Antibiotic Resistance – Today's Challenges, Tomorrow's Solutions

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ReAct--Action on Antibiotic Resistance

Medical Innovation—Changing Business Models

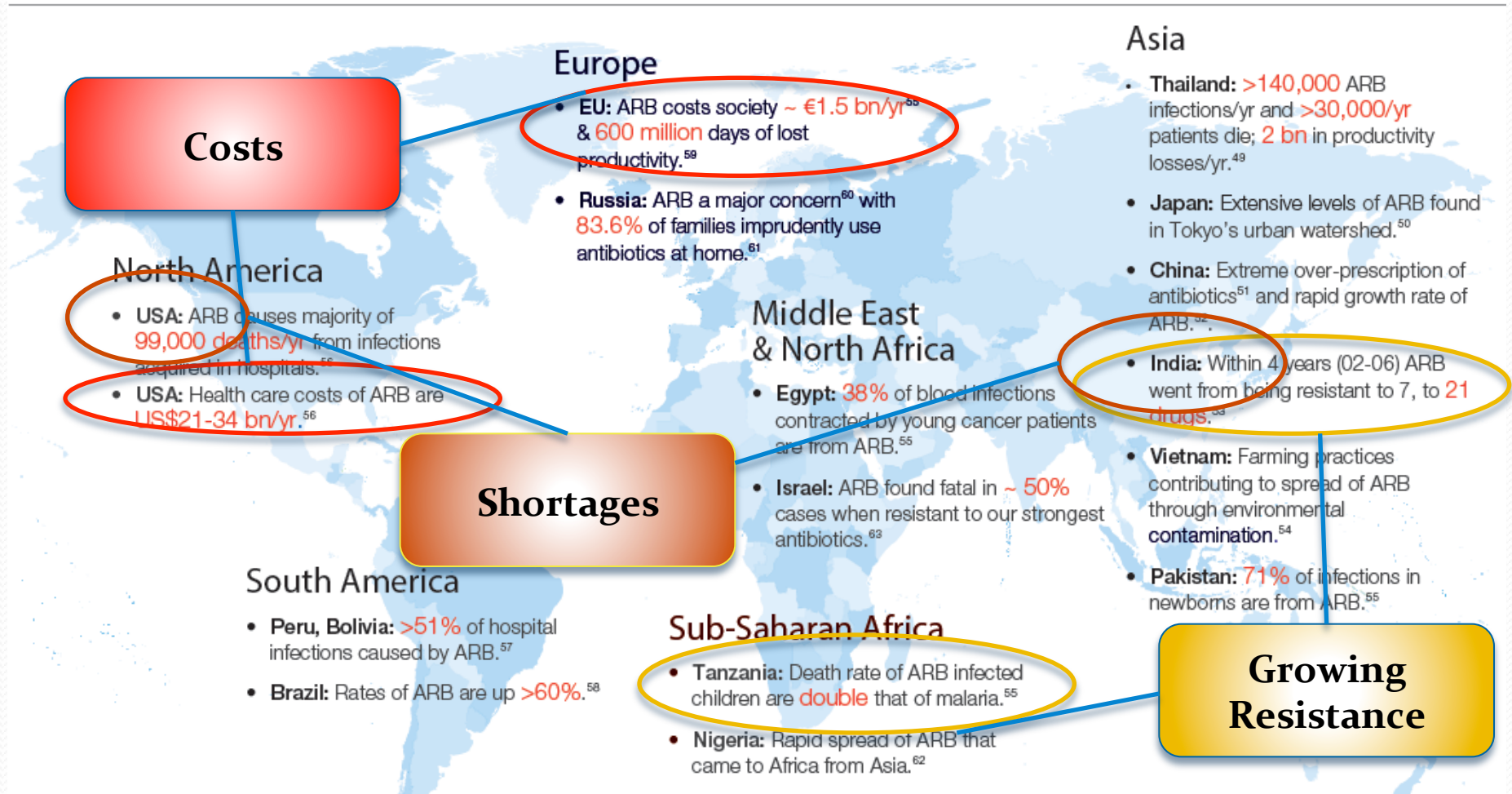Geneva, Switzerland
05 July 2013

Antibiotics Success Story

Table 3. Antibiotic-Mediated Mortality Reductions for Specific Infections

Disease	Pre-Antibiotic Mortality Rate	Antibiotic Mortality Rate	Change in Mortality
Community Pneumonia [53]	~ 23%	~ 7%	−16%
Nosocomial Pneumonia [54]	~ 60%	~ 30%	−30%
Bacterial Endocarditis [112–115]	~ 100%	~ 25%	−75%
Bacterial Meningitis [116–117]	>80%	<20%	−60%
Skin Infection [55, 118]	~ 11%	<.5%	−10%
By comparison, treatment of myocardial infarction (i.e., heart attack) with aspirin or streptokinase [119]			−3%

Source: Infectious Diseases Society of America (IDSA). Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. *Clinical Infectious Diseases* 2011; 52 (S5): S397-428.
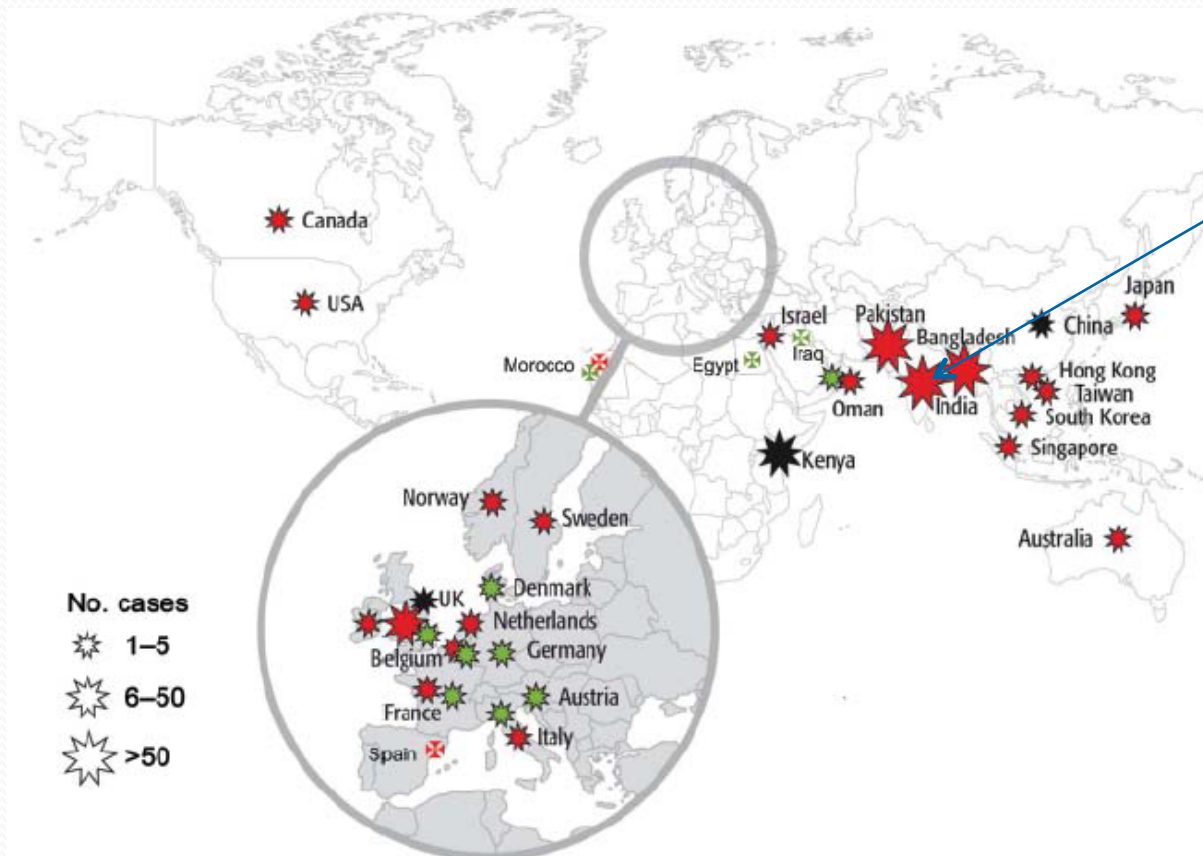
Antibiotic Resistance is a Global Threat

