Designing Economic Incentives for Antimicrobials: Implementation in the U.S. Context

Hotel Monaco
700 F St NW, Washington, DC 20004
November 9, 2016

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Designing Antimicrobial Economic Incentives for Implementation in the U.S.

Gregory Daniel, PhD, MPH
Deputy Director, Duke-Margolis Center for Health Policy
Clinical Professor, Fuqua School of Business

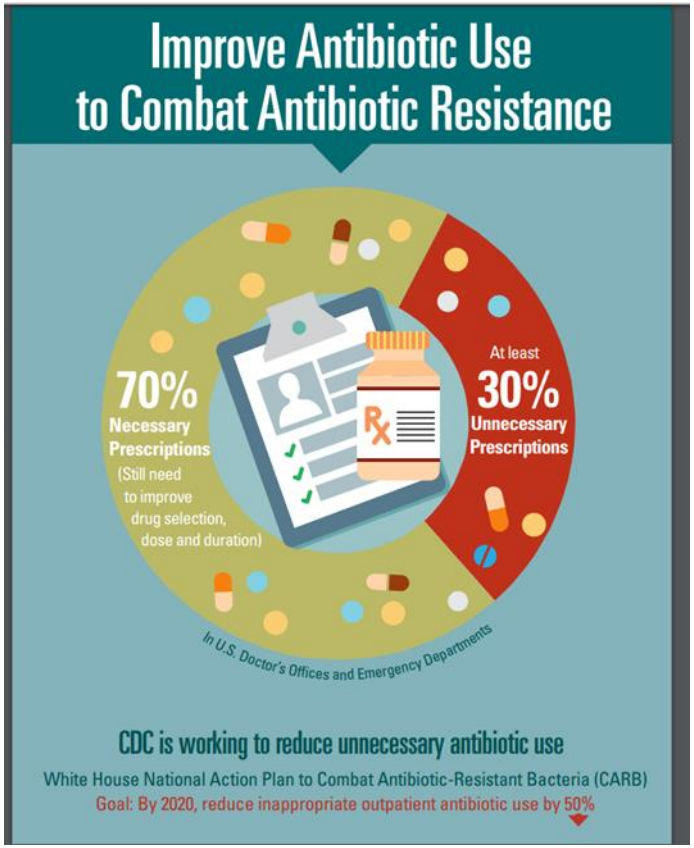
November 9, 2016

Current state of antimicrobial resistance (AMR)

- **Antibacterial drug resistance:** Growing global public health threat poised to worsen due to overuse, misuse and current market failures.
- **Weak drug pipeline:** Need investment and development of novel antimicrobials and other drugs to prevent or treat active infections
  - Difficult to develop drugs when microbes remove drug from cell or undergo mutations that lead to resistance
  - Clinical development is challenging because of a lack of rapid diagnostics and difficulty enrolling patients
  - Challenging market conditions due to low sales volumes & prices due to effective stewardship and low-cost generic competition that limit clinical uses, which limit ROI
  - Efforts mostly focused on improving the R&D and regulatory processes by lowering regulatory hurdles and by providing financial support.

Inappropriate use of antibiotics drives resistance

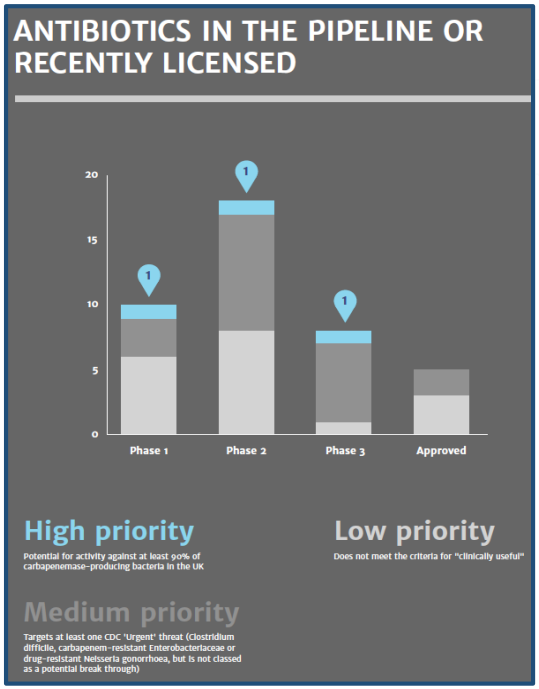
- In 2009, **antibiotic expenditures in the U.S. in all healthcare settings totaled $10.7 billion**: $6.5 billion (61.5%) in the outpatient setting, $3.6 billion (33.6%) in the inpatient setting and $526.7 million (4.9%) in long-term care.
- **One third of these antibiotic prescriptions is inappropriate**
- Reducing misuse and overuse of antimicrobials will result in healthcare savings and slowing of antibacterial drug resistance
- Antibacterial drug resistance reduces the resources we have available to combat infections



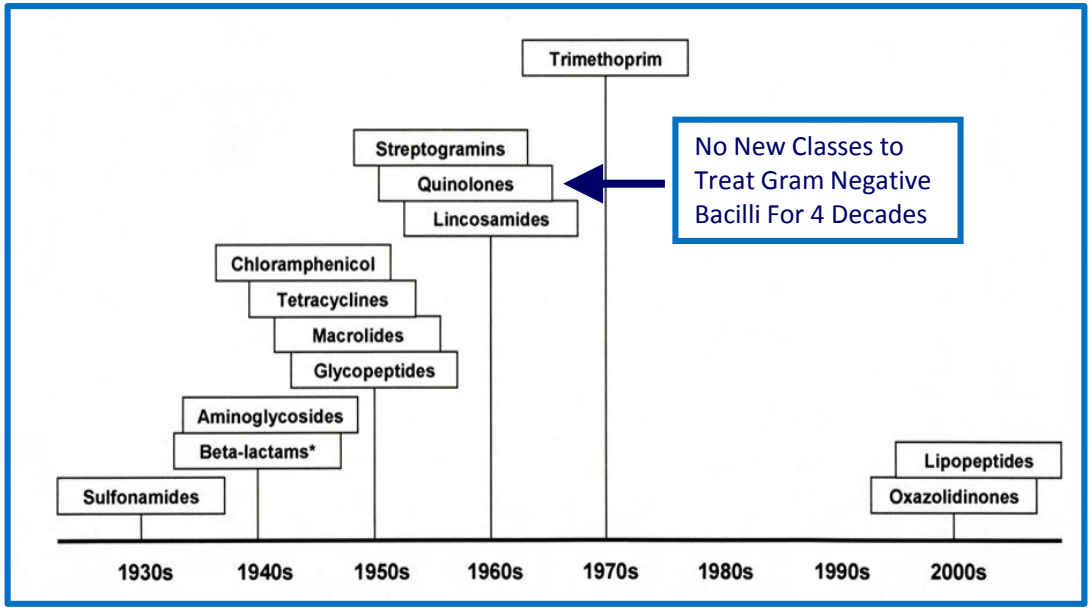
From Suda et al, *J. Antimicrob. Chemother.* (2013)

