Enabling drug discovery & development to address the crisis of antibacterial resistance: New tools, new pathways & remaining challenges

John H. Rex, MD
SVP & Head of Infection Global Medicines Development, AstraZeneca
Non-Executive Director & Consultant, F2G Pharmaceuticals
john.rex@astrazeneca.com

The opinions expressed herein are my own.

Slides happily shared – just drop me a note.

Introductions

- Board-certified MD: Internal Medicine & ID
- Career
  - Fellow in ID: NIH/NIAID (1987-92)
  - Assistant Professor → Professor, UT Med School-Houston, (1992-2002)
    - Focus: Medical Mycology (life-threatening fungal infections), Critical Care, Hospital Epidemiology
  - VP → Senior VP Infection, AstraZeneca (2003-present)
    - Focus: Developing antibacterial agents for life-threatening infection, creation of regulatory and economic tools to support same
- Ex-AZ work
  - Cross-industry work on antibiotic development issues (PCAST & more)
  - Co-creator of IMI ND4BB (New Drugs 4 Bad Bugs) program
  - Non-Executive Director, F2G Pharma (UK Biotech, antifungal agents)
  - Advisor to Wellcome Trust, London, UK

My biases

- I am employed in the pharmaceutical industry. I also have equity in pharmaceutical companies and provide consultative support and advice to various pharmaceutical companies
- So, please do be clear on my bias:
  - As a board-certified internist and ID specialist, I am terrified by the problem of antibacterial resistance.
  - I firmly believe that we need new therapeutic options, I believe that a combination of public and private investment is required for these to be created, and I am working hard to ensure that this happens

