

Perspectives on stimulating industrial research and development for neglected infectious diseases

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Abstract This paper summarizes recent thinking on stimulating industrial research and development (R&D) for neglected infectious diseases and argues that it is critical to enlarge the value of the market for medicines and vaccines through, for example, global purchase funds. The most important economic barriers to R&D are that the commercial markets are small and that individual purchasing power is severely limited, even though the number of patients may be very large. Since R&D costs for all diseases are high, this means that returns will not cover investments. Various mechanisms have been proposed to address this economic imbalance (accepting that other barriers will also need to be considered). Economic devices which reduce the costs of R&D — push factors — are useful, but our review suggests that high costs do not explain the shortfall in R&D. Economic devices which address the lack of viable markets have been termed pull factors and are designed to create or secure a market, thereby improving the likelihood of a return on investments. One pull mechanism is the commitment in advance to purchase a product that meets specified criteria, if invented. The purchase-precommitment approach has a number of attractive features. For example, it only rewards successful outputs rather than supporting research that may not succeed. Pull programmes effectively mimic the market and lead companies to favour lines of attack that they believe will lead to marketable products. Overall, a combination of push and pull mechanisms is likely to represent an attractive approach. This could combine, for example, increased funding for public laboratories, public–private partnerships in R&D, purchases of underutilized existing products, and a precommitment to purchase new drugs and vaccines when developed.

Keywords Communicable diseases/drug therapy; Orphan drug production; Drugs, Investigational/supply and distribution; Drug industry; Motivation; Research/economics; Private sector; Financial support; Cost-benefit analysis; Patents (*source: MeSH*).

Mots clés Maladie transmissible/chimiothérapie; Médicament orphelin; Médicament phase recherche/ressources et distribution; Industrie pharmaceutique; Motivation; Recherche/économie; Secteur privé; Aide financière; Analyse coût-bénéfice; Brevet (*source: INSERM*).

Palabras clave Enfermedades transmisibles/quimioterapia; Producción de medicamentos sin interés comercial; Drogas en investigación/provisión y distribución; Industria farmacéutica; Motivación; Investigación/economía; Sector privado; Apoyo financiero; Análisis de costo-beneficio; Patentes (*fuelle: BIREME*).

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Voir page 740 le résumé en français. En la página 740 figura un resumen en español.

Introduction

While 50% of global health research and development (R&D) in 1992 was undertaken by private industry, less than 5% of the money was spent on diseases specific to less developed countries (1, 2). Of the 1223 new chemical entities marketed worldwide between 1975–96, only 13 were developed specifically for tropical diseases (3). Despite this, private industry has discovered several drugs for serious

disease threats in less developed countries, including malaria, tuberculosis, hepatitis B, river blindness, meningitis, leprosy, sleeping sickness, and trachoma. Moreover, the development of globally applicable medicines and vaccines has led to important advances in public health in developing countries.

At the same time, every biopharmaceutical company has a limited number of R&D programmes in their portfolio, which are regularly reviewed against each other. Fundamentally, the process tends to favour those projects with a higher probability of success and which, if successful, would serve markets with a larger monetary value. Consequently, there is lower investment in diseases such as tuberculosis and malaria, despite their high global disease burden, compared with the level of investment in “industrialized-country” diseases. As a result, there is general agreement that new mechanisms and in-

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centives are needed to encourage industrial R&D in underresourced diseases. In this paper, some recent thinking about ways to stimulate industrial R&D for neglected infectious diseases is examined, and it is argued that enlarging the value of the market for medicines and vaccines through, for example, global purchase funds, is a critical step toward stimulating R&D in these diseases.

Barriers to R&D

A joint working group of WHO and the pharmaceutical industry identified five barriers limiting industry engagement in new R&D on neglected infectious diseases (4), as described below.

The state of the science

The lack of understanding of some diseases, coupled with the complexity of the science and technology involved, makes the prospect of finding new medicines and vaccines uncertain and therefore risky. This lack of understanding limits the investment that it is prudent for industry to make. Publicly-funded basic research, often carried out by research institutions and universities, has been important in stimulating the applied work undertaken by the pharmaceutical industry, although industry is increasingly performing basic scientific research as well.