There are very few antimicrobial drug candidates in the pipeline

- According to Pew Charitable Trusts, there are currently 37 antibiotics in phase I-III testing (in contrast, in 2015, there were 836 drugs in the pipeline for cancer)
  - Few antibacterial compounds treat the most urgent unmet needs
  - Based on published attrition rates, only 10-11 of the 37 antibacterial compounds will be approved
- No new classes of antimicrobial are being brought to market



From "Securing New Drugs for Future Generations: The Pipeline of Antibiotics", The Review on Antimicrobial Resistance. May 2015



From Joe Larsen at Duke-Margolis Antimicrobial Expert Workshop, July 21, 2016

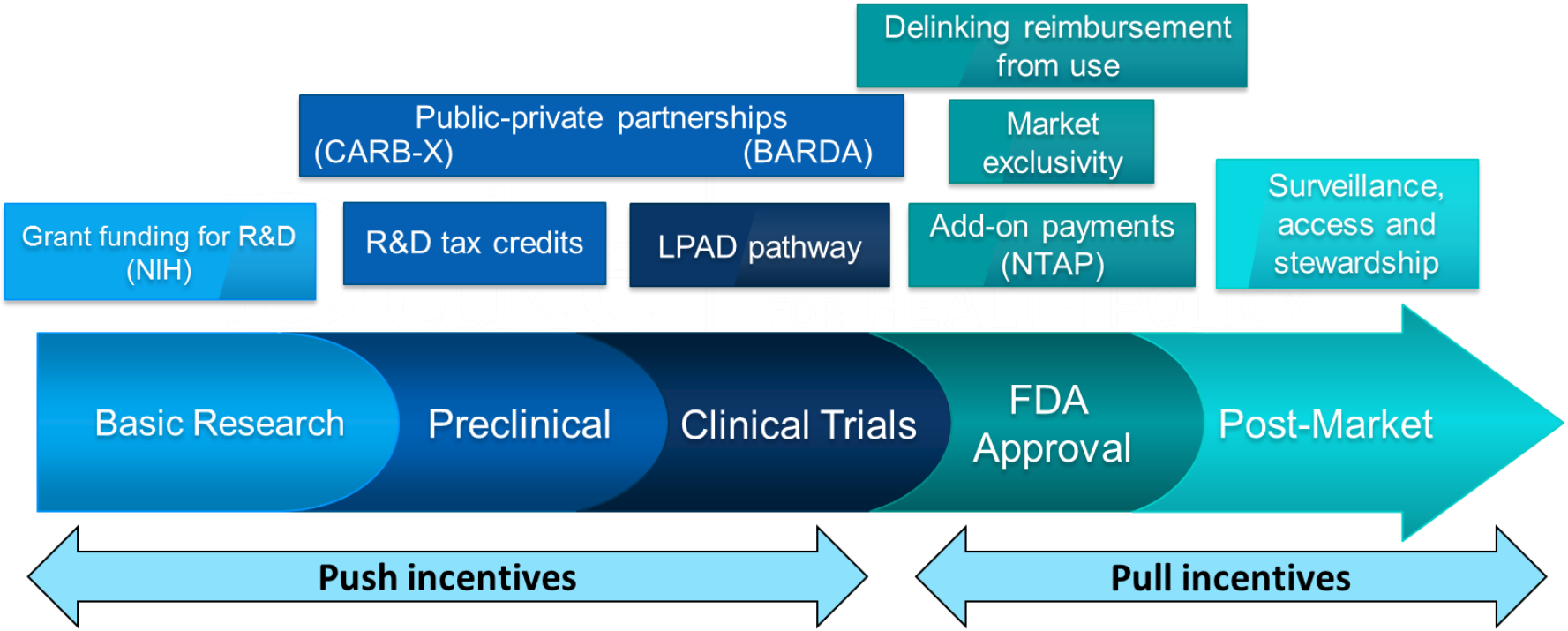
Global efforts have identified essential steps

- **Chatham House**, the Royal Institute of International Affairs, an independent policy institute based in London, released a report on business models for antimicrobial development in October 2015
- **DRIVE-AB**, 16 public and 7 private partners from 12 countries, developing recommendations on: use and stewardship, economic models, and management and communication
- **The Review on Antimicrobial Resistance** is commissioned by, and reports to, the UK Prime Minister, but it operates autonomously of government control - a final report was released on May 19th, 2016

Convergence of principles:

- **Provide grant funding to encourage R&D of antimicrobials**
- **Implement pull incentives that delink reimbursement from sales volume**
- **Coordinate globally on surveillance and development efforts**

Incentives for antimicrobials can support all stages in the development of priority antibiotics



Developing U.S. approaches aligned with global proposals

- **Part of comprehensive strategy** to provide pull incentive in combination with other push incentives
- **Public funding**: Leveraged by global proposals and private payments for antibiotics to provide an adequate reward for drug development for high priority antibiotics at lowest feasible public cost
  - Obtaining advanced commitment to U.S. appropriations in a tight budget environment is difficult
- **Rapid access to funds upon approval for drug addressing high-priority needs**:
  - Manufacturer's access to funds can be tied to the value of the drug
  - Front-loaded payments, but occur over time to promote value and access goals
- **Movement from fee-for-service (FFS), volume-based reimbursement to value-based reimbursement**: U.S. is moving toward episode- and person-level alternative payments tied to value of care rather than volume

Core principles for antimicrobial incentives

Innovation

- Enable small and large developers to succeed
- Keep current developers in antimicrobial space
- Incentivize developers to return to the space

Sustainability

- Incentives are developed to be sustainable over time
- Strive for a sustainable business model that can be achieved through enhanced predictability
- Allows for flexibility of reward over time as development goals met

Access

- Support stewardship and appropriate use
- Integration and coordination with global efforts (stewardship and access for low income country)

Duke-Margolis Center's approach

Goals:

- **Identify promising economic "pull" incentives, including reimbursement reforms, that incentivize development, support stewardship and value, and can be feasibly implemented in the U.S.**
- **Outline a path for implementation within the U.S. healthcare system**

Strategy:

- Engage broad-based stakeholder and expert group to identify and develop promising models
- Examine outputs from DRIVE-AB, AMR Review Team, other global and U.S proposals
- Develop policy recommendations on the most viable economic incentives that could be implemented in U.S.
- Disseminate research findings through several public outlets, including publications and presentations at relevant meetings.

