Economic Incentives for Antibiotics: the DRIVE-AB Approach

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BU LAW

CHATHAM HOUSE
The Royal Institute of International Affairs

DRIVE AB
RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

Acknowledgements

- Chatham House Working Group on
- New Business Models for Abx (2013-present)
- DRIVE-AB (IMI/ND4BB) (2014-present)
- Longitude Prize (rapid POC abx dx) (2014-present)
- Consultancies with companies (Roche/Genentech/PureTech) but all fees donated to Habitat for Humanity or MSF
- CDC Working Group on AMR (2012-2014)
- Eastern Research Group Report for US DHHS (2011-2014)

All comments today are my own opinions and
do not necessarily reflect the positions held by my colleagues

Overview

1. Tripod
2. Economics
3. Law

1. Tripod
2. Economics
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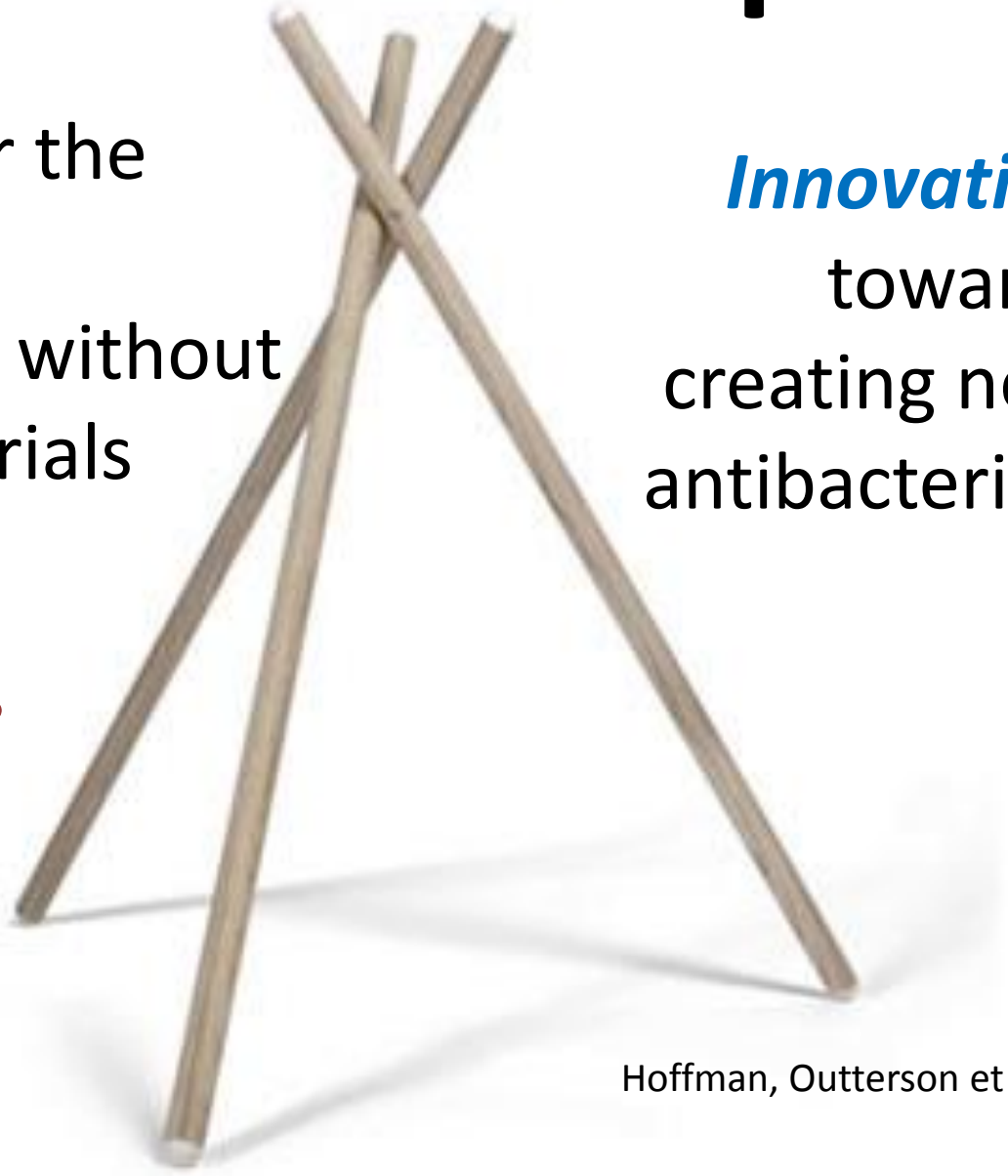
The Antibiotic Tripod

Access for the millions of people without antibacterials

Innovation towards creating new antibacterials

Sustainable use of novel antibacterials



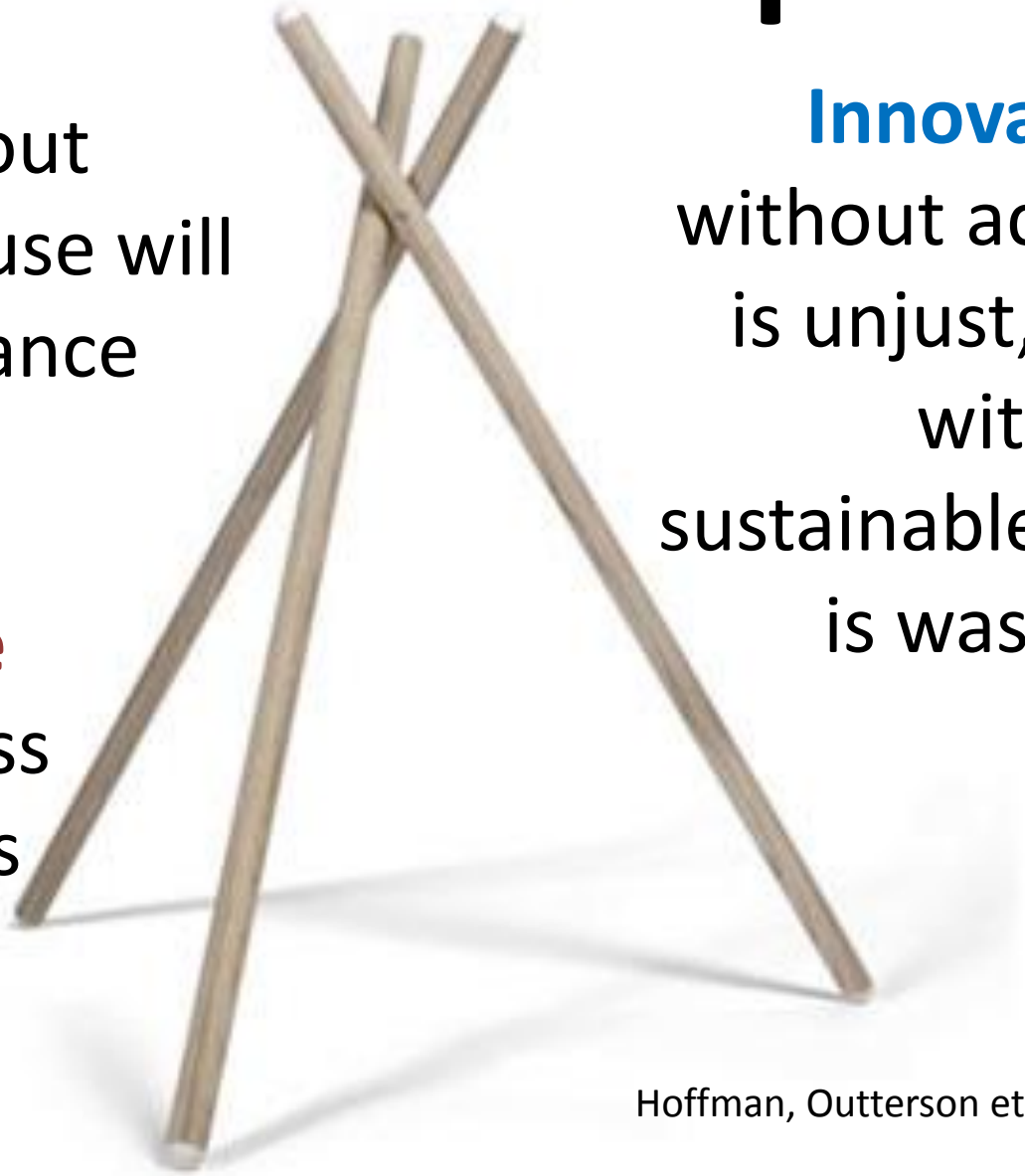
Hoffman, Outterson et al. (2015)

The Antibiotic Tripod

Access without sustainable use will speed resistance

Innovation without access is unjust, and without sustainable use is wasteful

Sustainable use constrains access and undermines innovation



Hoffman, Outterson et al. (2015)

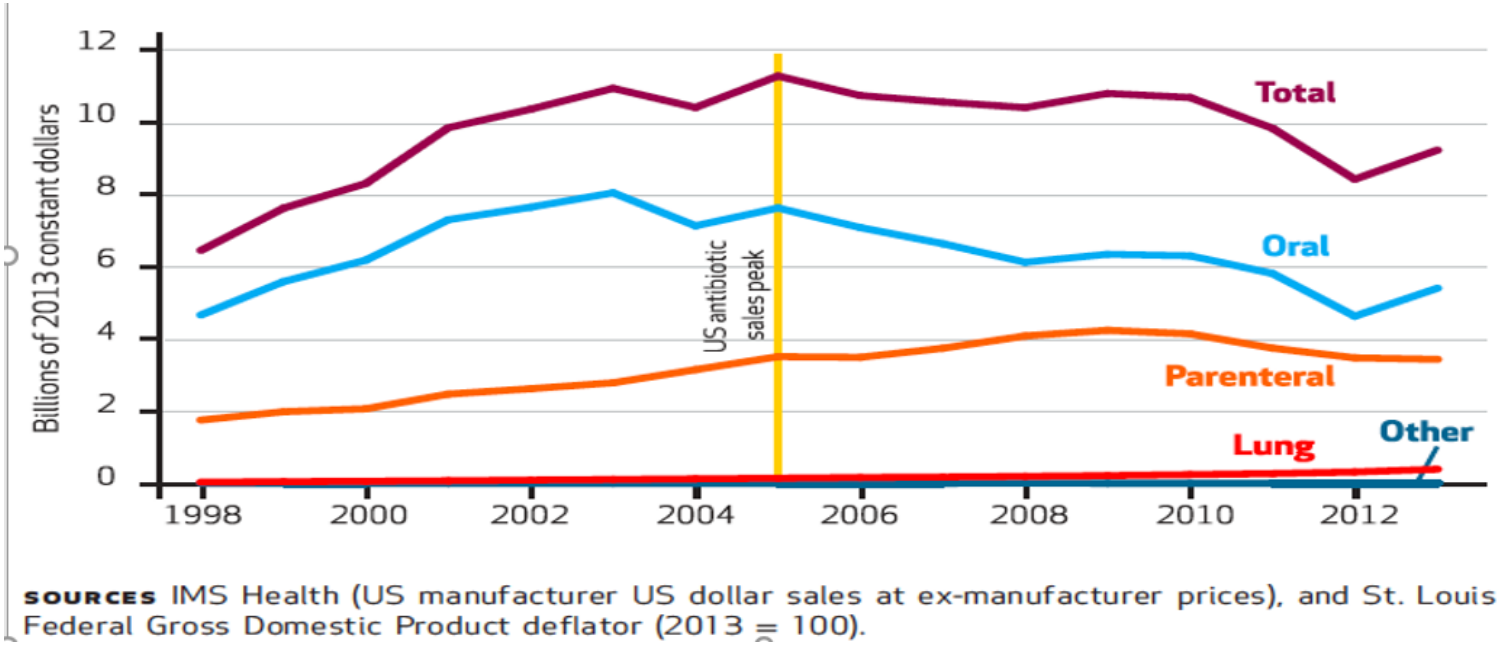
1. Tripod
2. Economics
3. Law

Peak antibiotics

EXHIBIT 2

US Antibiotic Sales For Human Use, In 2013 Constant Dollars, By Mode of Administration, 1998-2013

Billions of 2013 constant dollars

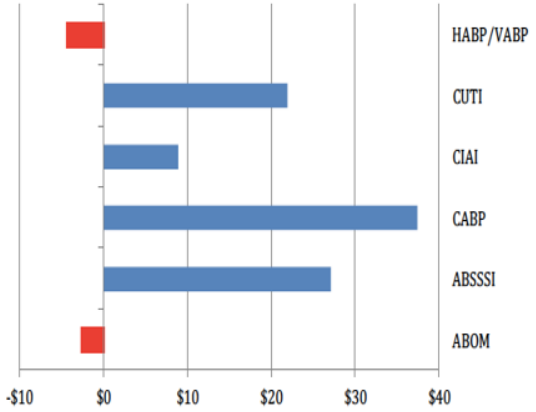


Text Version

Outterson K, et al. *Repairing the Broken Market for Antibiotic Innovation.* 34 HEALTH AFFAIRS 277-85 (Feb. 2015).

Private NPV

- Private NPV variable across indications
- CABP has the highest private NPV & HABP/VABP the lowest

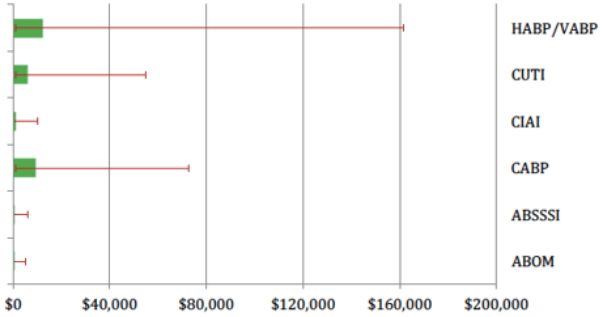


	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Private ENPV	-$3	$27	$37	$9	$22	-$4

ERG for DHHS 2014

Social NPV

Figure 6. Sensitivity of Estimated Social ENPVs by Indication for a New Antibacterial Drug (in $ Million) – Error Bars Represented 90% Confidence Bounds



	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Social ENPV	-$487	$584	$9,375	$1,069	$6,065	-$12,166

ERG for DHHS 2014

Text Version

Annual US private and social ENPV by indication, in millions of US$

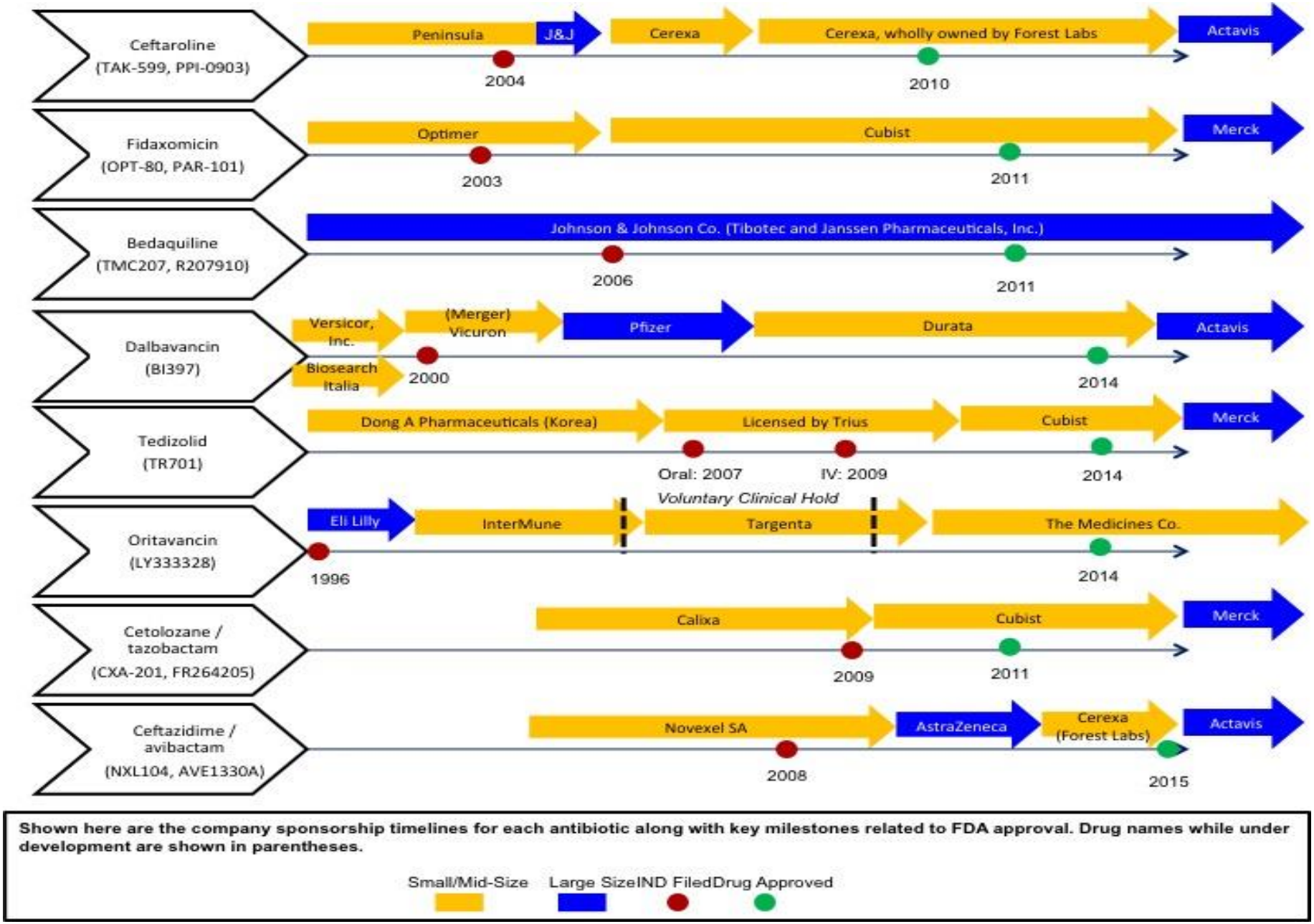
Adapted from ERG for DHHS 2014


Bad Bugs
Need Drugs
10x'20
Ten new ANTIBIOTICS by 2020

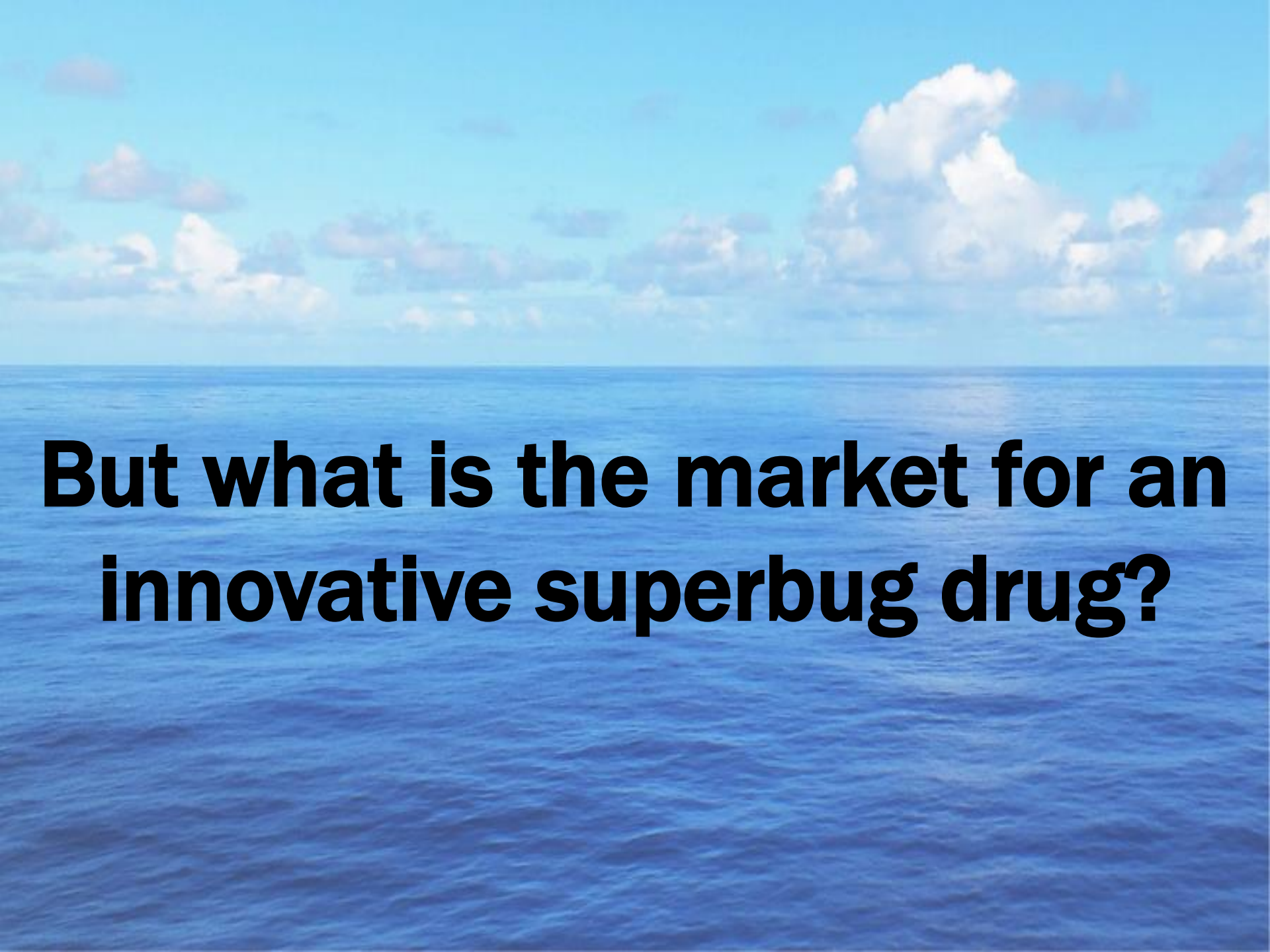
FDA J01 NMEs (2010-15)

ceftaroline fosamil (Oct. 2010)
fidaxomicin (May 2011)
bedaquiline (Dec. 2012)
dalbavancin (May 2014)
tedizolid (June 2014)
oritavancin (Aug. 2014)
ceftolozane/tazobactam (Dec. 2014)
ceftazidime/avibactam (Feb. 2015)

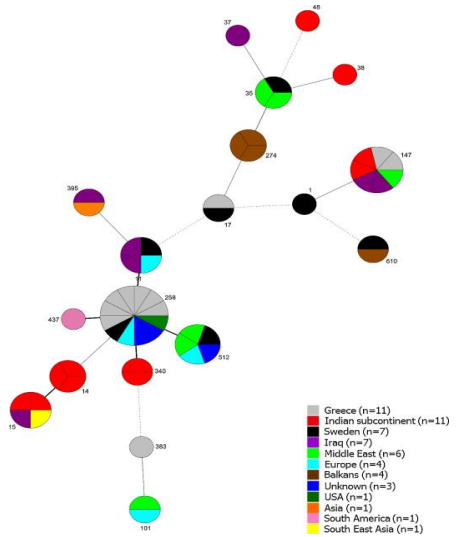
"Recently marketed antibiotics are more expensive but have been approved without evidence of clinical superiority." Deak, Outterson, Kesselheim, Powers. Annals Intern Med June 2016



Source: Deak, Outterson, Powers & Kesselheim, Annals Int Med 2016 (online first)


But what is the market for an innovative superbug drug?

CRE in Sweden



Greece (n=11)
Indian subcontinent (n=11)
Sweden (n=7)
Middle East (n=6)
Europe (n=4)
Balkans (n=4)
Unknown (n=3)
USA (n=1)
Asia (n=1)
South America (n=1)
South East Asia (n=1)

Löfmark S et al. DRU 2015

- National mandatory reporting 2007-13
- 24 clinical infections, 70 other colonized
- 81% associated with travel abroad
- 84% with hospitalization abroad
- Only 1 transmission chain in a Swedish hospital
- 28% possibly XDR
- 1 case – colistin only

Commercial Impact

- Sweden
  - 24 cases over 7 years, every case was susceptible to at least one current abx
  - **Market value of a CRE drug in Sweden = 0**
  - **But insurance value might be many millions/year**
- USA
  - 9,000 estimated cases 2011
  - If same pattern as Sweden, expect **<250 US cases in 2020 susceptible to colistin only**

Rex & Outterson, Lancet Infect Dis 2016

CDC Strategy

- CRE – target 60% decline by 2020 through aggressive measures
- Similar patterns for other diseases
  - 50% decline in *c. difficile*
  - Nosocomial MDR *Pseudomonas* – ↓35%
  - MRSA BSI – ↓50%
  - Invasive pneumococcal <5 and >65 -- ↓25%

National Strategy for Combatting Antibiotic-Resistant Bacteria (White House, Sept. 2014, Table 3)

Prop'd Rule on ASPs as a CoP

June 13, 2016

This document is scheduled to be published in the Federal Register on 06/16/2016 and available online at http://federalregister.gov/a/2016-13925, and on FDsys.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Parts 482 and 485

[CMS-3295-P]

RIN 0938-AS21

Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH) Changes to Promote Innovation, Flexibility, and Improvement in Patient Care

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Proposed rule.

Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH)

iPhone 7®

Welcome to the next generation

Dimensions: 5.51 x 2.63 x 0.25 inches
5.5 " frameless touchscreen
Digital home button with built-in touch ID at frame
Wireless charging
New A X chip with 64-bit architecture
New iOS 10

Wall Street's View

- US CRE market = $400-600M / year
- 4-5 relatively undifferentiated drugs will be in that market by 2018, including:
  - ceftazidime/avibactam (approved 2/15)
  - meropenem/vaborbactam
  - eravacycline
  - plazomicin
  - relebactam
- **@$10k/course = implied 40k – 60k courses / year**
- **My query: How will they sell that much?**

Alan Carr, Needham, Antibiotic R&D Update 15 (April 6, 2016).

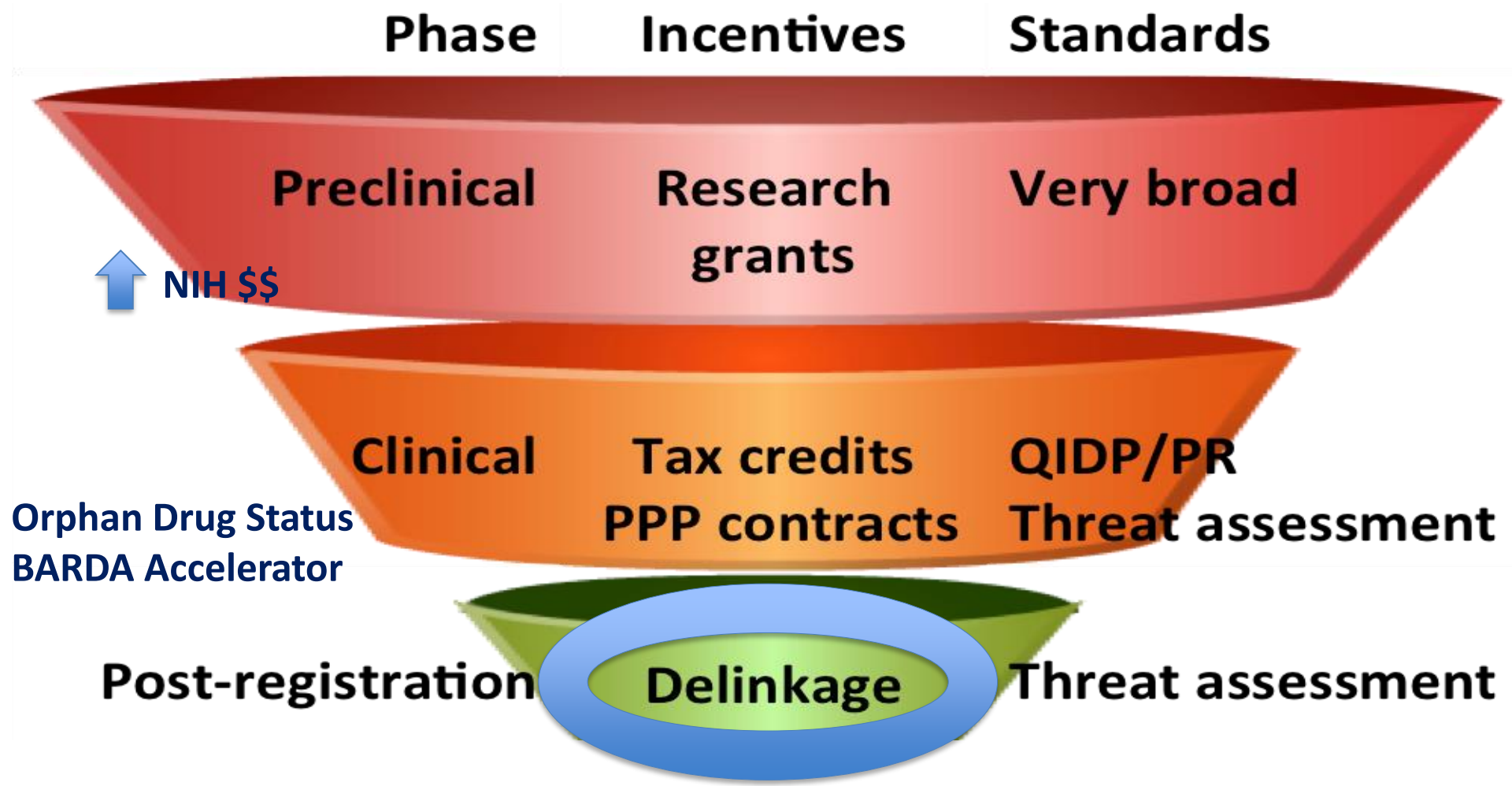
Bottom line

- Few cases, should decline
- Volume per case may decline
- Shrinking, unattractive market for innovative, targeted abx
- Unless marketing

1. Tripod
2. Economics
3. Law


3161
ENGINE
COMPANY
3181

Incentives



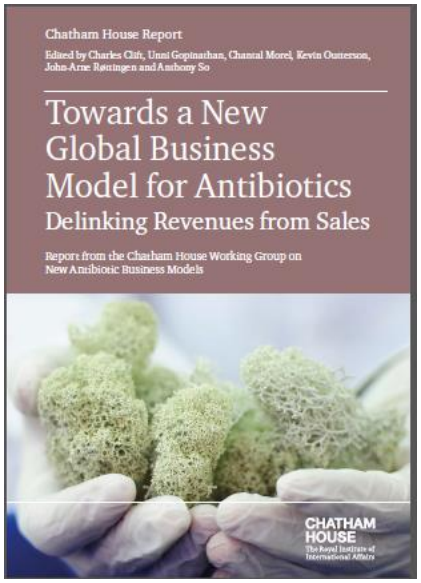
Chatham House, Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales Oct. 2015

Convergence of principles

G7 GERMANY 2015

WORLD ECONOMIC FORUM

- Need for both “push” and “pull” mechanisms
- Delinkage (i.e., revenues delinked from volumes sold)
- Access and sustainable use are integral
- Global collaboration and financing necessary



Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

OECD

BETTER POLICIES FOR BETTER LIVES

World Health Organization

DNDi

Drugs for Neglected Diseases *initiative*

DRIVE AB

RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

EUROPEAN COUNCIL

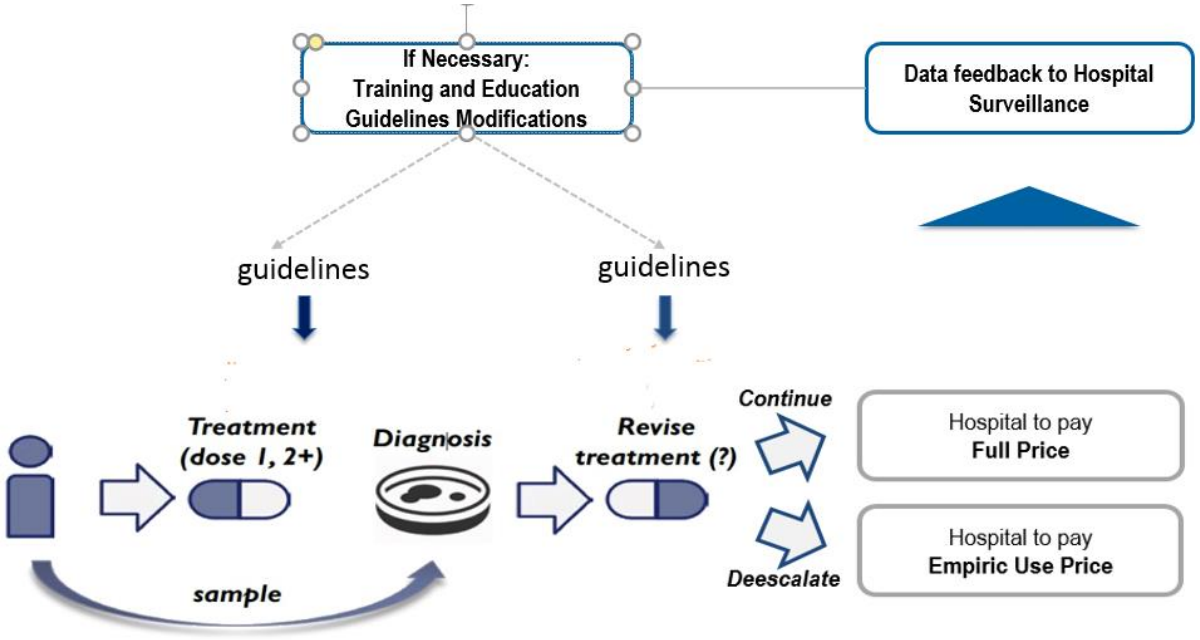
June 17, 2016: “Actively engage in initiatives and proposals to implement a new business model to bring new antibiotics to the market, including models in which investment costs or revenues are de-linked from sales volumes.”

