ENGELBERG CENTER for Health Care Reform at BROOKINGS

Incentives for Change: Addressing the Challenges in Antibacterial Drug Development

Engelberg Center for Health Care Reform
The Brookings Institution
Washington, DC
February 27, 2013

Antibiotic Delinkage

Brookings/FDA

Feb. 27, 2013

Kevin Outterson

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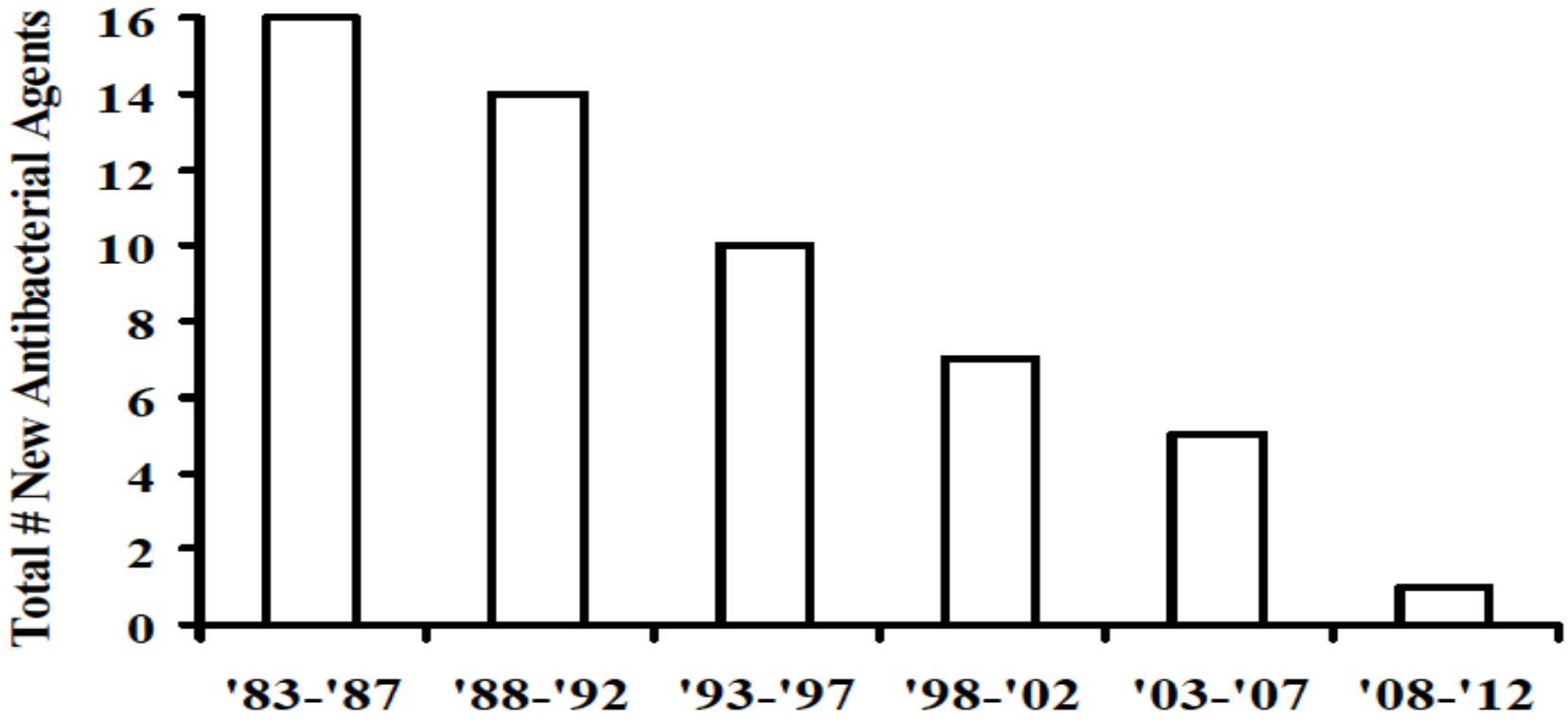
BU LAW

Table 1: Antibiotic Approvals (1983-Present)



Source: IDSA's 2004 Bad Bugs, No Drugs report (modified)

Spellberg/IDSA. House Energy & Commerce Comm., June 9, 2010

From the Boston Business Journal
:http://www.bizjournals.com/boston/stories/2005/10/17/daily65.html

Oct 20, 2005, 12:01pm EDT

Cubist posts record sales, narrower losses for third quarter

Staff *Boston Business Journal*

Cubist Pharmaceuticals Inc. says third-quarter 2005 revenue reached record levels and losses continued to narrow, driven by a continued increase in sales of its signature drug Cubicin.

The Lexington, Mass., company (Nasdaq: CBST) reported $31.8 million in revenue for the quarter ending Sept. 30, up considerably from the $19.4 million in revenue reported during the same period last year.

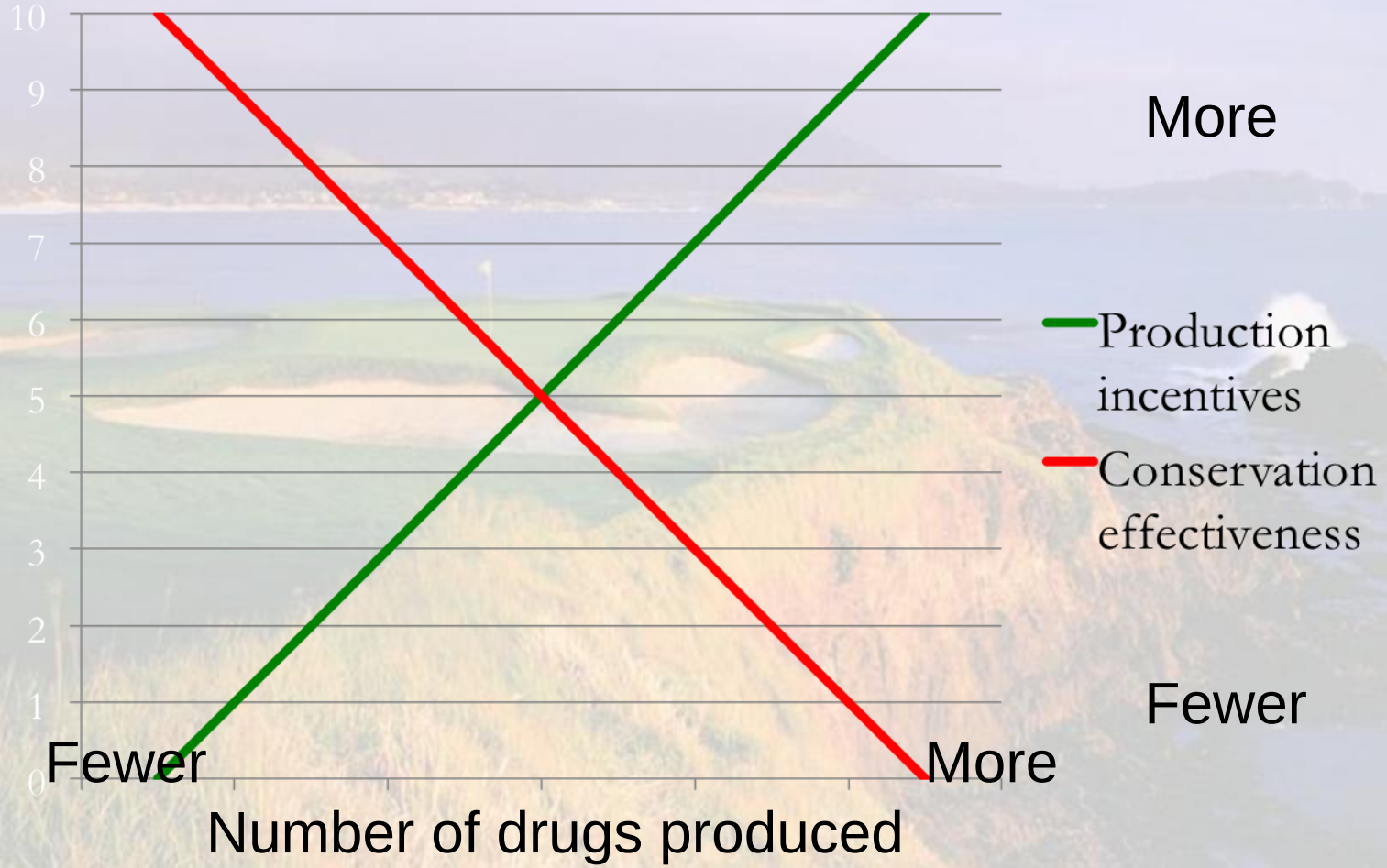
Goal: Lowest achievable ID burden

- Vaccines
- Infection control
- Better antibiotics
- Stewardship
- Public health

Design parameters

- Simultaneously solve for both production and conservation
- Begin with inpatient & OPAT abx
- The ecology of resistance is a complex system – the solutions might also require complex, integrative designs

Opposing incentives

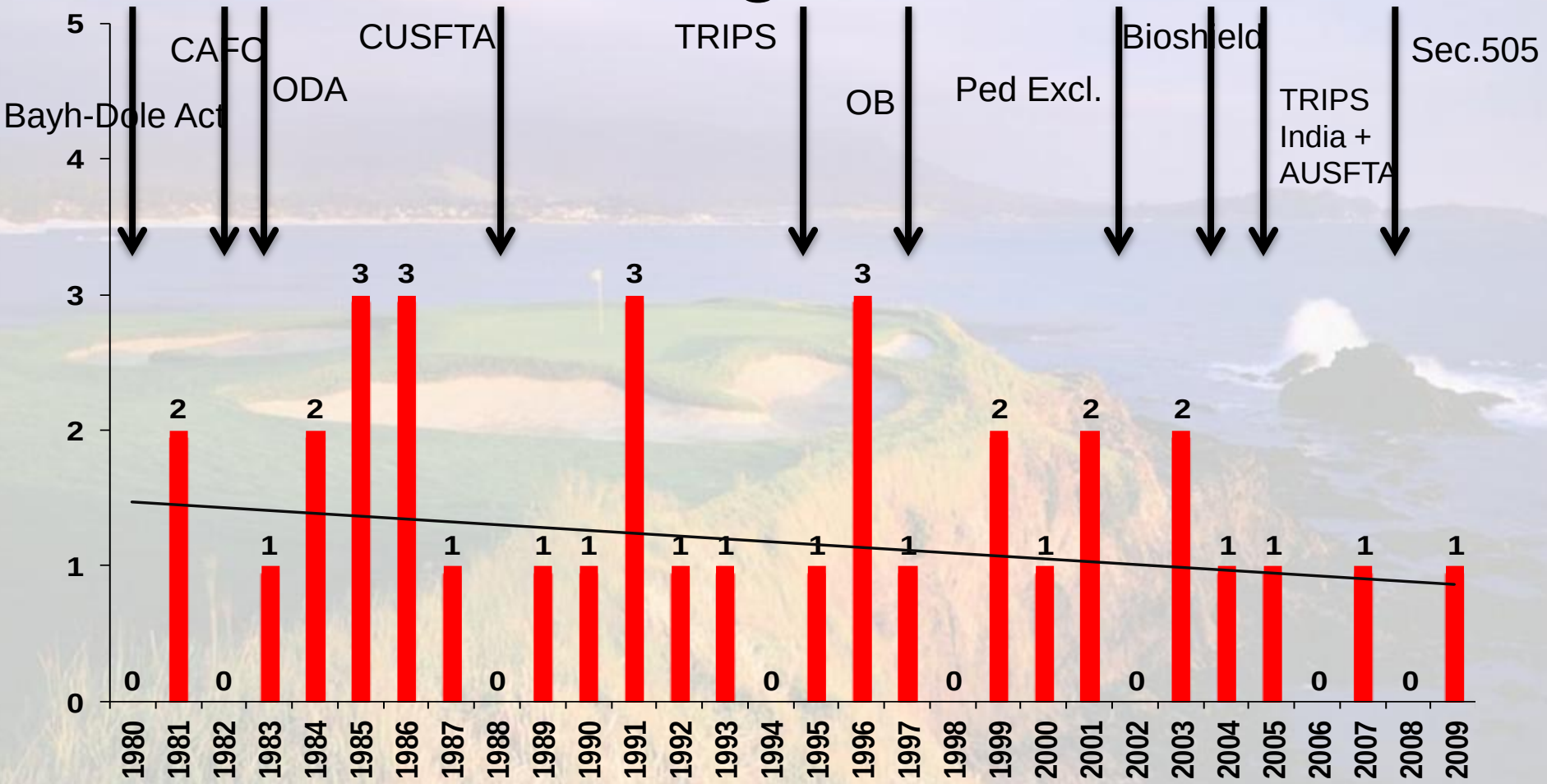


With linkage

- Providers, patients & drug companies lack financial incentives to conserve
- Successful conservation reduces sales & innovation
- No business model for infection control & conservation

