Working Group on Research & Development

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Program on Global Health and Technology Access
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I. Areas for Innovation

R&D across the continuum of care: Vaccines vs. diagnostics vs. drugs

- Method of prioritization
- Tradeoffs and synergy among these areas

- Decrease need for antibacterial use → Vaccines
- Improve the rational use of antibacterials → Diagnostics
- Accelerate the development of new antibacterials → Drugs

Prioritization on anticipated reduction in resistance—can we propose a framework for modeling?

- The incidence of macrolide resistance significantly reduced since the introduction of pneumococcal vaccines in Georgia, US

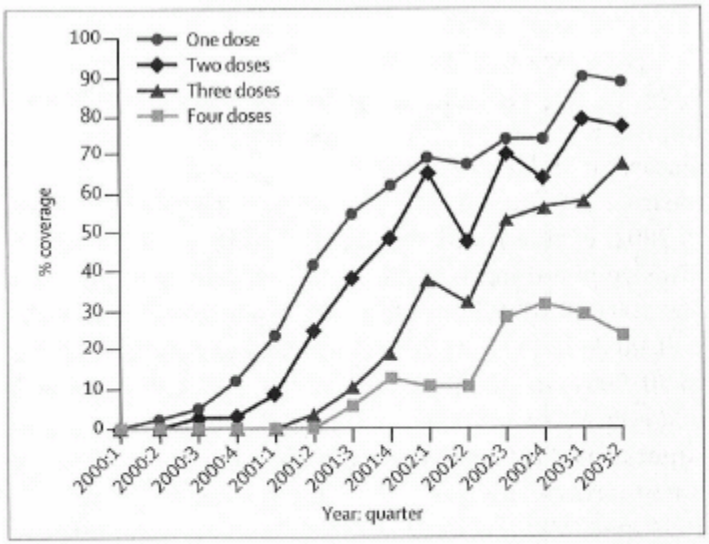
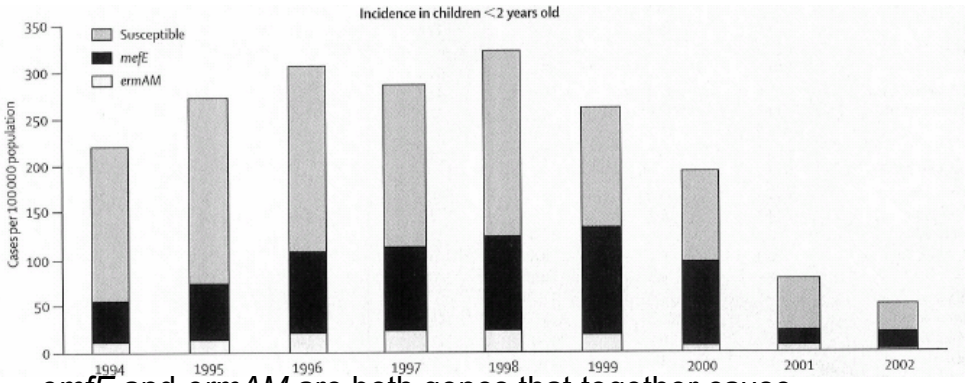


Figure 2: **Pneumococcal conjugate vaccine coverage in Atlanta, 2000–2003**
Percentage of children aged 19–35 months in two central metropolitan Atlanta counties (Fulton and DeKalb) of HD-3 who had received at least one, two, three, or four doses of the vaccine. Data are expressed by quarter of 2000, 2001, 2002, and the first half of 2003.

