RENEGOTIATING THE ROLE OF PUBLIC HEALTH R&D

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ABSTRACT

Public health research and development (R&D) in developing countries is generally both underfunded and misdirected. Using data from national R&D surveys, it is shown that the health R&D is directly predominantly at basic and applied research, with experimental development and commercialisation being funded and undertaken by business enterprise. This model has worked admirably in the development of new health products for which large and profitable markets exist. However it has failed in delivering innovative products and services that meet the needs of low margin public health markets, especially in developing countries; this failure demands a new role for the state in such countries. Using data from a case study on the treatment of tuberculosis in South Africa, it is argued that public funds will earn high returns if used for new product development (NPD) in addition to supporting basic R&D. Such a model has worked well in the defence sector, where governments have played an active role in NPD. Following an established model of product development partnerships, it is concluded that increased investment by governments of developing countries in close-to-market products and services will lead to improvements in public health outcomes at lower net cost.

Key words: public health, research, funding, new product development, developing countries

INTRODUCTION

Government funding of health-related research and development (health R&D) has grown significantly in most developed countries over the last 50 years and now accounts for about 17% of all government expenditure on R&D (OECD, 2009), an increase of more than 50% since 1990 (see Figure 1). Given that the total global government expenditure on R&D is about 30% of total expenditure, public-funded health R&D now amounts to at least $82.6 billion[1] per annum (Grueber and Studt, 2013).

[1] All monetary values in this article are quoted in United States dollars, expressed in purchasing power parity (referred to as $ PPP).

Despite this substantial R&D expenditure, public health continues to lack the essential products and services to provide an effective, low cost alternative to private healthcare, particularly in developing countries (Moran et al., 2009). It is contended that the reason for this gap between R&D and innovative new products capable of meeting the needs of public health, is not a consequence of the inefficiency of health R&D performed with public funds, nor is it a perceived reluctance of public health systems to absorb new products and services; instead it is due to the narrow focus of this research on basic research vs. new product development (NPD).

In this article, evidence in support of this contention or proposition is presented. The initial section provides an overview of global R&D, which is followed by a more detailed discussion on the funding of health R&D. The impact on the quality of care in the public health sector as a result of the latter's narrow focus on basic research is then discussed. It is argued that the present arrangement allows for the control of the public sphere by private interest, and deepens the social inequalities that have become a feature of modern capitalism (Piketty, 2014). The arguments in support of a re-allocation of public health R&D in developing countries are supported by a case study of the treatment of tuberculosis (TB) in South Africa. In the final section, proposals for the redirection of this funding towards product and service innovation through the funding of product development partnerships are made; it is concluded that these changes could assist the redistributive intent of the state and help to improve public health services.

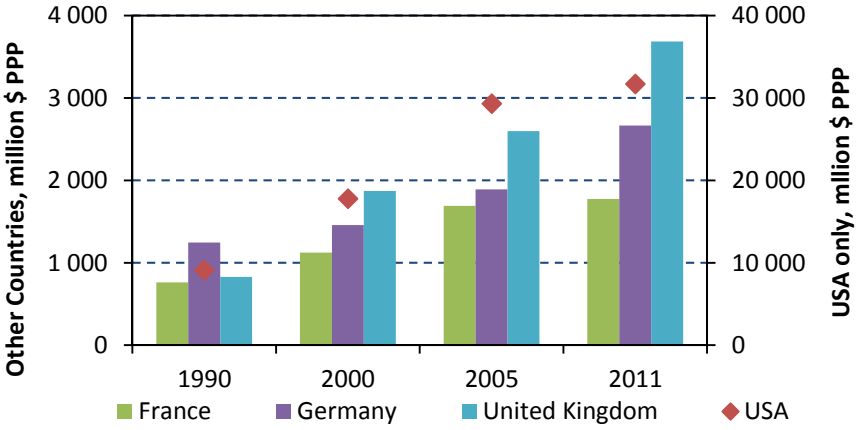

Figure 1. Growth in global health R&D funding ($ PPP; 1990 - 2011)