Duke-Margolis Antimicrobial Advisory Group

Private Payers:
- Aetna
- ExpressScripts
- Intermountain Healthcare
- Kaiser Permanente

Public Payers:
- Centers for Medicare and Medicaid Services

Patient Advocate:
- Foundation to Combat Antimicrobial Resistance

Small Manufacturers:
- Achaogen, Inc
- Melinta Therapeutics
- Spero Therapeutics

Large Manufacturers:
- AstraZeneca
- GlaxoSmithKline
- The Medicines Company

Societies:
- Infectious Diseases Society of America

U.S. Government:
- U.S. Food and Drug Administration
- Centers for Disease Control and Prevention
- Biomedical Advanced Research and Development Authority

International organizations:
- The Review on Antimicrobial Resistance
- DRIVE-AB
- Center for Disease Dynamics, Economics & Policy

Academics:
- Boston University School of Law
- Duke University Schools of Medicine and Business
- Harvard School of Public Health

Overview of today's sessions

Session I: **Transferable exclusivity voucher**

Session II: **Market Entry Reward**

Session III: **Value-based Reimbursement Contracts**

- Each session will open with an overview of the proposal
- Opening speaker will be followed by a reaction panel
- We encourage all audience members to participate in the discussion of these models

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Session I

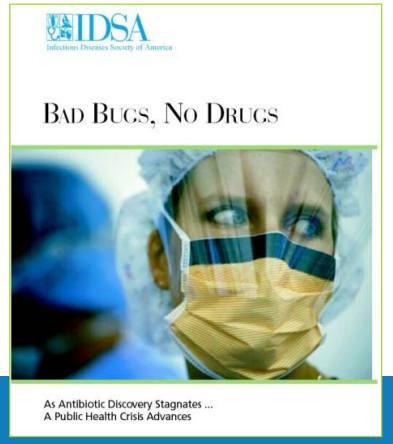
Transferable Exclusivity Voucher

Infectious Diseases Society of America

Transferable Exclusivity Vouchers for the Antimicrobial Market

Amanda Jezek
Vice President, Public Policy and Government Relations
Infectious Diseases Society of America

November 9, 2016



Agenda

- Concept of transferable exclusivity vouchers
- Pros and Cons
- Addressing potential challenges
- Political environment
- Policy context

Transferable Exclusivity Vouchers: Basic Concept

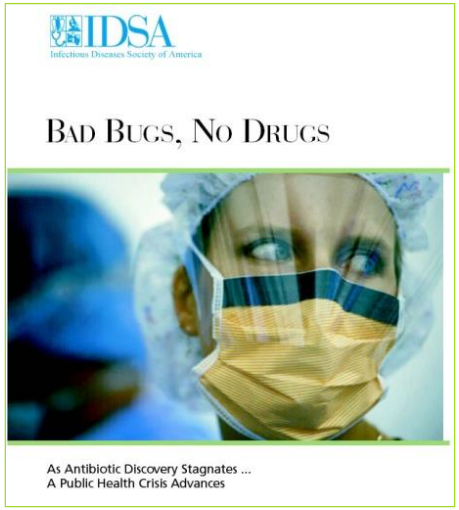
- A company that receives FDA approval for a new antibiotic would obtain a voucher to extend the exclusivity period of another drug.
- A company that earns the voucher could sell it to another company.

- Many details to consider:
  - Which antibiotics would be eligible?
  - Length of extended exclusivity?
  - Drugs on which voucher can be used?
  - Stewardship?

2003: Duke University professor and researcher: Henry Grabowski

Transferable Market Exclusivity: a pull-based incentive that affords companies a defined period of market exclusivity that can be applied to any compound, thus facilitating R&D spending on a different “socially desirable but unprofitable medicine”

IDSA: 2004



Critical Priority: Establishment of a "wild-card patent extension linked to R&D for antibiotics to treat targeted pathogens.

- Two-year patent extension
- New antibiotic that treats a targeted pathogen
- Require company to commit 10-20% of profits derived from the patent extension to additional targeted antibiotic R&D

PCAST: 2014

Reward successful developer of an important antibiotic with a 'tradable voucher' that provides a short extension to the patent life or market exclusivity period of any drug. The developer could sell the voucher to another company with a blockbuster drug whose patent is soon to expire.

- Example: For a mature blockbuster drug with $4 billion in annual sales, a three-month extension would yield $1 billion in additional sales – corresponding to profits of $800 million
- Would delay generics. "Why should patients taking a statin drug (or their insurers) bear the financial burden of incentivizing antibiotic development?"
- Would leave innovation decisions up to the free market.
- Would not require direct appropriation from the Federal discretionary budget, although a portion of the cost would be borne by CMS as a payer.

Johnson & Johnson Testimony: 2014 Energy and Commerce Committee Hearing

Transferable Market Exclusivity (TME):

- Successful examples of extended exclusivity stimulating product development:
  - Orphan drugs
  - Pediatric exclusivity
- Decouples the investment toward development of an antibiotic from the market success of the antibiotic
- Guardrails could be incorporated into a TME model to ensure, for example, that a TME period or voucher cannot be applied to on-market pharmaceutical products for which fewer than four years of patent life remain.
- Support the inclusion of TME in a larger package of policy incentives for antibiotic R&D

2015: 21st Century Cures Act (discussion draft only)

Conveyed Exclusivity (proposed by Reps. John Shimkus (R-IL) and Gene Green (D-TX):

- Option to convey up to 12 months of the 5-year extension of exclusivity provided to Qualified Infectious Diseases Products (QIDPs) by the GAIN Act to a different (non-QIDP) drug
- Would require companies electing this option to donate:
  - 5% of profits attributable to the conveyed exclusivity to the National Institutes of Health to fund antimicrobial resistance research
  - 5% of profits attributable to the conveyed exclusivity to patient assistance programs that include the disease for which the drug receiving the conveyed exclusivity is intended to treat

Transferable Exclusivity Vouchers: Pros

- Does not require upfront government funding or annual congressional action
- De-linked from the sales or use of antibiotics
- Potentially powerful incentive for companies

Transferable Exclusivity Vouchers: Drawbacks and Potential Solutions

Challenges	Potential Solutions
Increases costs in other areas of healthcare	Cap voucher (in value or duration)
Can negatively affect generic market	• Voucher will only be awarded to new drugs (not applicable for previously approved drugs) • Company that will be using the voucher must declare which drug the voucher will be used on at least 4 years prior to exclusivity expiration
Does not encourage stewardship	Link quality reporting requirements (e.g., efficacy, length of hospital stay) to receipt of voucher
Could be poorly targeted to needed antibiotics	Limit eligibility to drugs that meet criteria set by public/private partnership group, which will identify unmet need based on periodic reviews of infection rate, resistance, and the drug pipeline
Sale of drug would still be FFS, but providing drugs for free would undermine stewardship	Drug provided at cost of production with penalty for improper use

→ ***Ten years after implementation of voucher program, the GAO could conduct a study to determine the effectiveness of the vouchers and whether the voucher program should continue***

Source: Duke Margolis Center for Health Policy

Another approach

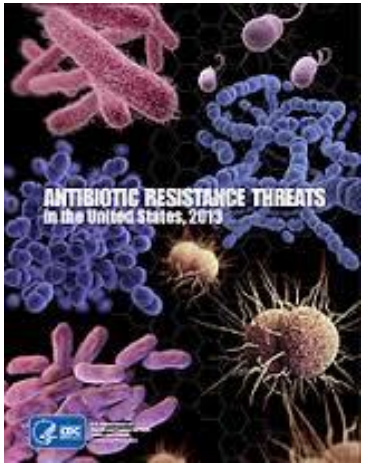
The federal government could sell exclusivity vouchers and use the proceeds to finance market entry rewards.

