A New Sustainable Model of Antibiotic R&D

Brad Spellberg, MD FIDSA FACP
Chief Medical Officer
LAC+USC Medical Center
Medical Director of Biosciences for LA County

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Perspective

Sustainable Discovery and Development of Antibiotics — Is a Nonprofit Approach the Future?

Travis B. Nielsen, Ph.D., Eric P. Brass, M.D., Ph.D., David N. Gilbert, M.D., John G. Bartlett, M.D., and Brad Spellberg, M.D.

IDEAS AND OPINIONS

Annals of Internal Medicine

Ensuring Sustainability of Needed Antibiotics: Aiming for the DART Board

Brad Spellberg, MD; Travis B. Nielsen, PhD; David N. Gilbert, MD; Andrew F. Shorr, MD, MPH, MBA; and Eric P. Brass, MD, PhD

The initial boom of antibiotic discovery led experts in ... New Act (5). Unfortunately, this list includes many or

The Future of Antibiotics and Resistance

Brad Spellberg, M.D., John G. Bartlett, M.D., and David N. Gilbert, M.D.

PERSPECTIVE

N ENGL J MED 368;4 NEJM.ORG JANUARY 24, 2013

World Changes, Solutions Evolve

- I was THE card-carrying incentive guy during the Abx R crisis in the early 2000s
  - 2004 1st author publication led to IDSA White Paper, Bad Bugs, No Drugs
  - 2008 1st author IDSA Call to Action paper
  - 2010 wrote the pipeline/incentive paper in NAM Abx R Workshop Summary
  - 2011 1st author IDSA Policy paper
  - Congressional briefings to House & Senate Staffers for IDSA
  - Testified for IDSA before House HEC, leading to GAIN
- Not anymore

What Has Changed?

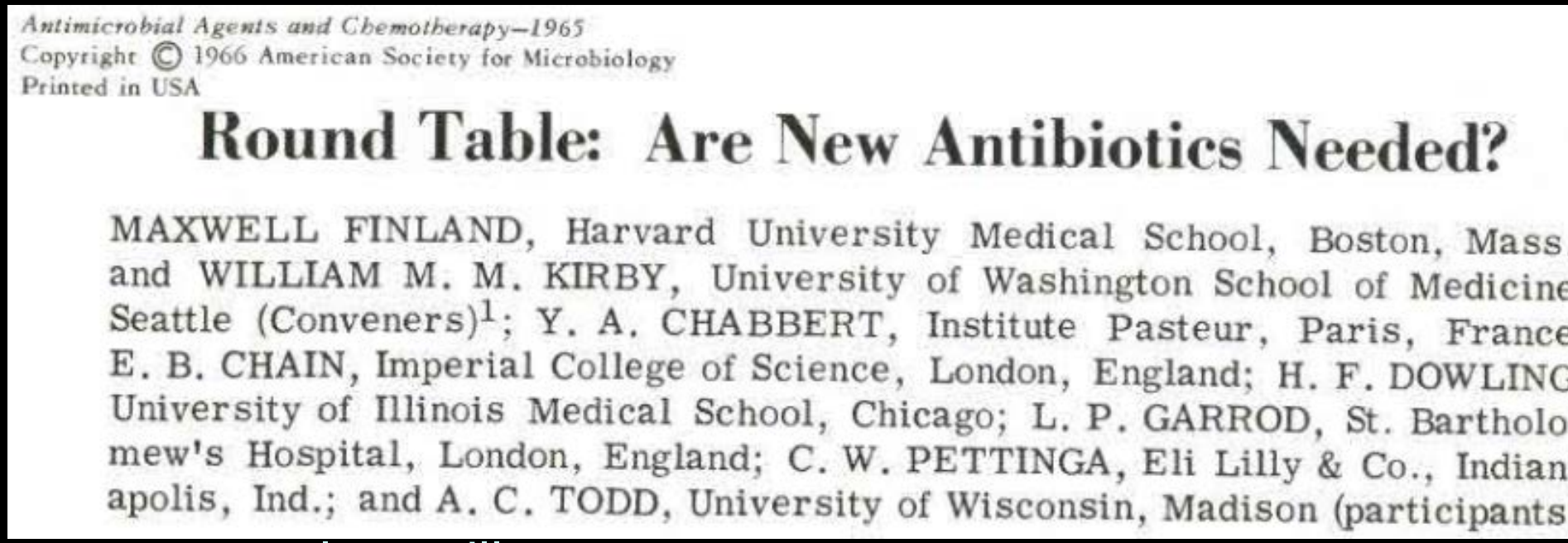
- Resistance rates declining now
- New abx approvals marked improvement, fastest, most robust since mid ‘90s
- Wastage of money subsidizing me-toos
- New vantagepoint at the health system level as CMO
  - Outside the ID Industrial Complex echo chamber
- Have learned more about the past