In the United States, each year we have

CDC 2013 estimate

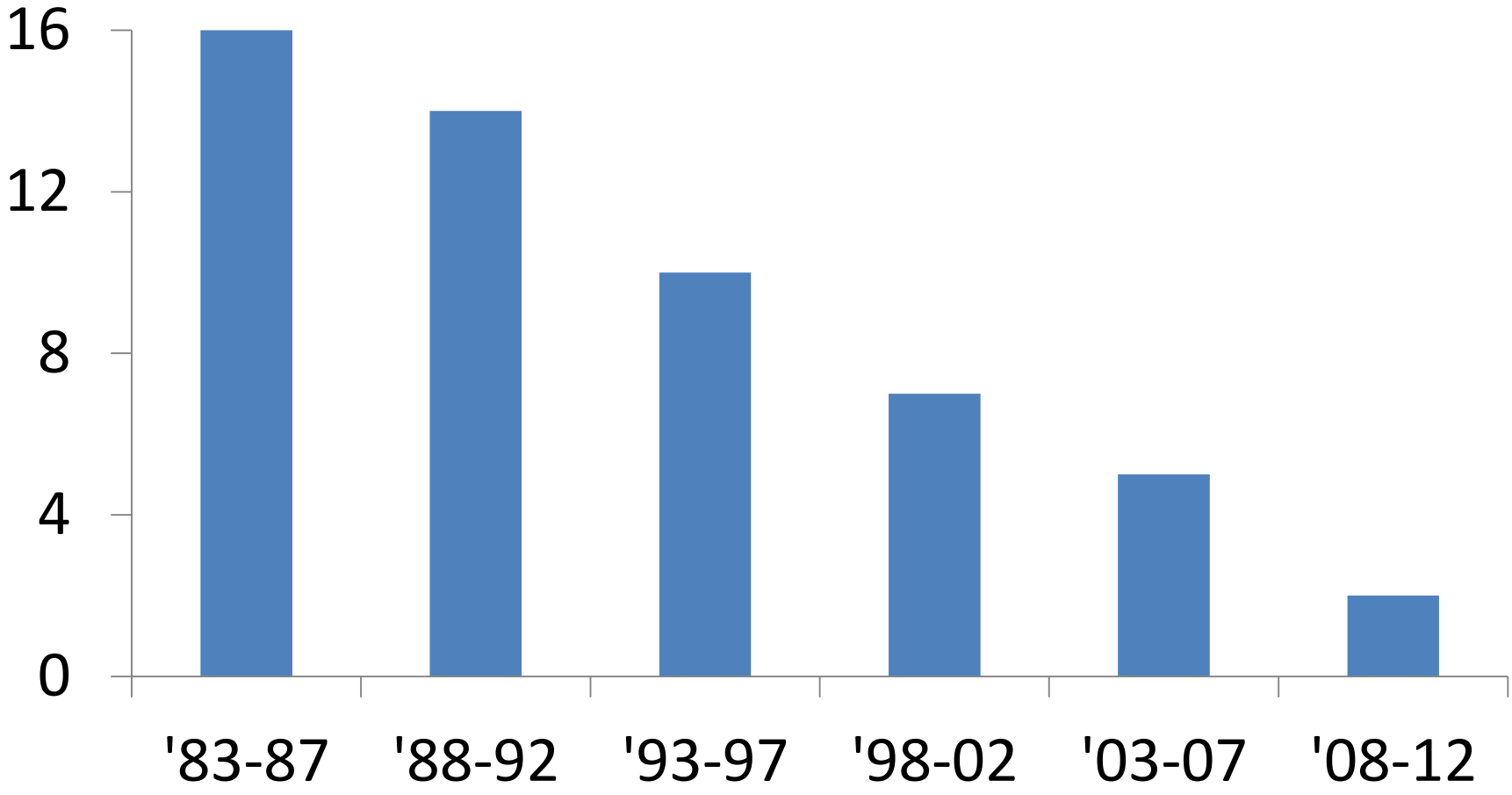
23,000 deaths/year

≅

One jumbo jet crash every week

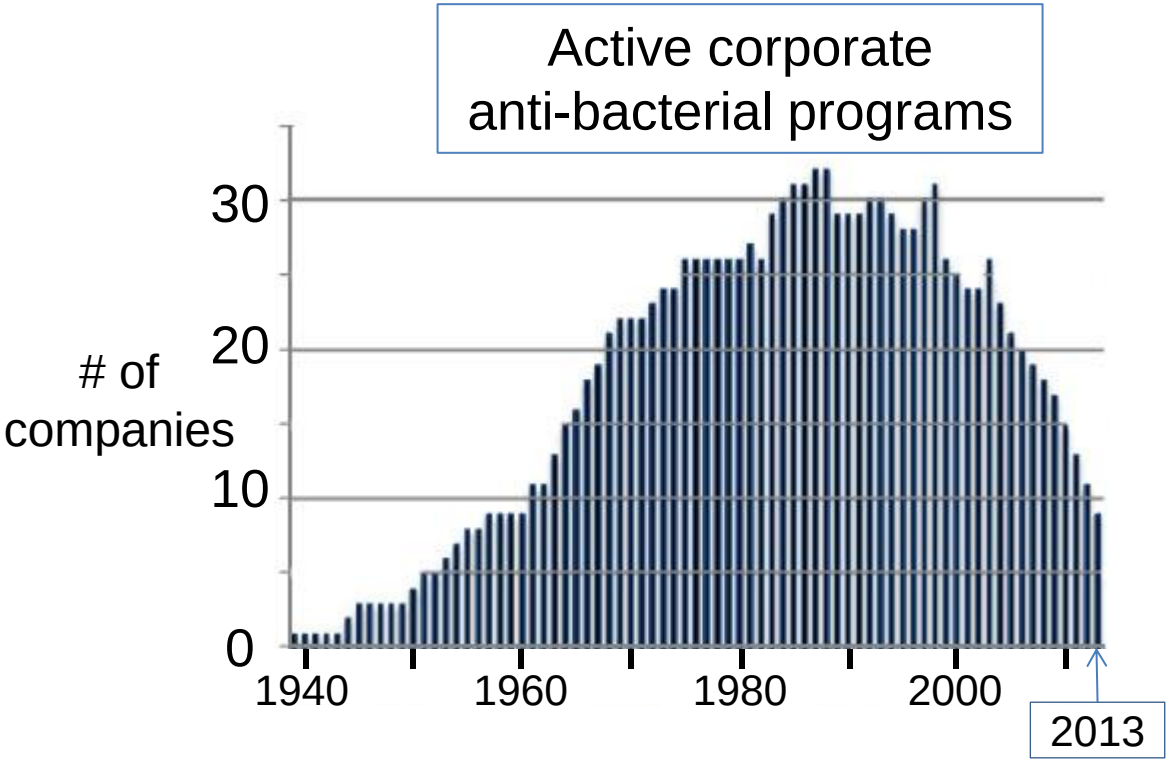
In the face of this, few new drugs!

Rate of new antibacterials over 30 years[1]

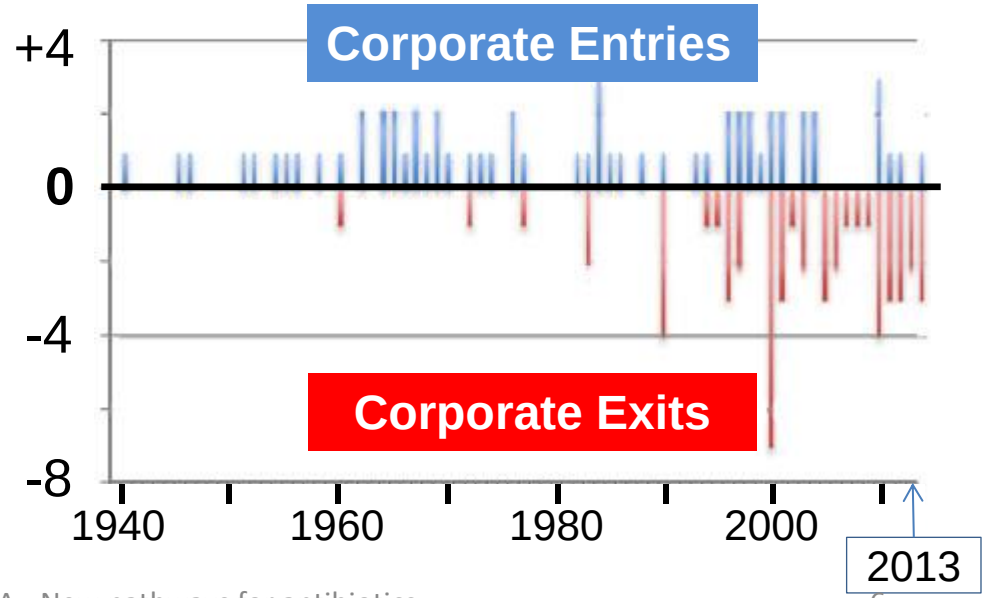


[1]Boucher et al. Clin Infect Dis 56:1685-94, 2013. Note: This graph does not show several recent new approvals. But, the overall message remains correct – very few new drugs!

Consistent with this, the number of active companies in 2013 was the same as in 1960!



I'm pleased to see new companies emerging since 2013, but we have a lot of ground to reclaim



Graphic adapted from Kinch MS et al. Drug Discovery Today, July 2014.

Why so few drugs and companies?

- I think of this in three big buckets
  - It's **hard to discover** new antibacterial antibiotics
    - Bacteria don't want to die! Antibiotics walk a narrow line between killing bacteria and harming patients
  - It's **hard to develop** new antibacterial antibiotics
    - An ethical issue means we can't use simple superiority designs but must instead take a more difficult path[1]
  - The current **economics** of antibacterials are poor
    - New antibacterial drugs will be gladly received …
    - … but held in reserve (more on this below)

[1]This topic deserves an hour on its own. In brief, infections can be lethal and you can't deliberately test vs. placebo or against an agent known to be ineffective. As a consequence, antibiotic development requires use of the more difficult non-inferiority (active control) designs.