- Financing mechanism for market entry rewards that does not require up front government funding or annual congressional action

- As part of a “delinkage” approach, market entry rewards could be linked to more robust stewardship policies

Political Environment: Momentum for Addressing Antibiotic Resistance, New Antibiotics

United Nations



Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Political Environment: Public Outcry on Drug Costs

Policy Context

CARB National Action Plan

- Increased BARDA, NIAID, DoD efforts
- CARB-X: Biopharmaceutical Accelerator
- Antibacterial Resistance Leadership Group
- FDA exploring new approaches
- Stewardship requirements in hospitals and LTCs

21st Century Cures Act

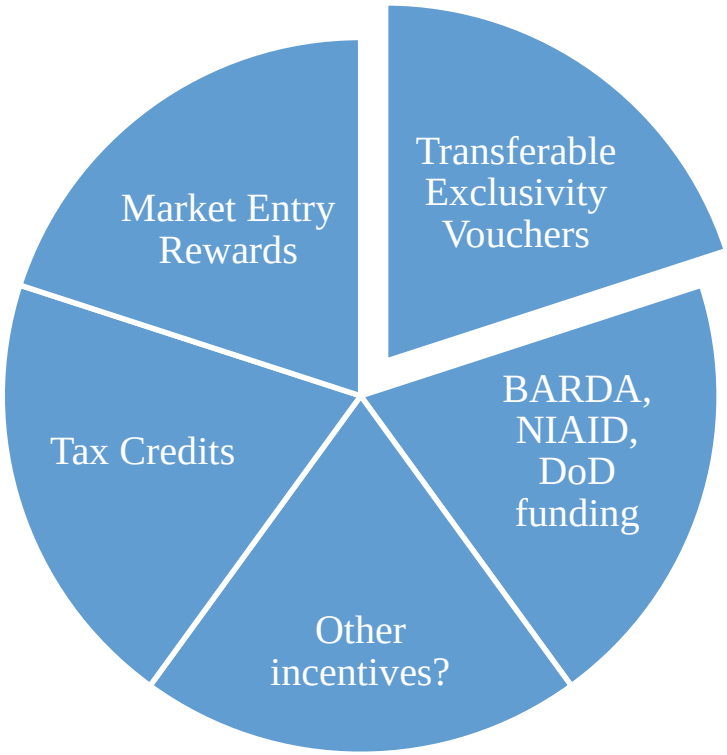
- Limited Population Antibacterial Drug (LPAD) Approval Pathway
- Breakpoints
- Passed House 2015, Senate HELP Committee 2016; working toward final deal

2017

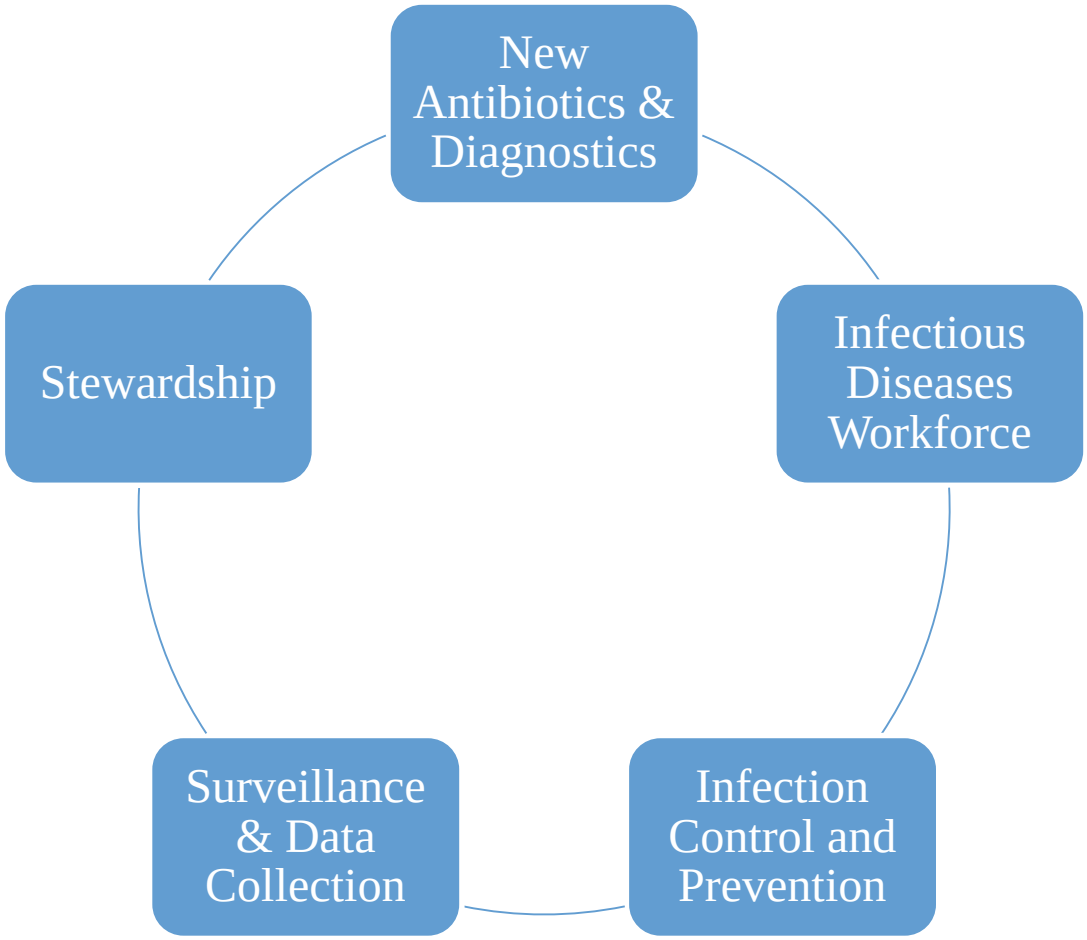
- PDUFA legislation will provide another opportunity to move antibiotics incentives

Final thoughts: Multiple Push and Pull Incentives are Needed

Transferable exclusivity vouchers may be part of the solution



Final Thoughts: Comprehensive Approach is Needed

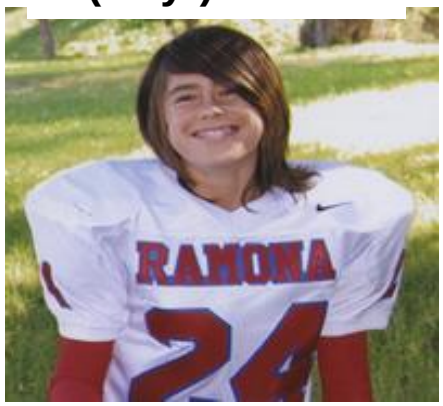


New Antibiotics: Inaction is Not an Option

Premature Death

Rebecca Lohsen
(17 yr)--Dead

Mariana Bridi da Costa
(22 yr)--Dead



Carlos Don
12 yr)--Dead

Ricky Lannetti
(21 yr)--Dead

Life-Altering Disability

Tom Dukes: colostomy, lost 8” colon

Addie Rerecich, 11yo
Double lung transplant
Stroke, nearly blind
$6 million hospital bill