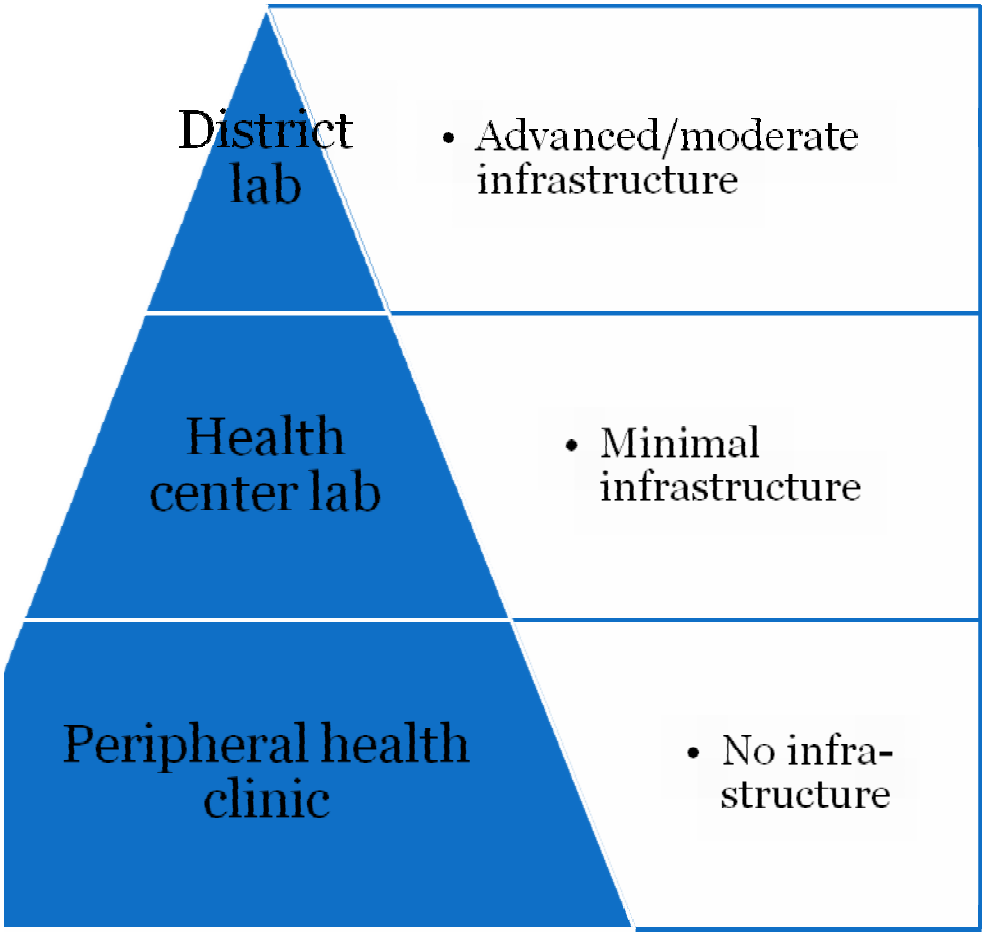


emfE and *ermAM* are both genes that together cause 95%-98% of macrolide resistance in *S. pneumoniae*

Stephens D.S., et al, *Incidence of macrolide resistance in Streptococcus pneumoniae after introduction of the pneumococcal conjugate vaccine: population-based assessmen*t, The Lancet; Mar 5-Mar 11, 2005; 365, 9462

Synergy Among Technologies:

RAND analysis on theoretical diagnostic tools (Nature, 2006)



	ALRI	Malaria
	Measure: unnecessary txs saved	
Perfect test	180,300	153,500,465
Next-to-perfect test	105,200	141,845,100
Perfect test	375,100	427,162,689
Next-to-perfect test	254,200	396,095,397
Perfect test	404.300	528,941,121
Next-to-perfect test	N/A	487,901,105

Note: Perfect tests: Sensitivity-1, Specificity-1
Next-to-perfect tests for ALRI: Sensitivity-0.95, Specificity-0.85
Next-to-perfect tests for malaria: Sensitity-0.95, Specificity-0.95

Source: Hay Burgess, D.C., J. Wasserman, and C.A. Dahl, *Global health diagnostics.* Nature, 2006.

Landscape: Making Use of Old and New

- *Novel therapy:* Mapping of alternative therapies, some derived from traditional folk remedies, and the state of their clinical evaluation, analysis of potential market opportunity

- *Complementary therapy:* Other technologies that would diminish our use of antibiotics, e.g., biofilms that reduce catheter-related infections

- *Combination therapy:* Explore combination therapies that can improve compliance, diminish side effects, and reduce the occurrence of resistance in different pathogens

II. Diagnosing the problem

Identifying Gaps in Therapeutic Access—Antibacterials

- By number of drugs being approved

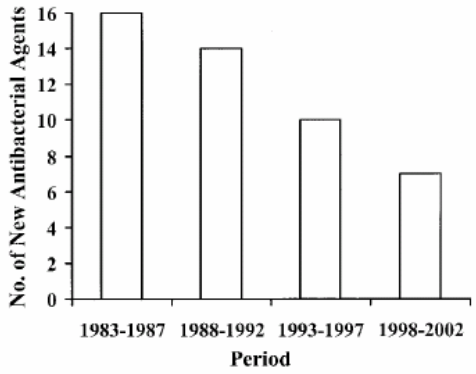


Figure 1. New antibacterial agents approved in the United States, 1983–2002, per 5-year period.

Source: Spellberg B., *Trends in Antimicrobial Drug Development: Implications for the Future*, Clinical Infectious Diseases, 2004; 38:1279-86

- By presence of novel mechanisms

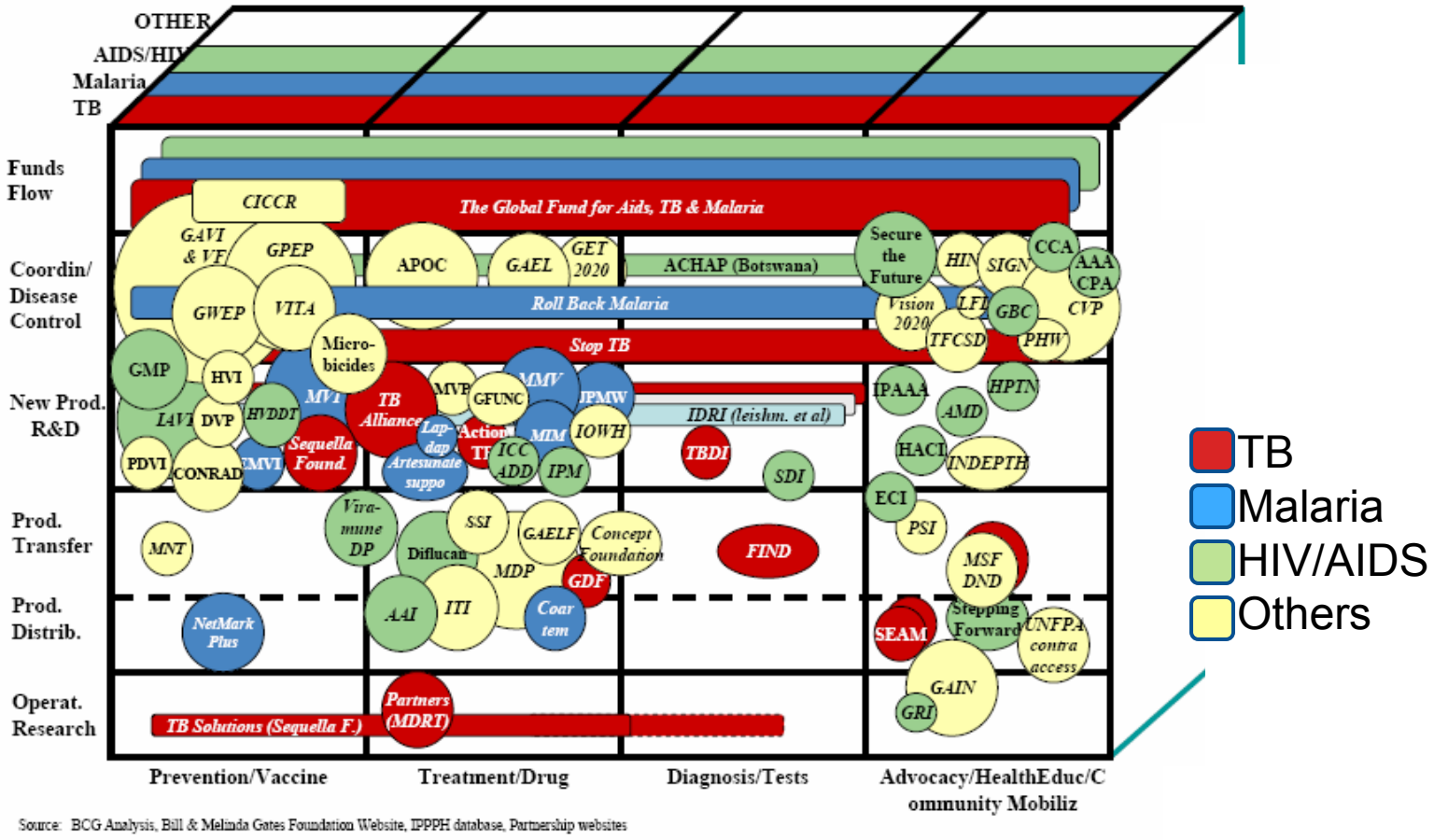
Table 1. New antibacterial agents approved since 1998.

