R&D Incentives for Neglected Diseases

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Motivation

- In 2007-8 I was asked to act as economic advisor of a newly founded Innovation Park for Life Sciences located in Siena

- The «Toscana Life Sciences» (TLS) Park www.toscanalifesciences.org

- TLS was supported by Local and Regional authorities, a major Bank and Foundation, the five Universities located in Tuscany.

Motivation

- The TLS Park had two main missions:
- 1) Incubate «innovative» start up firms operating in the life sciences (vaccines, drugs, diagnostis, bioinformatics etc.)
- 2) Support research groups working on rare and neglected diseases
- As economic advisor of TLS I was asked to investigate some of the main economic issues concerning such diseases.
- This is how I first became involved in the topic.

Motivation

- My work mostly concerned R&D investments and economic incentives for neglected diseases.

- The presentation, partly based on my papers, will try to offer a broad perspective on the issue.

Introduction

- Neglected Diseases (NDs) is a wide class of diseases sharing a common feature

- They lack potential market revenues, and so pharmaceutical companies are reluctant to invest in R&D to develop new, or better, treatments.

- The reason why market potential is missing differs between the following two main categories of NDs.

- RARE DISEASES (RDs)

- INFECTIOUS AND TROPICAL DISEASES (ITDs)

Introduction

- *Rare Diseases*, by definition (each of them) affect a small portion of the population. Hence, market potential may be weak because of too few cases to treat. There could also be difficulties to find enough patients for clinical trials (quantity problem)

- *Infectious and Tropical Diseases* lack market potential because they mostly affect a (large) number of individuals living in developing countries, who are too poor to afford paying for treatment (price problem)

- Hence, profit seeking big pharmas would typically not find it convenient to invest in risky and expensive R&D initiatives with very low, or no, revenues to expect.

- For this reason, in recent years a concern by public and private institutions, both at national and inter(supra)national level, mounted on how to provide treatment for those affected by NDs

Introduction

- The challenge was tackled in a variety of ways, with a range of organizational forms and types of incentives, differing between RDs and ITDs and across geographical areas.

- As for RDs the main instrument in US, EU etc. was legislative. The so called «Orphan Drugs» Legislation (US 1983, Japan 1993, Australia 1998, EU 2000) in this case acted as an economic incentive, driver, for pharmaceutical firms to invest in R&D for RDs.

- For ITPs initiatives were mixed. Some of them are also included in the Orphan Drugs Legislations but, at the same time, Public-Private-Partnerships (PPP) developed since the early 2000s to fight specific diseases. Moreover, the mechanism of «Priority Review Vouchers» was suggested in (2006), enacted as a Law in the US (2007), and recently proposed also for Europe (2010)

Rare Diseases

- Considering the medical literature, population of reference, and national health programs the (*prevalence*) ratio $\frac{patients}{population}$, defining RD, can vary within the range of $\frac{1}{1000}$ and $\frac{1}{200.000}$

- The prevalence criterion is typically accompanied by the request that a disease should be life threatening or chronically debilitating.

- The European Organization for RDs (EURORDIS) estimates a number of RDs in between 5000 and 7000, 80% of which due to genetics.

- About 350 mln people world wide are affected by RDs. (circa 30 mln in EU and 25 mln in North America)

- The «paradox of rarity» is illustrated by the ratio $\frac{350.000.000}{7.000} = 50.000$. That is, a single disease may affect a limited number of people in the world, but altogether numbers are very large (about 5% of world population)

Rare Diseases

- With the increase in R&D costs (almost 1$bln) to develop a new drug, due also to more rigid regulation, profit seeking companies did not find it profitable to invest in R&D for such diseases, with low perspective revenues.

- Hence, how was the issue of treating RDs tackled?

- Introducing *economic incentives* for companies to invest in R&D through the «Orphan Drug» Legislations (ODLs)

- With some variations among countries, main cornestones of ODLs are:

  i) market exclusivity for a number of years after approval (independent of patent status)
  ii) tax incentives on (parts of) R&D investments (US)
  iii) fast-track approval and free support to filing

Rare Diseases

- Both in the US ad EU the ODL was considered successful, leading to a meaningful number of new marketed drugs treating Orphan Diseases.

- Much remains to be done to meet patients needs, though a lot has been achieved already.

- But what kind of *economic incentives* are the ones in ODLs and why were they apparently so successful? Push or pull incentives?

- It is a mixture of measures. Not a single, simple, explanation. We now briefly discuss each of them

Rare Diseases

- ***Market Exclusivity*** is a form of so called «*pull incentive*», that is financial resources accruing to the firm upon successful registration.

- Lenghtening exclusivity provides a stronger monopolistic position that could go beyond the one guaranteed by patents.

- A longer monopoly period enhances perspective revenues, hence expected profitability from R&D investments.