Thank you

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Session II

Market Entry Reward

Market Entry Rewards

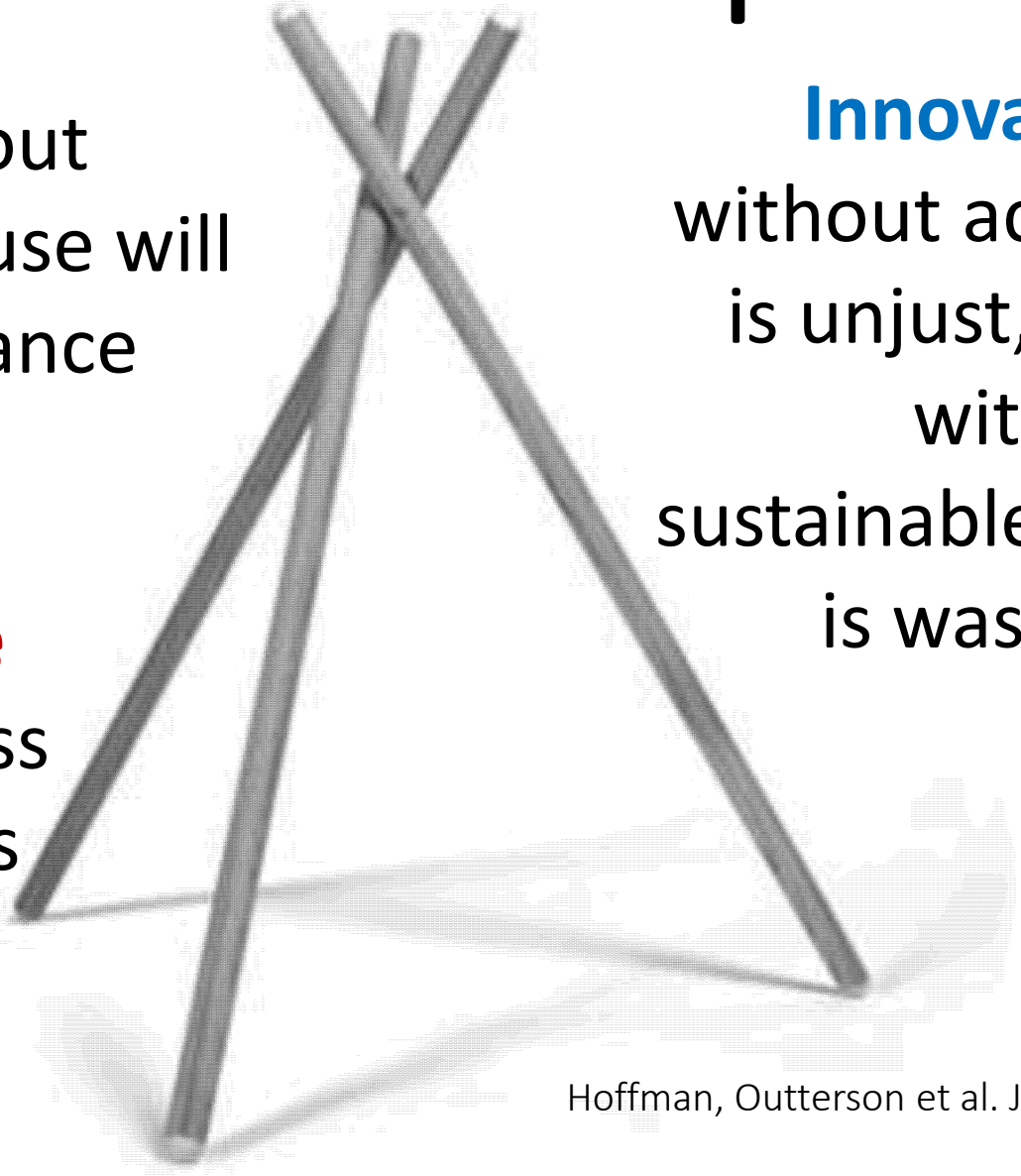
Kevin Outterson
Boston University

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. JLME 2015

Convergence of principles

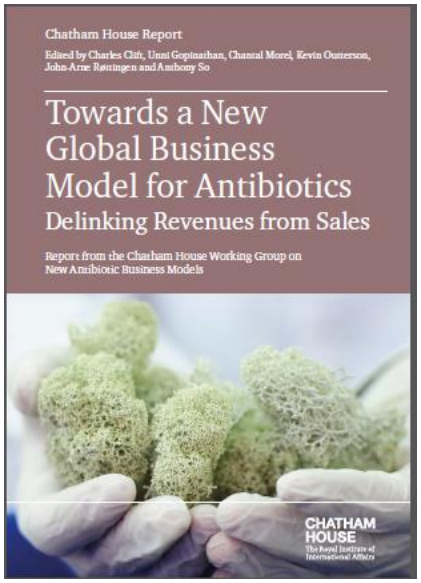
G7 GERMANY 2015

WORLD ECONOMIC FORUM

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

- 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



OECD
BETTER POLICIES FOR BETTER LIVES

World Health Organization

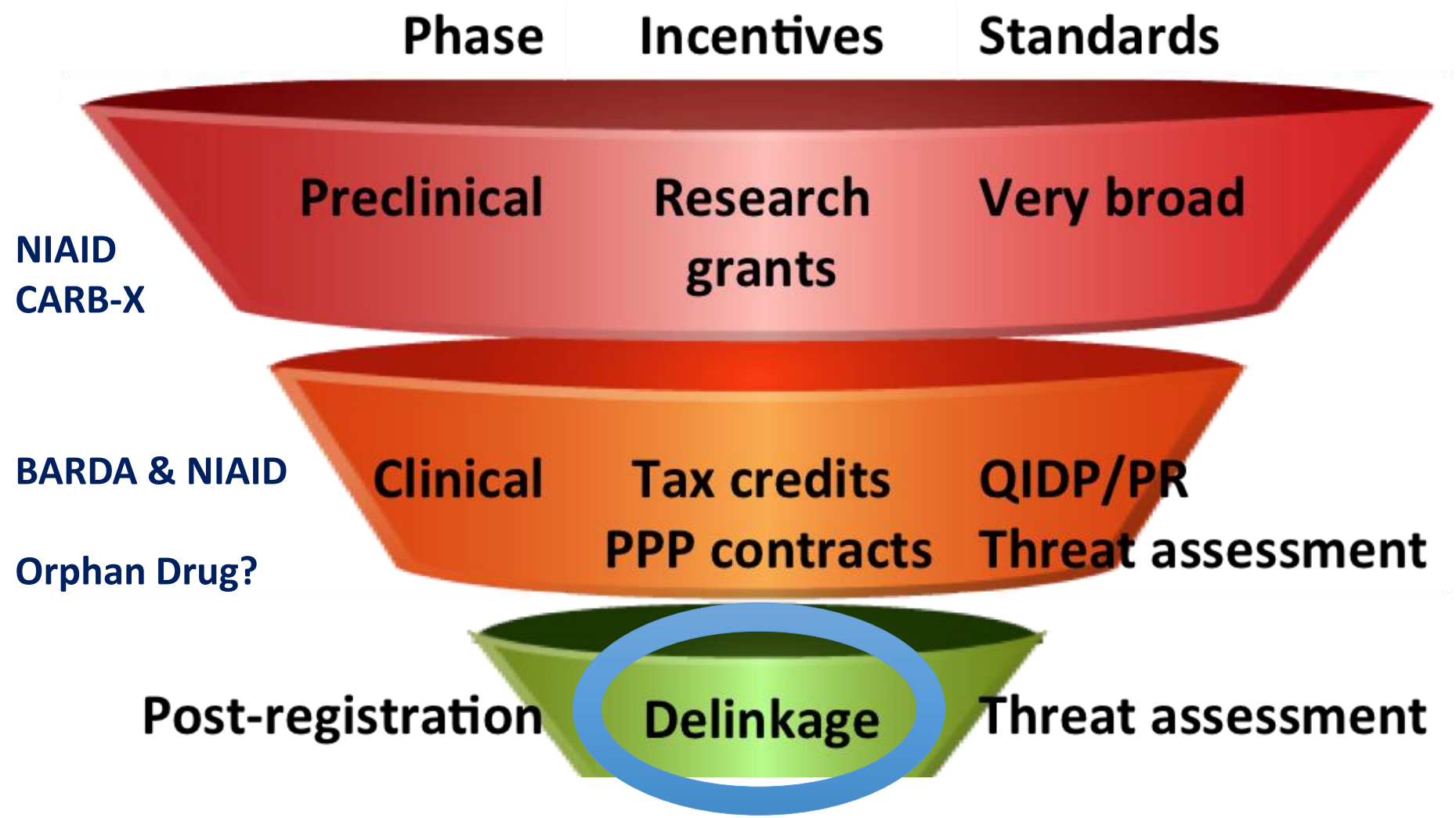
DNDi
Drugs for Neglected Diseases *initiative*

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."

US Incentives



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

Market Entry Rewards

1. Structure
2. Magnitude
3. Adjustments
4. Other rules
5. Funding

Market Entry Rewards

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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.

Structure

- Guaranteed, unambiguous payment upon FDA registration
- Size of payment varies with TPP
- Payment spread over 5 years
- No profits from sales volume
- Conditions for stewardship & global access

Market Entry Rewards

1. Structure
2. Magnitude
3. Adjustments
4. Other rules
5. Funding

Magnitude

	Payments from governments	Expected NPV benchmark at commencement of R&D
Sertkaya et al[11]	$919 million (spread over entire R&D process and at registration; USA only)	$100 million
Sharma and Towse[18]	$2·5 billion ($500 per year for 5 years)	$300 million
Review on Antimicrobial Resistance[19]	$2–4 billion (paid 3 years after registration)	Not stated

All values are in US$. R&D=research and development.

Table 1: **Nominal and expected net present value (NPV) estimates of the needed size of antibiotic delinkage payments**

Taking the smallest estimate, roughly adjusted to 2017 dollars = $1b total or a base payment of $200m a year paid for five consecutive years after FDA registration.

Market Entry Rewards

1. Structure
2. Magnitude
3. Adjustments
4. Other rules
5. Funding

Adjustments

	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