Drug	Year approved	Novel mechanism
Rifapentine	1998	No
Quinupristin/dalfopristin	1999	No[a]
Moxifloxacin	1999	No
Gatifloxacin	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin	2003	No
Daptomycin	2003	Yes

[a] The mechanism of the streptogramins (quinupristin and dalfopristin) is closely related to that of the macrolide/lincosamide families [63].

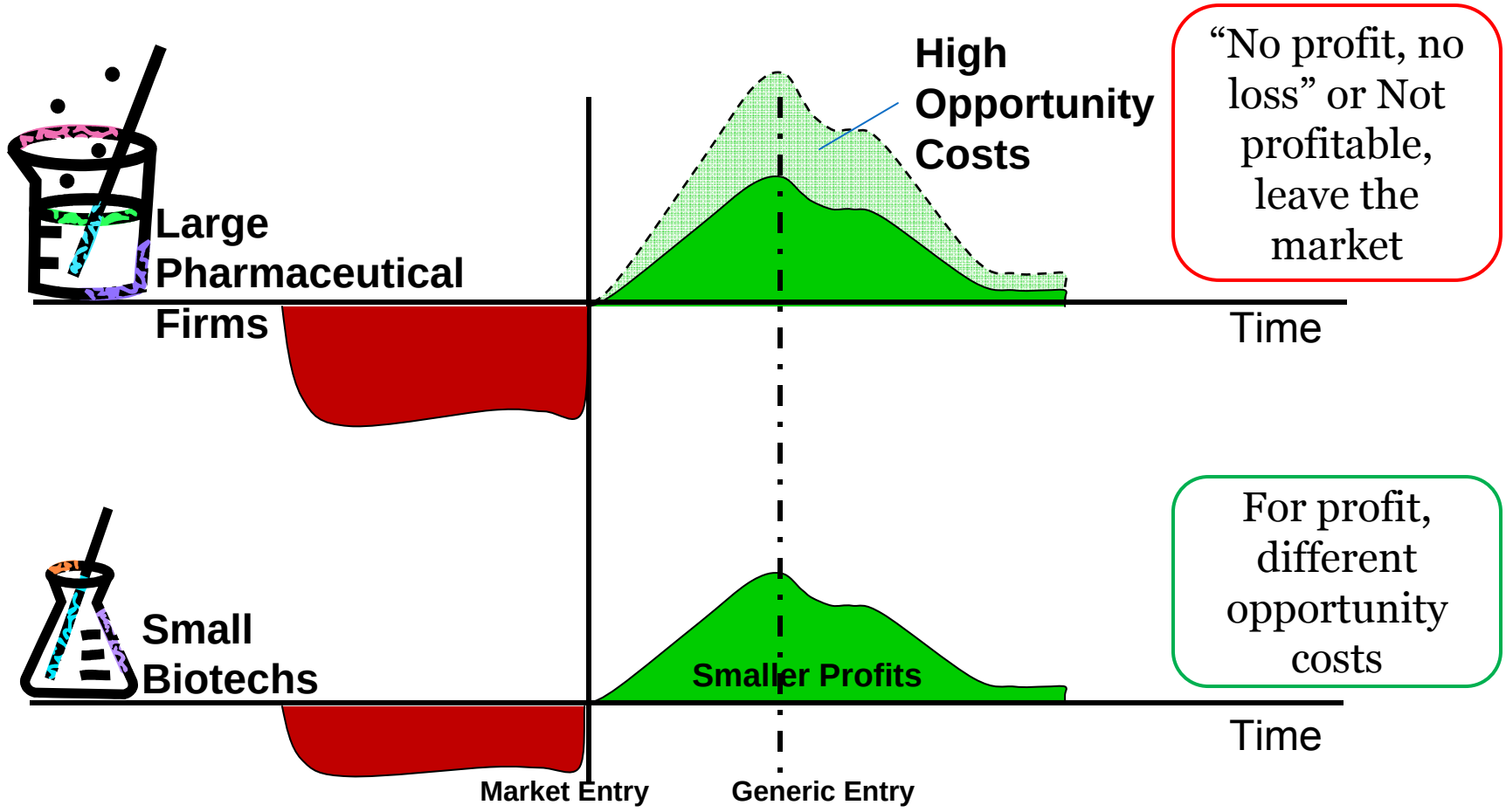
Source: Pray L., *Antibiotic R&D: resolving the paradox between unmet medical need and commercial incentive*, InsightPharma Reports, 2008, p37