- Since Orphan Drugs are typically very expensive (for the price to compensate for low quantity) certainty of *reimbursement* by healh care providers is also very important, otherwise sales would suffer, and R&D costs could not be recovered.

Rare Diseases

- **Tax-Credits (US)** subsidy, cost reduction, based on R&D expenditures. Once the Orphan Drugs designation has been awarded firms can deduce from tax a given % of the R&D expenses. This amounts to subsidizing and reduces costs.

- Tax-credits are not conditional on successful discovery, and in this sense they act as «*push incentives*», that is financial resources available to the firm before (or during) the development process.

- However, they are conceded only conditionally upon R&D investments having been made, and in this sense they act as «*pull incentives*».

- Therefore, they can be seen as «*hybrid incentives*»

Rare Diseases

- **Fast Track Approval and Support to Filing** the former, accelerating entrance in the market, works as a «pull incentive» while the latter as «push incentive» since it would be enjoyed even if discovery does not succeed.

- To recapitulate, measures in the ODLs are *a mixture of push and pull incentives*.

Infectious and Tropical Diseases

Dimitri. Lancet IDs (2010). Data WHO 2004, G- Finder 2009

	R&D = x_i $	$\sum_{k=1}^{i} x_k$	DALYs= D_i (mln)	$\sum_{k=1}^{i} D_k$	Deaths= d_i (thous)	$\sum_{k=1}^{i} d_k$	$\frac{\sum_{k=1}^{i} x_k}{2385117816}$	$\frac{\sum_{k=1}^{i} D_k}{332,4}$	$\frac{\sum_{k=1}^{i} d_k}{11590}$
1 Rheumatic fever	1670089	1670089	5,1	5,1	280	280	0,0007	0,01	0,02
2 Trachoma	1679711	3349800	1,3	6,4	0	280	0,001	0,02	0,02
3 Leprosy	5619475	8969275	0,2	6,6	5	285	0,004	0,02	0,02
4 Typhoid and paratyphoid fever	9117212	18086487	Na	Na	600	885	0,007	Na	0,08
5 Bacterial pneumonia and meningitis	32517311	50603798	104,6	111,2	4240	5125	0,02	0,33	0,44
6 Helminths	51591838	102195636	12	123,2	47	5172	0,04	0,37	0,45
7 Dengue	82013895	184209531	0,7	130,2	18	5190	0,08	0,4	0,45
8 Diarrhoeal diseases	113889118	298098649	72,3	202,5	2000	7190	0,12	0,61	0,62
9 Kinetoplastids	125122839	423221488	4,1	206,6	110	7300	0,18	0,62	0,63
10 Tubercolosis	410428697	833650185	34	240,6	1400	8700	0,35	0,72	0,75
11 Malaria	468449438	1302099623	34	274,6	890	9590	0,55	0,83	0,83
12 HIV/AIDS	1083018193	2385117816	57,8	332,4	2000	11590	1	1	1
GINI INDEX								0,52	0,55

Infectious and Tropical Diseases

- The problem with ITDs is lack of purchasing power by the patients.
- Mergers and acquisitions in the pharmaceutical industry increased the size of companies which became mostly interested in developing «blockbuster» drugs.
- As a result weak, or no, perspective revenues rendered such diseases more likely to be neglected.
- However, since the early 2000s the situation started to change.
- A number of new initiatives of various types began to take place, involving pharmaceutical companies, non-profit organizations, public institutions.
- Most of the initiatives are not-for-profits. We now discuss some of them

Infectious and Tropical Diseases

- **Public Private Partnerships (PPP)**

- Not-for-profit entities, involving public institutions but also industry groups. Some notable examples are:

- Medicine for Malaria Venture (MMV) (1999)
- Tubercolosis (TB) Alliance (2000)
- Drugs for Neglected Diseases (DNDi) (2003)
- Institute for One World Health (IOWH)
- Global Alliance for Vaccines and Immunisation (GAVI Alliance) (2000)

- Notice that some big pharmas, such as Novartis, took the initiative of setting their own institutions devoted to NDs, which however do not have a fully blown PPP connotation. (Novartis Institute for Tropical Diseases, NITD)

- PPP do not own infrastructures but typically operate as virtual coordinators of labs, gathering funds, supporting the various development phases of a treatment as well as its delivery on the field.

Infectious and Tropical Diseases

- **Advanced Market Commitment (AMC)** (2007)

- Advocated by Prof. Michael Kremer (Harvard) in 2005, is an innovative way to create a market for specific vaccines

- In 2007, five countries (Canada, Italy, Norway, Russia, UK) together with the Bill & Melinda Gates Foundation committed 1,5$ bln to purchase vaccines for pneumococcal diseases, killing about 1,6 mln people per year

- Purchase would be made as long as the vaccine proves to have all the needed characteristics of efficacy and safety.

- AMC is a pure example of «*pull incentive*», as funding becomes available only upon successful discovery. The risk faced by firms with pull incentives should be eliminated by the sponsors' reputation.