Discovery and Development are being well supported

- You've heard this morning about
  - New tools for diagnosis of bacterial infections
  - New pathways for approval of antibacterial drugs
- New tools for discovery are also emerging
  - **Supporting the science:** Substantial support (money and technical skills) from government (EC, US) & foundations
  - **Widening the net:** Global collaborations focused on finding and testing compounds with structures that are complete different from anything ever tested before
- Personal view: We will see new agents emerge
  - … and it will be possible to develop them

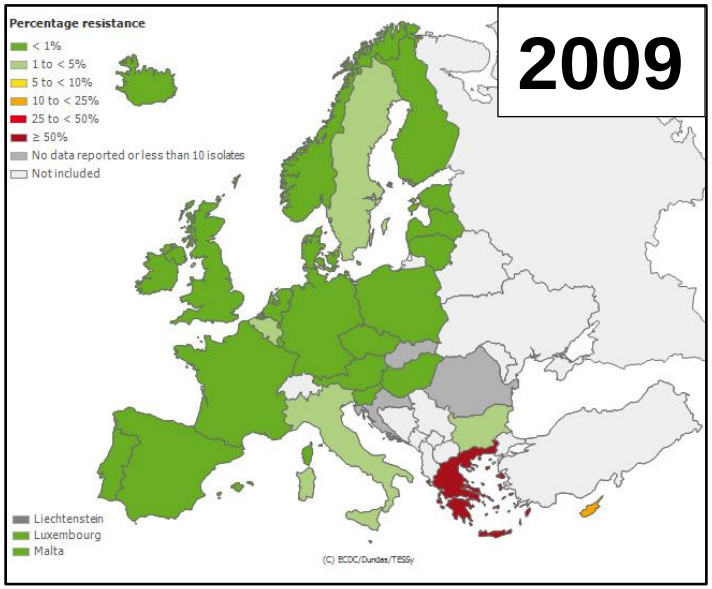
We need to rethink the economics

- New antibacterial antibiotics would be welcomed
- But, the response will be
  - "Thank you! That's a very important new drug!"
  - "Indeed, it's so important that we're going to save it and not use it unless we must!"
- That's exactly the response we should have
  - That's good antibiotic stewardship!
- But, this creates an economic challenge
  - Let's look at this more closely…

Let's now look further via the lens of three questions about the area

- How rapidly does resistance emerge? How much advance notice do you get? When do you need to start searching for that new antibacterial antibiotic?
- Why won't the market consistently pull new antibacterial agents forward in a timely fashion?
- What does it cost to create an antibacterial antibiotic? If one can project a positive NPV (net present value) of $50m, why wouldn't you invest?

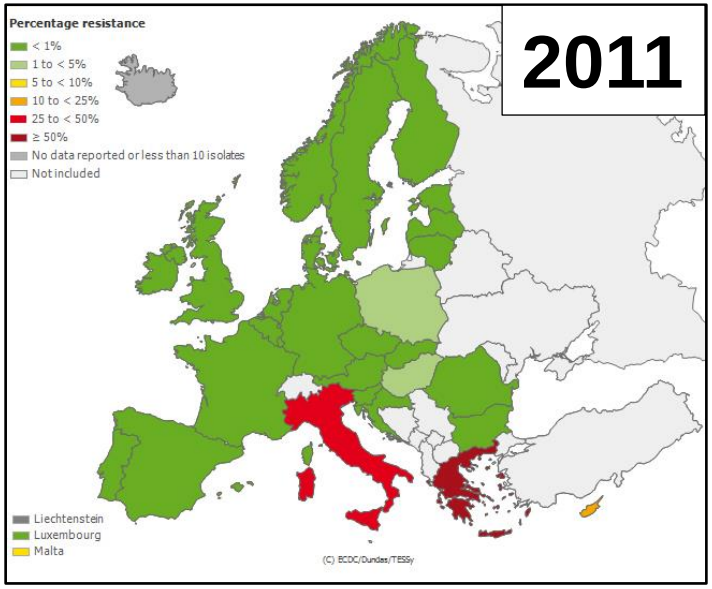
Q: How fast? A: Quickly!

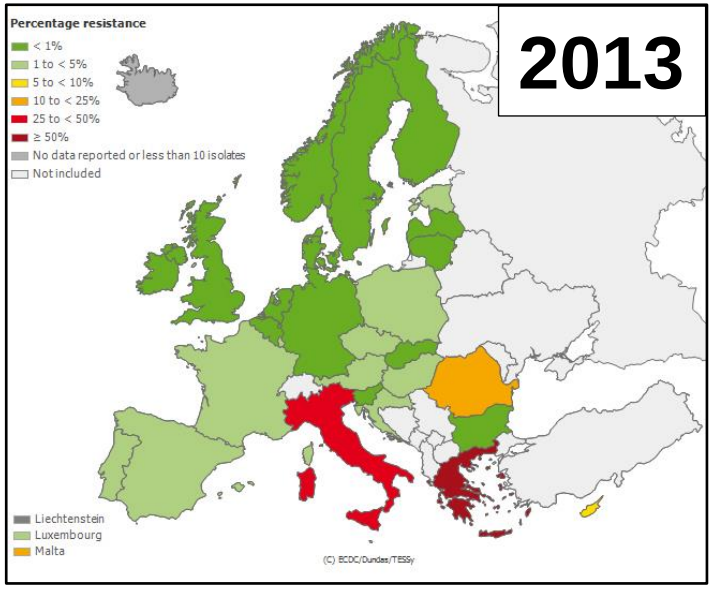


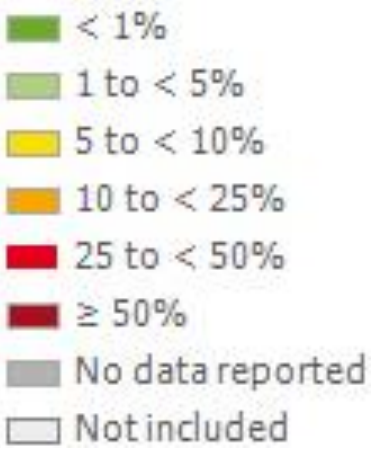
Shown is the % carbapenem non-susceptible for *K. pneumoniae* in Europe, 2009-2013

- Italy: From 1-5% to 25-50% in two years
- Romania: From <1% to 5-10% in two years

