Financing Innovation for Antibiotics

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Introduction

- Antibiotics are fundamental for modern medicine
- But antimicrobial resistance (AMR) became one of the major urgent threats to public health
- Recent estimates attribute to AMR more than 33 000 deaths in the EU in 2015 (Cassini et al., 2019), and 1.27 million deaths globally in 2019 (Murray et al., 2022), and this is growing
- While need of new antibio therapies is growing, little innovation has been observed over last decades and pipeline of AMR related clinical trials is very weak

Introduction

Incentives for innovation provided by intellectual property protection work for other medicines

But AMR market seems to suffer from a **market failure**:

- Stewardship policies to slow down resistance leads to low quantities
- Hard to get high prices (risk of overuse too large)
- Externalities across countries

$\rightarrow$ this results in limited commercial attractiveness and provides poor value for developers and investors

How to solve the market failure?

- Reward for innovation needs to be large enough
- Development cost in the order of several billions €
- Standard patent exclusivity protection unlikely to provide large enough prices or large enough quantities
- Solutions entail :
  - either **delinking** revenue from sales volume
  - or **conditioning** treatments to diagnostic tests to control quantities and guarantee large prices

How to solve the market failure?

- Patents confer monopoly power over a fixed duration, during which innovator can (try to) recoup their investment, but may not guarantee a business model
- Small number of patients (orphan diseases), limited ability to pay (drugs for LDCs), and externalities (antibiotics, vaccines) may create a wedge between social and private values of innovation

$\rightarrow$ Alternative approaches with granting **cash prizes** or **advanced market commitments** (Michael Kremer and coauthors)

How to solve the market failure?

- But the large development cost requires some multilateral approach
- Cash prizes achieve delinking but multilateral contributions requirement is subject to **international free riding**
- Classic public good underinvestment (climate change)
- Policy responses have up to now been insufficient

Policy proposals

- **Push incentives**: Global AMR action fund
- **Pull incentives**:
  - US GAIN Act in 2012 (additional exclusivity period for Qualified Infectious Diseases Products)
  - European Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI) proposal
  - UK subscription pilot model (fixed revenue independent of quantity) would need to be adopted more widely
- Lack of new-antibiotics pipeline impending bacteriological pandemics raises concerns about current push and pull mechanisms weakness

Policy proposals

- **Transferable Exclusivity Extensions** or **Vouchers**
- Inventor given a patent extension right of given duration
- This right is tradable: can be used directly or sold to entity willing to extend an exclusivity period
- 2018 US REVAMP Act planned TEEs for priority antimicrobials
- TEE scheme to support antimicrobial innovation is currently under consideration in Europe (Revision of EU General Pharmaceuticals Regulation)
- Dubois, Moisson, Tirole (2023) provide an economic analysis of such mechanism

Philosophy of Vouchers

- What vouchers attempt to do
  - Solve the free-riding problem: Each country (if all-inclusive European scheme) must pay in this new currency. European Medicine Agency can delay approval of generics (and translate timing of data protection accordingly)
  - Voucher presumably will be sold to pharma with most profitable blockbuster
  - No free lunch: no upfront cash payment but a cost in terms of market power (borne by consumers, insurance companies, social security system, taxpayers, depending on the country)
- Is this alternative "currency" socially more or less costly than a cash payment?

What Vouchers do not do

- Like prizes, build on set reward for innovation
- Any pull scheme requires a Target Product Profile and a measure of the medical benefit
- Vouchers, like subscription model, agnostic as to whether the associated incentive is commensurate with what is needed to encourage innovation (whether social surplus loss on patent protection (or cash transfer) compare with the social surplus generated by new antibiotic)

Model overview

- Assume that inventor's reward has been set (at right or wrong level). Question: paid in which currency?
- Cost-over-reward ratio captures \$-worth social surplus loss for \$1 of additional benefit to inventor awarded TEE
- To be compared with cost-over-reward ratio of cash prize, $1 + \lambda$, where $\lambda \geq 0$ is marginal cost of public funds
- Not straightforward because after exclusivity, markets are not perfectly competitive