AN OVERVIEW OF GLOBAL R&D FUNDING

Global R&D funding was forecast to reach $1.62 trillion in 2014, equivalent to an average expenditure of 1.8% of global gross domestic product (GDP) (Grueber and Studt, 2013). The top 10 countries account for 80% of the total expenditure, the top 40 countries account for 97%. South Africa's expenditure of $6 billion represents 0.4% of the global total and falls below the average ratio of gross expenditure on R&D (GERD) to GDP (0.76% vs 1.77%) (Department of Science and Technology, 2014a).

In the more detailed discussion of global R&D, it is important to understand three important terms and how they are used in the R&D policy literature. Firstly, the measurement of R&D distinguishes between funding and performance. GERD and government's proportion of GERD (known as GovERD) refers to the performance of R&D, whereas the term Government Budget Appropriations

or Outlays for R&D (GBAORD) is used to describe government funding of R&D. The distinction is important, especially in the health sector, since public funding generally exceeds public performance, with governments providing significant funding to private entities for health-related R&D. In this article, government funding for health R&D is defined as that proportion of GBAORD allocated to the socio-economic objective (SEO) of 'health' (Young, 2001).

Secondly, data on government funding of the health sciences is generally not collected as a separate category. As a result, it may not be possible to determine the proportion of GBAORD that is used for health-related R&D. In South Africa, R&D expenditure by socio-economic objective is reported and includes health within the general category of 'society' (the other categories are defence, economic development, environment and advancement of knowledge). Alternatively, R&D surveys may report on the funding of the socio-economic category 'health and environment' which has been used as a proxy for health funding where available (OECD, 2009).

Finally, R&D surveys generally report on expenditure by Frascati category, where the latter includes basic research, applied research and experimental development. An example of expenditure breakdown by these categories is shown in Figure 2. The definitions for these three categories, used universally by country-wide R&D surveys, are as follows (OECD, 2002):

- *basic research*: experimental or theoretical work undertaken primarily to acquire new knowledge about observable phenomena and facts, not directed toward any particular use
- *applied research*: original investigation to acquire new knowledge directed primarily towards a specific practical aim or objective
- *experimental development*: systematic effort, based on existing knowledge from research or practical experience, directed toward creating novel or improved materials, products, devices, processes, systems, or services.

In practice, a R&D project or portfolio may straddle several categories, or fail to match the definitions of any category; however the approach remains central to the analysis of R&D data, being widely used and reported.

A more detailed analysis of global R&D funding of GBAORD reveals the following important points:

- defence R&D as a percentage of GBAORD is less than 10% in most countries with the exception of the United Kingdom (15%) and USA (57%);
- health R&D funding is provided mainly by business enterprise (60%) with governments contributing only 35%;
- the allocation of funding by Frascati category is entirely different between the two agencies, with government funding focussing on basic and applied research, and business funding on experimental development (see Figures 1 and 2); this profile is common to much of civil R&D;
- this profile of expenditure by Frascati category is not common to all GBAORD; in the defence sector, government funding may cover 75% of the total R&D performance, of which 80% involves late stage or close-to-market R&D, otherwise known as experimental development (see Figure 3).

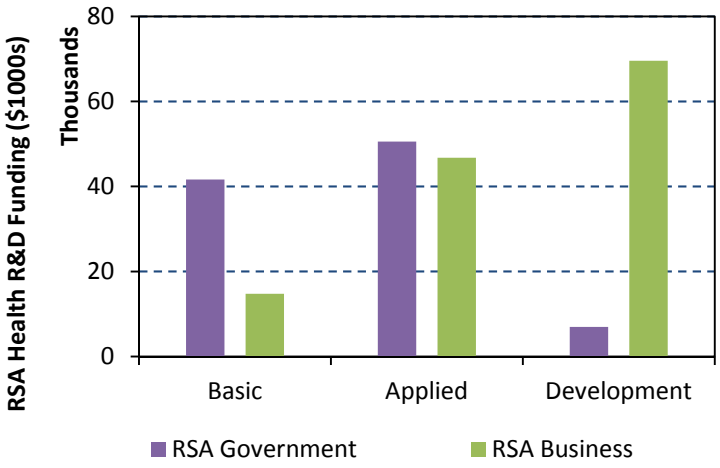

Figure 1. Funding of health R&D in South Africa (2011)