The death rate more than doubles[1] with these resistant bacteria







Source: EARS-NET (http://www.ecdc.europa.eu/) and Patel 2008 Infect Control Hosp Epidemiol 29:1099

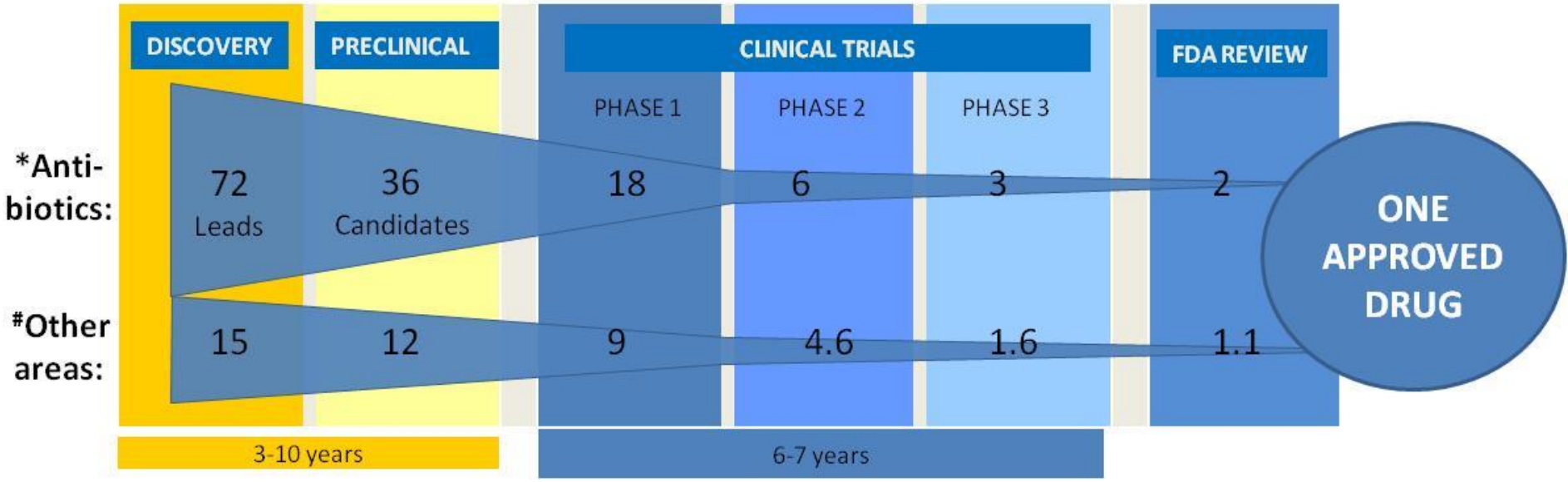
Q: Can we prevent resistance?
A: Only somewhat

- Clever approaches to dosing and use of combinations can reduce the rate of development of resistance
- Careful Infection Control practices can reduce the rate of spread of resistant bacteria

- But, there's never (ever!) been a drug that was resistance-proof
- Every use, whether correct or incorrect, leads inexorably to development of resistance
- Explosive outbreaks remain possible

Q: When do you need to start searching for that new antibacterial antibiotic?

A: It takes 10-20 years to make a drug



We need to be looking **now** for the antibiotics we want in 2030!

**Hit to Phase 2 based on novel mechanism AB discovery (GSK) #Based on Paul, et al (2010), Nature Reviews Drug Discovery 9: 203-214.*

For today, let's look at this through the lens of three questions about the area

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The two kinds of antibiotic value

Usage-based income captures only one of them

- **Obvious:** Using them to treat an infection
  - *Such usage-based sales revenues are how companies currently expect to generate a return on investment*
- **Subtle:** Knowing I *could* use them to treat
  - This may actually be the bigger value!
  - When you fear inability to manage an infection…
    - At the extreme: Chaos & panic (Ebola)
    - Day to day: Avoiding needed and useful medical care, avoiding travel → disruption of commerce & daily life
  - *(Near) zero usage is actually the goal for all antibiotics*

I like to think of this as *"The problem of drugs 8, 9, & 10"*

- IDSA[1] has called for 10 new drugs by 2020
  - And we really need 20 by 2030
  - Having a diverse pipeline is our only real defense!
- The first few are so acutely needed that they are likely to be profitable
- But drugs 8, 9, and 10 will struggle
  - And it will only be worse for nos. 18, 19, and 20
- This is a problem we have to solve!

[1]*IDSA = Infectious Diseases Society of America*

Are there realistic alternatives to company-based approaches?

- Pharmaceutical development is complex
  - You have to continue development, register globally, ensure pharmacovigilance, and maintain a supply chain
  - This requires years of effort by highly motivated teams
- My view: A combination of public and private investment is the only realistic approach to an ongoing diverse pipeline
  - Permitting appropriate profit for successful innovation (and no profit without successful innovation!) ensures that companies have "skin in the game"
  - This, in turn, ensures the needed energy, efficiency, focus

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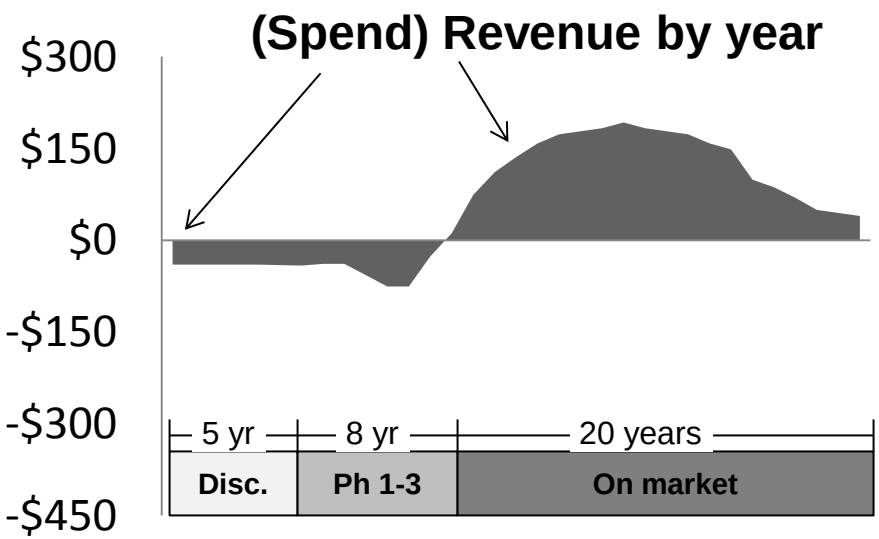
What motivates companies?