Audience Quiz

"The needs are multi-fold—to overcome the problems of resistance, to use against gram-negative bacillary infections...more active and less toxic ones for fungal infections, better ones against mycobacteria...and for the prevention and treatment of viral infections."

—who wrote this and when?

Answer: 1965



Antimicrobial Agents and Chemotherapy—1965

Printed in USA

Round Table: Are New Antibiotics Needed?

MAXWELL FINLAND, Harvard University Medical School, Boston, Mass
and WILLIAM M. M. KIRBY, University of Washington School of Medicine
Seattle (Conveners)[1]; Y. A. CHABBERT, Institute Pasteur, Paris, France
E. B. CHAIN, Imperial College of Science, London, England; H. F. DOWLING
University of Illinois Medical School, Chicago; L. P. GARROD, St. Bartholo
mew's Hospital, London, England; C. W. PETTINGA, Eli Lilly & Co., Indian
apolis, Ind.; and A. C. TODD, University of Wisconsin, Madison (participants

--Courtesy Glenn Tillotson

- Those who do not learn from history are doomed to repeat it; or
- "New ideas are often based on the recognition of old truths."—D. Gilbert

Should We Rush New Abx?

"There is a possibility that not many new antibiotics remain to be discovered, and if so it is better that they should be introduced one by one at fairly long intervals."