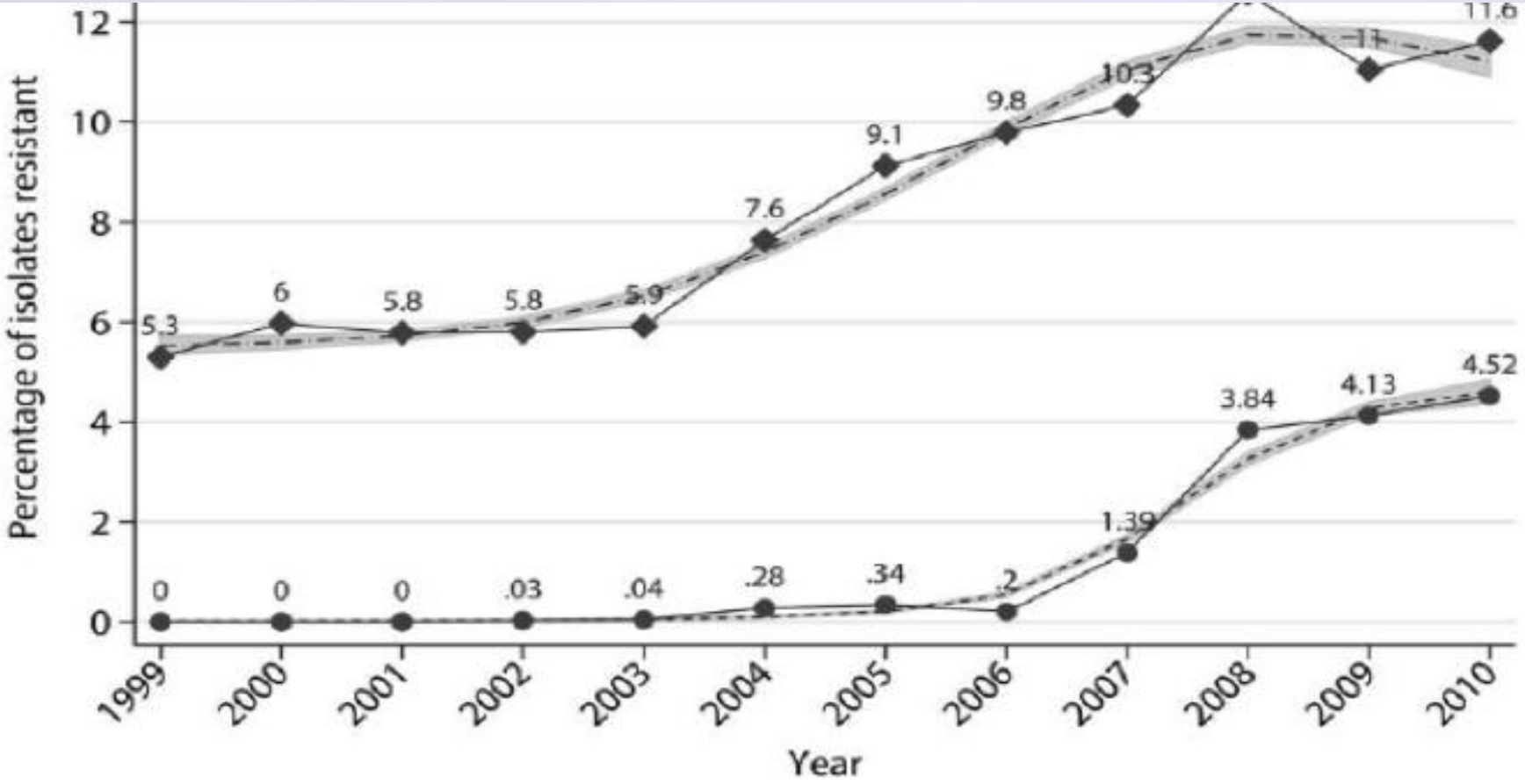
See R. Laxminarayan; K. Outterson; E. Kades; A.S. Kesselheim; A. Malani; R. Saver; S. Mechoulan.

Systemic Antibacterials Approved by the FDA (1980-2009)
Marketed Drugs, Linear Trend



Outterson et al. 2013 (in peer review)