- We can't *make* companies do this work … we have to make them *want* to do this work[1]
- We must address several basic tensions
  - We want to minimize use of *all* antibacterial antibiotics
  - We want to have new(er) antibiotics available on demand
  - We want those antibiotics developed before the epidemic
- How can we do this?
  - Noting that "All models are wrong, but some are useful"[2]…
  - … let's now look at a model that may be instructive

[1]Spellberg B. The antibacterial pipeline: Why is it drying up, and what must be done about it? Appendix A in Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies: Workshop Summary, Institutes of Medicine, 2010. Accessed online at http://www.nap.edu/catalog/12925.html on 11 July 2013. [2]GEP Box and NR Draper in *Empirical Model-Building and Response Surfaces*, 1987, John Wiley & Sons, New York, NY.

The cost of creating an antibacterial
An EU-based analysis



- The typical antibacterial lifecycle can be modeled from start to finish[1]
- The model allows for failed drugs
- Spend and revenue by year are based on industry average data
- Note the Phase 3 bump in spend
- And then a sales curve: ~10 years of protected sales and then ~10 years of declining sales

- Approximate total spend (years 1-13): $600m
- Approximate total sales (next 20 years): $2,500m
- **But, we've forgotten about NPV!**

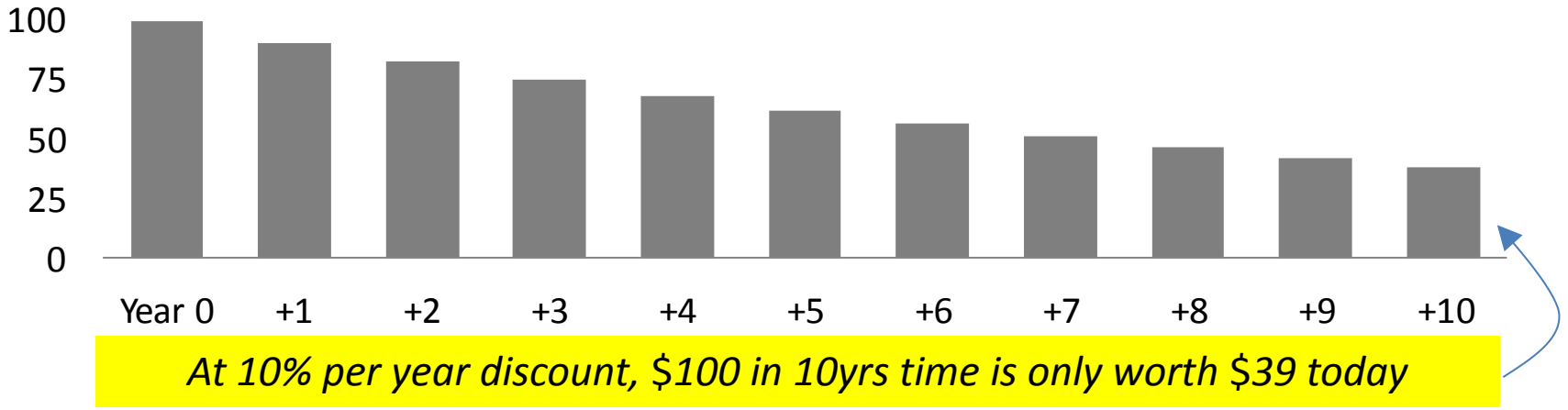
[1]Sharma, P. & Towse, A. New drugs to tackle antimicrobial resistance: analysis of EU policy options. OHE website, 2011; Spellberg et al. Nat Rev Drug Discov 11: 168., 2012

Before we go further, we interrupt this presentation...

Sidebar: NPV (Net Present Value)

How much is an investment worth in today's terms?

- Cash today is worth more than a promise of cash tomorrow (or in ten years)
- Based on cost of capital, risk, etc., it is typical to discount 10% per year
- The math is the inverse of interest on a loan:
  - $100 today = $100; $100 in a year = $90; $100 in two years = $81, etc.[a]