Figure 17: Spread of Antibiotic-Resistance Bacteria (ARB)[x]

Costs

Shortages

Growing Resistance

Europe
- **EU:** ARB costs society ~ €1.5 bn/yr[55] & 600 million days of lost productivity.[59]
- **Russia:** ARB a major concern[60] with 83.6% of families imprudently use antibiotics at home.[61]

North America
- **USA:** ARB causes majority of 99,000 deaths/yr from infections acquired in hospitals.[55]
- **USA:** Health care costs of ARB are US$21-34 bn/yr.[56]

South America
- **Peru, Bolivia:** >51% of hospital infections caused by ARB.[57]
- **Brazil:** Rates of ARB are up >60%.[58]

Middle East & North Africa
- **Egypt:** 38% of blood infections contracted by young cancer patients are from ARB.[55]
- **Israel:** ARB found fatal in ~ 50% cases when resistant to our strongest antibiotics.[63]

Sub-Saharan Africa
- **Tanzania:** Death rate of ARB infected children are double that of malaria.[55]
- **Nigeria:** Rapid spread of ARB that came to Africa from Asia.[62]

Asia
- **Thailand:** >140,000 ARB infections/yr and >30,000/yr patients die; 2 bn in productivity losses/yr.[49]
- **Japan:** Extensive levels of ARB found in Tokyo's urban watershed.[50]
- **China:** Extreme over-prescription of antibiotics[51] and rapid growth rate of ARB.[52].
- **India:** Within 4 years (02-06) ARB went from being resistant to 7, to 21 drugs.[53]
- **Vietnam:** Farming practices contributing to spread of ARB through environmental contamination.[54]
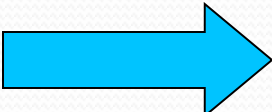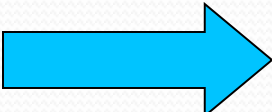- **Pakistan:** 71% of infections in newborns are from ARB.[55]

Spread of NDM-1 Producing Enterobacteriaceae

New Delhi sewage sites

Source: Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infectious Disease* 2011; 11: 355-62.
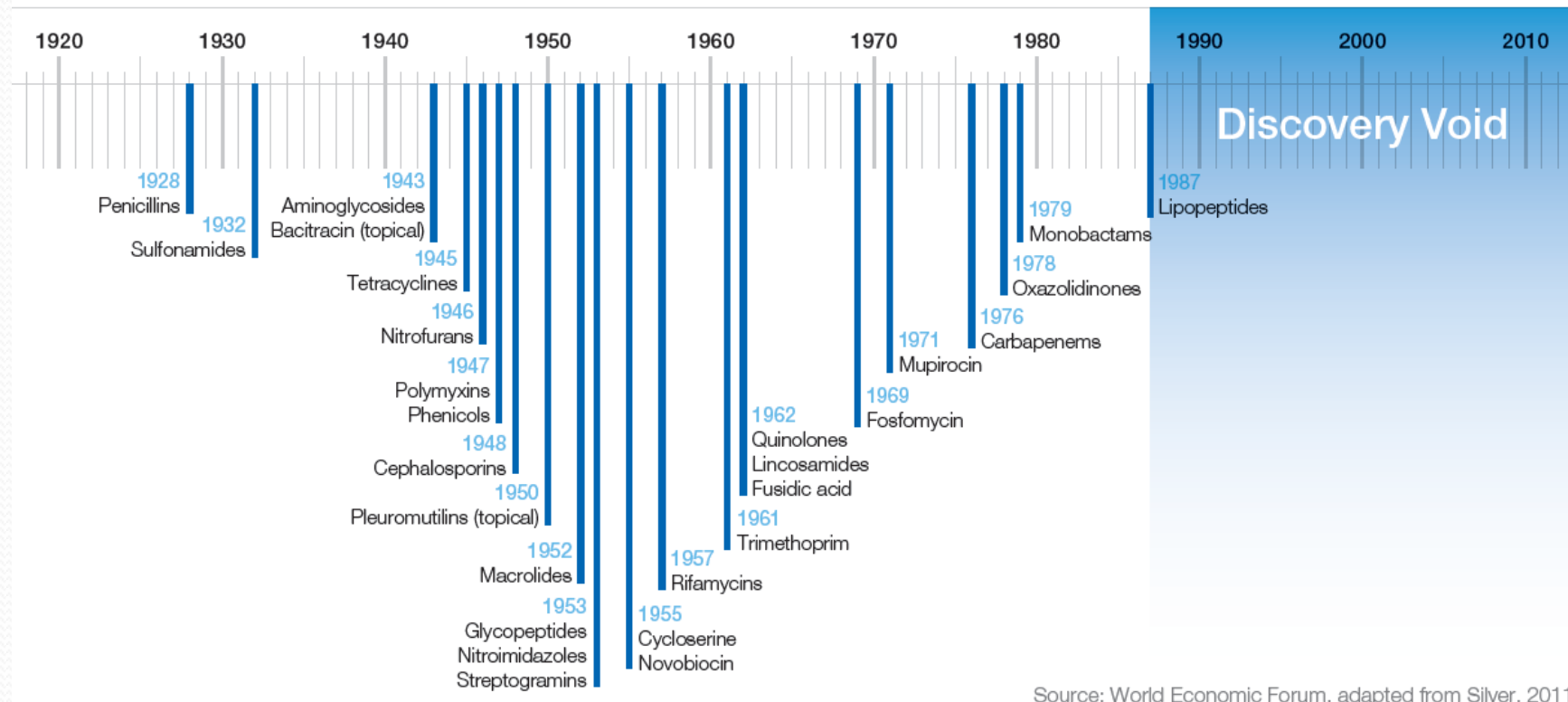
Source: Nordmann P, Naas T, Poirel L. Global Spread of Carbapenemase-producing *Enterobacteriaceae*. *Emerging Infectious Diseases* 2011; 17 (10): 1791-1798.