Also consider a much smaller but long-term “market access” payment to support warm mfg base

Adjustments

- Target Product Profile (previous slide)
- Clawback for federal grants & tax credits (assumed in ERG)
- Global coordination

Market Entry Rewards

1. Structure
2. Magnitude
3. Adjustments
4. Other rules
5. Funding

Other Rules

- Payment rules must be guaranteed when R&D decisions are made (i.e., grandfathered for > decade)
- “On ramp” process during Phase 2
- Payments cease if drug withdrawn from market or key conditions violated
- Generics may need special rules

Market Entry Rewards

1. Structure
2. Magnitude
3. Adjustments
4. Other rules
5. Funding

Funding

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

2 – AMR Review; 3- Hollis & Ahmed NEJM 2013; 4- Outterson & McDonnell, Health Affairs May 2016

Tweeting antibiotics R&D @koutterson

Research papers at Google Scholar & SSRN

Kevin Outterson
Boston University

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Session III

Value-Based Reimbursement

Path to Sustainability with Value-Based Reimbursement for Antimicrobials

Gregory Daniel, PhD, MPH
Deputy Director, Duke-Margolis Center for Health Policy
Clinical Professor, Fuqua School of Business
November 9, 2016

Increasing the value of health care delivery

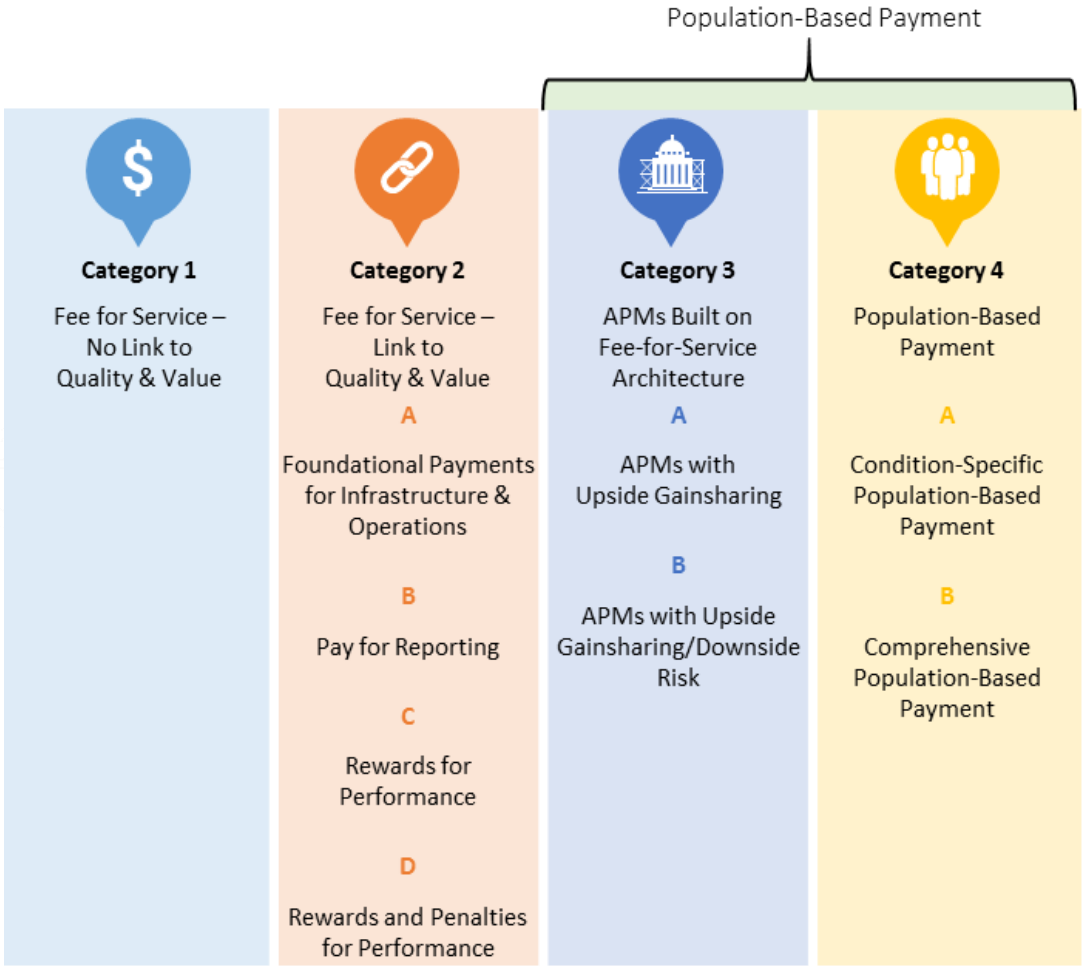
- As health care expenditures rise, more emphasis is on value and quality
- Providers and payers implementing alternative payment models (APMs)
  - Shift from volume and intensity to patient-level payments that enable more flexibility in how services are provided
  - Higher payments for better measured results and lower overall costs
  - Provide support for care coordination and innovative care delivery
  - Create new financial accountability for providers… Will affect incentives for use of costly therapies – particularly those with low impact on outcomes
- Challenging for health care providers
  - Steep learning curves in shifting to new payment structures, requiring new patient care capabilities and capacities to bear financial risk
  - Increasingly complex drug and device pipeline with high prices and traditional FFS payments that aren't aligned with shift