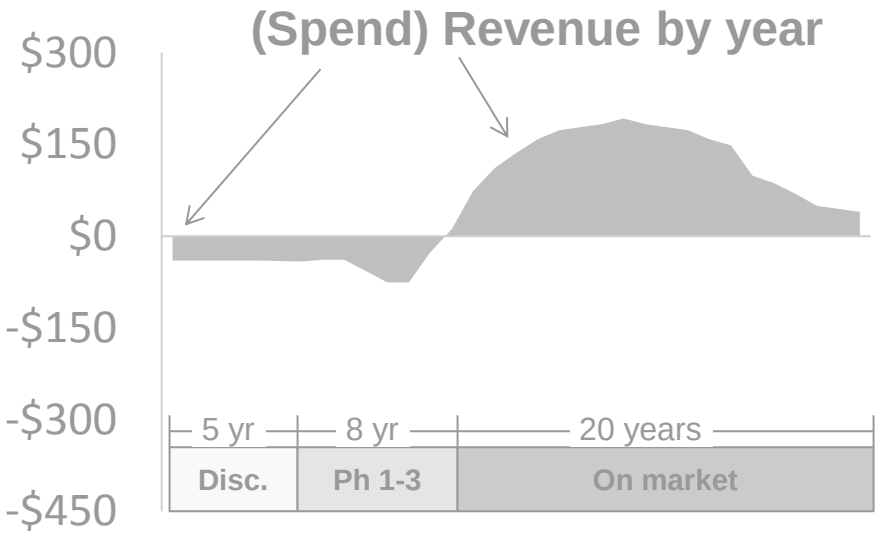


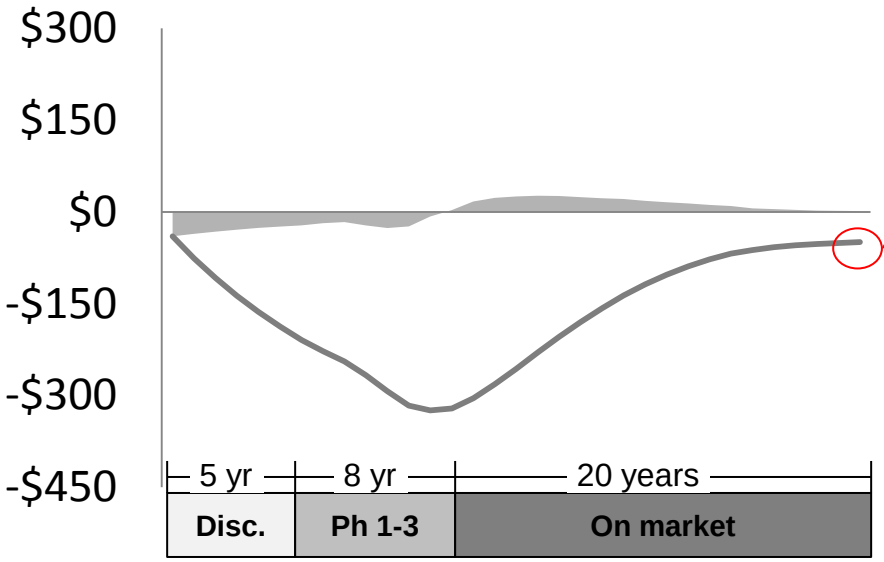
- A project's NPV is calculated by
  - Computing sales less costs for each year (Annual Net Cash Flow)
  - Each future year's Cash Flow is discounted to today
  - The total across all years is the **Net Present Value**
- **Any NPV > 0 means you've created (at least some) value**

a. Actually, I've simplified a bit here – the actual values are $91, $83 … but this simpler way of thinking about it is close enough for illustrative purposes

Now, back to the story…

The very real effects of NPV math





- **Now, consider this in NPV terms**
- From the standpoint of year 0 (the day you decide to start discovery), the graph below shows spend & revenue discounted 10%/year
- The line below is the cumulative NPV
- In NPV terms, these 33 years of work produce a loss of around $50m
- And think about the capital at risk and the timeline to the return. Even at +$50m, this would be unattractive

Recent US-based analysis: same result

- Comprehensive model for drugs for 6 key indications (ABOM, ABSSSI, CAP, cIAI, cUTI, HAP-VAP)[1]
- NPV of the new drug always < $40 million
- Value to the patient was MUCH higher
  - As much as $12 billion
- Thus, these EU- and US-based models show that
  - Starting antibacterial R&D is not financially rational, at least not with traditional R&D costs and approaches
  - We (society) undervalue these drugs

[1]Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Eastern Research Group. Analytical framework for examining the value of antibacterial products. Report to US DHHS. http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

That's a problem we must solve

- To restore vitality to the pipeline and ensure we have the life-saving drugs we will need in the future,

- We have to move these models back into consistently positive territory

And, we're trying now to do just that…

Global Leadership: A partial list

2003 et seq: IDSA: “Bad Bugs, No Drugs”

17 Sep 2009: (EU) Swedish presidency
- “Innovative Incentives for Effective Antibacterials”

7 April 2011: WHO World Health day on AMR
- “No action today, no cure tomorrow”

17 Nov 2011: (EU) ND4BB program
- PPP for Discovery & Development

2011 forward: (US & EU) FDA & EMA
- A steady stream of new guidances

2012: (US) GAIN Act (see subsequent slide)

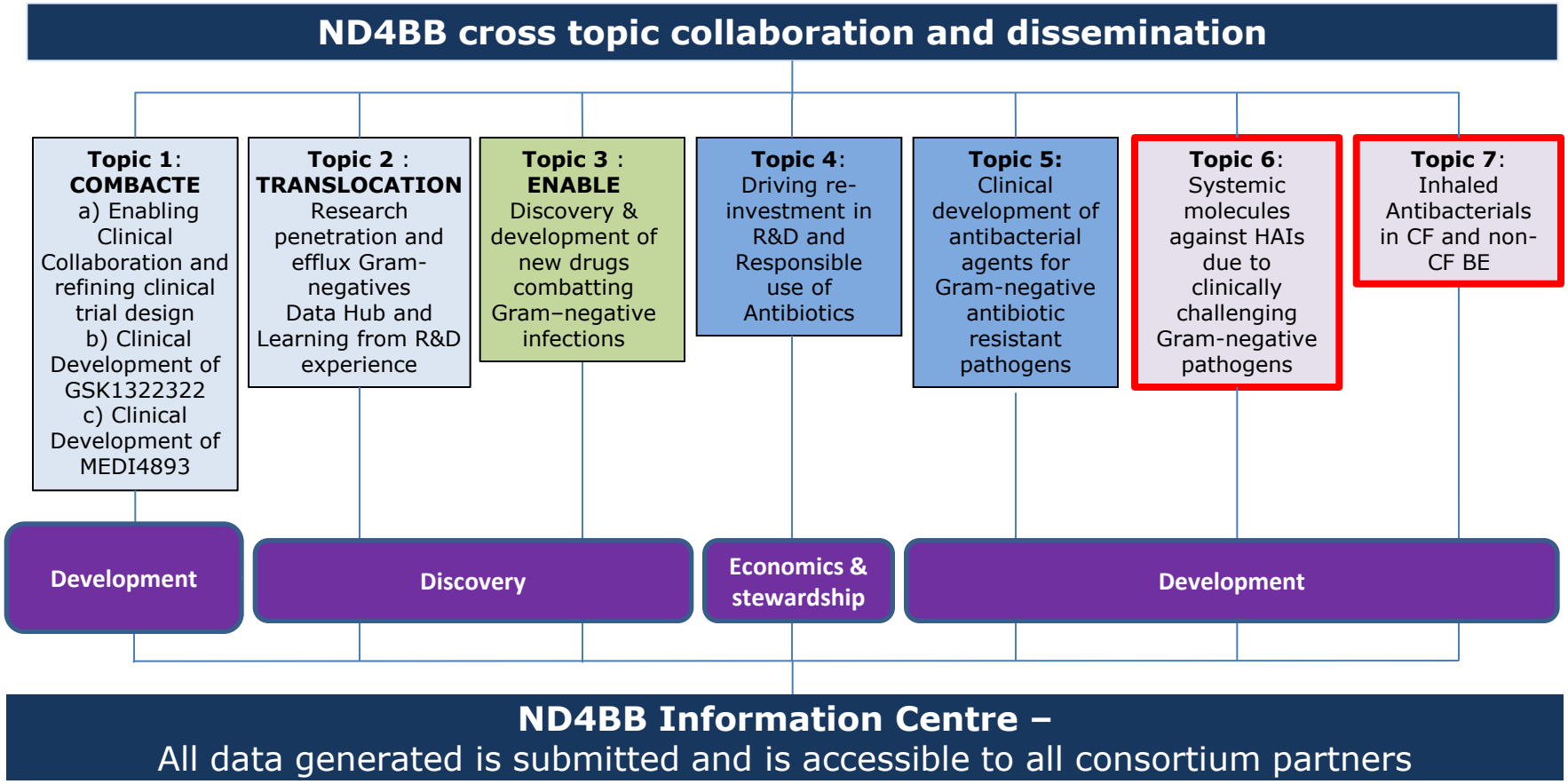
3-4 Oct 2013: (EU) Chatham House Conference
- “Antimicrobial resistance: Incentivizing Change Towards a Global Solution”