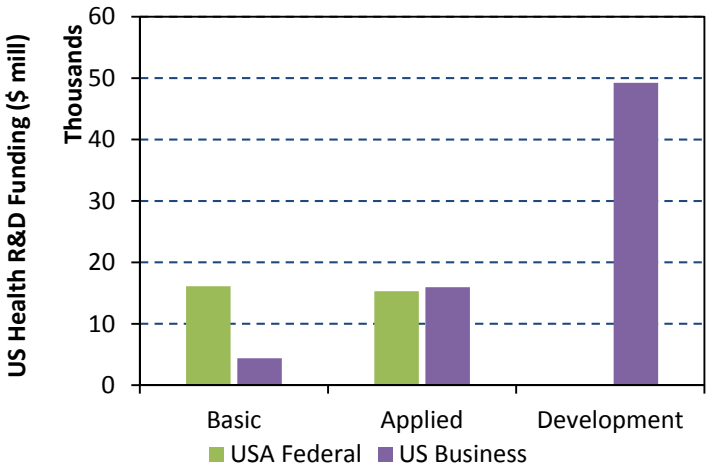

Figure 2. Funding of health R&D in USA (2008)

The observations from this analysis are fundamental to an understanding of main argument in this article and the commonly accepted roles of public vs. private R&D. It is clear that non-defence GBAORD conforms to the standard assumptions about the role of public funded R&D, namely that this should be focussed on early-stage, fundamental research, that it should not compete with, or crowd out, private R&D, that it should be directed at the development of new public knowledge, and that it should not attempt product or service commercialisation given that public performance agencies have limited knowledge and/or understanding of market needs. It is widely believed that governments and their public sector agencies are generally poor at understanding markets and the need for new products; slow to develop the required expertise for product commercialisation; and unresponsive to efficiency measures due to the absence of strong market competition, the presence of which is purported to drive successful innovation (Hart et al., 1997; Shirley and Walsh, 2001).

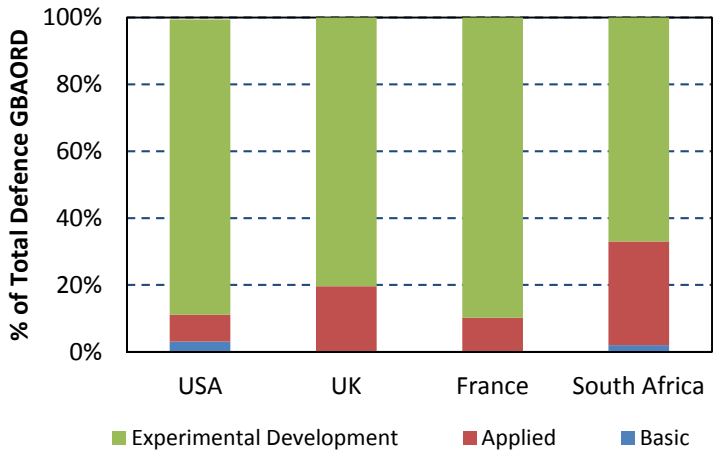

Figure 3. Government funding of defence R&D by Frascati category for USA, UK, France and RSA

The division of roles between public and private is particularly evident in the health sector; governments spend large sums on health-related R&D, mostly in the form of basic and applied research, the benefits of which accrue to the private sector. The new therapies, developed by the private sector using knowledge developed from public investment, may then be marketed and sold to public health facilities at significant margins (Walwyn, 2013a). This 'role-based' model, although globally ubiquitous, has numerous disadvantages as listed in Table, and raises the question as to why the state cannot act as its own product development and commercialisation agency.