Infectious and Tropical Diseases

- **Priority Review Vouchers (PRV)** (2007)

- Proposed in 2006 by Ridley-Grabowski-Moe (Duke), and enacted by the US 2007, is a mechanism that tries to spur R&D for NDs by linking their «market» to the «standard markets» for drugs

- It works as follows: any company registering a drug for a NDs (specified in the Law) is entitled to receive a voucher, that could be used to prioritize review of any drug in the pipeline of the registering company, or sold to another company.

- The value of such an accelerated (one year) entrance in the market by a top selling drug (3$bln NPV) is estimated to be about 300$mln.

- PRV has been crititised for being too weak an incentive.

- Recently, Ridley-Sanchez (2010) proposed to introduce PRV also in EU.

Infectious and Tropical Diseases

- To summarize, there have been a number of different initiatives supporting R&D for ITDs
- PPP are institutions where risk of losses are shared and where incentives are hybrid
- AMC and PRV are typical examples of «pull incentives»
- This broad overview illustrates that various types of schemes were used .

R&D Incentives for Neglected Diseases

- The work by Michael Kremer induced an interesting debate on which, between *«push and pull incentives»,* fare better to stimulate R&D for NDs.
- Kremer advocated *«pull»,* since *«push»* incentives can be particularly prone to opportunistic behaviour by firms and lose effectiveness.
- The proposal was very well received by the Gates Foundation and, indeed, since then Kremer's Professorship at Harvard was entitled to Gates.
- The debate has been lively and hosted in a variety of outlets (academic publications, official documents, blogs etc.)
- For this reason I have been trying to contribute to identify the main driving forces behind these two classes of incentives, using a stylized scheme.
- Though simple, the underlying assumptions are sufficiently general and should help capturing the main elements (Dimitri, Plos One, 2012)

R&D Incentives for Neglected Diseases

- (***No incentives***) Consider a profit maximizing firm and no incentives. Suppose that
- C are R&D investments, $p(C)$ the success probability, R future net revenues, $\Pi(R, C)$ the firm profit function. Then the firm profit is given by

$$\Pi(R, C) = \begin{cases} R - C & with\ probability\ p(C) \\ -C & with\ probability\ (1 - p(C)) \end{cases}$$

- And its expected profit by

$$E\Pi(R; C) = p(C)R - C$$

- Assuming decreasing returns from R&D investments, $p'(C) > 0$ and $p''(C) < 0$, the profit maximizing C would solve the following condition

$$p'(C) = \frac{1}{R}$$

R&D Incentives for Neglected Diseases

- (***R&D Incentives***) Suppose now an external sponsor provides linear incentives (funds) to maximize C

$$F(C) = F + bC,$$

- where F is a fixed amount and $0 \leq b \leq 1$.

- (*Push incentives)* Push incentives imply that

$$E\Pi_{push}(R; C; F(C)) = \begin{cases} R + F(C) - C & with\ probability\ p(C) \\ -C + F(C) & with\ probability\ (1 - p(C)) \end{cases}$$

- and the expected profit now is

$$E\Pi_{push}(R; C; F(C)) = E\Pi(R; C) + F(C)$$

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- Hence the profit maximizing R&D level C_{push} of investment solves

$$p'(C_{push}) = \frac{1-b}{R}$$

- Implying that the firm optimal R&D investment now increases with respect to when no incentives are availlables.

- (*Pull incentives)* Firm profits would now be

$$\Pi_{pull}(R; C; F(C)) = \begin{cases} R - C + F(C) & with\ probability\ p(C) \\ -C & with\ probability\ (1-p(C)) \end{cases}$$

- and

$$E\Pi_{pull}(R; C; F(C)) = E\Pi_{push}(R; C; F(C)) - \big(1-p(C)\big)F(C)$$

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- Therefore, for all C

$$E\Pi_{pull}(R; C; F(C)) < E\Pi_{push}(R; C; F(C))$$

- and, in general, with co-funding,

$$C_{pull} < C_{push}$$

- Notice however that if $F(C) = F$, that is constant funding, then

$$C = C_{push} < C_{pull}$$

- Namely with constant funding, push incentives are unable to increase the R&D investment level obtainable without incentives, which is lower than the R&D effort induced by pull incentives.

R&D Incentives for Neglected Diseases

- Limitations of the analysis given by the assumptions (for example decreasing returns from R&D investments)

- Then, hybrid schemes such as «Pay–As-You-Go» could be a good compromise to improve risk-sharing and payoffs.

R&D Incentives for Neglected Diseases

Conclusions

- Neglected Diseases are now *less neglected* than they were before the 2000.
- A number of initiatives have been taken to spur R&D effort for both Rare and Infectious Tropical Diseases.
- Some appear to be less neglected than others (HIV, TB, Malaria)
- Hybrid forms of economic incentives seem desirable
- Progress has been made but much is still to be done

Thanks for your attention