Boom-Bust Antibiotic R&D

- Discovery boom began in 1940, lasted until 1960—bust through the 1960s

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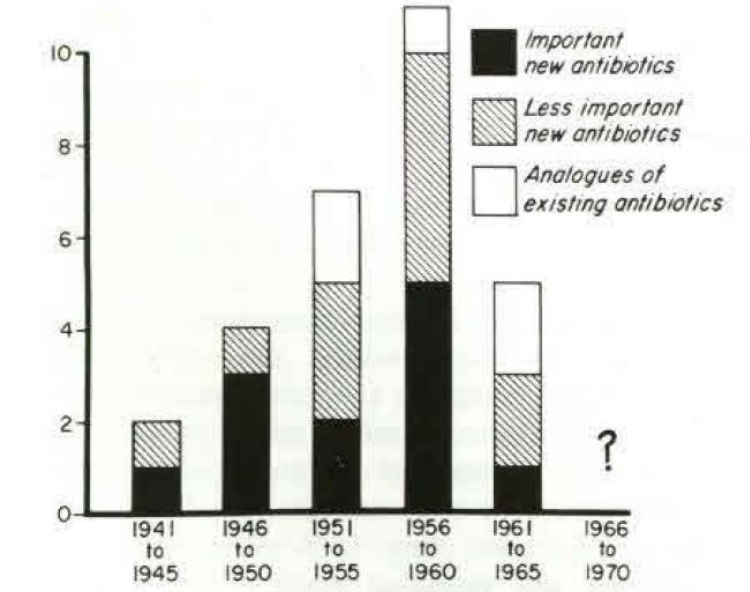
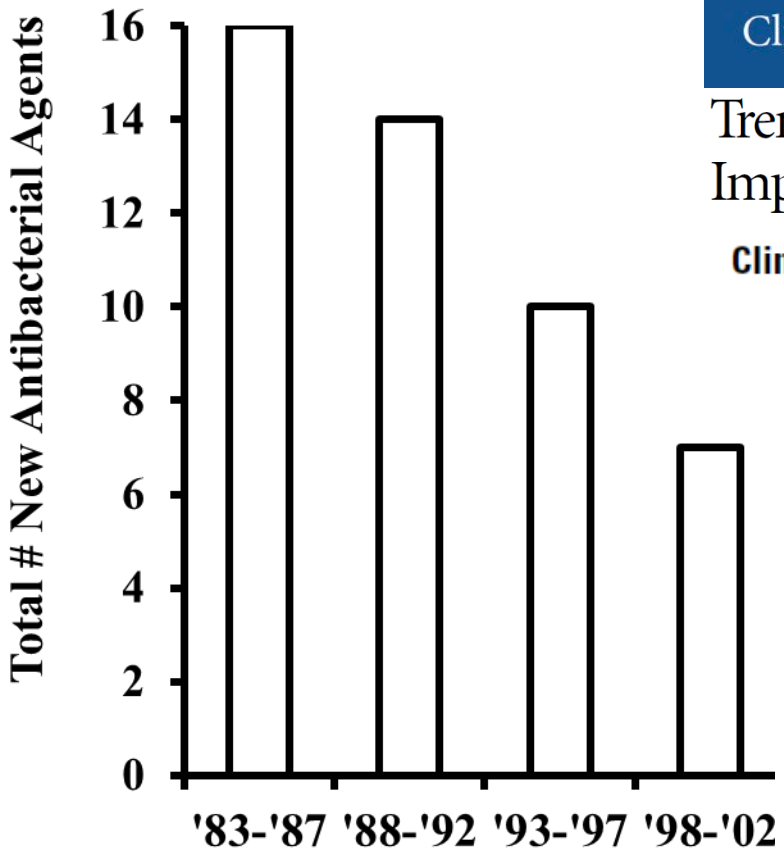


Fig. 2. *Antibiotics arranged by years of their introduction, and classified by importance.*