DRIVE-AB Shortlist

Incentive/Model	Type	Type of innovation stimulated	Delinkage
Grants	Push	Early phase research	n/a
Non-Profit Antibiotic Developer	Push	Incremental innovation and development with a higher risk profile	n/a
Diagnosis Confirmation Model	Pull	Greater diversity of broad and narrow-spectrum antibiotics with significant improvements	No
Partial Delinkage	Pull	Rarely used, emergency antibiotics	Yes
Market Entry Rewards	Pull	Most pressing public health threats	Yes

Diagnosis Confirmation Model

A diagnosis-driven, dual-price model built on stewardship components



This is a diagnosis confirmation model and it is a diagnosis-driven, dual-price model built on stewardship components.

Partial Delinkage

Text Version

Market Entry Rewards

Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach

John H Rex, Kevin Outterson

Lancet Infect Dis 2016; 16: 500–05

AstraZeneca Pharmaceuticals, Waltham, MA, USA, F2G Pharmaceuticals, Eccles, Cheshire, UK, and University of Texas Medical School-Houston, Houston, TX, USA (Prof J H Rex MD); and Boston University School of Law, Boston, MA, USA, and Chatham House, London, UK (Prof K Outterson JD)

Despite the life-saving ability of antibiotics and their importance as a key enabler of all of modern health care, their effectiveness is now threatened by a rising tide of resistance. Unfortunately, the antibiotic pipeline does not match health needs because of challenges in discovery and development, as well as the poor economics of antibiotics. Discovery and development are being addressed by a range of public–private partnerships; however, correcting the poor economics of antibiotics will need an overhaul of the present business model on a worldwide scale. Discussions are now converging on delinking reward from antibiotic sales through prizes, milestone payments, or insurance-like models in which innovation is rewarded with a fixed series of payments of a predictable size. Rewarding all drugs with the same payments could create perverse incentives to produce drugs that provide the least possible innovation. Thus, we propose a payment model using a graded array of benchmarked rewards designed to encourage the development of antibiotics with the greatest societal value, together with appropriate worldwide access to antibiotics to maximise human health.

Text Version

Continuation of article results and annual payments made to manufacturers.

	Annual payment*
Drug approved at US FDA and European Medicines Agency to treat at least one defined infection‡ caused by at least one or more pathogens listed on the CDC 2013 threat assessment as either urgent, serious, or of concern to public health[2]	Base payment†
Has a clinical spectrum of activity on the label that includes one or more urgent pathogens on the CDC 2013 threat assessment§	Bonus equal to one base payment
Has a clinical spectrum of activity on the label that includes one or more serious pathogens on the CDC 2013 threat assessment§	Bonus equal to 50% of a base payment
Is the first approved drug to act via a given mechanism of action¶	Bonus equal to a base payment
Is the second, third, or fourth agent approved to act via a given mechanism of action	Bonus equal to 75% of a base payment for a second agent, 50% for a third agent, or 25% for a fourth agent
Is the fifth or subsequent agent to act via a specific mechanism of action but offers a medically relevant improvement in safety, efficacy, or ease of dosing	Bonus equal to 10% of a base payment
Delivery of agreed paediatric commitment studies‖	Payments based on model or separate contract open to tender
Is approved for a second, third, or fourth defined infection‡ for a specific agent‖	Bonus equal to 25% of a base payment
Approved in oral dosage form‖	Bonus equal to 25% of a base payment

http://thelancet.com/journals/laninf/article/PIIS1473-3099(15)00500-9/fulltext

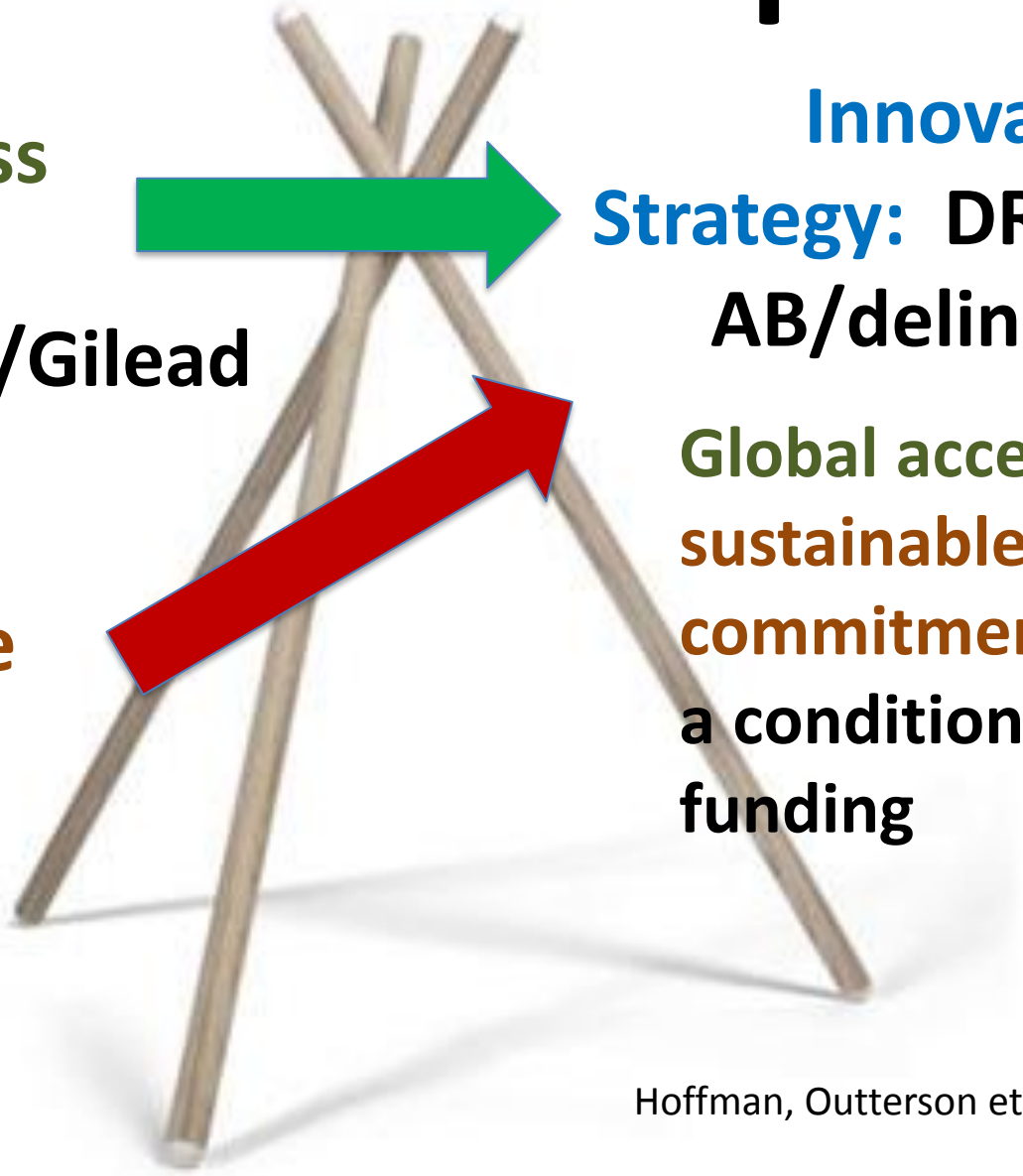
The Antibiotic Tripod

Global Access Strategy:
MSF/CDDEP/Gilead

Innovation Strategy: DRIVE-AB/delinkage

Sustainable Use Strategy:
WHO/CDC

Global access & sustainable use commitments as a condition of funding



Hoffman, Outterson et al. (2015)