Table 1. Advantages and disadvantages of public vs private innovation

Sector	Advantages	Disadvantages
Public	Better integration with operational units (such as health systems) Addresses areas of public need rather than potential for private profit Develops internal expertise Protects against non-contractible cost reduction with deleterious effects	Slow to respond Competes with the private sector May present significant challenges to public research institutions in terms of accessing the required clinical and pharmacological skills
Private	More efficient Faster (time to market) Less risk for the public sector (licensing of successful product and no upfront R&D) Generally faster pace of innovation	More expensive (the quality-adjusted life year consistently overestimates the value of therapy; as a consequence, the state is forced to purchase products and services at inflated prices) No development of capacity in the public space Delayed implementation due to high cost (affordability issue)

Over the last two decades this traditional structure of relative roles within the national system of innovation has shifted slightly, with an increasing use of product development partnerships (PDPs)

financed by donors and government agencies (Chatelain and Ioset, 2011; Grace, 2010; Moran et al., 2010). PDPs are often explicitly established and managed to do experimental development and commercialisation; for example, a recent review of US government support for global health product development lists over 350 projects covering the development of new drugs and vaccines (preclinical to Phase 3), diagnostics and contraceptives, with government involvement including funding, joint R&D, use of infrastructure and secondment of expertise (Policy Cures and Global Health Technology Coalition, 2012).

PDPs are changing the perception that governments should not support pharmaceutical product development and commercialisation. However the success of PDPs seems to have done little to change the funding patterns of governments in developing countries, which have failed to either increase their overall health R&D budgets, or re-allocate these budgets to product development and incremental innovation. As noted in the introduction, the main proposition of this article is that public health in developing countries can be significantly improved by shifting funding from early to late stage R&D. The benefits of such a change in strategy are now illustrated using the public health programme for TB prevention, treatment and control as a case study.

A CASE STUDY OF TB

Expenditure on TB treatment

Despite being preventable, treatable, and curable, TB is the second leading cause of death (after HIV) due to an infectious disease (Frick and Jiménez-Levi, 2013), with South Africa being one of the highest incidence countries (World Health Organization, 2013). As a consequence, the country has one of the largest treatment programmes in the world; the present treatment cost is about US$ 350 million or an average of about $685/patient (Pooran et al., 2013; South African National AIDS Council, 2011).

The treatment of active drug-sensitive TB (DS-TB) requires 6 months combination drug therapy to effectively eliminate the infection. A breakdown of DS-TB treatment costs, adapted from Pooran et al. (2013), is shown in Figure 4; about 54% of the total costs are incurred as a consequence of the diagnostic and monitoring needs of the patient with only 27% being due to the actual drugs. Although the present regimen has more than 60 years of clinical evidence and experience, it has not been evaluated systematically in a recent standardised clinical trial. As a consequence, it is clear that there is potential for improved regimens of shorter duration and fewer drugs (Mitnick et al., 2009), requiring less monitoring and having a higher level of a successful treatment outcome.