Resistance



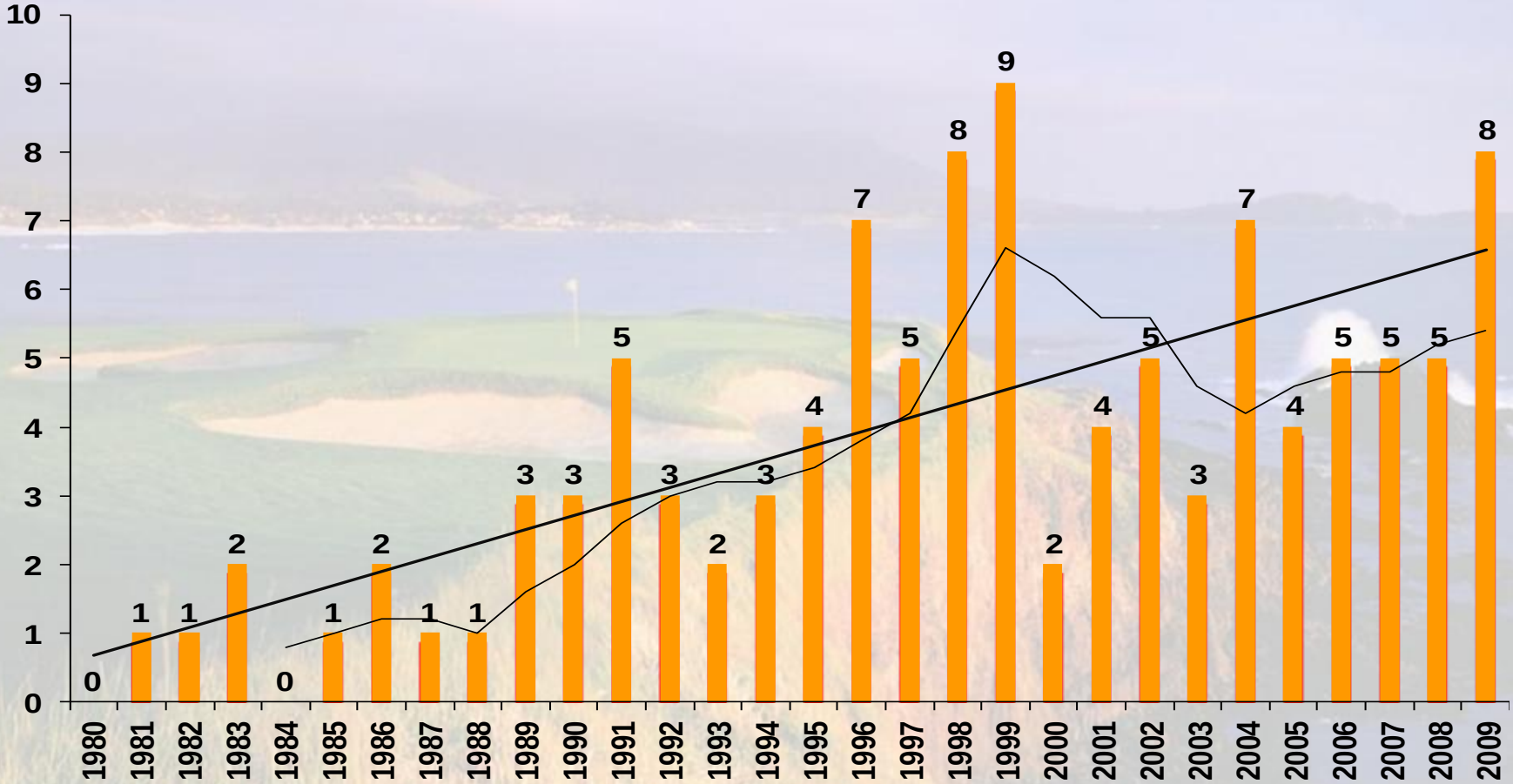
Braykov NP et al, ICHE March 2013

Which tools?

- NPV benefits of *ex ante* patent changes & faster approvals are smaller than front-loaded tax & prize incentives
- Reimbursement bonuses would magnify market signals
- Consider ancillary consequences

ERG Study (pending, 2013)

Antineoplastic & Immunomodulating Agents Approved by the FDA (1980-2009). Marketed Drugs, Linear Trend & 5 Year Moving Average



Outterson et al. 2013 (in peer review)

Key elements

- Separate unit sales from revenues
- Increase total rbx (social value)
- Conditioned on conservation targets set by expert group
- Permit long-term drug-bug market coordination by all institutions

Kesselheim AS Outterson K. Health Affairs 2010; Yale J. Health Policy, Law & Ethics 2011.

Models

- LPAD I & II
- CMS P4P
- Payor licenses (capitation)
- AQC/CC & Part C
- Global prize (aHIF)
- Strategic Antimicrobial Reserve

Kesselheim AS Outterson K. Health Affairs 2010; Yale J. Health Policy, Law & Ethics 2011.

Models

	Public	Private
Global	• aHIF	
US	• LPAD II • CMS P4P & C • Strategic reserve	• LPAD I • Capitation • AQC/CC

LPAD I

- Faster approval/limited population
- Significantly higher reimbursement (set by market)
- Higher price & limited label constrain demand (conservation)
- IDSA & Tier C proposals

LPAD II

- Faster approval/limited population
- Significantly higher reimbursement (minimum price?)
- Explicitly delinked with immediate, conditional cash flow unrelated to unit sales (~$50mm/yr)
- Rempex proposal

Strategic reserve

- LPAD II, with very low unit sales and much longer LPAD period
- Higher bonus, based on long-term strategic considerations
- Very rare, but valuable

Kesselheim AS Outterson K. Health Affairs 2010; Yale J. Health Policy, Law & Ethics 2011.

CMS P4P

- Quality initiative
- NTAP
- Very significant DRG bonuses for appropriate use & infection control (billions, not millions)

Capitation

- Patent owner licenses use of the drug to plans
- Reimbursement is PMPM, not unit sales
- Akin to a carve out
- Significant coordination issues with all private models

AQC & Part C

- Private plan quality initiative
- Plan bonuses for infection control & appropriate use
- CMS could also encourage in Part C

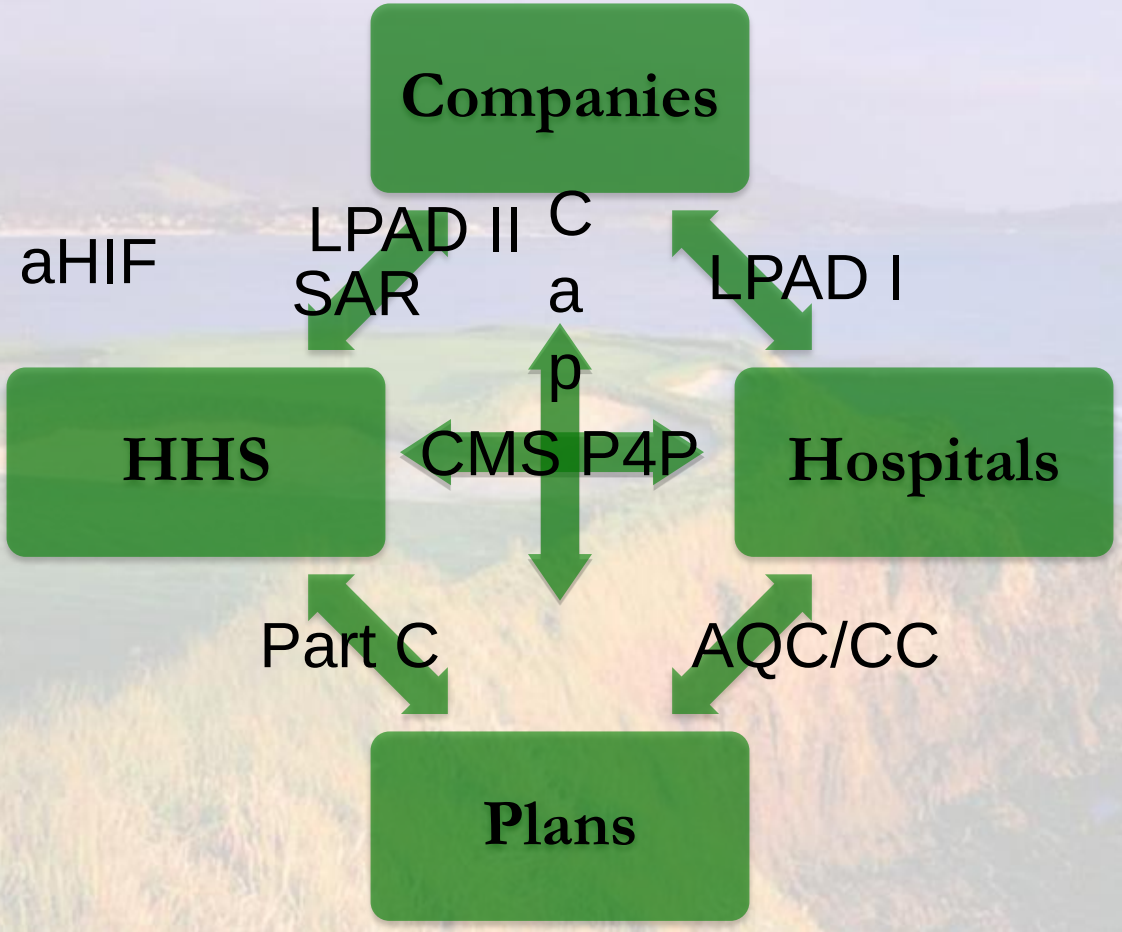
aHIF

- Global coordination problem
- See Aidan Hollis' presentation on the antibiotic Health Impact Fund

Design questions

- Who has the best information?
- Who is best positioned to change behavior?
- Who do we need to incentivize?
- What data do we want to collect?
- How do we measure success?