Framing Technology Policy Options

- **Decrease need for antibacterial use** → **Vaccines**

- **Improve the rational use of antibacterials** → **Diagnostics**

- **Accelerate the development of new antibacterials** → **Drugs**

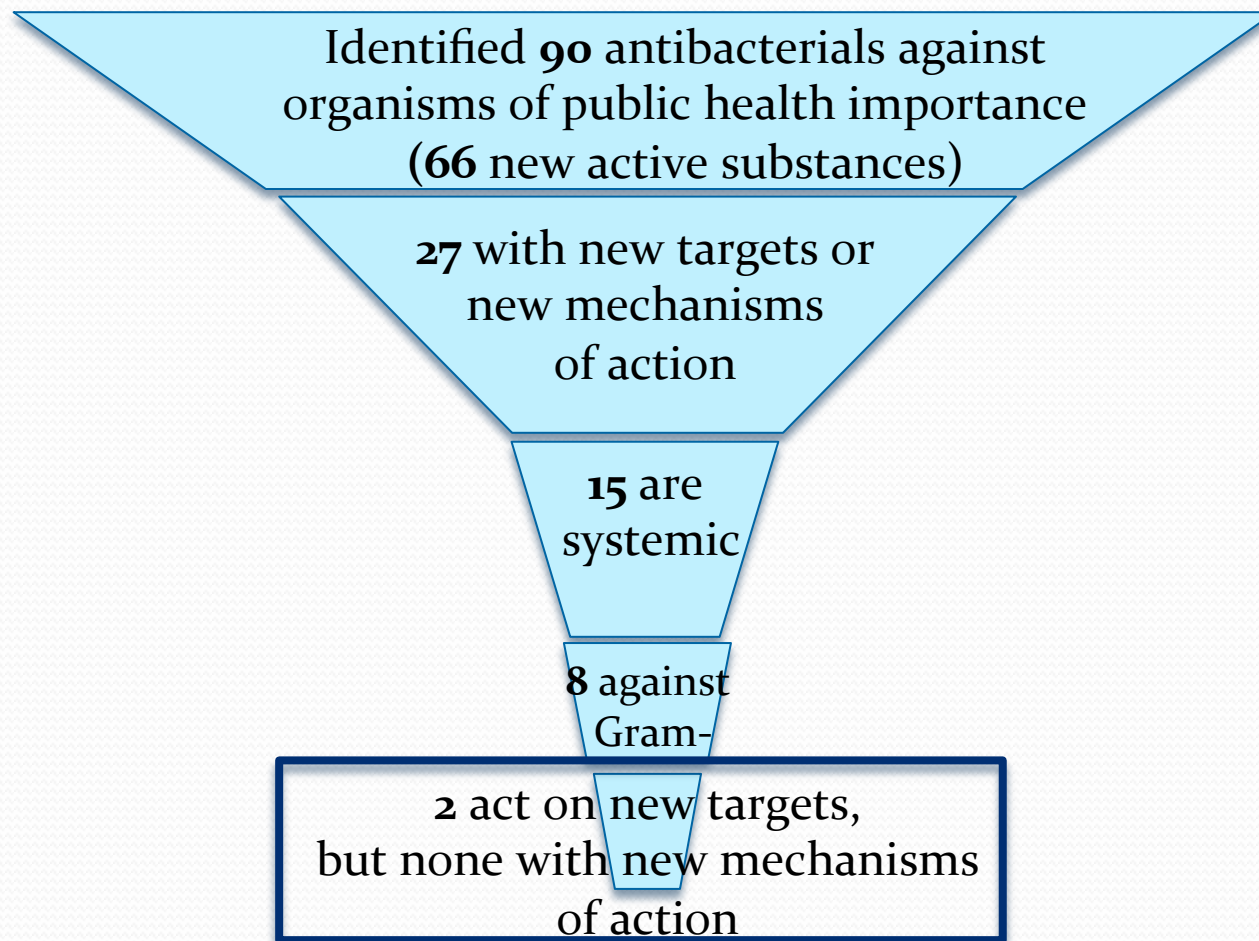# Few Novel Classes of Antibiotics

The Antibiotic Discovery Void:
The discovery dates of distinct classes of antibiotics. No new classes have been discovered since 1987.

Source: World Economic Forum, adapted from Silver, 2011

Faltering Pipeline for Antibiotics

EMA-ECDC-ReAct analysis

Identified **90** antibacterials against organisms of public health importance (**66** new active substances)

27 with new targets or new mechanisms of action

15 are systemic

8 against Gram-

2 act on new targets, but none with new mechanisms of action

Source: Freire-Moran, et al. Critical shortage of new antibiotics in development against multidrug-resistant bacteria—Time to react is now. *Drug Resistance Updates* 2011; 14: 118-124. Available at http://www.sciencedirect.com/science/journal/13687646/14/2