Boom-Bust Antibiotic R&D

- From the 1970s-early 1990s, 2nd boom
- Then the 2nd bust from ’90s-’00s



Clinical Infectious Diseases MAJOR ARTICLE

Trends in Antimicrobial Drug Development: Implications for the Future

Clinical Infectious Diseases 2004; 38:1279–86

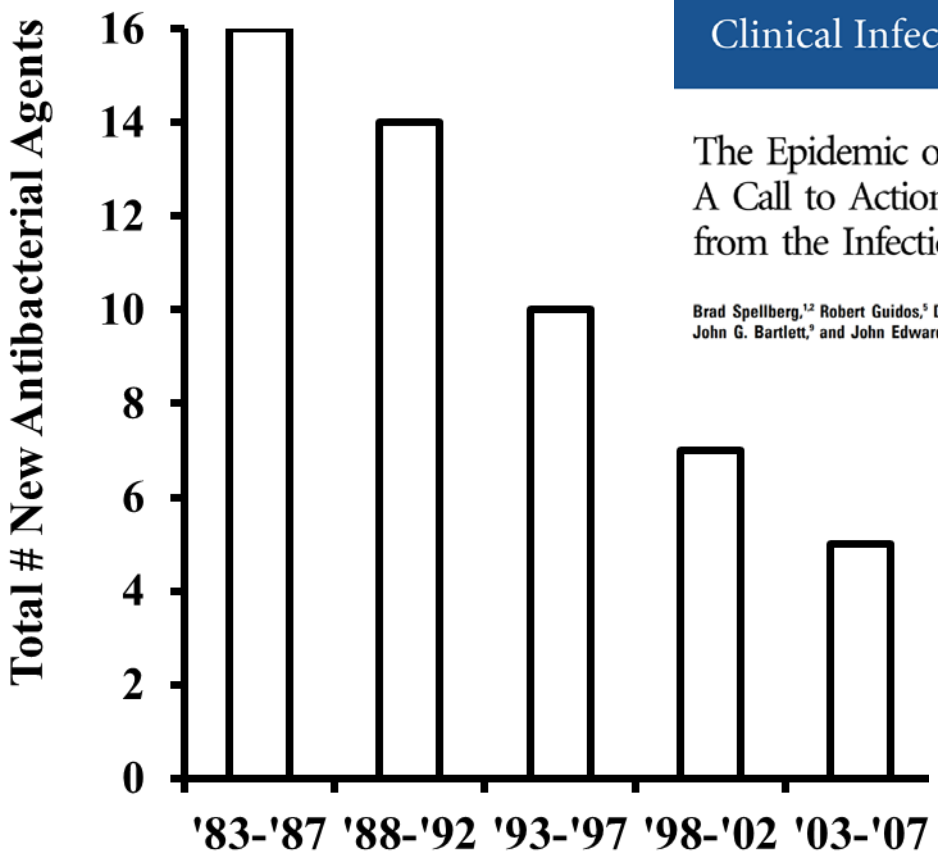
6 antibiotics in development

Boom-Bust Antibiotic R&D

- During that 2nd bust: 90's-'00s
  - MRSA exploded into communities
  - CRE appeared
  - CRAB spread
  - CRPA spread
  - XDR TB

Boom-Bust Antibiotic R&D

- Extensive advocacy efforts launched



Clinical Infectious Diseases

IDSA PUBLIC POLICY

The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America

Brad Spellberg,[1,2] Robert Guidos,[5] David Gilbert,[7] John Bradley,[3,4] Helen W. Boucher,[8] W. Michael Scheld,[6] John G. Bartlett,[9] and John Edwards, Jr.,[1,2] for the Infectious Diseases Society of America

The Nadir

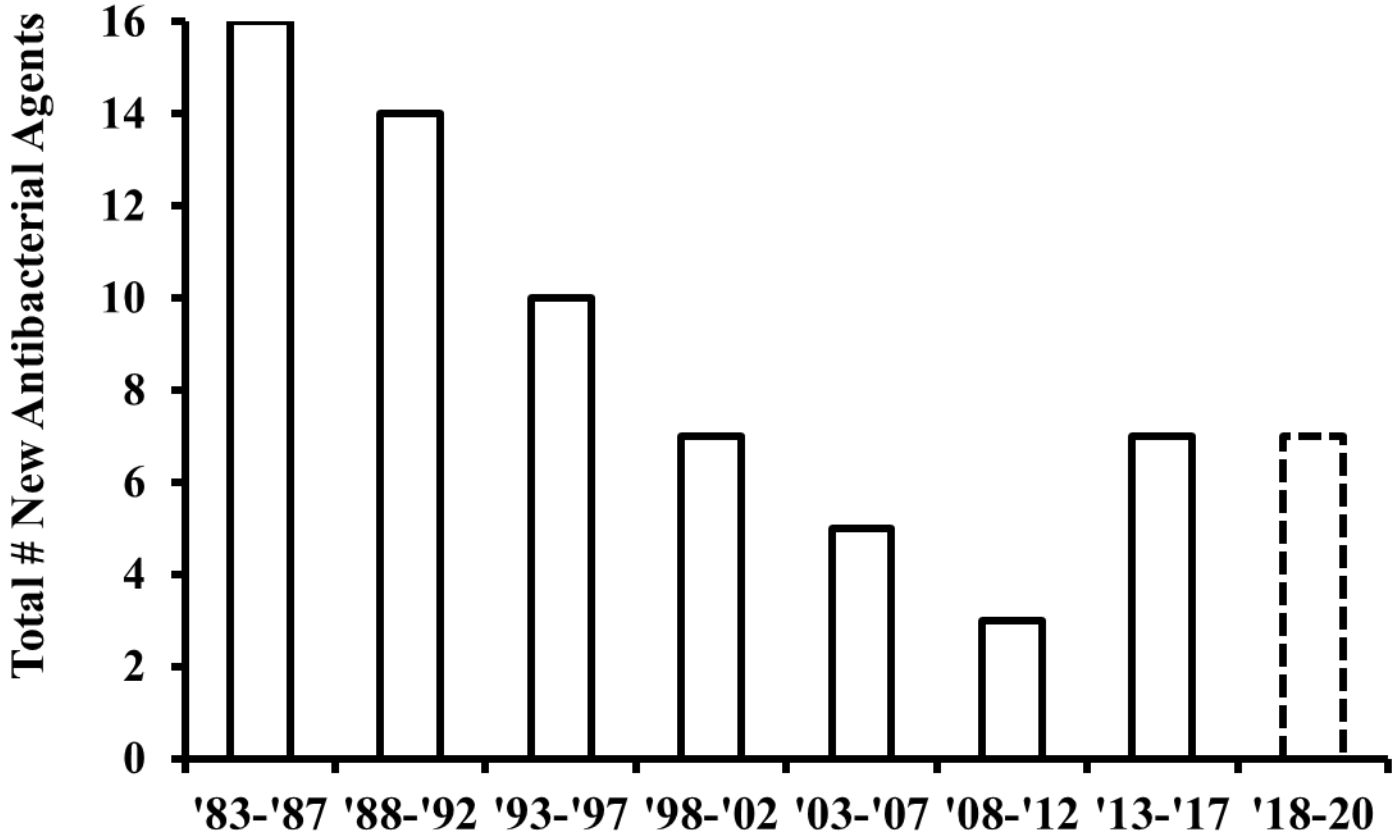
- The period from 2008-2012 was the nadir