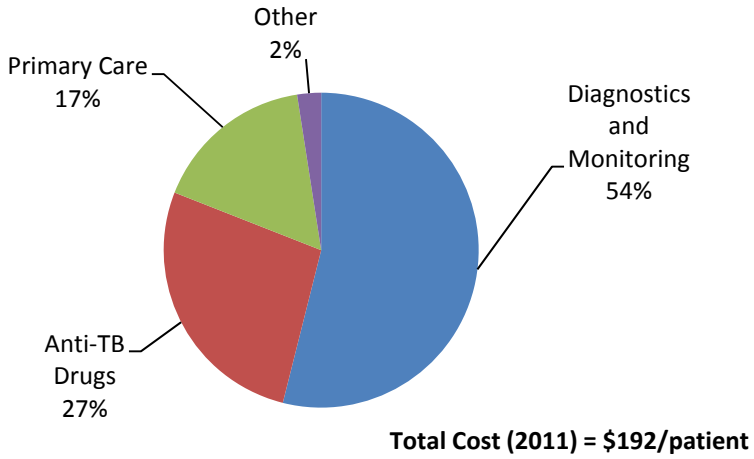

Figure 4. Breakdown of costs per DS-TB patient in South Africa

The treatment costs for both MDR-TB and XDR-TB are much higher, mainly as a consequence of the disproportionate contribution of drugs and hospitalisation (Mitnick et al., 2008). Unfortunately, DR-TB is all too often a death sentence for many people globally, due to inadequate access to treatment and the complex, toxic, and lengthy treatment (Logan, 2013). In 2011, 32% of the national TB budget for South Africa was used for DR-TB, but this number has been rising and is now closer to 50% as a consequence of improved case detection and a higher reported incidence of DR-TB case (South African National AIDS Council, 2011).

A wide range of factors affect TB risk, including gross domestic product per capita, population structure, levels of inequality and poverty, poorly ventilated indoor environments, and HIV prevalence (Akachi et al., 2012; Richardson et al., 2014). A more detailed understanding of the relationship between these factors and TB incidence would be helpful in being able to treat the disease. Combined with studies on the major components of treatment cost, epidemiological factors and the drug regimen itself, R&D could help considerably in reducing the overall treatment costs and eventually numbers of TB patients. As noted by Diel et al. (2014), without innovative tools to control and treat TB disease, it is unlikely the cost of TB to national programmes will drop. A prioritised TB R&D portfolio could deliver such tools and introduce significant savings for TB programmes. In the next section, present expenditure on TB R&D is reviewed.

Expenditure on TB R&D

The most recent survey on TB R&D expenditure reports a total expenditure of $627 million, of which $238 million and $87 million were spent on drug and vaccine development respectively (Frick and Jiménez-Levi, 2013). The bulk of the funding was provided by public sector (61%) and philanthropic organisations (20%), with the two largest donors being the National Institute of Health ($169 million), and the Bill and Melinda Gates Foundation ($112 million). The private sector contributed 18% of the total, which the report describes as an 'unprecedented pullback' compared to previous years (Frick and Jiménez-Levi, 2013). In a separate study on registered clinical trials, TB studies have remained unchanged at a total of three (out of 4,182) trials over the period 2007 to 2010 (Fisher et al., 2014). The low levels of funding relative to the funding for other diseases and to the scale of TB incidence has prompted several authors to call for higher levels of commitment by funders, particularly from public sources in the affected countries (Ma et al., 2010; Walwyn, 2013b).

Expenditure on TB R&D in South Africa is less than 0.4% of the treatment programme (Frick and Jiménez-Levi, 2013), although this is considered to be an underestimation of the actual value. Data on TB, HIV and malaria R&D expenditure has been collected as part of the National R&D Survey since 2005/6 and is reported to have reached about $200 million per annum (Department of Science and Technology, 2014b). The disaggregation of this figure between the three diseases is not possible, and it is likely that more than 50% of the total is allocated to HIV research, with the actual TB expenditure being about 20% of this total. However the bulk of this funding is sourced from international funders and not from local sources, either public or private. Actual public funding of TB research (rather than performance of research) is considered to be about $21 million, or about 7% of the total treatment cost.

Methodology

This research has followed a quantitative, case study methodology based on the analysis of secondary data obtained from various sources. Areas of potential cost savings were identified by an initial analysis of the present TB treatment costs, listed according to their contribution to the total programme. The impact of a variety of possible R&D projects, including the development of new vaccines, drugs, drug regimens, diagnostics and systems, on these costs was then considered. In each case the potential costs savings were calculated using a net present value (NPV) approach in which the cost savings were extrapolated over a 15 year period and the final value weighted according to the likelihood of project completion to give a risk-adjusted NPV (Svennebring and Wikberg, 2013). The assumed discount rate was 8%.