Scientific bottlenecks: Upstream science

	HTS to Lead	Lead optimization to Development Candidate (DC)	DC to Ph 1 start	Ph 1 to Ph 2 start	Ph 2 to Ph 3 start	Ph 3 to File	File to Launch
	2yr	3-5yr	1yr	1yr	2yr	2yr	1yr
*Novel Antibacts:	7%	50%	50%	33%	50%	67%	25%
#Industry average (all therapeutic areas)	**80%**	**85%**	69%	**54%**	34%	70%	**91%**
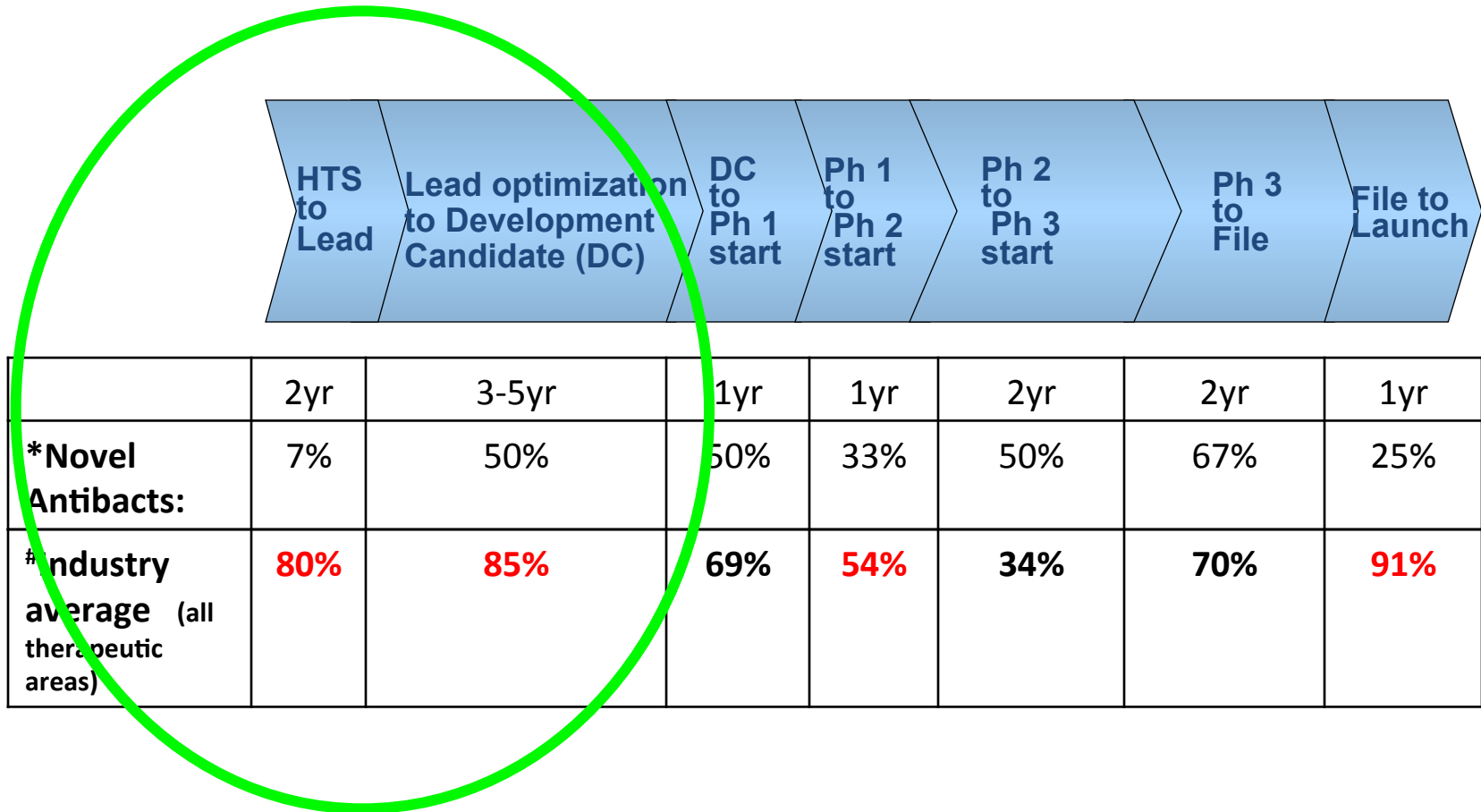
*Hit to Phase 2 starts based on GSK data. Phase 2 and Phase 3 success based on Centers for Medicines Research (CMR) 2003 averages for antibacterials (likely based on agents from established classes). #Paul, et al (2010). Nature Reviews Drug Discovery 9: 203-214.

Financial Bottlenecks:
Net Present Value, by Drug Class

Project therapeutic class	Risk-adjusted NPV x $1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable antibiotic (Gm+)	100
Oral contraceptive	10

Market Life Cycle of a Drug

Return on Investment

R&D Investment

Drug Invention

Market Entry

Generic Entry → Multiple Generic Producers
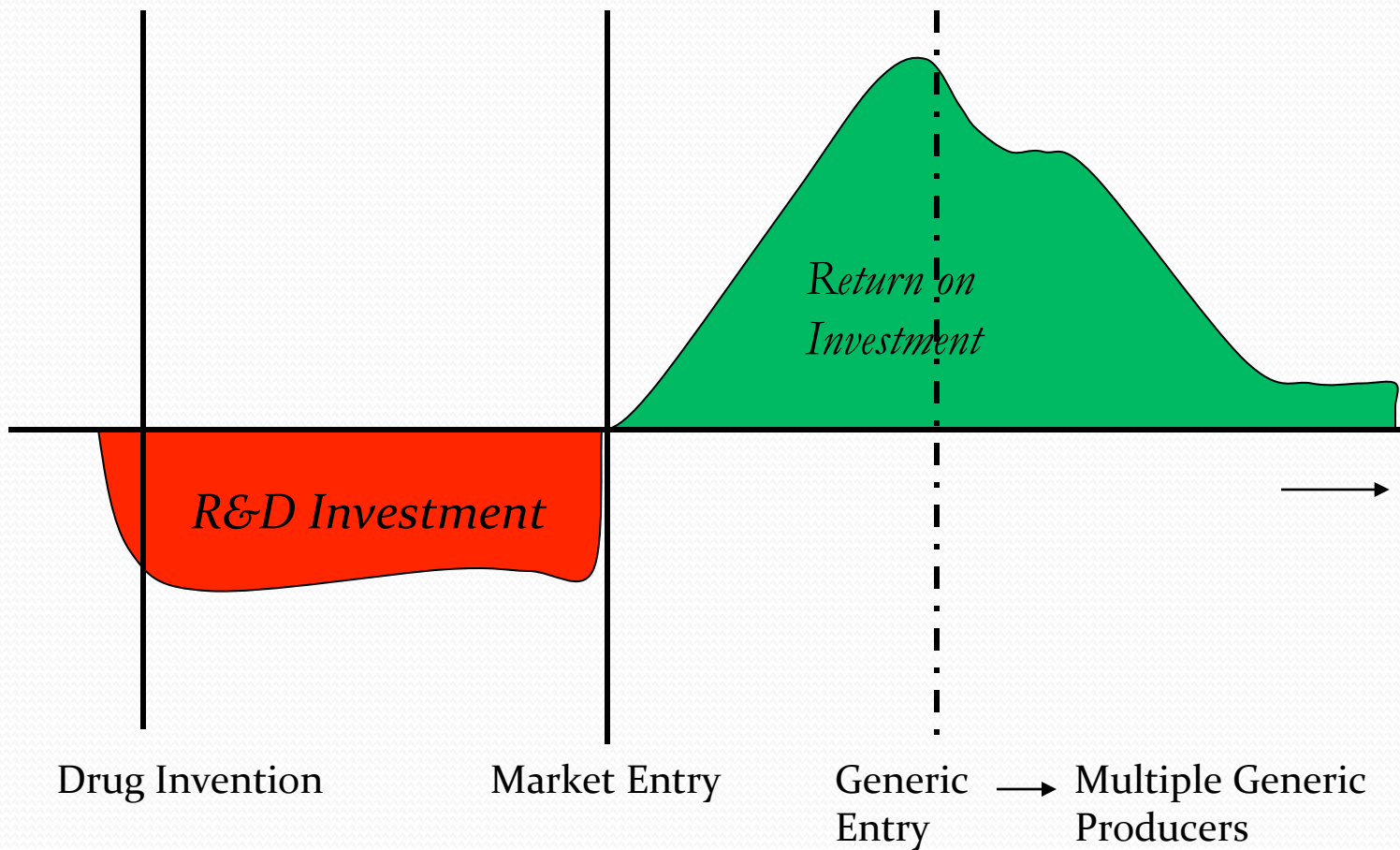
Reengineering the business model

- *Tiering*: Preferential treatment for one segment of the market over another

- *Pooling*: Lowering transaction costs by bringing R&D inputs or outputs together

- *Push*: Decrease R&D Cost

- *Pull*: Ensure return on investment (ROI)

