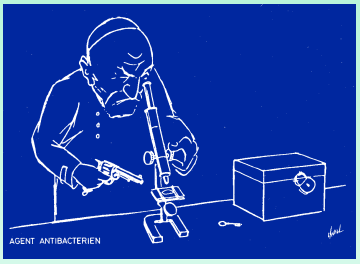
14

The paradoxes of antibiotic value

- New antibiotic usage
  - "Congratulations! Well done! Important for us all!"
  - "Indeed, it is so important that let's not use it"
- New antibiotic pricing
  - "New drug was only non-inferior to old (generic) drug"
  - "Why should anyone pay more than cost of old drug?"
- But if new antibiotic not available when needed?
  - "We have an outbreak NOW!"
  - "How can it possibly take 10 years to find a new drug?"

15

Conclusions



16

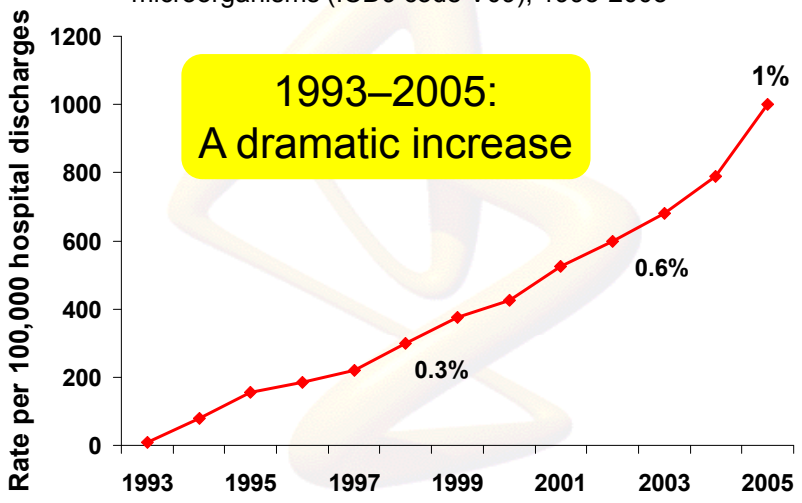
Lessons learned

- Effective antibiotics do amazing things
  - Modern medical care is not possible without them
- Discovery of antibiotics is hard
  - Start early. You can't just open the taps
- Antibiotic discovery & development is iterative
  - Stay with it. Must support through early steps
- The paradox of resistance
  - Don't expect direct superiority. Indirect proofs are key
- The paradoxes of antibiotic value
  - Must recognise & reward the true value of innovation

17

Resistance never sleeps: Perennial need

US hospital discharges with diagnosis of infection with drug-resistant microorganisms (ICD9 code V09), 1993-2005



Data from US Healthcare Cost and Utilization Project

18

The heart of the matter

"... the countermeasure that saves the day during a quick-hitting public health emergency can often take years to discover, develop, manufacture, and distribute."

Kathleen Sebelius, Secretary DHHS
1 Dec 2009
AMA 3rd National Congress on Health System Readiness

19

Recommendations (1 of 2)

- Take a broad view on what is needed
  - Create conditions for a diverse long-term pipeline
  - Recognise that the true value of an antibiotic (or antibiotic class) emerges slowly
  - Continuous innovation is the best way to have options
- Increased dialogue on regulatory issues
  - Regulatory pathways: Consistent, stable, feasible
  - Ensure that gateway indications (e.g., CAP, skin) are accessible for both oral-only and IV drugs
  - Support creation and use of diagnostics for both the regulatory approval process & routine care

20

Recommendations (2 of 2)

- Reward the innovation of antibiotics
  - Early rather than late; more push than pull
  - Early: Orphan drug-like rules for antibiotic R&D
    - Tax incentives or credits; Research grants; Awards
  - Late: Patent extensions & exclusivity
  - Innovative: Product development partnerships, call options
- Recent EU discussions on antibiotics
  - Sept 2009: EU Conference on Innovative Incentives
  - Sept 2010: Follow-up conference
  - April 2011: WHO World Health Day

21

Exciting events

IDSA Initiative, Dec 2009

European Union Council: 1 Dec 09

...within 24 months, develop a comprehensive action-plan, with concrete proposals concerning incentives to develop new effective antibiotics ...

US legislative activity: GAIN Act
(Generate Antibiotic Incentives Now)

World Health Day: 7 April 2011

Antimicrobial resistance: no action today, no cure tomorrow

22