Insufficient access

Weaknesses in country-level physical, medical, financial, and political infrastructure mean that many existing products needed by people in developing countries are not being purchased by patients, health care facilities, governments, or nongovernmental organizations. There is a very real danger that even if new products are developed, they will not be purchased and made available to those who need them. While some existing products suited to developing countries are widely purchased and used, many others are not. In many cases, weaknesses in health infrastructure in developing countries mean that patients never see a health care provider and receive a diagnosis or prescription, let alone the care necessary to make effective use of some medicines. While this paper focuses exclusively on medicines and vaccines, it is often the case that other interventions are more appropriate and this fact should not be minimized.

Thus, there is the prospect that many patients with acquired immunodeficiency syndrome (AIDS) in Africa, for example, would not automatically benefit from antiretrovirals, even at dramatically lower prices. Antiretrovirals require diagnosis, monitoring, and long-term maintenance of demanding treatment regimens that are difficult to sustain without adequate infrastructure and support. Some technologies are easier to deliver than others, however, and inexpensive off-patent vaccines in the WHO's Expanded Programme on Immunization (EPI) package reach 74%

of the world's children. Even though coverage is far from adequate in many areas, it is estimated that this programme saves three million lives each year. Part of the reason that the EPI has been so successful compared to other inexpensive treatments is that vaccines require far less infrastructure and resources to deliver than many other products. In many developing countries, access is a particularly complex problem, requiring political will and a commitment of new resources. It is basically an issue of inadequate personal and societal resources for delivering healthcare, purchasing medicines, vaccines, diagnostics, and other technology.

Fear that intellectual property protection will be inadequate

Industry continues to be concerned about protection for innovation because of challenges to the principle of intellectual property and the lack of enforcement of international intellectual property rights. At the heart of the biopharmaceutical industry is the patent system, a legislative device designed to provide exclusive rights to innovators so that they can realize the benefits of innovative activity over a limited period. Patent legislation represents a careful balance between the desire to foster innovation and the need to avoid underutilization of the product due to higher prices brought about by patent protection. Proposals to alter the existing balance should be regarded with caution. Undermining patent protection could discourage innovative activity on the part of industry, while strengthening patent protection could come at the expense of reduced access. Thus, it is desirable to look for solutions that enhance both research incentives and access.

Identifying priorities

Insufficient information about the number of patients, the effectiveness of existing products and patient access makes it difficult for companies to identify priority markets. Good country-level data about the incidence and prevalence of diseases and the prospects of patients seeking and receiving appropriate medical care are important components for establishing viable markets.

Poor expected market returns

Clearly, in the case of neglected infectious diseases, the number of those afflicted is very large, but their individual purchasing power is generally small. Thus, markets for new medicines and vaccines are small as well. At the same time, since companies expect R&D costs for developing-country medicines and vaccines to be at least as great as they are for products for industrialized countries, the small commercial estimates of market size for some diseases create doubt that returns will cover investments. Currently, it is not financially feasible for private industry to match the level of research investment that is socially justified.

Economic approaches to overcoming the poor-returns barrier and encouraging private sector

R&D on neglected diseases are discussed below, while recognizing that further work is also needed on other barriers, such as basic science and health care infrastructure.

The economics of an R&D programme

Development of new medicines and vaccines requires a long period of costly investment in research and testing, followed by a period of returns. Measures of the R&D costs of a new chemical entity (NCE) must take into account the fixed and variable costs of product discovery and development, the cost of failures, and the time value of money spent. Estimates of the average cost of product development vary. One study found that the capitalized average cost per approved NCE was approximately US\$ 313 million dollars in 1991 (5). In a review of studies of NCE costs, Kettler found that the cost of an NCE launched today can approach US\$ 600 million (6). The main factors pushing up NCE costs include longer development and approval times, larger and more complex clinical trials, increased expenditures on new technologies, and shifts in the product portfolio towards riskier, more expensive therapeutic categories.