Identifying Shortfalls in Funding



Source: BCG Analysis, Bill & Melinda Gates Foundation Website, IPPPH database, Partnership websites

PDPs: Incentives vary among firms



Financial incentives for the industry

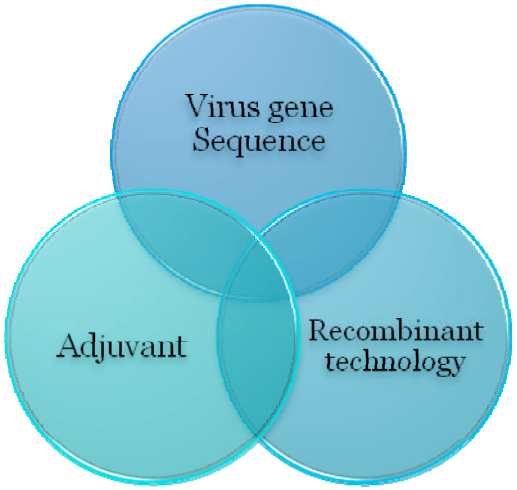
- *Net present value:* Industry's estimates of Net Present Value (NPV) of antibacterials are low (Projan, 2003).

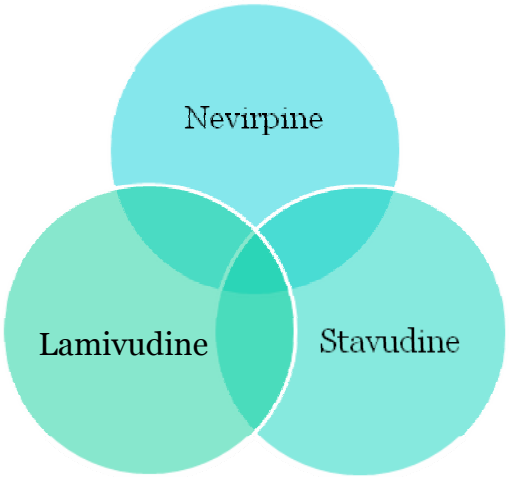
- *Heterogeneity of industry:* Opportunity costs for small and large firms are different. Small firms may see more value in commercializing products in the smaller markets of neglected diseases (Moran, 2005).

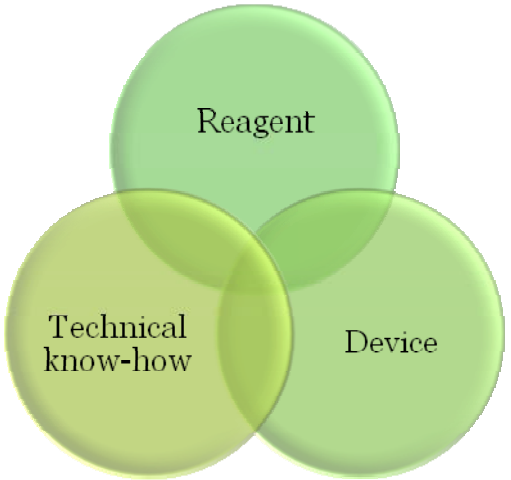
- *Public sector capital.* Strategic use of public and philanthropic funding may be able to leverage additional private sector resources, especially during a period of economic downturn that has dried up venture capital for IPOs.