<u>During this period:</u>

- Push incentives took hold
  - Wellcome Trust, NIAID, BARDA
- MRSA became an Abx non-issue
- GNB drugs began late development
- GAIN passed in 2012—pull incentive
  - QIDP, Extended exclusivity, Priority review

The New Boom

- The result of all this advocacy & incentives



The New Boom

- New Abx approvals at their fastest clip since the mid 1990s—tripled in 15 years
- 42 new Abx in development (increase 7-fold from 2004)
- MRSA/VRE non-issues for new Abx
- 6 new CRE agents approved
- 2 new Acineto drugs approved, and 1 old drug can be repurposed
- 2 new Pseudomonas drugs approved

The New Boom

- We have not been in this good a shape with respect to new Abx in 25 years

- So what's the problem?

Antibiotics Approved Since 2009

Year Approved	Drug	Resistant Pathogen(s) Covered	Body Site of Pivotal Trials	Primary Unmet Need	Comment
2009	Telavancin	MRSA / VRE	Skin, Lung	No	Potentially important for bloodstream infections, but developed instead for community skin and lung infections
2010	Ceftaroline	MRSA	Skin, Lung	No	
2012	Bedaquiline	TB	Lung	Yes	1st New TB Drug in 50 Years
2014	Tedizolid	MRSA / VRE	Skin	No	Potentially important for bloodstream infections or osteomyelitis–developed instead for skin infections (and tedizolid similar to generic linezolid)
2014	Dalbavancin	MRSA / VRE	Skin	No	
2014	Oritavancin	MRSA / VRE	Skin	No	
2014	Ceftolozane-Tazobactam	CRPA	Abdomen, Urine	Yes	Efficacy for CRPA only; not for CRE
2015	Ceftazidime-avibactam	CRE	Abdomen, Urine	Yes	1st CRE drug
2017	Delafloxacin	MRSA	Skin	No	Competing with >30 MRSA skin abx
2017	Meropenem-Vaborbactam	CRE	Abdomen, Urine	Yes	2nd CRE drug
2018	Plazomicin	CRE	Urine	+ / -	3rd CRE drug
2018	Eravacycline	CRE, CRAB	Abdomen	+ / -	4th CRE drug
2018	Omadacycline	MRSA	Skin, Lung	No	Not studied for GNB, might cover CRE
2019	Imipenem-Relebactam	CRE	Abdomen, Urine	+ / -	5th CRE Drug
2019	Pretamonid	XDR TB	Lung	Yes	Developed by Non Profit (TB Alliance)
2019	Lefamulin	MRSA	Lung	No	Numerous CAP Tx on market
2019	Cefedericol	CRE (Acinet / Steno)	Urine	+ / -	6th CRE drug; concerns re Acinet / Steno