Tiering and the Bottom Billion

Global Burden of Disease by Country Income level, 2008

World Bank Income Level	Trypanosomiasis	Leishmaniasis	Tuberculosis	Lower Respiratory Infections
Non-low income	**13,812 (25%)**	**17,923 (70%)**	**939,424 (70%)**	**2,417,430 (70%)**
Low income	**40,477 (75%)**	**8,057 (30%)**	**402,347 (30%)**	**1,045,864 (30%)**

Strategic Collaboration—What If...We Pooled

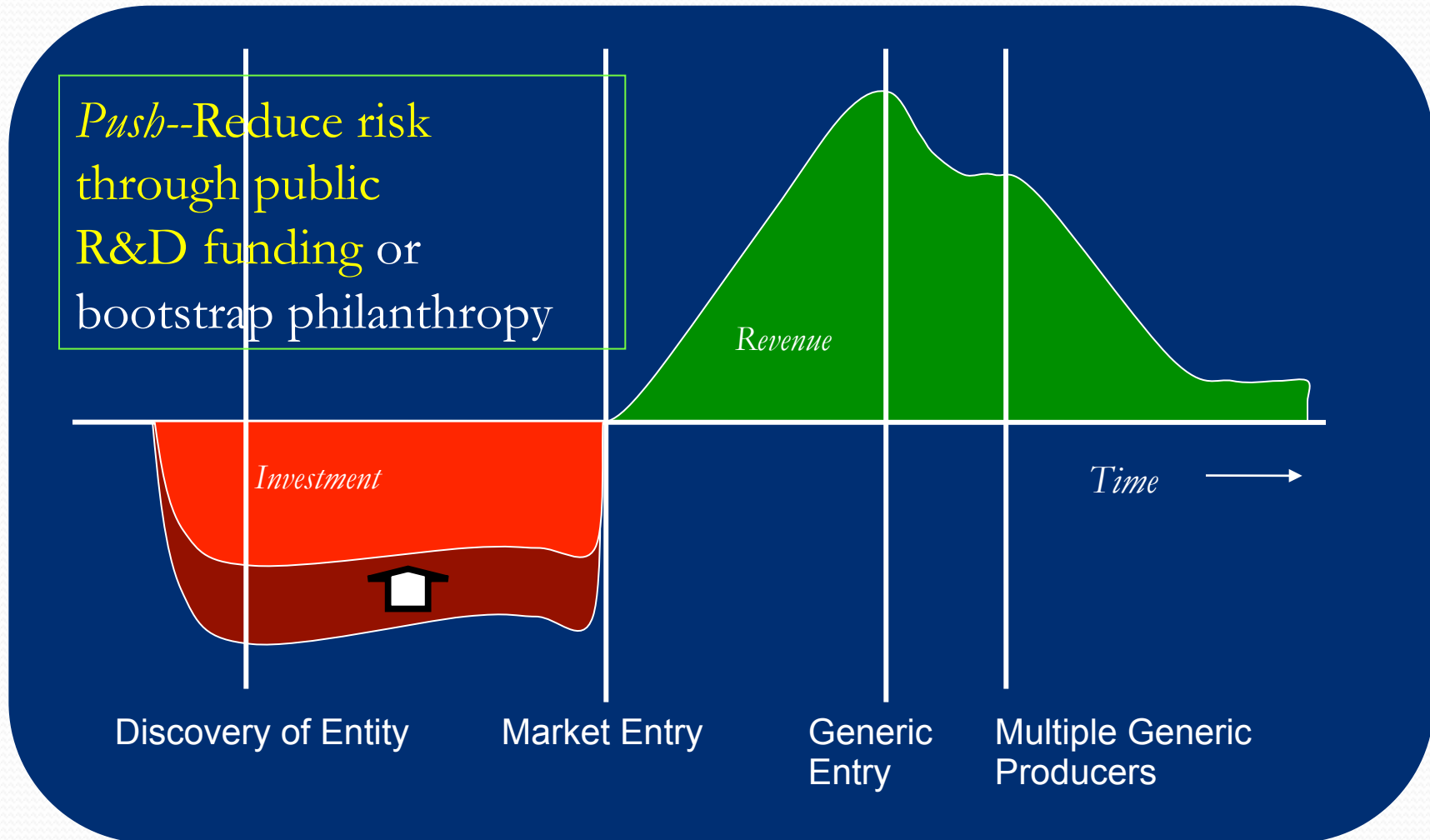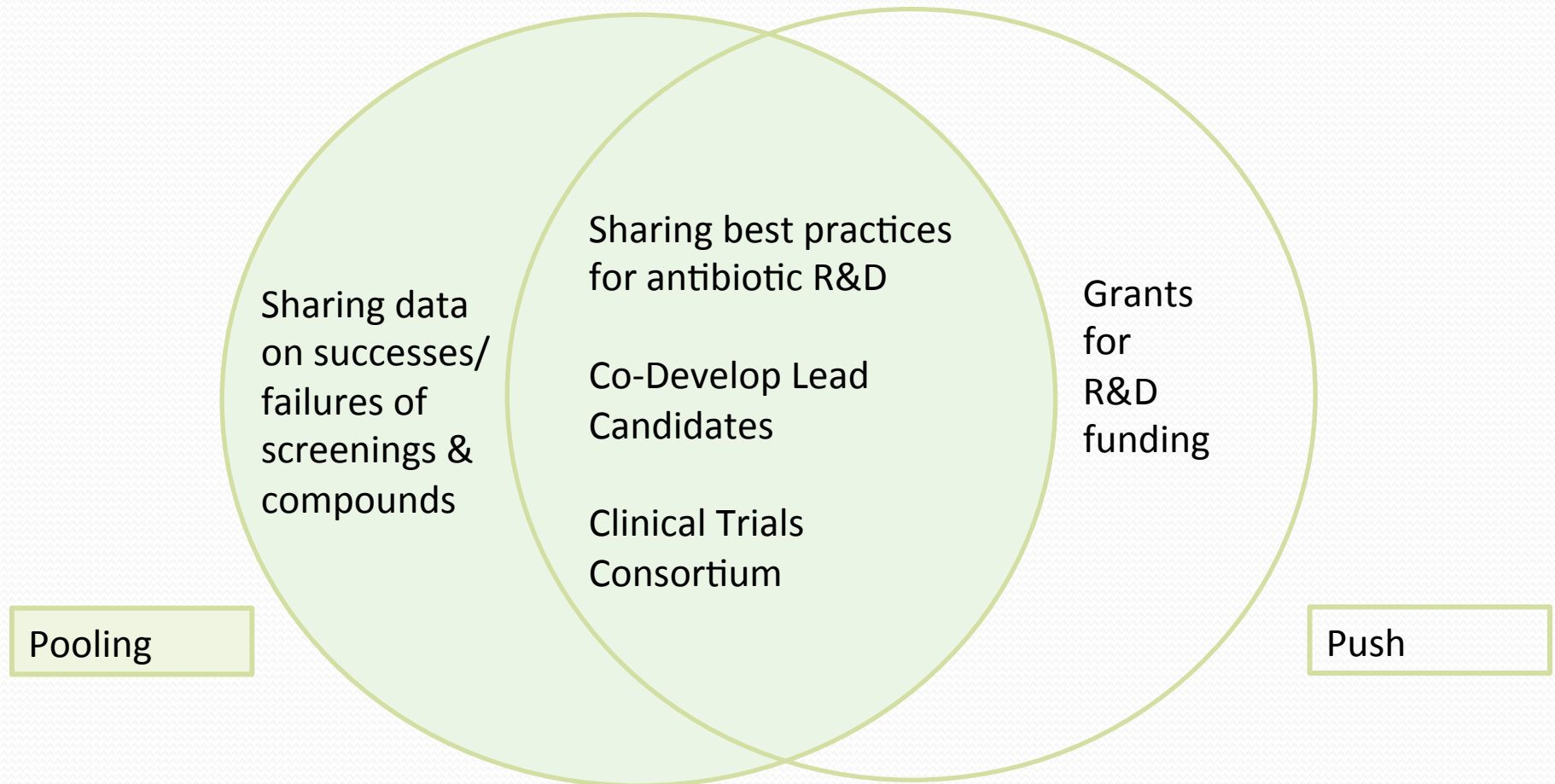| Compound libraries	• GlaxoSmithKline open collection of 13,533 compounds inhibiting malaria for public R&D.
Clinical trial data	• Coalition Against Major Diseases pooled control arms of clinical trials on Alzheimer's disease.
Combination treatments	• Global Alliance for TB Drug Development, Gates Foundation and the Critical Path Institute work to shave years off the regulatory approval of TB combination regimens.