Funding:

1. Federal $
2. Pay or play
3. User fee
4. Transferable exclusivity vouchers (with guardrails)

2 – AMR Review; 3- Outterson & McDonnell, Health Affairs May 2016

Urgently Needed:

1. Serious, targeted economic incentives
2. Fully integrated tripod solution
3. Global coordination

Papers on Google Scholar & SSRN

Tweeting antibiotics R&D @koutterson

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Additional slides

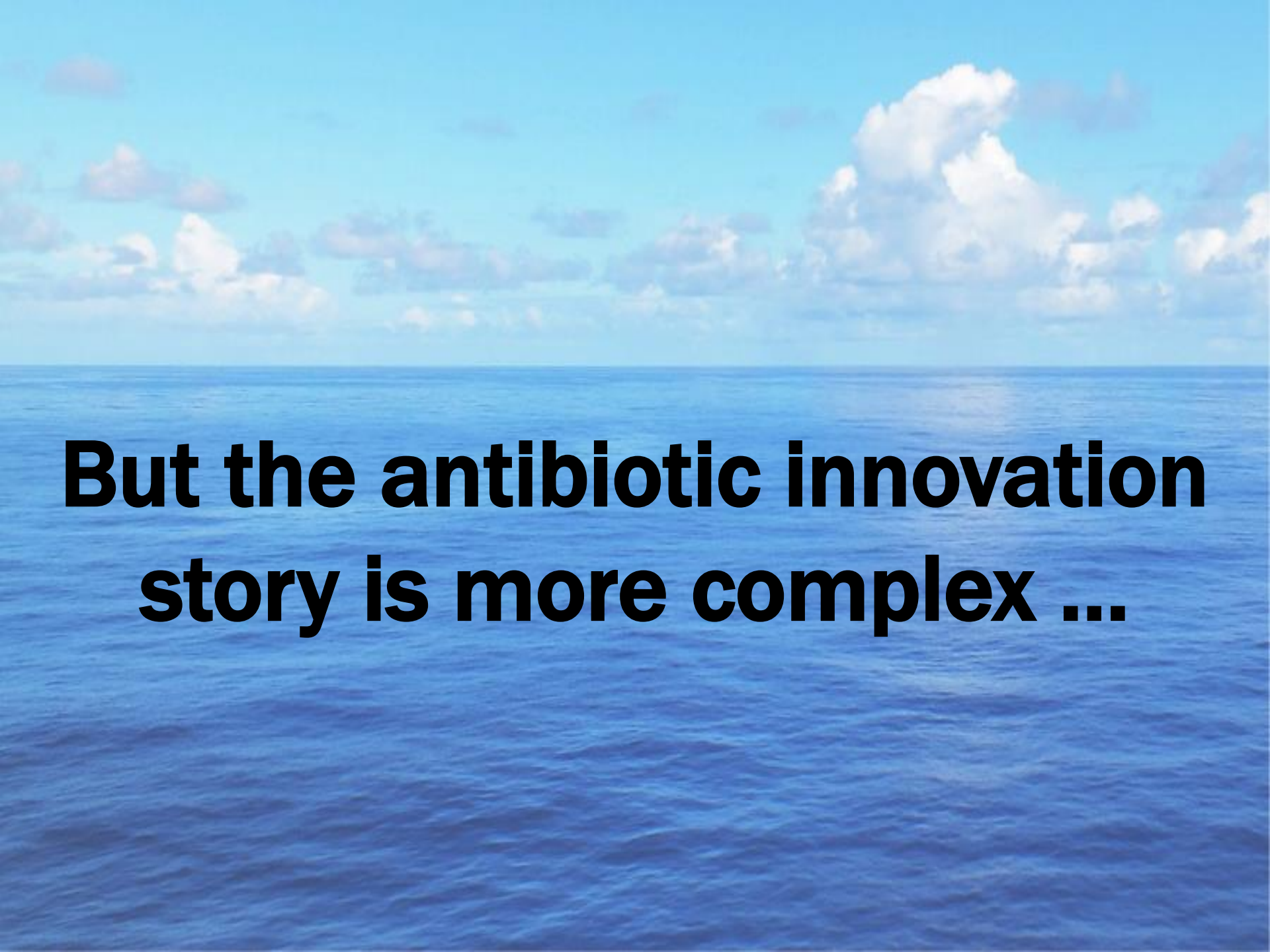
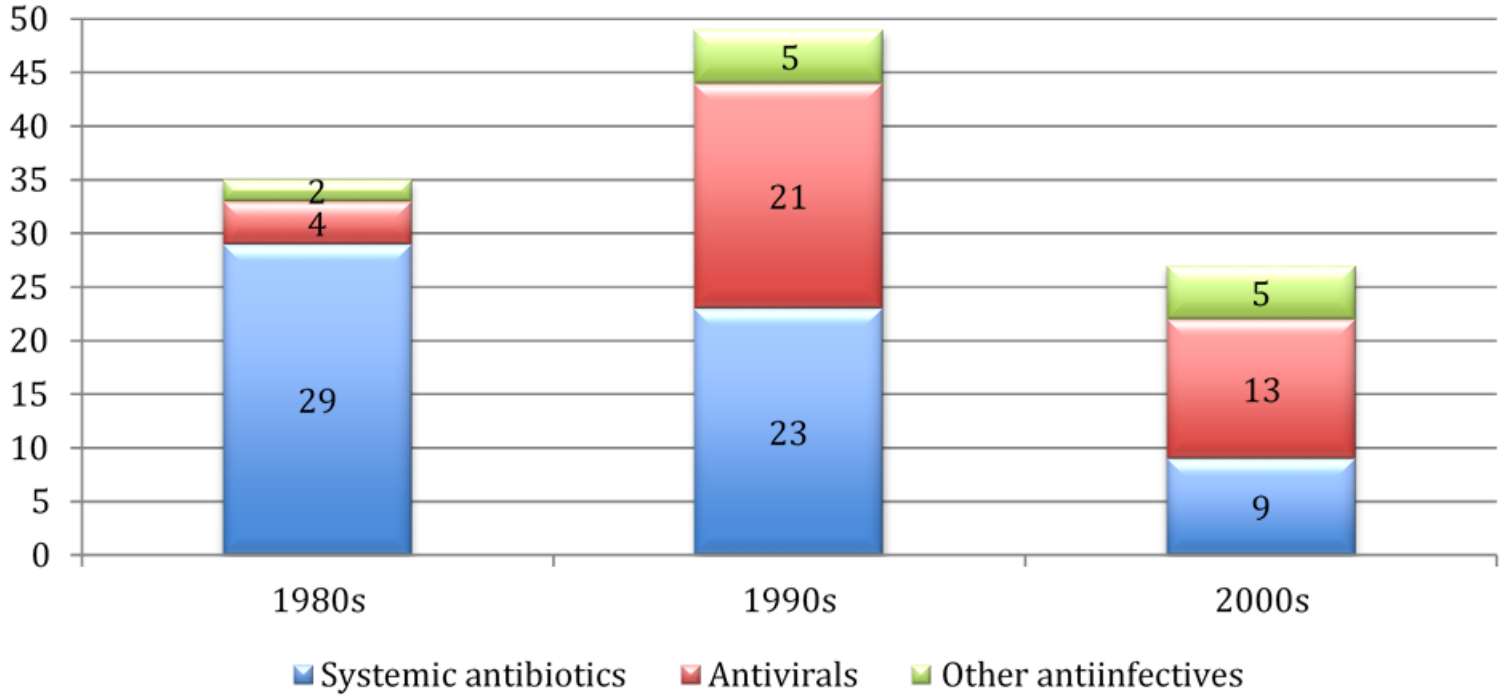

But the antibiotic innovation story is more complex ...

Exhibit 1

New Systematic Antiinfectives Not Withdrawn in the U.S. as for August 1, 2013, by Decade of FDA Approval, 1980-2009

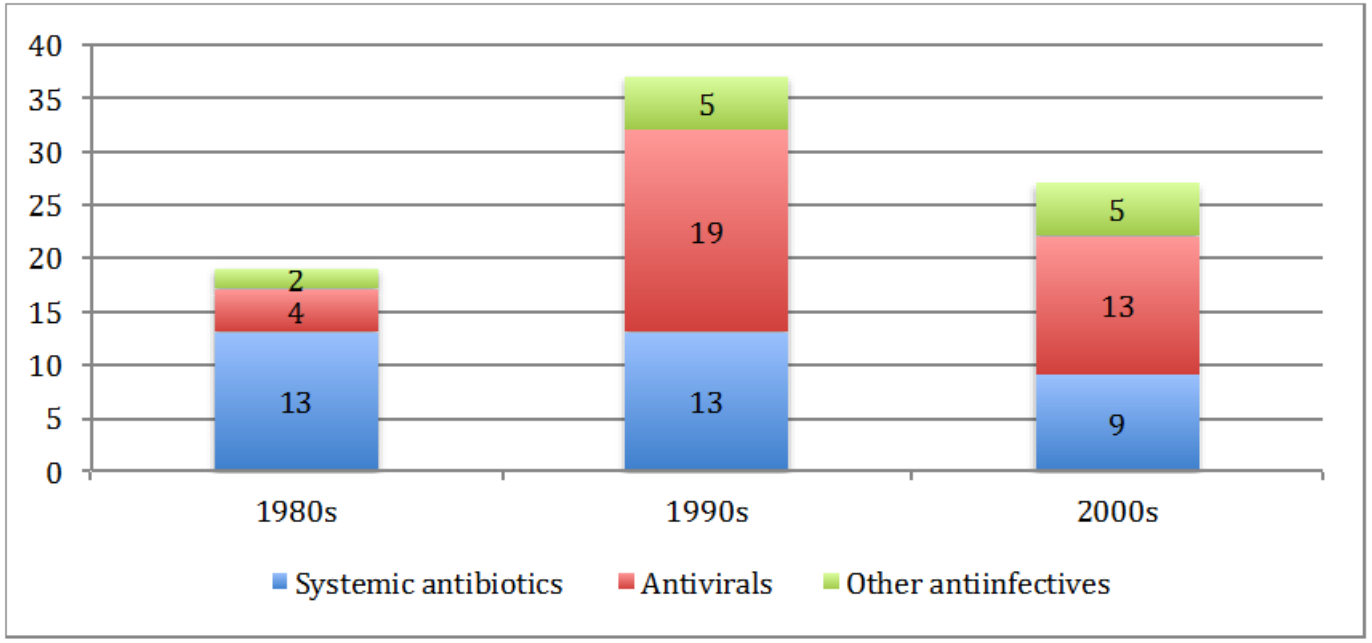


Text Version

Outterson, Powers, Seoane-Vazquez, Rodriguez-Monguio, Kesselheim JLME 2013

Exhibit 4

New Systematic Antiinfectives Not Withdrawn in the U.S. as for August 1, 2013, by Decade of FDA Approval, 1980-2009



Text Version

Outterson, Powers, Seoane-Vazquez, Rodriguez-Monguio, Kesselheim JLME 2013


We need higher quality antibiotics, with targeted incentives

EXHIBIT 2

Slide 7

US Antibiotic Sales For Human Use, In 2013 Constant Dollars, By Mode of Administration, 1998-2013

Billions of 2013 constant dollars

	1998	2000	2002	2004	2006	2008	2010	2012
Lung	0	00	0	0	0	0	1	2
Other	0	00	0	0	0	0	0	0
Parental	2	2	3	3.5	3.5	3.8	4	4.7
Oral	4.4	6	7.8	5.5	5.8	6	6.1	5
Total	6.4	8	10.1	10.2	11	10.2	10.4	8.2

Sources IMS Heath (US manufacturer US dollar sales at ex-manufacturer prices). And ST. Louis Federal Gloss Domestic Product Deflator (2013=100).

Mind the Gap

Slide 11

Name	Private	Social
ABOM	-$3	$487
ABSSI	$27	$584
CABP	$37	$9,375
CIAI	$9	$1,069
CUTI	$22	$6,065
HABP/VABP	-$4	$12,166

Partial Delinkage

Slide 29

- This image is a second version of a partially delinked model that is sometimes called insurance model, or a Cap and Collar Incentive. An Insurance License is an annual license paid to a manufacturer to have access to a specific antibiotic, up to a specified volume. If the threshold volume limit (sometimes called the “collar”) is exceeded, then the payer would be charged an additional amount (either per treatment or a fixed amount to a higher threshold). In a variation of this model (the Cap and Collar Model), there is an additional threshold (the “cap”) where there is revenue-sharing between the manufacturer and the payer.
- The chart shows that in the early years when the drug is instilling well, the government would give you money to bring it up to that low revenue figure. In years later, if more of the drug was sold, most of that revenue would go back to the government, so it's a sharing of risk.

Market Entry Rewards

Slide 30

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EXHIBIT 1

slide 37

New Systematic Antiinfectives Not Withdrawn in the U.S. as for August 1, 2013, by Decade of FDA Approval, 1980-2009

Year	Systematic Antibiotics	Antivirals	Other Antiinfectives
1880s	29	23	9
1990s	4	21	13
2000	2	5	5

EXHIBIT 4

Slide 38

New Systematic Antiinfectives Not Withdrawn in the U.S. as for August 1, 2013, by Decade of FDA Approval, 1980-2009

Year	Systematic Antibiotics	Antivirals	Other Antiinfectives
1880s	13	4	2
1990s	13	19	5
2000	9	13	5