2014: (US) PCAST Report

Public-Private Partnerships
In the US: NIAID & BARDA

- NIAID: Antibacterial Resistance Program
  - Extensive array of preclinical services
  - Phase 1 clinical units
  - ARLG (Antibacterial Resistance Leadership Group)
  - Master protocols (I-SPY as a model)
- BARDA (Biomedical Advanced Research & Development Authority)
  - Several public-private partnerships established to date

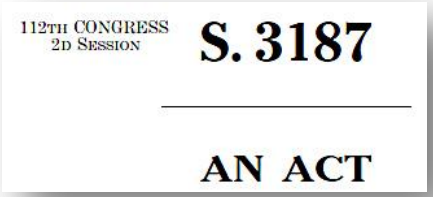
In the EU: IMI's ND4BB program (New Drugs For Bad Bugs)



IMI = Innovative Medicines Initiative

Call 6 | Call 9 | Call 8 | Call 11

And finally, economics
In the US…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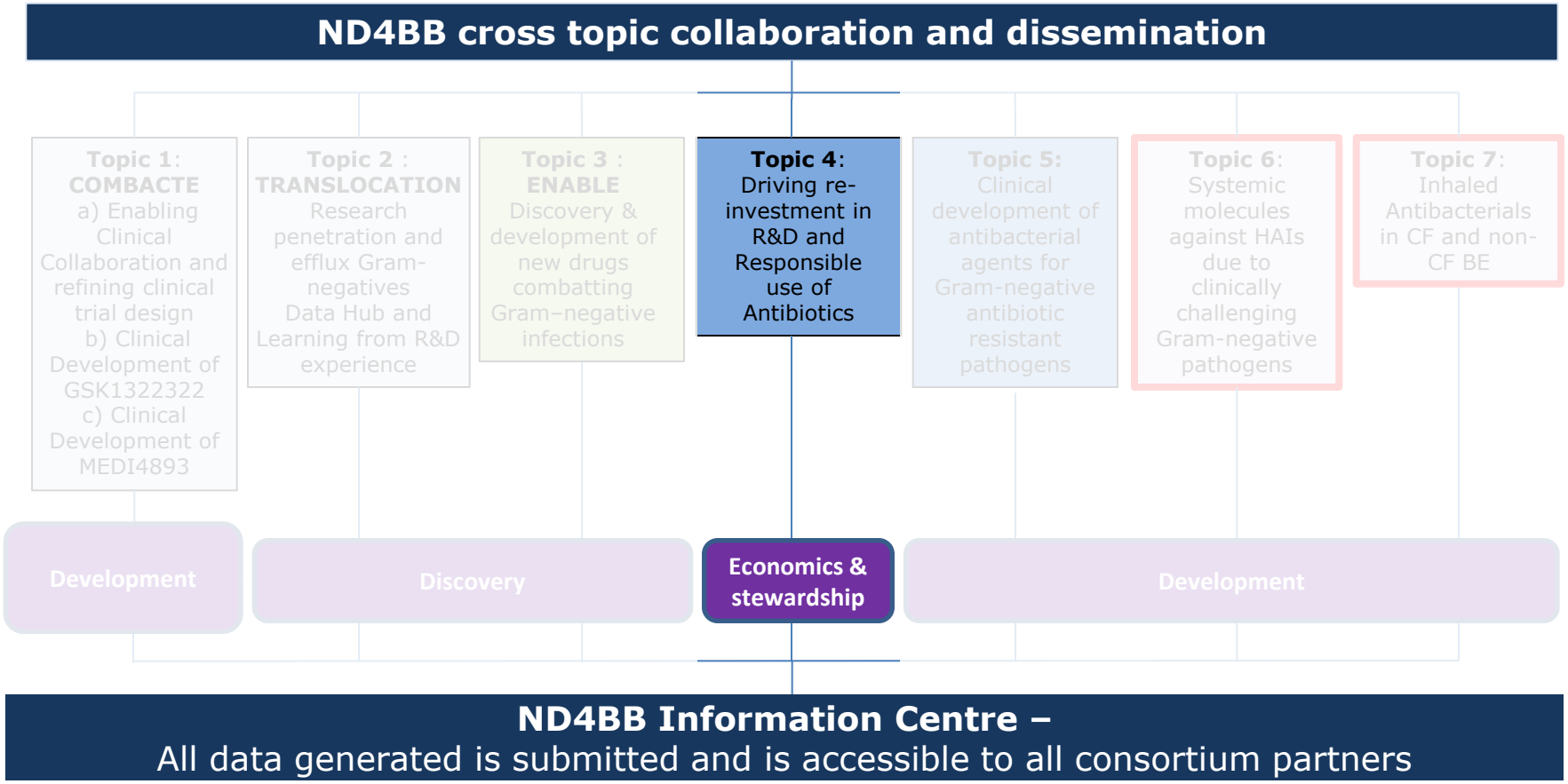
AN ACT