Cash flow


Companies
aHIF
LPAD II
SAR
C
a
p
LPAD I
HHS
CMS P4P
Hospitals
Part C
AQC/CC
Plans

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De-linking Return on Investment from Sales Volume for New Antibacterials

James Anderson, GSK European Government Affairs

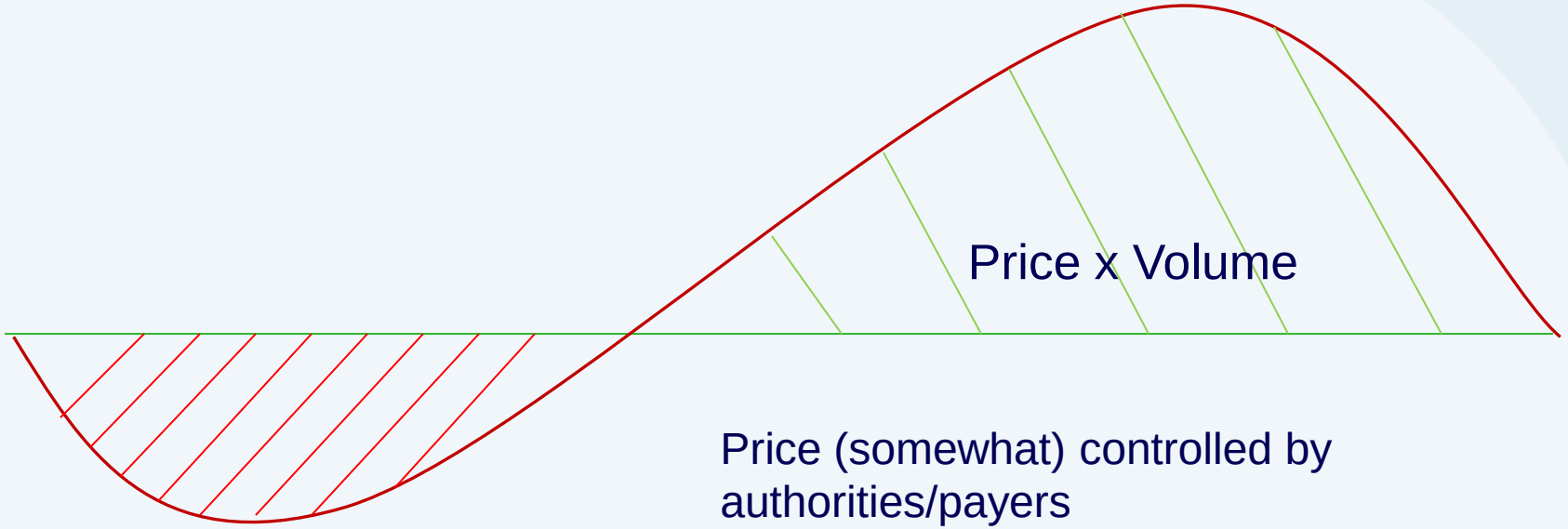
Brookings Institute, February 27th

Summary of Presentation

- Why a de-linked model to reward antibacterial R&D makes sense for both developers and public health
- Principles needed when designing a de-linked system
- Ball-park economics to make it work
- Challenges that will need to be addressed
- Partnership for post-license activities to jointly minimise inappropriate use

Disclaimer: this presentation has been prepared to contribute to today's debate and should not be interpreted as a GSK proposal. GSK Public Policy Position on Incentives for Antibacterial R&D is available on our website at:
http://www.gsk.com/content/dam/gsk/globals/documents/pdf/Policies/GSK-antibacterial-randd.pdf

Typical Pharmaceutical Economic Model: Return is driven by sales volume



Price (somewhat) controlled by authorities/payers

Volume (somewhat) driven by company and competition

Investment is largely controlled by need to demonstrate safety & efficacy

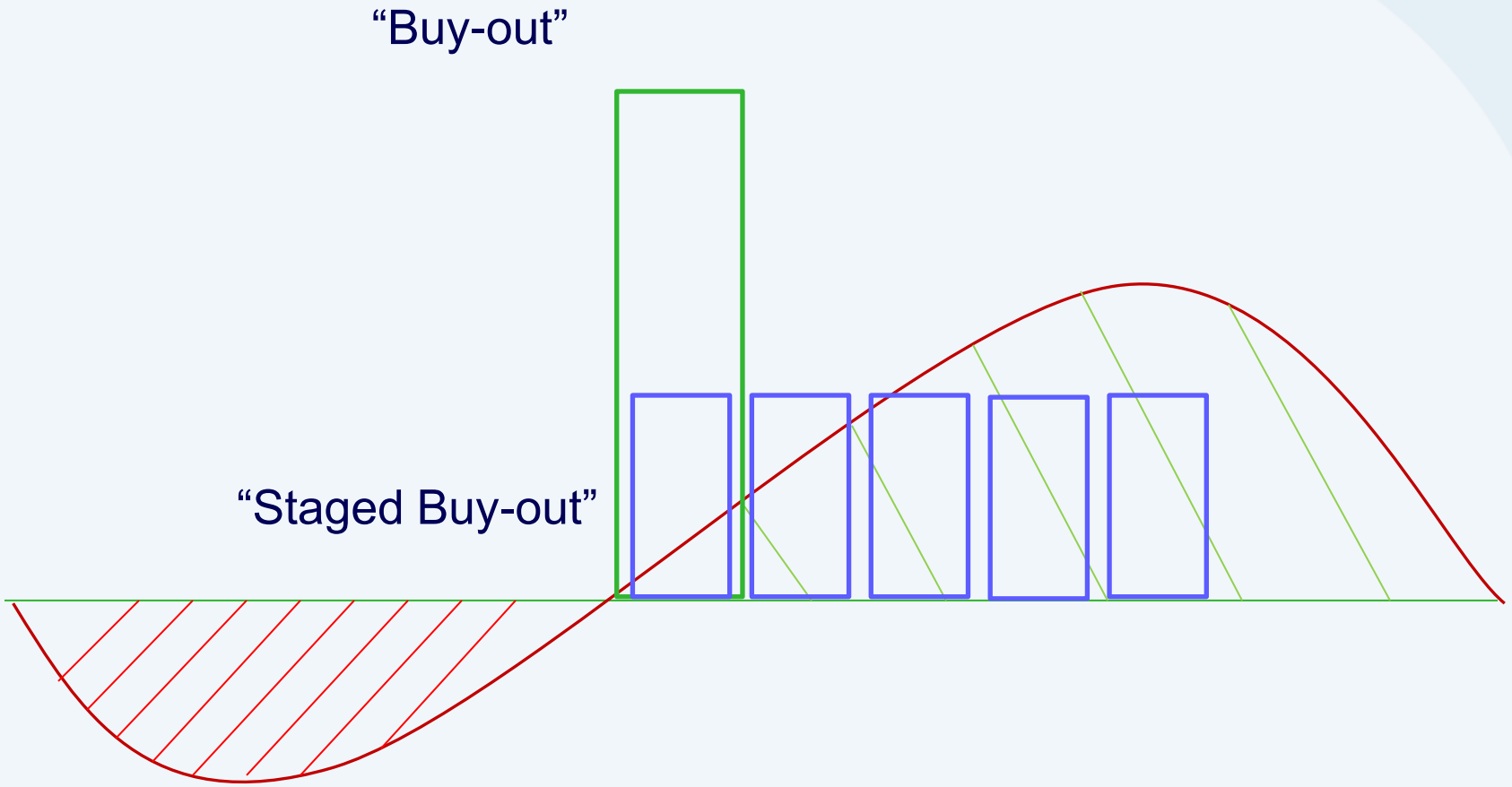
Industry recognises that this model:

- Works for most products: higher volumes deliver more health benefit
- Does not work for antibiotics: higher volumes deliver health benefit but sometimes contribute to resistance. LPAD type approaches exacerbate need for delinked model (smaller patient populations etc)

Principles of a De-linked ROI model

- Payments to successful developer of novel antibiotics need to be sufficient to attract further investment
- Payments should remove or significantly reduce the incentive for developer to want to sell more volume
  - Main payment triggered by successful license approval
  - Product provided at cost
- Payments must be predictable and decision process transparent
  - Target pre-specified by public bodies
- New products must be made available to patients who need them, wherever they are in the world
- If rewards are linked to additional responsibilities on industry, these should be calculated separately. For example, purchasers should contract separately for supporting services such as:
  - Further clinical studies
  - Identifying inappropriate levels of use
  - Educating Doctors and Encouraging appropriate use

De-linked model to deliver against these principles

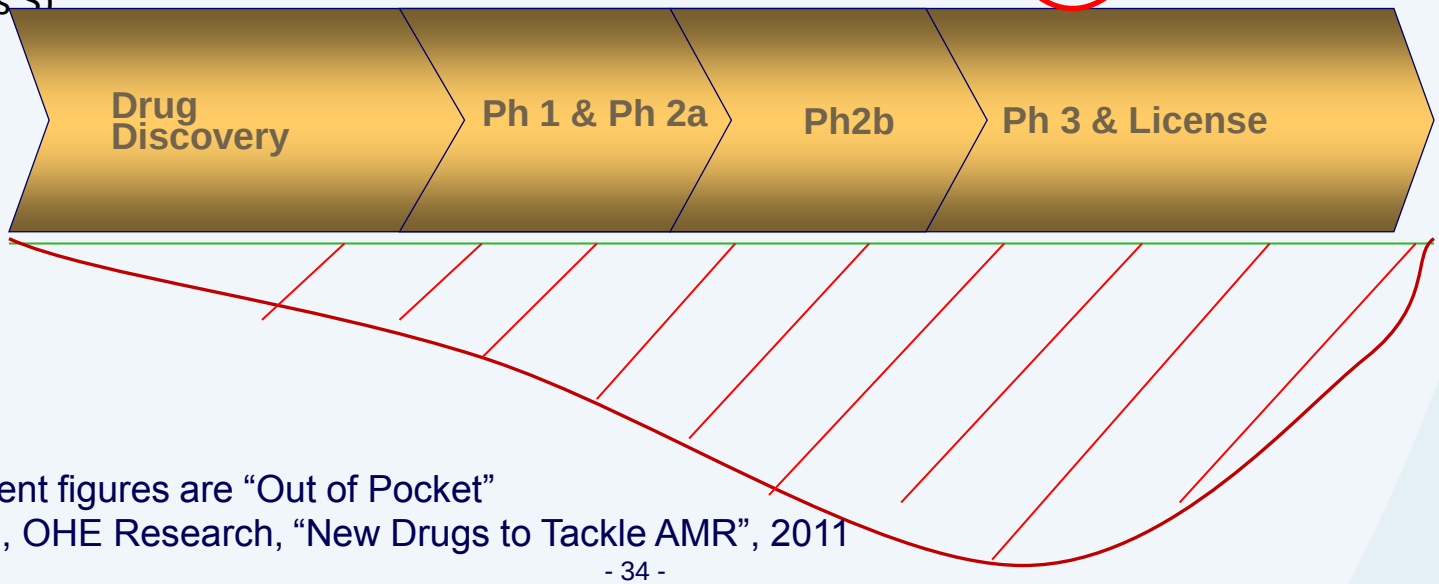


Timing of Commercial Commitment is Key

Public/Private Funding

Purchase Commitment

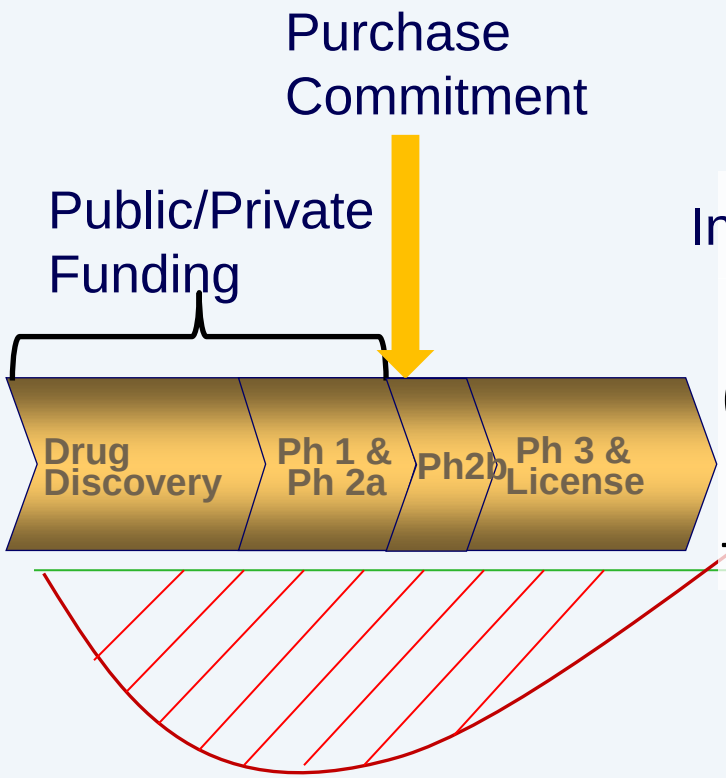
	Preclinical	Phase I	Phase II	Phase III	Approval	**Total**
Mean Investment per phase (millions $/molecule)	18.5	15	40	150	40	**264**
Probability of success	35%	58%	52%	79%	91%	
# of molecules to start each phase to ensure 1 approval	13.1	4.6	2.7	1.4	1.1	
Total Investment to ensure 1 approval (millions $)	243	69	107	210	44	**673**