Problems with the New Boom

- Most of the Abx we get from industry simply don't address unmet need
- Even those that started addressing unmet needs now are me-toos (e.g., CRE)
- And the drugs don't sell well when they hit the market

Calls for More Incentives

- ID Industrial Complex wants profit subsidies
- On top of extensive push incentives already in place
- In the face of massive government deficits and historically high debt
- For an industry despised by the public

Why Is the Market Failing?

- Short course Tx for Abx—getting shorter
- Antibiotic stewardship, declining resistance
- Pricing

<u>The real issue underlying these?</u>

- Antibiotics are commodities
- >90 on the market

Why Is the Market Failing?

- Each new Abx captures decreasing share of an ever increasingly crowded market
- This situation will only worsen over time as more Abx are approved
- Resistance only creates a small market for new agent--<15,000 cases/year for XDR

ID Industrial Complex Wish

- Give $1-2 billion of pure profit subsidy to rich investors and pharma per new Abx—just hand them this money
- Over and over...for each new Abx...in perpetuity
- And companies given these subsidies will choose to develop drugs we need for small markets, rather than me-too drugs

Is This Realistic?

- Pharma is the most unpopular industry sector, >70% public thinks they make too much money
- Multi-trillion dollar deficits, $30 trillion in debt
- Populism sweeping the globe

For-Profit Motive for Abx Is Dead

- Maybe instead of arguing with the capital markets, we should listen to them
- In a capital market, if you can't distinguish your product from others on the market, you should go out of business
- If you charge non competitive prices, you should go out of business
- YOU DON'T ASK THE TAXPAYERS TO BAIL YOU OUT IF YOU'RE A CAPITALIST

Other Problems

- Right now, our targeting of new drugs is dreadful
- QIDP list includes: MRSA, VRE, *C. difficile*, CRE, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*
- New incentives proposed to be based on QIDP

Non Profit

Advantages of a non-profit model

- Can focus on/target unmet need
- No need to satisfy insatiable revenue growth
- Revenues of millions to tens of millions ok
- Don’t aggressively market—rely on experts
- Tap into non-dilutive push incentives and also license or sell to for-profit at later stages of development

Non Profit

Structure of a non-profit model

- Endowment (e.g., $300 million); 3-4%

Operating budget $10-12 million per yr

- 15-25 FTEs internal: $5-8 million/yr
- R&D budget: $3-4 million/yr
- Admin/IPO/Overhead: $1 million/yr

Non Profit

- R&D budget does not cover clinical trials
- Leverage existing push incentives
- Leverage later stage outlicensing opportunities
- The non profits are the bullpen—they develop to late pre-clin/phase I
- When unmet need is there, rapid clinical development can proceed