There is no reason to suppose that developing new vaccines or medicines for neglected diseases will vary significantly from this pattern. Indeed, the complexities of the scientific challenges involved make it possible that products for these diseases will cost as least as much to develop as current NCEs. For example, the cost of developing a NCE can be estimated by considering R&D spending and the number of new product launches at a company or industry level. A major research-based pharmaceutical company with audited R&D spending of US\$ 1.5 billion is doing well if it launches two or three NCEs annually. Total industry R&D was of the order of US\$ 40.8 billion in 1999, excluding capital expenditure, of which approximately two-thirds was spent on NCEs. In the 1990s, on average 41 NCEs were launched per year (7). Simple mathematics in both cases confirms the Kettler figures (6).

Economic devices which reduce the costs of R&D have been termed push factors, while those which address the lack of viable markets have been termed pull factors. If the availability of medicines and vaccines available for neglected diseases are to be expanded, the most cost-effective push and pull factors for motivating companies to engage in R&D for these diseases must be identified.

Push mechanisms

Push programmes are those that provide direct funding for research through, for example, grants to universities or government laboratories. Large government-funded research institutions play a vital role in basic research. The knowledge they create is a public good and provides an essential platform for

the downstream activities of biotechnology and pharmaceutical companies. In generating at least some of the basic foundation of knowledge, these activities save biopharmaceutical industry costs and can encourage investments in applied research. The largest public R&D expenditure worldwide was spent by the National Institutes of Health, USA, whose budget totalled US\$ 15.6 billion in 1999. But only a small proportion of this expenditure was related to medicines.

Publicly-funded “Manhattan-project” approaches, in which public funds are deployed to research and to develop products right through to the market, are proposed from time to time. However, experience with such programmes has revealed that they do not tend to be successful, and are vulnerable to efforts by scientists and research administrators to overestimate the chances of success and to divert resources to non-core activities. The disastrous effort of the United States Agency for International Development to develop a malaria vaccine is a case in point (8). Other push programmes make their contribution directly to companies through, for example, R&D tax credits and small business grants, and there are a growing number of product R&D-related ventures. Examples of push programmes and issue that need to be considered are listed in Table 1. Although these push mechanisms are often useful, a review of current legislation and evaluation of the instruments available for offsetting R&D costs suggests that the cost of R&D per se does not explain the market’s failure to undertake sufficient R&D in some diseases (4). Private companies often do make very risky and expensive investments in the development of medicines for which a substantial market is expected. For neglected diseases, we believe that insufficient market attractiveness or viability, relative to the likely cost and level of risk inherent in R&D, is a more serious barrier than the cost of R&D itself. Our working assumption is that substantial industrial investment in neglected disease R&D will occur only if expected rates of return are broadly equivalent to those anticipated from R&D in conventional areas. If this is the case, then on their own none of the instruments in Table 1 would provide enough inducement for the large pharmaceutical companies to expand their investments in neglected diseases. This conclusion notwithstanding, some of the instruments in Table 1 remain valuable: for example, in disease areas where the science is insufficiently advanced, they are likely to be needed to jump-start discovery.

Pull mechanisms

Pull incentives are designed to create or secure a market, thereby improving the likelihood of a return on investments. Pull mechanisms reward output — the actual creation of a new medicine or vaccine — rather than input. They therefore cost nothing unless they lead to development of usable products.

Table 1. **Push mechanisms for industrial R&D**

Mechanism	Considerations
Research in public and university labs	- essential for basic science; - less well suited to the later stages of product development.
R&D tax credits	- widely used to encourage R&D within a particular region; - only income-earning companies benefit.
Public investment in applied research (alone or in conjunction with private industry)	- examples include International AIDS Vaccine Initiative and Medicines for Malaria Venture; - hard to pick “winners”; - danger of politicization of funding decisions; - difficulty of shutting down failed programmes.
Sharing of R&D costs between companies	- sharing R&D presumes sharing returns — not attractive in absence of improved market returns; - most applicable to precompetitive research; - potential antitrust difficulties.
Establishment of local development facilities (Phase III-trial support)	usefulness varies by disease/location.
Fast-track regulatory review	helpful, especially to small companies, but unlikely to be sufficient to encourage more R&D.