The risk-adjusted NPV was then compared to estimated development costs and the difference used to identify priority areas for a public health R&D portfolio. A more detailed description of the methodology and the options for cost savings are given in the original dissertation submitted by Jongihlati (2013).

Results

In comparison with other projects, such as the development of novel diagnostics and new drugs, the study revealed that improvements on current TB treatment regimens offered the highest potential returns, with the two priority areas being a reduction in the total treatment time for XDR- and MDR-TB from 20 months to 9 months, as per the expected outcomes of the STREAM trial (Nunn et al., 2014); and the optimisation of the DS-TB regimen through shorter treatment duration and fewer drugs/dose of drugs as per recommendations of an expert opinion (Mitnick et al., 2009). Further details follow.

Reduction in DR-TB treatment time

Recent evidence from a cohort of 206 patients in Bangladesh suggested that the recommended treatment time for DR-TB can be reduced from 20 to 9 months (Nunn et al., 2014). The patients were treated throughout with high-dose gatifloxacin, clofazimine, ethambutol and pyrazinamide supplemented by prothionamide, kanamycin and double-dose isoniazid during a four-month intensive phase. This radical shortening of the treatment period proportionally reduces both hospitalisation and drug savings. Based on the revised unit costs, the methodology as outlined earlier and allowing for an annual 10% reduction in patient numbers due to improved DR-TB

management, the risk-adjusted net present value of the potential savings for the South African TB programme is calculated to be $24.9 million.

These savings must be compared to the trial costs for the development of the new regimen. Although the total costs for the STREAM (standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant TB) trial are not available, it is reported that the USAID funding, which covers the bulk of its ongoing expenses, is $8.3 million (The Union, 2013). In other words, the overall return on investment to the South African government, should this project have been funded entirely from its coffers, is calculated at 200% and the internal rate of return at 62%.

This example illustrates clearly the main argument of this article; in the event of significant expenditure by national governments on public health programmes, it makes economic sense to invest in close-to-market technologies which can reduce the extent of this expenditure. In the case of DR-TB, which costs the South African government $129 million per year, an estimated cost saving of $25 million could be achieved from an initial expenditure of $8 million, should a revised formula for the funding of public health R&D be adopted.

Optimisation of DS-TB regimen

Similarly, the optimisation of the DS-TB regimen could deliver much-needed cost savings and make sound economic sense. It has already been suggested that the standard regimen for the treatment of DS-TB can be improved by optimising the doses of rifampin and rifapentine, thereby permitting shorter therapy (four months or less) and ensuring better outcomes (Mitnick et al., 2009). The same reference also proposes the use of inhaled or split dosing and the use of new classes of drugs. It is considered that the main priority for a new regimen is to identify a drug cocktail which has a more effective sterilizing activity or ability to "kill mycobacteria that persist after the initial days of multi-drug treatment" (Mitnick et al., 2009). Given our advancing knowledge about the pathogenesis of the disease and the emergence of new drugs, it is likely that this challenge can be overcome.

The impact of such optimisation has been modelled by assuming that a savings rate of at least 10% can be achieved on the current programme. This value is considered to be a conservative estimate since it does not allow for the additional savings as a consequence of improved treatment outcomes and eventually lower TB incidence. Using the programme costs as reported earlier, the risk-adjusted NPV of the savings is calculated to be $75.6 million.

The development of regimens based on new drugs is expensive and time consuming. For instance, it has been estimated that the recently-launched STAND (Shortening Treatments by Advancing Novel Drugs) trial will cost $58 million (Stop TB Partnership, 2014). However, even at this value, the project will have a positive return on investment (30%) and an internal rate of return (16%) which exceeds the average cost of capital. In summary, this second example also illustrates the main argument of this article, namely that governments should invest directly in health product development, although the returns are somewhat lower and the estimated initial investment a great deal higher than those presented in the first example.