Push – Diminishing R&D Risks

Push--Reduce risk through public R&D funding or bootstrap philanthropy

Revenue

Investment

Time

Discovery of Entity   Market Entry   Generic Entry   Multiple Generic Producers

Pooling and Push: Europe's Innovative Medicines Initiative(IMI)

New Drugs 4 Bad Bugs (ND4BB) Program

Sharing data on successes/ failures of screenings & compounds

Sharing best practices for antibiotic R&D

Co-Develop Lead Candidates

Clinical Trials Consortium

Grants for R&D funding

Pooling

Push

Source: *Based on* Innovative Medicines Initiative Website. Available at: http://www.imi.europa.eu/content/mission (Accessed 02 Jul 2013)

Push - Leveraging Public Sector Investments: Microbial Synthesis of Artemisinin

Gates Foundation

$42.6M →

$10.7M

One World Health (PATH)

$8 M →

UC- Berkeley

License

$12M

Amyris Biotechnologies

Sanofi Aventis
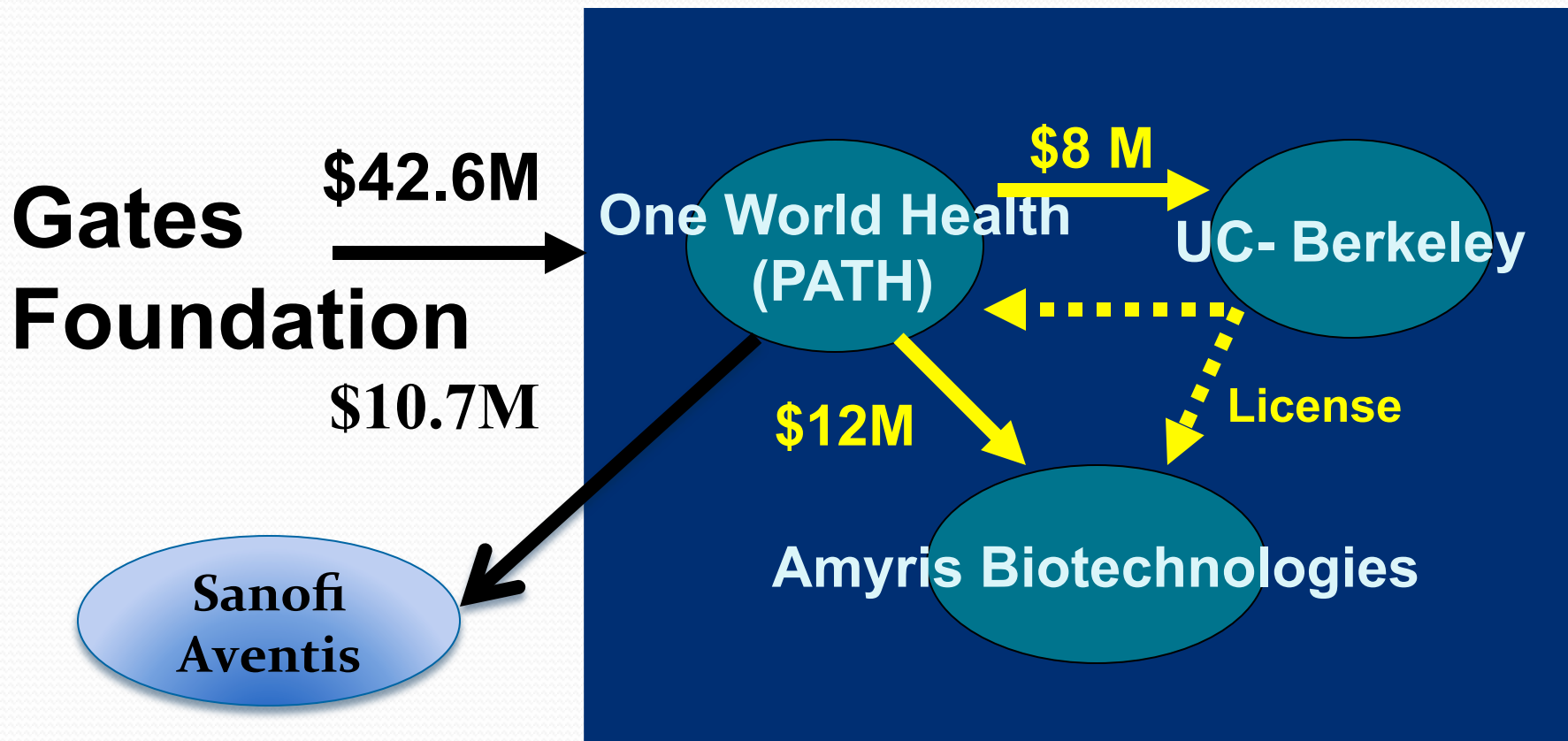
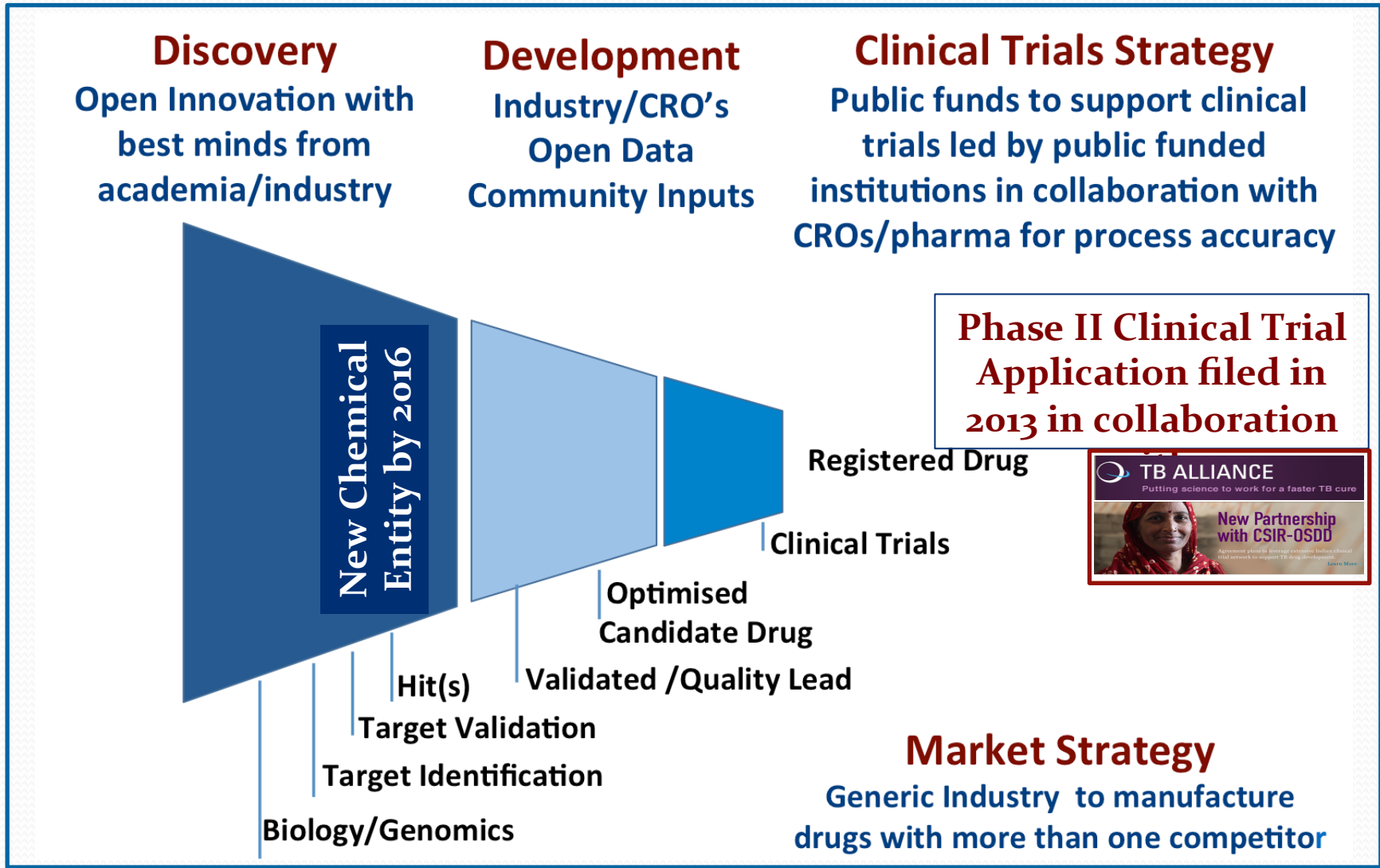# Pull – Reducing Risk of Resource-limited Market
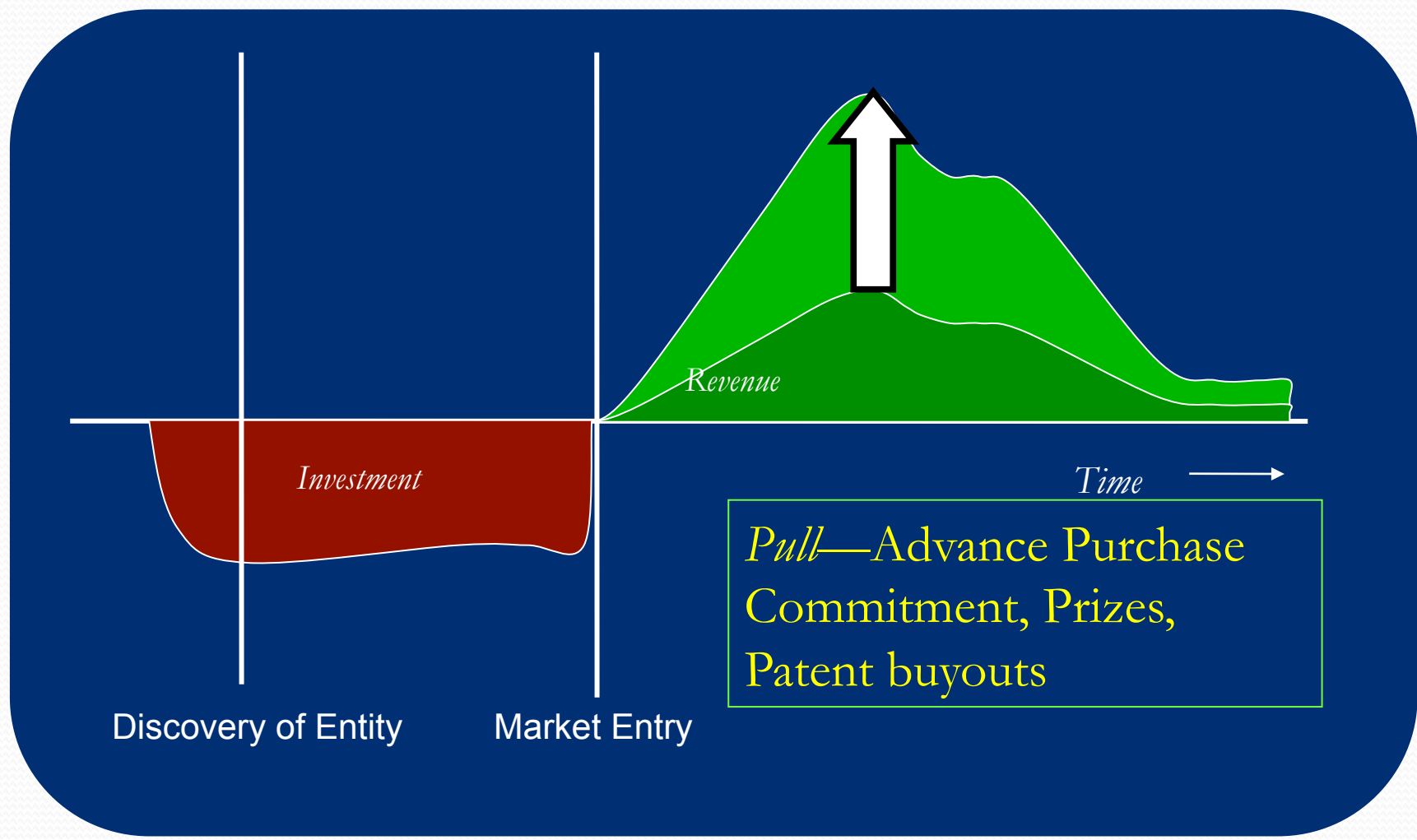
Reengineering R&D Value Chain – The 3Rs
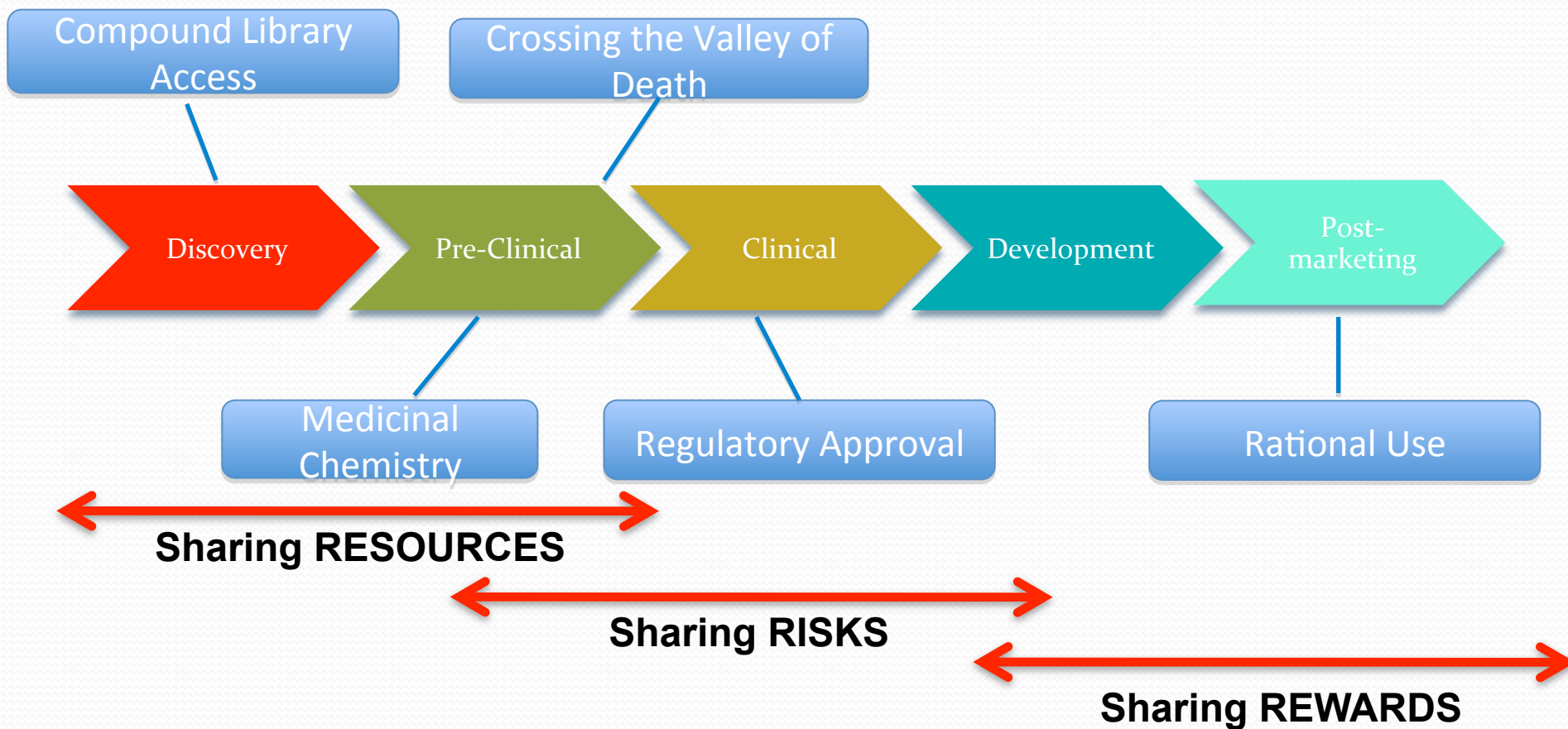
Source: So AD, Ruiz-Esparza Q, Gupta N, Cars O. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards.
British Medical Journal 2012; 344:e1782.
Available at: http://www.bmj.com/content/344/bmj.e1782?ijkey=TXeqN1NcCsPpzC1&keytype=ref