Note: all investment figures are “Out of Pocket”

Sharma & Towse, OHE Research, “New Drugs to Tackle AMR”, 2011

How much reward is needed – ballpark estimates



Level of Public Funding (Pre Phase 2)

Investment	0%	50%	100%
1 Molecule only ($264m)	6.6x	6.4x	6.1x
Including costs of failures ($673m)	4.6x	3.7x	2.8x

Multiple of Investment needed to deliver NPV*

Annual payments over 5 years of $350-500m* (globally)

* NPV discount rate 12%; NPV = $200m, assuming 50% public funding contribution
Model adapted from Sharma & Towse, OHE Research, "New Drugs to Tackle AMR", 2011

Industry's Role in a De-linked model

- Greater transparency on strategy and profit to stakeholders
  - Stakeholders & funders should have a say in strategy
    - Global committee to identify priority pathogens and update annually ("Target Product Profile")
    - AB R&D increasingly dependent on public funding (eg BARDA, DTRA, IMI, NIAID)
  - Reward framework developed jointly:
    - payments should reflect public funding;
    - profit should be calculated openly to be attractive but with 'caps'/agreed limits
  - Create further open innovation & partnerships amongst pharma (eg IMI ND4BB, COMBACTE clinical trial consortium etc)
- Partner with Public Health and Medical community to further facilitate appropriate use, (crucial for SMU)
  - Provide sales data for new antibacterials to healthcare institutions (GSK committed to this)
    - Creates transparency, encourages controls by healthcare institutions
    - Enables ID community to assess appropriate use
  - Communication/educational services covering product and appropriate use can be provided (at purchaser's request)

Challenges of any De-linked model – for discussion

- Global pooling mechanism for funds preferred: country by country negotiation impractical and free-rider risk
  - Incompatible with “normal” medicine spend: Pandemic analogy? Emergency preparedness?
- Global management of availability vs inappropriate use. Enforcement at a National & Institutional level, but are tools sufficient?
  - What about countries known to lack prescription controls?
- The loss of market forces to exert control over both price and volume causes challenges:
  - Who and how to decide which molecules meet the criteria for reward? Need to avoid cross resistance – how does this impact selections?
  - How to set the amount of reward? Should this ever be re-assessed?
  - How does money flow?
  - Do we need to re-introduce a transfer price at institutional level, as a way to manage demand?

Conclusions

- Investment will be encouraged by a sufficient reward for successful licensing, under a de-linked model
  - Incentives will be much better aligned
  - High-level economics appear workable in principle
- A new form of holistic global partnership is needed to set R&D priorities, agree successful products and manage the use of new products
- Ideally, funding would be pooled globally and a global approach taken to balance product availability with inappropriate use
- Industry is well-placed to deliver some aspects of the products use cycle, but Public partners are better-placed to deliver others. Close collaboration is needed.
- Many details need to be worked out together

New Public Private Partnership model needed to manage new antibiotics optimally

Role	Devel-oper	Public Partners	Rationale
Manufacturing	+++		Has chemical expertise and can ensure capacity available
Further clinical studies	+++	+	Core area of expertise for developer. Public partners decide on studies. Who funds?
Educating doctors and encouraging appropriate use	+++	+	Developer has product expertise and staff. Would need to separate from standard salesforce. Public partners should define “appropriate” for each product
Monitoring product safety	+++	+	Core area of expertise for developer. Public partners need to help interpret data.
Identifying inappropriate levels of use	++	++	Developer can provide the localised data. Joint investigation capability to understand causes and design corrective action
Managing distribution	+	+++	Standard distribution systems not set up to control product flows. Needs centralised/global coordination by Public partners.
Encouraging good hygiene	+	+++	Not a core area of expertise for developer, but may be able to help. Core focus for Public partners.
Monitoring resistance		+++	Public monitoring systems effective and established
Enforcing appropriate use	+	+++	Public partners need enforcement tools: Industry can play facilitation role

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Antibiotic Health Impact Fund

Aidan Hollis
University of Calgary
and
Incentives for Global Health

The problem

- Corporate incentives are to maximize revenues without consideration of the resistance profile that emerges at the end of exclusivity
- “Stewardship” programs depress current revenues, harming incentives for innovation
  - Alternatively, stewardship provides a justification for high prices, which encourages companies to maximize volume.
- Firms should be *rewarded* for developing new products and protecting them from resistance
  - Can firms influence how their products are used?

Rewarding stewardship

Carrot only

- The simplest step: pay a reward to firms at pre-determined intervals for achieving specific measurable stewardship goals and resistance goals.
  - eg: $10m bonus if resistance in less than 2% of MRSA samples in US hospitals at the end of 10 years.
- Problem: unless these rewards are massive, the incentives will be too weak to have much effect on corporate behavior – and who will fund the rewards?

Stronger incentives

Carrot and stick

- The firm is offered a deal that allows it to earn more if it meets stewardship and resistance goals, while being penalized if it falls below certain thresholds.
  - In effect, the firm is partly funding its own rewards
- Implementation: the firm transfers a fixed share of its price to a third party, which in turn pays performance bonuses back to the firm.
- Requires supplementary funding to make it attractive.
  - Firms might be in part rewarded with extended exclusivity

Example

- Firm agrees to hand over 50% of its revenues on the drug to an “antibiotic protection fund”.
- APF commits to reward the firm with
  - 50% of the sum if it meets minimal stewardship and resistance targets
  - 100% of the sum if it meets all goals
  - 150% of the sum if it exceeds goals by pre-defined amount

Plausible funding mechanism

- Supplementary funding could be supported through a tax on all antibiotics use
- Since most antibiotics are generic, the prices would increase by the amount of the tax
- The tax would be directed towards rewarding good stewardship of new antibiotics.