- 2012: GAIN (part of FDASIA)
  - Generate Antibiotic Incentives Now
  - Extended exclusivity, priority review, fast track, and a requirement to generate new guidances
- 2014: ADAPT (LPAD), DISARM
  - Two more pieces of legislation now in discussion
  - ADAPT (LPAD): Further support for streamlining antibacterial development
  - DISARM: A fix for the NTAP[1] problem

[1]NTAP = New Technology Add-On Payments: The quick adjustment to DRGs made when a new technology emerges.

In the EU: IMI's ND4BB program (New Drugs For Bad Bugs)



IMI = Innovative Medicines Initiative

Call 6 | Call 9 | Call 8 | Call 11

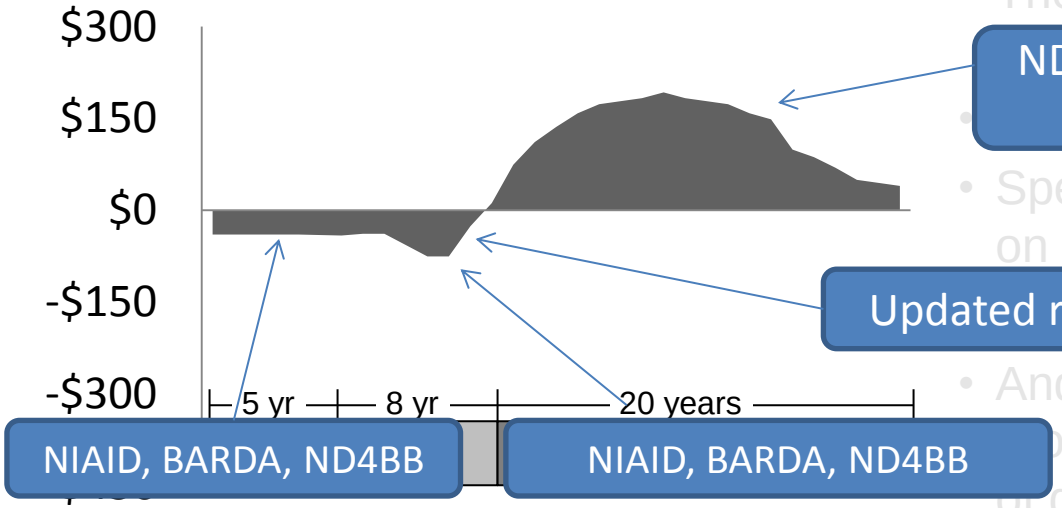
And in the EU…
ND4BB Topic 4: The DRIVE-AB Project

- Launch meeting: 6 Oct 2014
  - "Driving re-investment in R&D and Responsible use of antibiotics"
- Aim: Address the tension between economics & stewardship
  - Create a multi-disciplinary, multi-stakeholder community (16 public partners and 7 private partners from 12 countries) with an in-depth comprehension of challenges of antibiotic development
  - Develop evidence-based measures for responsible antibiotic use
  - Create implementable options for new commercial models that address the needs of multiple stakeholders
  - Validate options through modelling
- We expect DRIVE-AB to explore a broad range of approaches
  - In particular, we hope to see ways to separate (delink) usage from reward to the innovator. That is, reward should not be sales-based
  - Let's look at two possible tools...

Two intriguing economic ideas

- (Push) Refundable tax credits
  - For some percentage (e.g., 50%) of qualified expenses, the company either gets a tax credit (if the company has income) or receives a payment of that amount
  - Has immediate impact on NPV while also ensuring the company has "skin in the game" that ensures delivery
- (Pull) Insurance-based approaches
  - National acquisition at a fixed, predictable rate (e.g., US buys $100m/year of a new antibiotic for 5 years)
  - Annual fee guarantees availability of a certain number of courses of therapy, whether used or not
  - We should be pleased to buy but not use the drug, just as we are pleased when our life insurance does not pay off

We're now tackling the entire model!



- With support from NIAID, BARDA, ND4BB, & others plus the updated regulatory approach, we are truly taking a systems approach to this problem
- The Discovery and Development support + the updated regulatory approaches are already having an impact
- **Last step: Rethinking value and business models**

[1]The FDA & EMA have worked steadily to develop strategies to permit development of drugs in advance of widespread resistance.

Conclusions

Our head is round so that our thinking can change direction (Francis Picabia)

Summary

- Modern medicine depends on having a diverse, sustainable pipeline of antibiotics
  - Hip replacements, treatment of cancer, and care of premature infants hinge on having such drugs
- We're making progress on some fronts
  - Discovery is hard: *ND4BB, NIAID, BARDA are opening doors*
  - Development is hard: *Now improved!*
- The #1 problem remaining is the market model
  - To unleash the power of private investment in combination with public support, we must separate usage from return
  - This problem is being attacked, but it's far from solved. We could still fail

How will success look?

- We will have a **diverse, vibrant pipeline** steadily yielding agents with new (or improved) mechanisms of action
- The agents will be **developed in advance** of epidemic spread of the organisms for which they are needed
- We build an economic model for antibiotics that
  - … provides attractive **returns** for private investors
  - … considers the **value to society** when rewarding innovation
  - … **rewards (and requires) risk-taking** by small and large companies
  - … incentives the entire process, including **post-registration development**
  - … **drives antibiotic preservation** by avoiding volume usage incentives
  - … is applicable at a **global** level
  - … facilitates **access** to all patients with resistant infections
- Thank you for listening!