Intellectual Property issues around health technologies

- Vaccines
- Drugs, eg. Triomune for HIV/AIDS
- Diagnostic tools





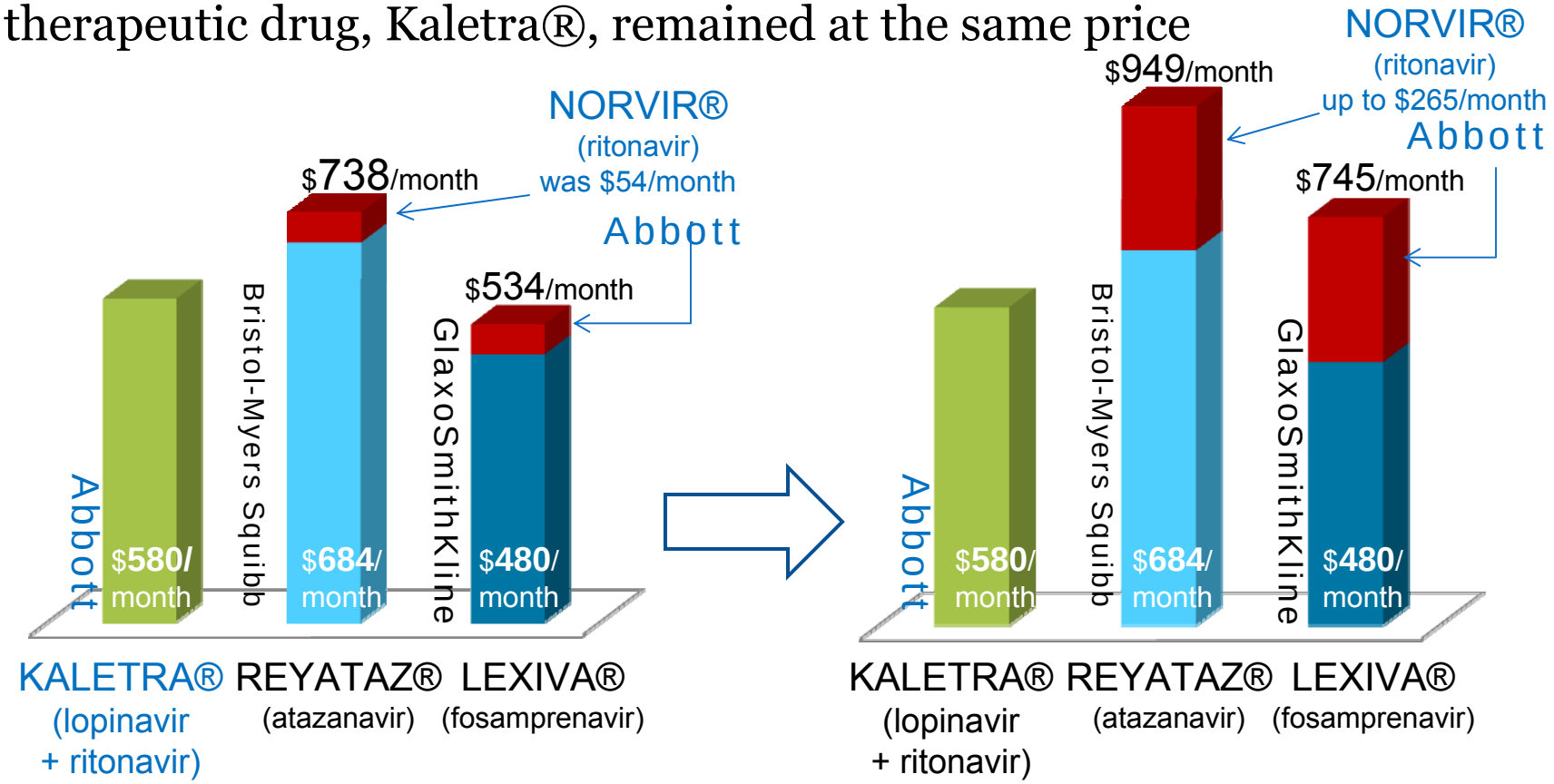


Producer: CIPLA, India

Source: W. Kaplan, *Fixed-dose combination (FDC) drugs availability and use as a global public health necessity: intellectual property and other ilegal ssues,* Background paper for Fixed□dose combinations for HIV/AIDS, tuberculosis, and malaria, WHO, 2003

Affordability: Case Study of Abbott's Norvir®

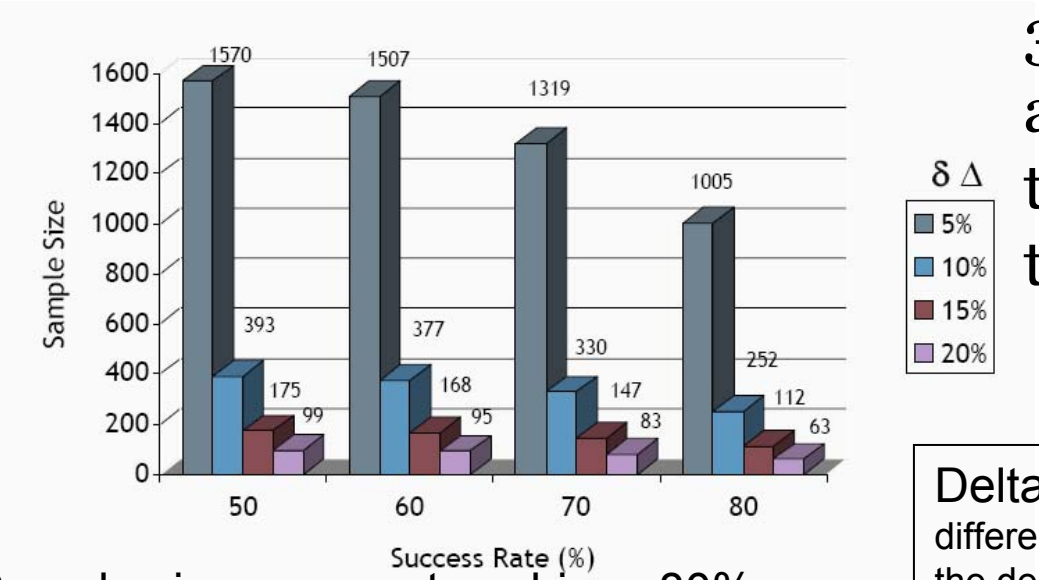
- In December 2003, Abbott increased its price on Norvir® (ritonavir) by 400% (from $54 to $265 per month), while its own combination therapeutic drug, Kaletra®, remained at the same price



Source: Vanessa Fuhrmans, *Abbott Lifts Price of Norvir 400%,* http://www.natap.org/2003/dec/123103_2.htm

Regulatory Issues: Delta and the impact on clinical trial sample size

- In early 2000, both the US and EU agencies changed their requirement on clinical trials to a more stringent 10% delta, which can increase in the costs and time associated with clinical trials
- However, anti-infective drug development enjoys a up to 35% success rate, which is almost four times higher than for any other therapeutic area



Sample size per arm to achieve 80% power

Delta: The largest clinically acceptable difference. For a given success rate, the smaller the delta (δ), the larger the sample size

Source: Mary Foulkes, *Non-Inferiority Specification of δ* (lecture slides), Johns Hopkins Bloomberg School of Public Health, accessed Nov. 2008

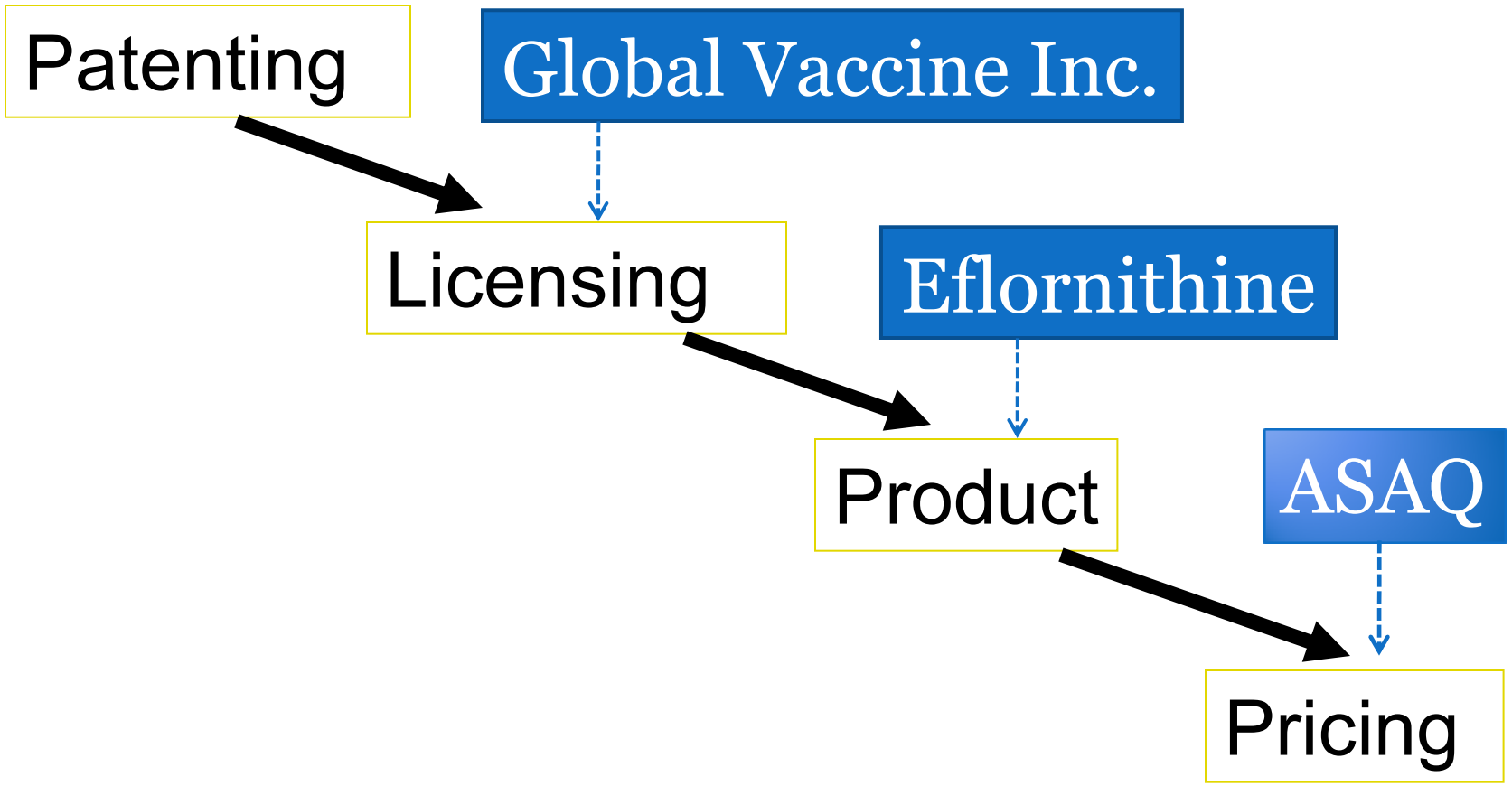
Tensions between broad and narrow indications

- Dilemma for the public: Guarding drug safety vs. Speeding up R&D for essential drugs
  - US FDA requires at least two "pivotal" trials to support registration.
  - Would shortcuts compromise patient safety?
- Dilemma for the industry: Broad spectrum drugs which require greater clinical trial testing vs. Narrow spectrum antibiotics with less market potential
  - How might this tension in the breadth of antibiotic spectrum be resolved?

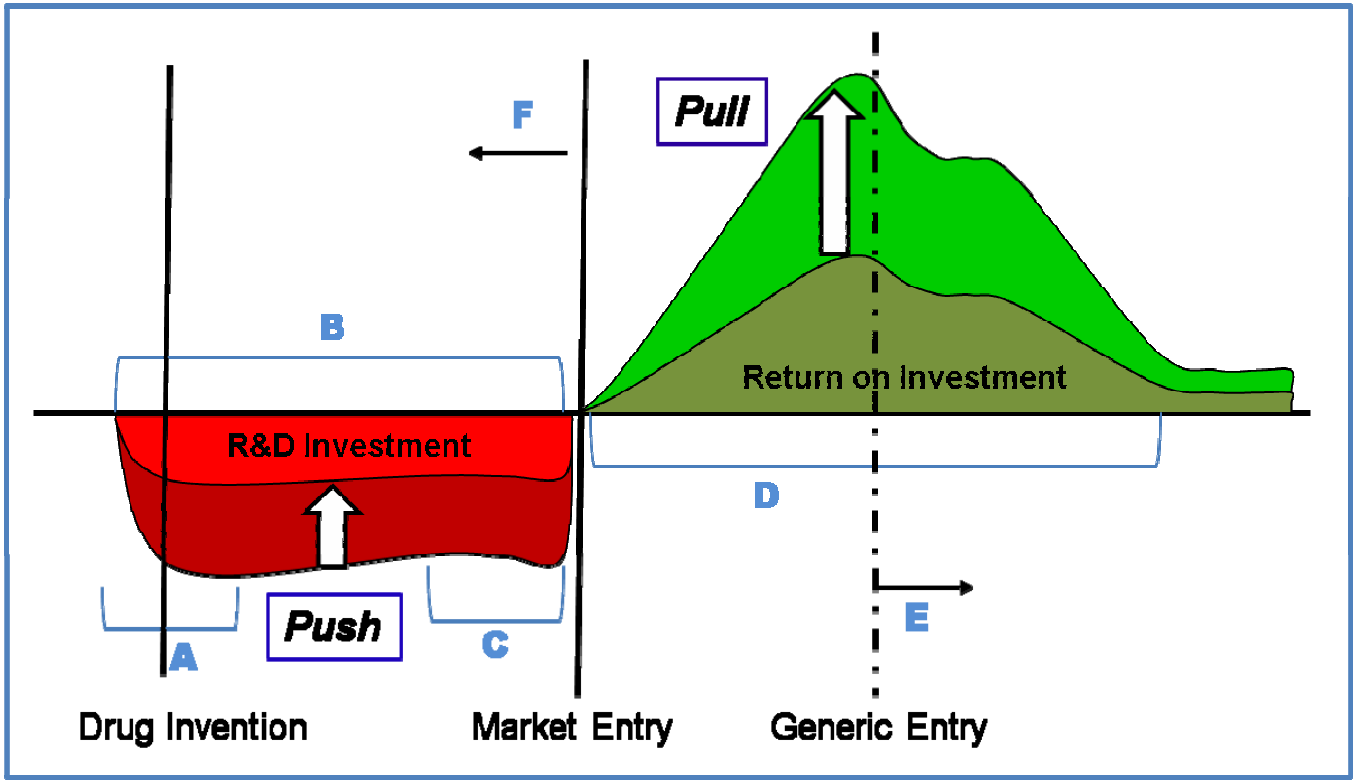
Source: Randall Brenner, Evelyn J Ellis-Grosse & Roger Echols, *Moving Goalposts– regulatory oversight of antibacterial drugs*, Nature Biotechnology, Vol24#12, Dec. 2006