Integrated Scheme of Abx R&D

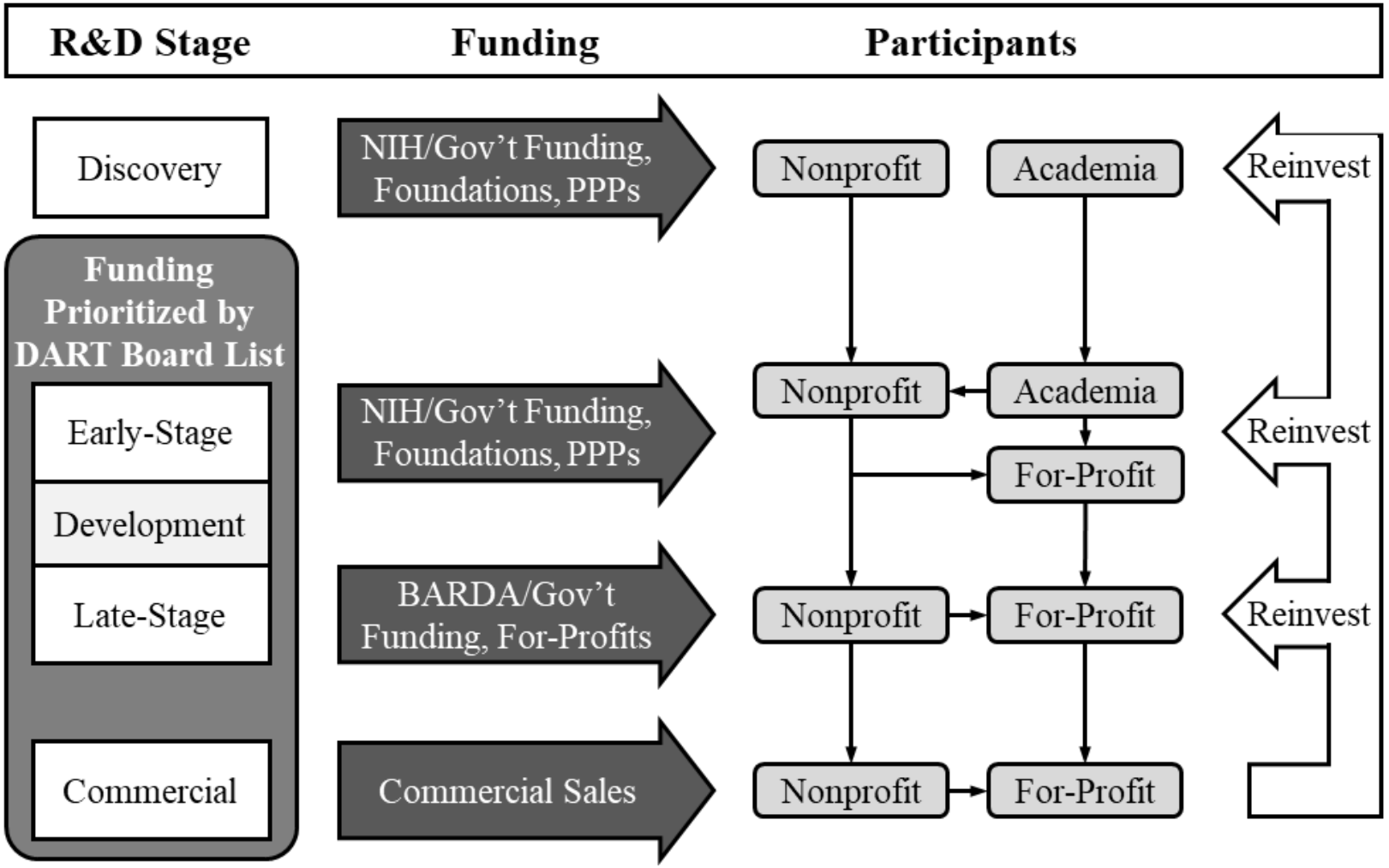


Figure. Schematic of a sustainable model for targeted discovery and development of new antibiotics.

How to Fund?

- Rich philanthropist
- Government funding

- $1 billion invested once to sustainably enable 3 non-profits to operate
- More sustainable than multi-billion dollar profit subsidies annually in perpetuity

Conclusions

- The for-profit motive for Abx is dead
- Thinking to sustain it by new, billions of dollars annual pharma profit subsidies is ID Industrial Complex prayer
- The market problem is due to over-crowding—it's a commodities market

Conclusions

- Clinging to past will not change the future
- We should want a small number of new, needed Abx approved every few years
- The future is not-for-profit with careful targeting of push incentives
- Can co-exist with and help sustain a more limited for-profit capital market

QUESTIONS?