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Are public-private partnerships the solution to tackle neglected tropical diseases? A systematic review of the literature

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Highlights:

- Introduction to the market failure of neglected tropical diseases;
- Assess the adequacy of public-private partnerships;
- A mapping of public-private partnership(s) per disease;
- No impact evaluation of public-private partnerships could be found;
- The literature on public-private partnerships is mainly descriptive;

Abstract

Pharmaceutical companies are reluctant to invest in research and development (R&D) of products for neglected tropical diseases (NTDs) mainly due to the low ability-to-pay of health insurance systems and of potential consumers. The available preventive and curative interventions for NTDs mostly rely on old technologies and products that are often not adequate. Moreover, NTDs mostly affect populations living in remote rural areas and conflict zones, thereby hampering access to healthcare. The challenges posed by NTDs have led to the proliferation of a variety of public-private partnerships (PPPs) in the last decades. We conducted a systematic review to assess the functioning and impact of these partnerships on the development of and access to better technologies for NTDs. Our systematic review revealed a clear lack of empirical assessment of PPPs: no impact evaluation analyses could be found, which are crucial to realize the full potential of PPPs and to progress further towards NTDs elimination.

Keywords: Public-private partnerships; Neglected tropical diseases;Health economics; Public health; Research and development

Introduction

Neglected tropical diseases (NTDs) are a diverse group of communicable diseases that affect more than one billion people, mainly across the developing world. The World Health Organization (WHO) lists 17 NTDs: Buruli Ulcer, Chagas disease, Dengue, Chikungunya, Dracunculiasis (guinea-worm disease), Echinococcosis, Endemic treponematoses, Yaws, Human African trypanosomiasis (sleeping sickness),

Leishmaniasis, Leprosy, Hansen disease, Lymphatic filariasis, Onchorcerciasis (river blindness), Rabies, Schistosomiasis, Soil-transmitted helminthiases, Taeniasis, Cysticercosis, Trachoma (1). It is common for people infected with NTDs to be hit by multiple pathogens; impairing physical and cognitive development, and leading to an estimated 534 000 death yearly (2). These diseases were associated with 26.06 million disability adjusted-life years (DALYs) (3). NTDs have a serious impact on work productivity: the largest of which seems to be due to blindness from onchocerciasis and severe manifestations of schistosomiasis (4). Overall, these 17 diseases have been estimated to cost billions of dollars to developing economies each year (3).

The development of new treatments and vaccines cannot be incentivized through the usual patent system, for the ensuing reasons. First, the patent system grants monopoly power to pharmaceutical companies, usually for a period of 20 years, to encourage investment in research and development (R&D). The resulting lack of competition enables pharmaceutical companies to recoup R&D investment costs by setting a market price well above the marginal cost of production. Pharmaceutical companies are hence reluctant to invest in R&D for diseases that predominantly affect low and middle-income countries (LMICs) because of the health insurance system and consumers' reduced ability-to-pay. Second, as LMICs are often characterized by poor local infrastructure and sanitation, lack of political commitment and bad governance in the health sector, lack of drug safety harmonization and weak legal frameworks, there can be no guarantee that a developed product will necessarily reach the population in need, thereby discouraging investment in R&D (5)(6)(7).

Translating this market failure into real facts, only five new therapeutic products were approved for NTDs between 2000 and 2011, accounting for less than 1% of the total products approved (i.e. 5 products out of 850). A significant share of the newly approved products instead targeted neuropsychiatric disorders (13%) and cardiovascular diseases (10%) (8). This issue was pointed out by Bill Gates who, in 2008, called for "creative capitalism"(9), which include push, pull and mixed (push-pull) schemes. Push schemes reduce upfront costs inherent to R&D activities through various grants and subsidies offered prior to product discoveries – examples include R&D grants and direct funding. Pull schemes, on the contrary, offer a variety of rewards that are contingent on successful product discoveries – examples include advance market commitment (AMC)

and priority review voucher (PRV). