CARB-X

Combating Antibiotic-Resistant Bacteria

BOSTON UNIVERSITY

Decennial Day:
Policy & Economic Innovations to Impact AMR

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Personal background & disclaimers

- Professor of Law at Boston University, working for the past 15 years on law & economic problems with antimicrobial innovation and reimbursement
- Founded CARB-X in 2016, now supporting the world's largest and most diverse preclinical pipeline of antibacterial products (next slide)
- No industry funding at all, only governments (US, UK, Germany) and charitable foundations (Wellcome Trust, BMGF)
- Speaking today solely as a professor, not on behalf of CARB-X or any of its funders

CARB-X accelerates innovative products against drug-resistant bacteria

Therapeutics, preventatives and diagnostics

Global partnership funds and advances high-risk projects with big-impact potential for patients

- Investing $480 million in 2016-22 to accelerate innovation addressing the global rise of antibiotic resistance
- Targeting the most serious antibiotic-resistant bacteria (CDC, WHO)
- Non-dilutive funding to product developers to drive innovation. Companies assume 10%-20% cost-share
- Non-profit public-private partnership

57 active PROJECTS* | **$305.2M** to date | **83** PROJECTS since 2016 | **11** COUNTRIES | **7** project GRADUATES | **2** graduates win contracts with BARDA

World's largest and most scientifically diverse early development portfolio … more to come

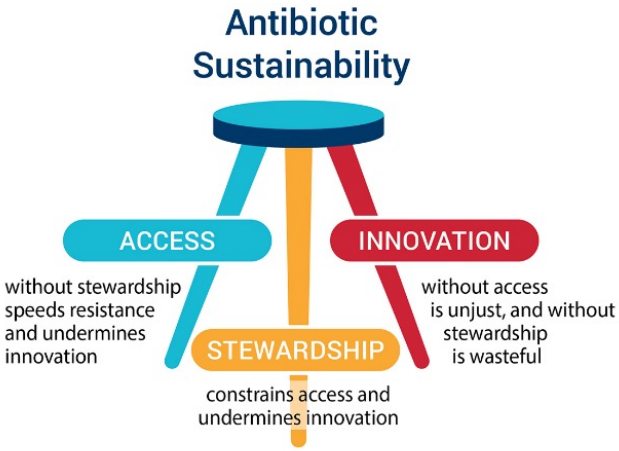
- 36 Therapeutics (new classes, novel targets, non-traditional)
- 14 Preventatives (vaccines, antibodies, microbiome, phage)
- 7 Rapid Diagnostics

* as of April 12, 2021

CARB-X | ASPR Assistant Secretary for Preparedness and Response Decennial Day | BARDA | wellcome | NIH National Institute of Allergy and Infectious Diseases | UKaid from the British people | Federal Ministry of Education and Research | Bill & Melinda Gates foundation

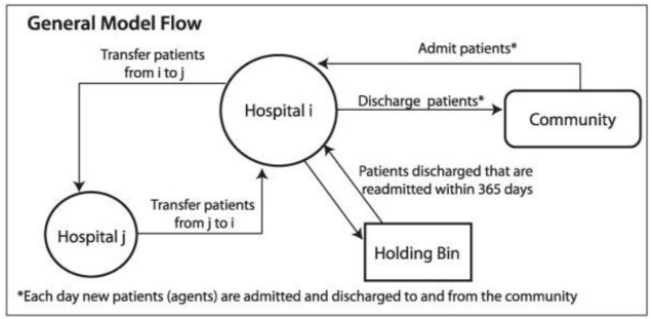
Antimicrobial innovation and stewardship interact with unexpected complexity

Tripod

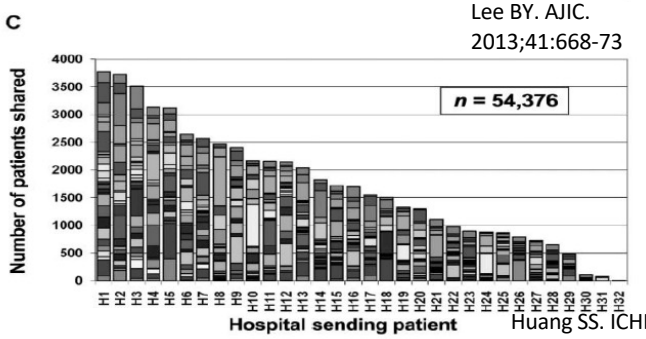


Hoffman S, Outterson K. JLME (2015)