Framework for Alternative Payment Models (APMs)

HCP LAN
Health Care Payment Learning & Action Network

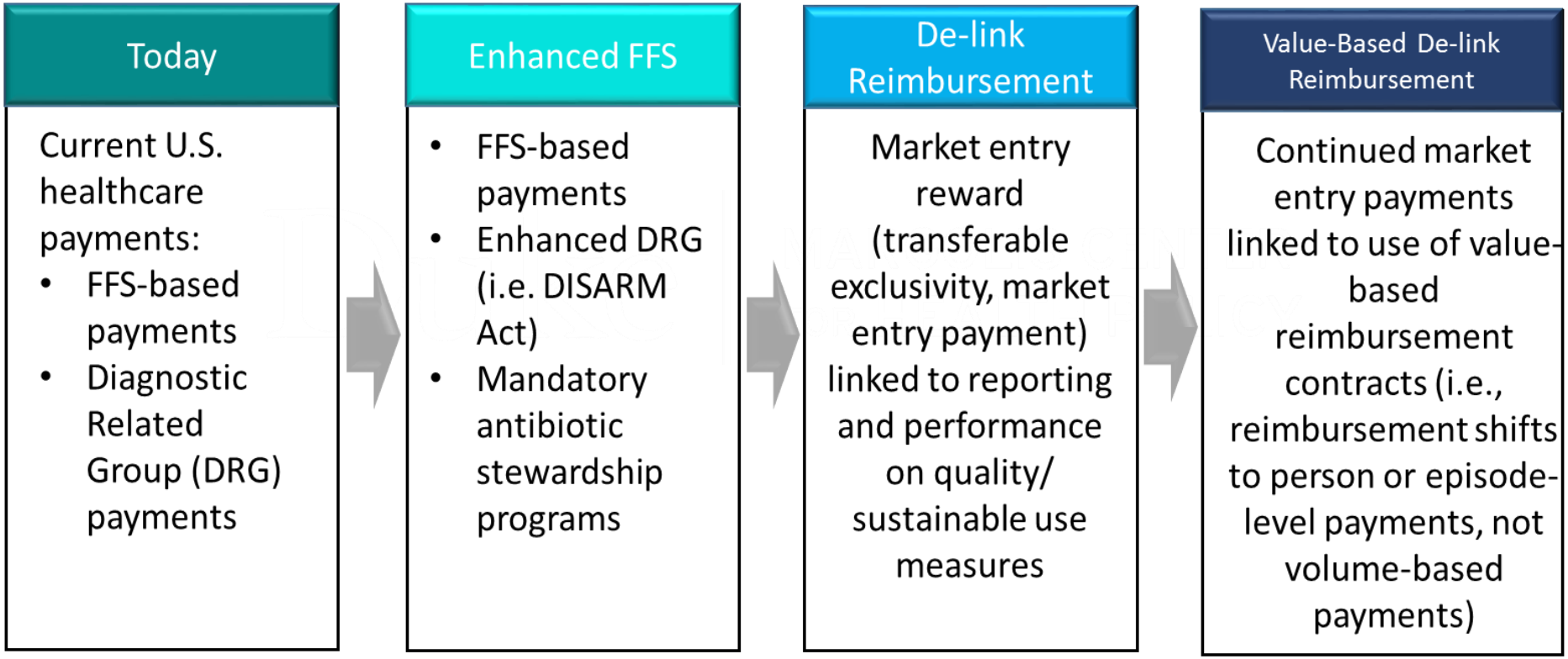
The framework is a step toward the goal of better care, smarter spending, and healthier people…

- for payment reform capable of supporting the delivery of person-centered care
- for generating evidence about what works and lessons learned



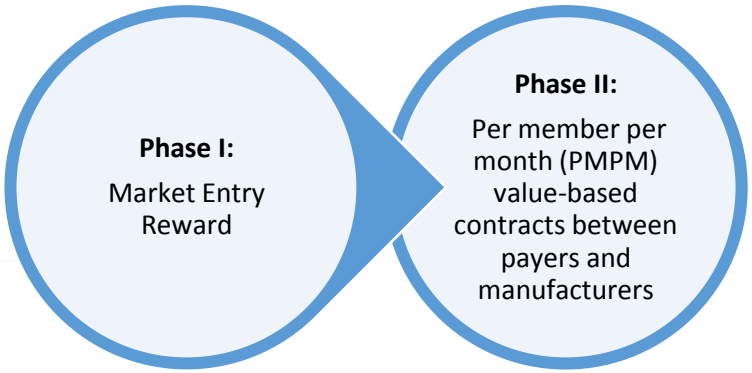
The framework situates existing and potential APMs into a set of categories.