III. Creating an Enabling Environment for R&D

Serendipity of Dual Markets



Push and Pull Incentives for Innovation



A: Bootstrap philanthropy

B: R&D Tax Credits

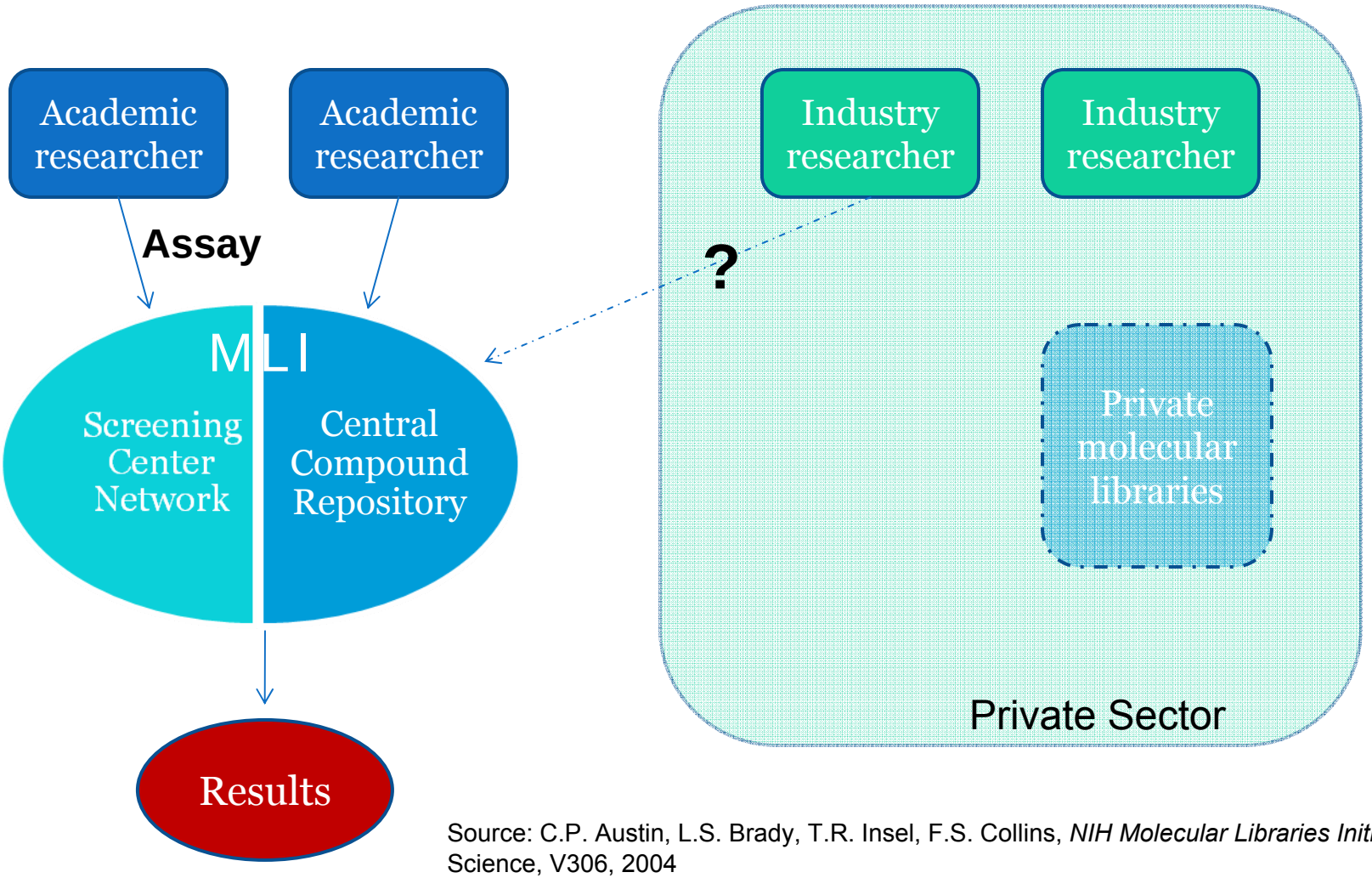
C: Public financing of clinical trials

D: Prizes

E: Wildcard patent exclusivity

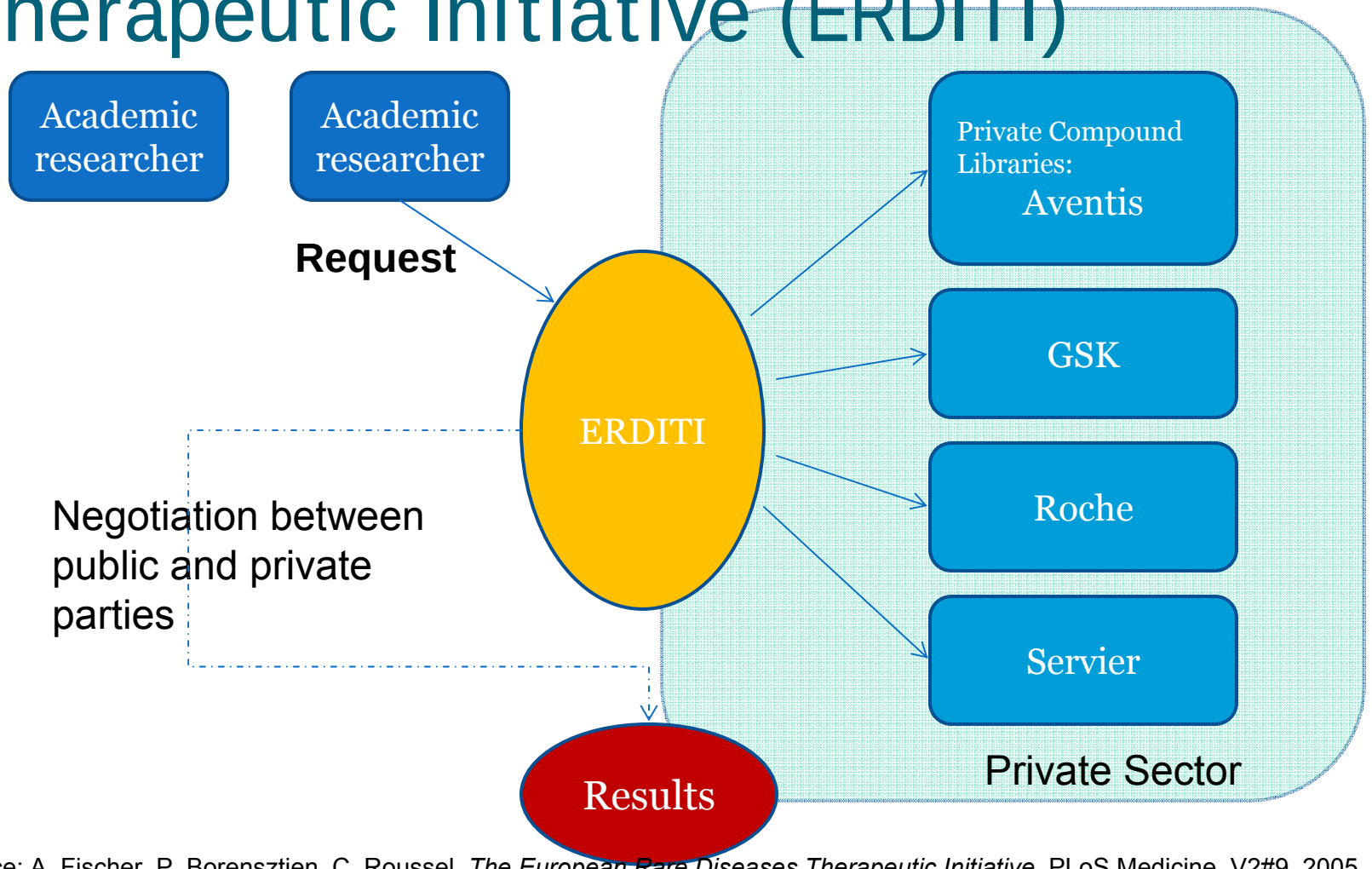
F: Priority review vouchers

Opportunities for Pooling:
Molecular Libraries Initiatives (MLI), US NIH



Source: C.P. Austin, L.S. Brady, T.R. Insel, F.S. Collins, *NIH Molecular Libraries Initiative*, Science, V306, 2004

Opportunities for Pooling: The European Rare Diseases Therapeutic Initiative (ERDITI)



Source: A. Fischer, P. Borensztien, C. Roussel, *The European Rare Diseases Therapeutic Initiative,* PLoS Medicine, V2#9, 2005

Proposed Framework for Discussion

- Technology Areas
  - Priority setting: By technology (Vaccines vs. Drugs vs. Diagnostics) and by disease area
  - Synergy among technologies
  - New, old (combinations) and complementary
- Diagnosing the Problem
  - Pipeline and funding shortfalls
  - Realigning financial incentives
  - Regulatory issues
  - Double bottom line of affordability, but rational use
- Creating an enabling environment for R&D
  - Dual Markets, Push and Pull, Pooling

Proposed Framework for Discussion: Some potential linkages

- *Surveillance:* Using diagnostic technology strategically to track resistance
- *Rational Drug Use:* Leveraging the use of diagnostics and vaccines to reduce unnecessary antimicrobial drug use
- *Infection Control:* Applying use of other technologies to improve infection control (e.g., biofilms)
- *Animal husbandry*: Considering how diagnostic technology might alert the public and policymakers of spread of resistance

Global Patient Safety Challenge III: Potential R&D Entry Points

- Time horizon: distance from benchtop to bedside, success through surrogate measures
- Different pathways
  - PDP
  - Technology in service of another topic area (e.g., diagnostic for rational use or as sentinel in food supply chain)
  - Alternative innovation approach
  - Realignment of financial incentives