Germsheds



Lee BY. AJIC. 2013;41:668-73



Huang SS. ICHE. 2010;31:1160-69

Tripod Economics: Innovation

- 15 NME antibacterials FDA approved since 1.1.2010[1]
  - Over-achieved IDSA's "10 by '20" goal by 50%[2]
- But:
  - 7/15 sponsors in bankruptcy or market cap <50% of R&D spend[1]
  - Median US sales $16m last year[1]
  - 37% of the small innovative antibiotic companies featured in the Access To Medicines Foundation Report left antibiotic R&D in last 2 years[3]
- Barriers:
  - Non-inferiority clinical trials,[4]
  - DRG reimbursement,[5]
  - Market does not pay for positive social values (positive externalities)[6]

1. Outterson K. (2021) (pending); 2. IDSA. CID 50 (2010) 1081–83; 3. Ardal CA. CID 71 (2020) 1994-99; 4. Rex JH. Nat Comms 10 (2019) 3416; 5. Outterson K. Nat Biotech 37 (2019) 1110-12; 6. Rothery C. Framework for Value Assessment of New Antimicrobials 2018.

Non-inferiority Clinical Trials for Antibiotics

Innovation Barriers

- Infections can be rapidly fatal and effective antibiotics can save your life, so superiority trials are ethical if and only if there are no effective antibiotics
- Non-inferiority trials are the tool that allows us to avoid that dire circumstance by developing new drugs *before* they are needed, *before* resistance is so extensive that nothing else works
- The oft-raised concern that NI trials are focused on infections such as cUTI misses the point that lab data accurately predicts the ability of the drug to retain activity when old drugs fail
  - Regulatory language is necessarily limited to the study that was done, but physicians never have data on all possible infections and are comfortable with estimating such utility
- In short, approval based on one or more well-designed NI trials ensures that the new drug is good-to-go when existing drugs lose utility
- Failing to recognize these principles has the perverse effect of penalizing companies that are working to prepare us for future resistance
- **But it is understandable when hospitals and payers don't want to spend more $ today on such drugs for the future**

Slide adapted from John Rex; see also Rex JH. Nat Comms 10 (2019) 3416.

DRGs Constrain Antibacterial Innovation

Example: Large Teaching Hospital in Boston

- The most common pneumonia codes:

MS DRG	ENC Adjusted Payment per Case	Variable Cost per Case	Contribution Margin per Case
193 - SIMPLE PNEUMONIA AND PLEURISY WITH MCC	$20,640	$8,464	$12,176
194 - SIMPLE PNEUMONIA AND PLEURISY WITH CC	$13,128	$4,959	$8,168

About 60% of their costs on these cases are fixed, leaving only 40% for the variable expenses

- Hospital's average cost for antibiotics for this population is **$36/day**. A novel product, cefiderocol, now labeled for HAP/VAP, is **$1100/day** WAC (~$1034 actual cost)
  - This antibiotic can save a life, but can wipe out most or all of the entire variable cost for the DRG.
  - The DRG guarantees hospitals a significant financial loss on the patient every time a novel antibiotic is used.
- Paying for inpatient antibiotics under the DRG puts a price cap on innovation.

Slide adapted from Antimicrobials Working Group; see also Outterson K. Nat Biotech 37 (2019) 1110-12

Market Does Not Pay for Positive Externalities

Table 2. The "STEDI" values of antibiotics

Value	Description of benefit
Spectrum	Replacing broad spectrum agents with narrow spectrum agents and thereby reducing collateral damage to the microbiome
Transmission	Avoiding pathogen spread to the wider population by effectively treating patients
Enablement	Availability of effective treatment enables other types of medical interventions (eg, surgery, oncology)
Diversity	Having a range of treatment options reduces selection pressure
Insurance	Having an agent available in case of a sudden or significant increase in the prevalence of pathogens resistant to existing agents

Outterson & Rex, Translational Research 2020
Table adapted from Rothery *et al.*[20]

- Who pays more for the narrow spectrum agent because it makes bacterial evolution less dangerous?
- How do you contract for a payment from the person who didn't get sick?
- Antibiotics are infrastructure, enabling modern medicine
- Easy to free ride (cancer patients are not paying for antibiotic R&D)
- No one is paying for diversity and insurance benefits, despite billions in social value

Any skimping on any of the above means antibiotic R&D < socially optimal

Tripod Economics: Stewardship

- CDC antibiotic resistance goals by 2025:
  - 20% ⬇️ HAIs; 10% ⬇️ CAIs; ⬇️ outpatient Rx; ⬆️ stewardship[1]
  - CDC estimates ~30% outpatient abx Rx ”unnecessary”[2]
- CMS ASP conditions of participation (Final Rule, 2019)
- “Shorter is better”[3] (and cheaper)
- All great news for patient health!!
  - But, if antibacterial innovation is driven by volume x price = revenues, then the net effect is to reduce the market size for innovation
  - Undesirable alternatives may be marketing, broader spectrum agents, or orphan-drug level prices

1. US National Action Plan on CARB (2020); 2. Fleming-Dutra KE. JAMA. 2016;315(17):1864-1873; 3. Spellberg B. JAMA IM. 2016;179(9):1254-55.

Tripod Economics: Solutions

1. Fix the DRG with the DISARM Act or a similar amendment to the IPPS Rule

2. Must be willing to pay for antibiotics NOT used in patients today and for antibiotics with target product profiles that the market has difficulty recognizing
   - STEDI values globally likely to exceed several dozen billion USD a year

3. Support innovation without undermining stewardship

Delinkage (paying for value, not volume) can be an efficient mechanism for 2 & 3

"Netflix" subscriptions:

Global total of subscription payments must total billions (not millions) per qualifying drug

Innovation Solutions

England

- Pilot program selection underway for 2 antibiotics
- Explicitly designed to pay for England's fair share of STEDI values, through HTA process

Sweden

- Contracting for availability in Sweden
- Not designed as an R&D incentive, but could be scaled
- 5 drugs in initial contracts, 3 were not previously launched in Sweden

USA

- PASTEUR Act (proposed by Senators Bennet & Young)
- 10-year subscription for highly novel new antibiotic
- Antibacterials are **infrastructure**, requiring long-term investment

Details at AMR Solutions (Rex blog)

Germ Shed Policy

- The Orange County studies quantify the movement of patients between facilities, both directly, and via the community[1-2]
  - Analogize to water sheds; polluters impose burdens (externalities) on those downstream
  - In germ sheds, poorly-performing institutions impose burdens on society and on downstream providers[3]
  - Germ shed characteristics are epidemiological, reflecting patient flow and community spread
- But payers reimburse providers as if they were discrete institutions, ignoring the larger epidemiological context[3]
  - "Polluters" go unpunished for downstream burdens & "nonpolluters" are not rewarded for downstream values
  - Single center studies on cost savings from ASPs can also miss the larger context

1. Lee BY. AJIC. 2013;41:668-73; 2. Huang SS. ICHE. 2010;31:1160-69. 3. Outterson K. Germshed Management. 2011.

Germ Shed Policy: Barriers

- Coordination between the providers in the germ shed (i.e., sharing ASP, IPC, and other resources with all other institutions in your germ shed)
  - But health care fraud & abuse laws make it a felony to give anything of value to a referral source
  - Antitrust enforcement authorities scrutinize coordination activities between competitors
- Coordination within a single health system or facility avoids these legal hurdles
  - But budgets are often siloed – downstream savings from ASPs won't necessarily flow back to the unit doing the work
  - The barrier here isn't law, but management
- Payers (such as CMS) could reward regional efforts to improve germ sheds
  - But, as with all things Medicare, the devil is in the details
  - Experience with value based payments and hospital acquired condition penalties has been mixed

Outterson K. Germshed Management. 2011.

Germ Shed Policy: Solutions

- State & federal support for germ shed coordination between the providers
  - Allow providers to coordinate without fear of antitrust enforcement within germ sheds on infection prevention and control as well as antibiotic stewardship programs
  - Amend fraud and abuse regulations & laws to similar ends
  - Federal & state encouragement, with funding
- Management
  - Measure and reward downstream impacts of IPC and ASP, not just reductions in the facility pharmacy budget
- Payers should support regional efforts to clean up germ sheds
  - Provide additional funding for germ shed coordination, outside of the CMS inpatient prospective payment system
  - Grants from CDC, as regional investments

Outterson K. Germshed Management. 2011.

Conclusions

- Markets and private coordination are unable to price significant externalities in both antibacterial innovation and infection prevention & control and antimicrobial stewardship
- As a result, investment in both is likely to be below socially optimal levels
- Innovation and stewardship interact in negative ways, potentially undermining each other
- Solutions that simultaneously solve for all of the above include:
  - CDC grants and legal reforms for improved germ shed coordination
  - Fix the DRG innovation cap with the DISARM Act
  - Invest in the future of antibacterials as infrastructure, through the DISARM Act