Cost over reward ratio

- Cost-over-reward ratio for a single country

$$\rho = \frac{S_{NE} - S_E}{\pi_E - \pi_{NE}}$$

- TEE preferred to prize if and only if $\rho \leq 1 + \lambda$, with λ cost of public funds.
- If generics were competitive, a reward of 1 € would imply a loss of consumer surplus greater than 1 €
- But empirical estimates show that an incentive reward of 1 € through a European voucher system would cost less to the consumer than 1 € (a fortiori less than social cost of 1 € cash award) in most European countries

Cost over reward ratio (union of countries)

- Cost-over-reward ratio for a union of countries
- In case of a cash transfer, assume the contribution of each country is proportional to country's income
- It is possible that countries do not favor a national TEE over a cash transfer but do prefer a union-wide TEE or the reverse
- Empirical analysis finds that for most countries a voucher is economically more efficient than a cash transfer to pay for innovation (which suffers from free riding problem anyway)
- Why can a voucher fund innovation at a lower cost than a cash payment?

A Simple Example

- On-patent drug sold at 1,000 € a dose, marginal cost of 100 €
- Demand of 100,000 doses per year
- Firm profit 90 millions, total insuree cost 100 millions

After exclusivity, generics enter and get, say, 50% market share

- Generic and branded prices at 400 €
- Total insuree cost: 40 millions instead of 100 millions
- Firms profit: 15 millions for generic and 15 millions for branded
- Branded company willing to pay 75 millions to get one year exclusivity extension while insuree lose 60 millions from extension
- Thus, with a cost to society of 60 millions, the branded company pays 75 millions for the voucher!

Empirical analysis overview

Empirical analysis:

- Use dataset of all drugs sold in 15 European countries over 2002-2012
- Compute estimates of cost-over-reward ratios of TEEs in each country, as well as in union composed of 15 countries in data
- *Findings:* Among 15 countries,
  - Country-level: all would prefer TEE scheme to cash prize,
  - Union-wide: 12 countries would prefer TEE scheme, 1 close to indifferent, while 2 prefer cash prize

Some theoretical results

Cost-over-reward ratio of TEE (ρ)

- weakly decreases with share of captive brand users
- exceeds 1 if and only if p_g sufficiently close to marginal cost c

Country i tends to prefer a (union-wide) TEE to a cash transfer if

- it spends relatively little on the on-patent branded drug with respect to its relative economic "weight" in union (share of union GDP)
- it has high generics prices (e.g. low competition among generics)

Empirics

- IQVIA sales data of prescription drugs in 15 European countries (Austria, Belgium, Finland, France, Germany, Greece, Ireland, Italy, Norway, Poland, Portugal, Spain, Sweden, Switzerland, UK) over 2002-2012

- Marginal cost?
  - Lower bound (0) reasonable for our sample (2002-2012) as very few drugs were biosimilars
  - Upper bound: for drug j, lowest price across countries i and dates t (reached only if very tough regulator in sample).

  Focus on upper bound: conservative estimate of cost-over-reward ratios ρ_j.

- Share of captives (measured) (1/4 to 1/2).