Examples of pull incentives and associated considerations are presented in Table 2.

Patents

From industry’s perspective, the prospect of a patent for a new medicine for any given disease is not a sufficient incentive to stimulate R&D because the rewards or value of the patent are low in this particular situation. A patent extension on the product in question would also have limited value as an incentive. By contrast, transferring the patent extension to a commercially viable product in industrialized-country markets would be attractive to many established companies. Patent extension on other products, however, would place a burden on those patients in need of the medicine for which the patent had been extended, increasing costs and potentially reducing access (depending on the country’s health care financing system). Compensation may be necessary in countries where patients contribute to the costs of their medicines. In countries where governments are the main purchasers of medicines and vaccines, extending the patent on an alternative product is roughly equivalent to paying for the new product directly, as it all comes out of the government budget.

Tax credits

In the USA, Senators Frist & Kerry and Representatives Dunn & Pelosi have proposed encouraging R&D on vaccines for AIDS, tuberculosis, and malaria, using both enhanced R&D tax credits and a tax credit for sales of vaccines to non-profit and international organizations. The tax credit for sales is

a pull mechanism: by raising the return to the seller, the credit increases the incentive to develop appropriate products. There are also advantages to purchasers, as tax credit may flow partly to them in the form of lower purchase prices. The proposed legislation thus also addresses the access problem. As with the purchase precommitment discussed below, tax credits for sales cost nothing unless an effective vaccine is actually developed and delivered. Tax credits for sales will only be effective if a non-profit or international organization is prepared to make the purchases which would be matched by tax credits, but given the interest from organizations such as the Gates Foundation in purchasing vaccines, tax credits could play an important role in the overall effort to develop and deliver medicines and vaccines for diseases.

Purchase precommitment

Finally, governments or private foundations could make a commitment in advance to purchase a certain quantity of a medicine or vaccine that meets specified criteria when, and if, it is invented (9–13). Such an approach is currently advocated by the United Kingdom government (14). This purchase precommitment could take the form of a contractual, binding agreement to buy any new product that meets the stated criteria. This commitment would be open to any firm that could develop the medicine or vaccine. The purchase commitment would have to be for a large enough quantity of the product to create a market of sufficient value to overcome the “inadequate market value”-barrier to research investments. The purchaser could then make the product available to developing countries at no cost, or in exchange for modest co-payments.

A respected consulting firm estimated that an annual market of US\$ 250 million would be needed to motivate pharmaceutical firms (15). Of course, the greater the potential market, the more firms will invest in R&D and the faster new products will be developed. Since the social value of these vaccines would be far greater than US\$ 250 million, larger commitments would be preferable. If donors were to commit to US\$ 300 million for a malaria, tuberculosis, or AIDS vaccine every year for 10 years (approximately US\$ 5 per person immunized), the net present discounted value of costs per disability-adjusted life year saved would be under US\$ 10, making this one of the world’s most cost-effective health interventions. Note that nothing would be spent unless vaccines were actually developed.

Aside from its cost-effectiveness, the purchase precommitment approach has a number of attractive features. As with other pull mechanisms it rewards successful outputs — the creation of a new medicine or vaccine with proven performance characteristics — rather than rewarding inputs into research that may not succeed. Push programmes too often allow researchers to exaggerate the potential for success to qualify for funds. Pull programmes such as the

purchase commitment lead companies to favour lines of attack that they believe will lead to marketable products. In this regard, the purchase commitment mimics the incentives a market provides.

Such a programme would address one of the key barriers to increased R&D investments, as described above. Since the government or private foundation that purchases the vaccines could make it available to those who need it, either for free or for a modest co-payment, access problems would be at least partly addressed. Intellectual property rights would be protected, since purchases would be made only from legitimate producers. Since the commitment would specify the number of doses to be purchased and the purchase price, market uncertainty would be reduced, and the size of the market would be increased.