Discussion

Several authors have called for policy reforms leading to more transparent, consultative and relevant allocation of health R&D budgets, and particularly public funds (Policy Cures and Global

Health Technology Coalition, 2012; Rao et al., 2014; Romero and Quental, 2014). For instance, the US government has been urged to maintain or increase its funding for global health R&D; increase focus on translational research (mainly clinical research) to fully leverage its global health R&D investments; and increase funding to partnering mechanisms that are focused on translation of global health research, including PDPs and other partnering approaches (Policy Cures and Global Health Technology Coalition, 2012).

In this article, similar policy reforms are being proposed. However the article is also advocating for a change within developing countries to the focus of public-funded health R&D, arguing that a greater proportion should be spent on experimental development (especially optimisation of treatment regimens) and less on fundamental science or basic research. The TB case studies presented show clearly that such expenditure can be justified from a purely economic return on investment consideration, given that the expenditure of public funds on TB treatment is high and significant savings can be made through improvements to the current drug regimens. In the process, a possible snowball effect could be achieved; higher efficiencies in TB treatment could release more funding for TB R&D, thereby realising greater savings and releasing further funds.

It is important to note that this policy recommendation is not arguing for a reduction in public funding of basic research, especially health R&D, in developed countries. The message of the Bamako Communique and other resolutions has been to stimulate health R&D in all countries but particularly developing countries. In the absence of any response, it is logical to argue for a re-allocation of existing resources in addition to new funds; this re-alignment should improve the impact of health R&D portfolios in these countries and seed further expansion. The re-allocation requires an overhaul of the present portfolio allocations, and new forms of partnership to address urgent public health needs. In the next section, the use of product development partnerships (PDPs) as an example of a new partnering structure is described.

THE EMERGENCE OF PRODUCT DEVELOPMENT PARTNERSHIPS IN GLOBAL HEALTH

Although important, the recruitment and retention of the competence required to support the clinical development of new pharmaceuticals, diagnostics or other health products will be a challenge for public research institutions (much of these skills presently lie in the private sector). Developed countries have partly addressed this issue by using PDPs as a means of meeting their needs for the capacity to develop innovative products for public health services.

The PDP model is a form of a public-private partnership with the specific purpose of developing new health products. Examples of such organisations include the Medicines for Malaria Venture, the Drugs for Neglected Diseases Initiative (DNDi) and the International AIDS Vaccine Initiative; examples of completed products include the drug combination of nifurtimox/eflornithine for the treatment of human African Trypanosomiasis, and fixed dose artesunate/mefloquine for the treatment of malaria, both of which have been developed by DNDi. The latter is an organisation created to respond to the “dire need of safe, affordable, easy-to-use and efficacious treatments for neglected patients” (Chatelain and Ioset, 2011).

PDPs are not-for-profit organisations which use the standard approaches of private sector companies (strict portfolio and project management, strong governance) to develop novel diagnostics, vaccines, medicines and other health products to serve neglected markets. The partnerships are funded partly by governments but mostly by donor organisations such as the Bill &

Melinda Gates Foundation and the Mellon Foundation. The model has been highly successful, with several accounts of good results (Mostert et al., 2014) including the report of the Australian Senate Foreign Affairs, Defence and Trade Committee, which concluded that Australia's initial 2013 investment of $10 million in four PDPs had "delivered a high return on investment, supporting a portfolio of 71 drug, 14 vaccine and 19 diagnostic projects" and expressed continued, strong support for R&D through PDPs" (Reddy and Spigelman, 2014).