India's Open Source Drug Discovery Initiative: The 3Rs at Work

Discovery
Open Innovation with best minds from academia/industry

Development
Industry/CRO's
Open Data
Community Inputs

Clinical Trials Strategy
Public funds to support clinical trials led by public funded institutions in collaboration with CROs/pharma for process accuracy

Phase II Clinical Trial Application filed in 2013 in collaboration

New Chemical Entity by 2016

Registered Drug

Clinical Trials

Optimised Candidate Drug

Validated /Quality Lead

Hit(s)

Target Validation

Target Identification

Biology/Genomics

TB ALLIANCE
Putting science to work for a faster TB cure
New Partnership with CSIR-OSDD

Market Strategy
Generic Industry to manufacture drugs with more than one competitor

Source: Zakir Thomas, Open Source Drug Discovery Initiative, India's Council on Scientific and Industrial Research, 2013.

Back to the Future
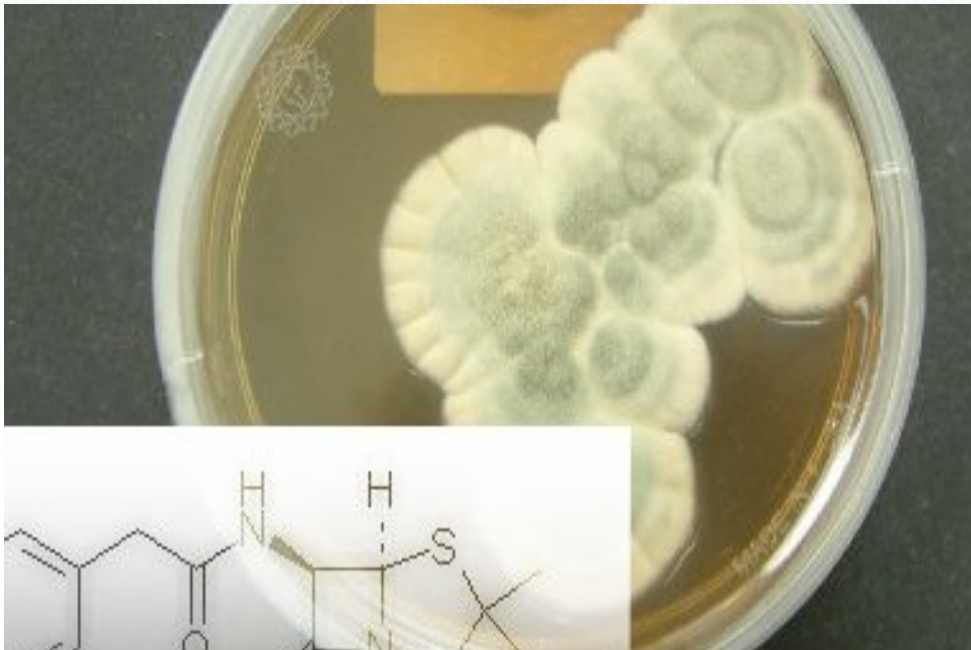
- 1929: Fleming's discovery of penicillin
- 1940: Florey and Chain's crucial experiment
- 1941 on: Committee on Medical Research assists to scale up penicillin production
- 1944: Twenty-one firms produce penicillin