The purchase precommitment approach does present some difficulties, however. First, while not without precedent in other industrial sectors, the use of a purchase precommitment to stimulate the development of a medical product is unknown in modern times. One consequence of this might be scepticism about the credibility of the commitment. If companies believe that the sponsor of such a commitment will renege on it, they will not invest. Procedures to enhance the credibility of the commitment are therefore important. One study examined legal issues surrounding a vaccine purchase commitment and concluded that it could be designed to be enforceable by the courts, as with earlier programs designed to boost production of manganese and of dairy products (16).

A different form of precommitment — a prize — has precedents. For example, the Kremer prize for human-powered flight successfully stimulated the development of the Gossamer Albatross and its historic flight over the English channel.

Another way to boost the credibility of a commitment would be to combine a commitment to purchase future products with enhanced purchases of existing products. For example, the Gates Foundation, in cooperation with the Global Alliance for Vaccines and Immunisation, is undertaking a large effort to improve use of underutilized vaccines, such as those for hepatitis B and *Haemophilus influenzae* B. This immunization programme is widely perceived as a successful model for effectively purchasing vaccines.

Purchase and delivery of vaccines that can be added to the existing childhood vaccine regimen are likely to be very cost-effective on their own terms. If R&D investment is to be increased, however, it will be necessary to supplement such purchases with explicit commitments to reward successful developers of future products. It may take 10 years of research to develop some of the needed products, such as a malaria vaccine. Another 10 years may then be required to recoup the R&D costs for such a product. If firms are to invest, they must therefore be confident that a market will be available in 10–20 years. The priorities of donor agencies change over time and a burst of enthusiasm by donors now

Table 2. Pull mechanisms for industrial R&D

Mechanism	Considerations
Extension of patent term or market exclusivity on new product	- key feature of orphan drug legislation; - market exclusivity on a product of low return is not very attractive.
Extension of patent term or market exclusivity on alternative product ("transferable patent extension")	- refers primarily to products in markets in industrialized countries; - potentially very attractive to established companies but is politically challenging; - burden placed on patients or payers for a different medicine in industrialized-country markets (although this may be offset by subsidies).
Tax credit on sales	- spreads the cost burden over the whole tax base; - attractive to legislators; - potential advantage to both purchaser and seller.
Purchase commitment, open to any firm, to buy a specified product and distribute to users	- theoretically attractive; creates a market where a market did not exist or was inadequate; - precedents exist, albeit not in medicine (8–11); - helps address price component of access problems; - may be best combined with increased purchases of existing products.

will not be enough to convince pharmaceutical firms that an adequate market will be available for their products in the future. Once a new product has been invented and the research investments already made, public health advocates and politicians have incentives to try to obtain the product as cheaply as possible. An explicit, long-term commitment to purchase a specified quantity of the product at a specified price, provided that it meets all the stated criteria, is thus likely to be an important component of any effort to increase R&D investment in the diseases that burden the developing world.

Conclusion

A combination of several of the push and pull mechanisms described above is likely to offer an attractive incentive for many companies to develop treatments for neglected diseases. Such an approach could combine, for example, increased funding for public laboratories, larger purchases of underutilized existing medicines and vaccines, and a precommitment to purchase new medicines and vaccines should they be developed. It is the view of one of the authors (DEW) that public–private R&D partnerships such as the Medicines for Malaria Venture may also represent an attractive model.

The fundamental question underlying the issues raised in this paper is who should pay? An approach such as that described above would require that industrialized countries be willing to underwrite the costs for developing countries. There is very limited scope for any legislation that does not come with funds attached. The preceding discussion makes clear how few non-financial options are available for tackling the barriers to R&D. While proposals without funding are not likely to succeed, however, it is clear that funds can

be spent in ways that maximize the potential for developing successful new products and minimize the chance of wasting public or private resources. While money is needed, it is not all needed at once, and risks can be reduced substantially through carefully designed policies and programmes. ■

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Résumé

Stimuler dans l'industrie pharmaceutique la recherche-développement concernant les maladies infectieuses négligées : perspectives

Le présent article fait le point des réflexions récentes sur la manière de stimuler dans l'industrie pharmaceutique la recherche-développement concernant les maladies infectieuses négligées. Il souligne qu'il est essentiel d'augmenter la valeur du marché pour les médicaments et les vaccins contre ces maladies en créant, par exemple, des fonds mondiaux d'achat. Les principaux obstacles économiques à la recherche-développement tiennent au fait que les marchés commerciaux sont restreints et que le pouvoir d'achat des particuliers demeure limité, même si les patients peuvent être très nombreux. Compte tenu du coût élevé de la recherche-développement pour toutes les maladies, le retour sur investissement devient très aléatoire.