Annual surveys of funding flows have reported that support for PDPs increased dramatically to 2009, but have since declined to about 12% of total global funding for neglected diseases, equivalent to $376 million in 2012 (Moran et al., 2013). Nevertheless PDPs remain an important model for NPD in public health, especially in developing countries. For instance, in 2013, the United Kingdom's Department for International Development (DFID) announced funding of $215 million over the next five years into nine PDPs to support the development of new drugs, vaccines, insecticides, diagnostic tools, and microbicides (Global Health Technologies Coalition, 2013). In a context of total global funding for health R&D reaching $240 billion, PDPs are one, albeit limited, mechanism whereby funding can be allocated to regions and diseases where it is most needed (Røttingen et al., 2013). In the next section, the expansion of this approach to encompass the new product and service needs of public health in general is discussed.

CREATING NEW MECHANISMS FOR PUBLIC HEALTH PRODUCT DEVELOPMENT

The success of PDPs in delivering urgently needed products for the treatment of neglected diseases raises the question of whether such a model can be more generally applied to NPD in the public sector. As already noted, governments spend significant amounts on health R&D yet urgent needs for new products and services to address public health priorities in many countries remain substantially underfunded (Røttingen et al., 2013). This gap between R&D expenditure and market need is essentially an issue of portfolio alignment. Although countries may achieve a degree of correlation between R&D expenditure and disease burden at the level of disease type (such as respiratory infections, heart disease and cancer) (Kinge et al., 2014), this expenditure is not analysed or aligned according to Frascati category. In other words, countries may fall into one of two categories, namely those for which there is poor alignment between R&D expenditure and disease burden, or those for which there is alignment but much of the public R&D is focussed on early stage research and of limited immediate utility to public health services. Although this is not a comprehensive analysis, there are no countries for which public funds are allocated to the further development of close-to-market, strongly aligned with disease burden, health products or services.

It has been argued that PDPs are undermining the global health governance and represent a "further deepening of the neoliberal management of individuals and populations, allowing private interest to become more embedded within the public sphere" (Ruckert and Labonté, 2014). This argument has been disputed by a group of economists who are concerned that a relentless attack on public institutions ignores an important role of the state in incentivising investment, building networks, and undertaking high risk R&D. Repeated calls for the public institutions to be downsized in order to 'unleash the power of entrepreneurship and innovation of the private sector' have been largely overdone, and could lead to a weakened state unable to deliver on economic growth and fostering radical innovation (Mazzucato, 2013).

Within this context of debate, it seems logical to argue for a compromise arrangement, in which one attempts to reproduce some aspects of private sector innovation and also PDPs within public sector NPD; these aspects could include:

- the use of strict portfolio and project management techniques to tackle R&D challenges
- the adoption of open innovation practices with partnerships working as virtual organisations
- highly specific initiatives focused on a clear goal or outcome (such as a new therapy for malaria)
- the assembly and retention of unique expertise not available within public sector facilities, including the ability to undertake commercial studies and market surveys
- the development of non-contractual allies in a collective effort to develop and improve access to health products.

Although this proposal may seem impractical, it is already in existence within the public-funded defence sectors of the larger systems of innovation (see Figure 3). As noted earlier, these public sectors already undertake significant NPD within a strong portfolio management and governance framework. The extension of this capability in the interests of health security, rather than national security, will require a change in R&D policy, the re-engineering of public research agencies and the re-direction of public funding.

CONCLUSION

The existing model of health R&D funding, in which the state eschews NPD and commits the bulk of its R&D expenditure to basic research, is unsuitable for the improvement of public health systems in developing countries. Although the allocation has worked admirably in the development of new health products for which large and profitable markets exist, it has failed in delivering innovative products and services that serve mainly low margin public health markets, as exemplified by the case study on TB. This failure demands a new role of governments in particularly developing countries to fund NPD leading to novel products which can strengthen their public health services.

The analysis has shown that this re-allocation does not contradict existing roles of the state and could be highly effective as long as the funding reforms are accompanied by the implementation of portfolio management, project management and governance procedures already in use within health PDPs. Regardless of who performs the research, it is apparent that increased investment by governments in close-to-market products and services will lead to future improvements in public health outcomes at lower net cost.

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