Extending the scope - # of drugs

Carrot, stick, and competition

- One way of extending such a system is to allow several drugs into the same system.
- Then each product would compete to achieve the best stewardship/resistance profile
- Revenues from one (unsuccessful) product might contribute to rewards to another one.
- A key difficulty here is that different products may have different stewardship opportunities and different risk profiles, so it is difficult to make them compete on this basis.
  - In principle, this is no worse than rewarding all on the same dollar basis.

Extending the geographic scope

Carrot, stick, competition, multinational

- Since antibiotic resistance has no respect for national borders, it makes sense to include as many countries as possible.
  - Fortunately this does not require universal cooperation.
- Countries could operate identical schemes nationally without any cooperation at all.
  - It would be more effective with wider cooperation.

antibiotic Health Impact Fund

- The multi-product, international system is the proposed antibiotic Health Impact Fund
- Such a system could potentially fully separate out the reward for innovation and stewardship from the price paid, achieving full delinkage.
- Rewards would depend on therapeutic benefits *and* stewardship/resistance targets
  - The firm would be rewarded for maximizing the sum of current and future expected health benefits
- One benefit is that poorer countries might be willing to extend patent protection – and hence stewardship opportunities – subject to obtaining the product at low prices.

Challenges

- 1. Getting global agreement
  - Since some countries will not participate, or lack prescription controls over antibiotic use, one approach is to apply high prices in those countries. This is essentially using the carrot and stick to influence country behavior.
- 2. Deciding on which drugs meet the criteria?
  - The aHIF approach is to hold out a pot of money and to allocate it according to which drugs offer the most value, as defined by a combination of achieved current *and potential future* health benefits. i.e. instead of up/down decisions, payment is proportional to benefits.

Measuring impact

- Which Abx are most valuable in the past and future?
- It would be impossible to get this just right. But it would be possible to move in the right direction:
  - Present value: QALY-based value, recognizing limited alternatives
  - Future value: agreed measures of stewardship and pre-determined resistance thresholds.

Thanks!

- More information on the Health Impact Fund approach is available at healthimpactfund.org
- A paper by Outterson, Pogge and Hollis on an antibiotic health impact fund is available at

  http://bit.ly/combatresistance

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Rewarding Antibiotic Development And Responsible Stewardship (RADARS)

Daniel Burgess
February 2013

Executive Summary

- **Objective of RADARS program**:
  - Create an economic platform to incentivize innovators to develop new antibiotics to combat resistant organisms
  - Preserve the usefulness of these antibiotics for as long as possible
  - Do so without creating an additional financial burden on hospitals
- **Program Structure**:
  - Designed to work hand-in-hand with QIDP/GAIN, LPAD
  - Guarantees innovators a minimum revenue level for 5 years at attractive pricing
  - Allows hospitals to be reimbursed (above DRG) for on-label use guided by stewardship programs
  - Government only pays for successes and does not have to pick winners prior to approval

RADARS: Basic Concepts

- HHS will set up an incentive program that will reimburse hospitals directly for the use of a new antibiotic (akin to current NTAP payments for Dificid® for *C. difficile*)
- Payment will only be made upon submission by the hospital of documentation showing that the patient had limited treatment options due to the presence of known or suspected resistant organisms consistent with the drug's QIDP designation
- Hospitals would be required to have an approved stewardship program in place to be eligible for reimbursement
- HHS/CMS payments would be over and above normal DRGs for the patient and would be designed to bring the net cost to the hospital to parity with standard existing treatment options

RADARS: Basic Concepts (Cont.)

- HHS would guarantee the innovator a certain minimum revenue stream per year at fixed prices for a period of 5 years (akin to Project BioShield)
- Per patient pricing would be high in the first year ($1,000-$1,500/day) to compensate for low initial volumes and correspondingly high production costs, but would decline over the 5 years to $500-$700/day
- The guaranteed minimum revenue would be $100 million in the first year and rise to $350 million in the 5th year (if total hospital purchases are less than this amount, HHS will pay innovator the difference)

Basic Concepts (cont.)

- NTAP-type payments would continue for 10 years, but the guaranteed revenue minimum to the innovator would only apply to the first five years
- Price per patient per day for years 6-10 would fall to $400-$500
- In exchange for these benefits, innovator agrees it will not promote the product through its sales force in any way; MSL's may be utilized for information exchange only
- No sales volume based incentive compensation permitted
- HHS/FDA would use QIDP (and/or LPAD) designation to define eligibility; no other application required
- Between the NTAP mechanism and BARDA/Project BioShield, all of the key components to implement this program are already in place--they would just need to be adapted and the funds appropriated

Economic Example for a New Antibiotic

Year	Purchase Commitment ($ thousands)	Price per Day of Treatment	Average Days of Treatment	Total Cost per Patient	Number of Patients Covered
1	$ 100,000	$ 1,300	10	$13,000	7,692
2	$ 200,000	$ 1,100	10	$ 11,000	18,182
3	$ 250,000	$ 1,000	10	$ 10,000	25,000
4	$ 300,000	$ 850	10	$ 8,500	35,294
5	$ 350,000	$ 700	10	$ 7,000	50,000

REMPEX Pharmaceuticals

Better Too Many than Too Few

- Program needs to err on the side of paying for too many new antibiotics rather than trying to identify the best few to fund
- On the Gram-negative side alone, we likely need 10-15 new antibiotics from a variety of classes
- Two examples from Rempex's portfolio illustrate this point:
  - Minocin® IV (minocycline for injection)
  - Biapenem (IV carbapenem)
- Drugs were either not developed for or pulled from the U.S. market by other companies due to "market considerations"
- Today, both are uniquely positioned to fight resistant infections that were not present when "no go" decisions were made

Can We Afford It?

- General consensus that failure to step up and address this issue could have disastrous public health and economic consequences
- RADARS **will** lead to many new antibiotics if they are there to be found—premium pricing for cancer and orphan diseases shows this
- The net cost to the health care system is likely to be modest at worst
  - Weinstein et al reported an average incremental cost of a resistant infection ranges from $18-30K based on data from 2000 (*Clinical Infectious Disease 2009;49:1175)*
  - The overall cost to the healthcare system based on 2000 resistance rates was estimated to be > $20 billion
  - Resistance rates have since doubled for many infections
  - Paying an incremental $10-15K to avoid a resistant infection would appear to be a bargain
- **The right question is can we afford not to?**

REMPEX Pharmaceuticals

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