Divers mécanismes ont été proposés pour tenter de remédier à ce déséquilibre économique – étant entendu qu'il faudra s'occuper aussi des autres obstacles. Les mesures économiques qui permettent de réduire les coûts de la recherche-développement – ce que l'on appelle les mesures dissuasives (*push factors*) – sont utiles, mais l'étude tend à démontrer que les coûts élevés n'expliquent pas à eux seuls l'insuffisance de la recherche-développe-

ment. Les interventions visant à remédier à l'absence de marchés viables – ce que l'on appelle les mesures incitatives (*pull factors*) – ont pour but de créer ou de s'assurer un marché pour améliorer les perspectives de retour sur investissement. L'un de ces mécanismes incitatifs consiste à s'engager par avance à acheter un produit répondant à des critères spécifiques si ce produit est inventé. Ce pré-engagement d'achat présente plusieurs avantages : il permet, par exemple, de ne « récompenser » que les efforts aboutis au lieu d'appuyer des recherches qui peuvent échouer. Les programmes incitatifs se calquent sur le marché et amènent les laboratoires à privilégier des recherches dont ils estiment qu'elles déboucheront sur des produits commercialisables.

Globalement, une association de mécanismes incitatifs/dissuasifs peut offrir une solution intéressante : on peut, par exemple, décider d'accroître le financement des laboratoires publics, de développer des partenariats public-privé pour la recherche-développement et d'acheter des produits existants sous-utilisés tout en s'engageant par avance à acheter de nouveaux produits et de nouveaux vaccins lorsqu'ils auront été mis au point.

Resumen

Perspectivas sobre el fomento de la investigación y el desarrollo industriales contra enfermedades infecciosas desatendidas

En este artículo se resumen las últimas ideas concernientes al fomento de las actividades de investigación y desarrollo (I+D) de la industria contra enfermedades infecciosas desatendidas, y se argumenta que es fundamental ampliar el valor del mercado de los medicamentos y vacunas mediante, por ejemplo, fondos de compra mundiales. Obstáculos económicos más importantes a la I+D son las pequeñas dimensiones de los mercados comerciales y las serias limitaciones del poder adquisitivo de los individuos, pese a que el número de pacientes puede ser muy elevado. Dado que los costos de la I+D para todas las enfermedades son elevados, los ingresos no permitirán cubrir las inversiones efectuadas.

Se han propuesto diversos mecanismos para corregir ese desequilibrio económico (aceptando que también habrá que tener en cuenta otros obstáculos). Los instrumentos económicos que reducen los costos de I+D –factores impulsores– son una valiosa ayuda, pero nuestro análisis lleva a pensar que los altos costos no explican el déficit de I+D. Los instrumentos económicos concebidos para solucionar la falta de mercados viables

es lo que se conoce como factores atractores, esto es, factores que tienen por objeto crear o asegurar un mercado y mejorar así las probabilidades de rendimiento de las inversiones. Un mecanismo atractor consiste por ejemplo en comprometerse por adelantado a adquirir un producto que satisfaga determinados criterios, si finalmente se descubriera. La idea de un compromiso previo de compra presenta varias ventajas, entre ellas la de que así sólo se recompensan las soluciones eficaces, en lugar de apoyar investigaciones que pueden fracasar. Los programas atractores simulan efectivamente el mercado y llevan a las empresas a potenciar las líneas de ataque que creen que pueden desembocar en productos comercializables.

En general, una combinación de mecanismos impulsores y atractores será probablemente la fórmula más idónea. Ello puede traducirse, por ejemplo, en la implantación simultánea de una mayor financiación para los laboratorios públicos, alianzas público-privadas en I+D, compras de productos existentes infrautilizados, y el compromiso previo de adquirir nuevos medicamentos y vacunas una vez desarrollados.

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