Path to value-based reimbursement



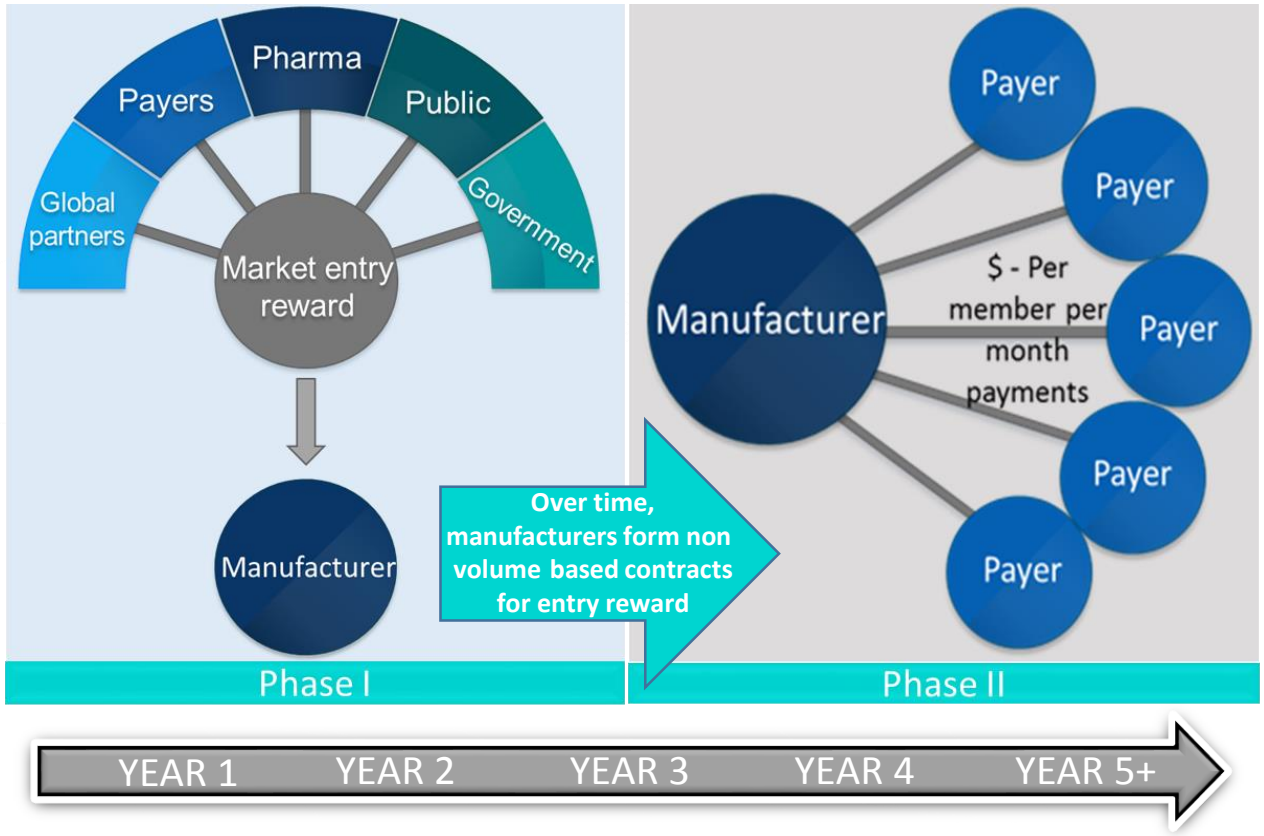
Phased-in approach to value-based reimbursement

- The FFS payment scheme does not align payers, providers, and drug manufacturers to use antibiotics appropriately
- Market entry reward provides quick access to funding but has built in incentives to transition to population-based payment
- Population-based payment (including PMPM or per-episode bundled payment tied to results) separates reimbursement from volume of drug used
  - Payment would be dependent on efficacy of drug and availability when appropriate
- Aligning payments for high-priority antibiotics with effective use in the covered population, rather than volume of sales, would encourage all parties to work together to use them appropriately

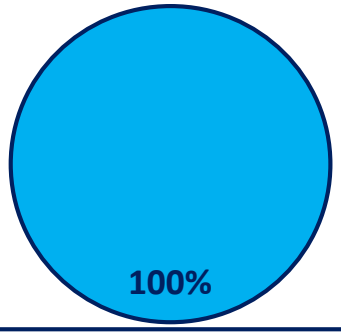


Phased-in approach to value-based reimbursement (cont.)

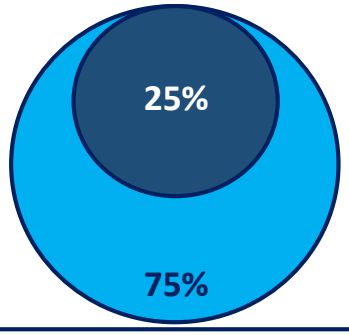
- Upon market entry, the manufacturer will receive a yearly payment, which would continue over 4-5 years and would be front-loaded, so the payment gets smaller over time.
- To continue receiving the payment, manufacturers would have to demonstrate that an increasing share of their payments for the drug are based on alternative, population-based payment contracts with the payers.
- The amount of payment will reflect the value (with appropriate accessibility) that the drug brings to the population of insured patients, rather than the volume used.



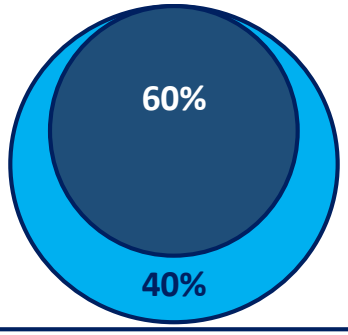
Phased-in approach to value-based reimbursement (cont.)



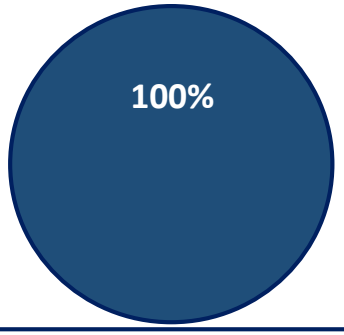
- Market entry reward will be delivered based on specific eligibility criteria set by an independent organization
- Recipients of the reward would be required to comply with established guidelines to ensure stewardship and appropriate use of the drug, while also being allowed to collect payments from insurers for access to the drug.
- Manufacturers will collect data on outcomes to inform future value-based reimbursement agreements



- Payments to manufacturers will be front-loaded, so they will receive a smaller reward while they start building non-volume-based contracts with payers
- Manufacturers would be required to support the collection of performance data demonstrating stewardship and appropriate use, as well as impact on patient outcomes and continued effectiveness of the antimicrobial.



- To continue receiving the market entry reward, manufacturers would have to demonstrate that an increasing share of their revenue for the drug is based on alternative, population-based payment contracts with the payers – not payments that are substantially based on volume of use.
- Some or all of the drug payments could be in the form of a per-member per-month (PMPM) fee to the manufacturer for access to the drug.



- The amount of payment will be determined via contracts with payers, reflecting the value (with appropriate accessibility) that the drug brings to the population of insured patients, rather than the volume used.
- Payers negotiate with providers to generate savings through appropriate use and providing the right drug for the right infection

TIME

Market entry reward from Antibiotic Innovation Fund

Per member per month (PMPM) from payers to manufacturers

Designing Economic Incentives for Antimicrobials: Implementation in the U.S. Context

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