(One-year) TEE values

Year	$\bar{V}_t^1$	$\bar{V}_t^2$	$\bar{V}_t^3$	$\bar{V}_t^4$	$\bar{V}_t^5$
2002	PLAVIX (2008)	ZOCOR (2002)	LIPITOR (2011)	NORVASC (2003)	PANTOZOL (2008)
	468,221	463,005	459,136	348,136	285,430
2003	PLAVIX (2008)	LIPITOR (2011)	NORVASC (2003)	PANTOZOL (2008)	ZYPREXA (2010)
	482,702	473,337	358,904	294,257	280,059
2004	PLAVIX (2008)	LIPITOR (2011)	PANTOZOL (2008)	ZYPREXA (2010)	SEROQUEL (2011)
	497,631	487,976	303,358	288,720	280,623
2005	PLAVIX (2008)	LIPITOR (2011)	PANTOZOL (2008)	ZYPREXA (2010)	SEROQUEL (2011)
	513,021	503,068	312,740	297,650	289,302
2006	PLAVIX (2008)	LIPITOR (2011)	PANTOZOL (2008)	ZYPREXA (2010)	SEROQUEL (2011)
	528,888	518,627	322,413	306,855	298,250
2007	PLAVIX (2008)	LIPITOR (2011)	PANTOZOL (2008)	ZYPREXA (2010)	SEROQUEL (2011)
	545,245	534,667	332,384	316,346	307,474
2008	PLAVIX (2008)	LIPITOR (2011)	PANTOZOL (2008)	ZYPREXA (2010)	SEROQUEL (2011)
	562,109	551,203	342,664	326,130	316,984
2009	LIPITOR (2011)	ZYPREXA (2010)	SEROQUEL (2011)	NEXIUM (2010)	TAXOTERE (2010)
	568,250	336,216	326,787	295,677	287,107
2010	LIPITOR (2011)	ZYPREXA (2010)	SEROQUEL (2011)	NEXIUM (2010)	TAXOTERE (2010)
	585,825	346,615	336,894	304,821	295,986
2011	LIPITOR (2011)	SEROQUEL (2011)	ZOMETA (2012)	SINGULAIR (2012)	VIAGRA (2012)
	603,943	347,313	149,702	147,214	128,432

Calibration

- *Measured:* quantities D_{ijt} and prices p_{ijt}, and thus fraction of captives x_{ij} (approx.), marginal cost c_{ij} (approx.), maximum WTP m_i (approx.)
- *Estimated:* scale of demand σ_i, curvature of demand k_i, marginal utility of income γ_i, regulator bargaining power α_i
- National TEE preferred to cash prize if

$$\rho_i \leq 1 + \lambda_i$$

- Country i favors a *union-wide* TEE over cash transfer iff

$$\rho_i^U \leq \frac{y_i}{\sum_{i'} y_{i'}}(1 + \lambda_i).$$

- Standard estimations of $1 + \lambda_i$: $[1.3, 1.5]$

Cost-over-reward ratios: national and union-wide

Country	ρ_i	$\rho_i^U \Big/ \frac{y_i}{\sum_{i'} y_{i'}}$
AUSTRIA	0.71	0.33
BELGIUM	0.84	1.31
FINLAND	0.44	1.36
FRANCE	0.78	1.09
GERMANY	0.64	0.59
GREECE	0.92	0.83
IRELAND	0.67	0.80
ITALY	0.85	0.46
NORWAY	0.96	0.36
POLAND	0.74	0.28
PORTUGAL	0.62	1.09
SPAIN	0.74	1.04
SWEDEN	1.00	1.80
SWITZERLAND	0.63	0.49
UK	0.73	0.64

Empirical results

- Results *suggests* that among 15 countries, 12 would quite unambiguously prefer a (union-wide) TEE scheme to (union-wide) cash transfer
- With higher estimates of marginal costs of public funds (in literature), all countries but one prefer TEEs over cash transfers.
- *Intuition:* From country-wide to union-wide,
  - Austria, Norway and Poland have a much lower share of (union) pharma expenses than share of (union) GDP.
  - Belgium, Finland, Portugal and Sweden are more "generous" on healthcare.

Conclusion

First economic analysis of TEE mechanism

- Provide a conceptual framework to study TEEs and provide estimates of their impacts
- TEE (surprisingly) seem better than cash prizes for a majority of countries in our sample

Pending questions:

- But, market power and strategic intertemporal bidding in the vouchers market may increase the cost-over-reward ratio
- Empirical estimates robustness? (in progress)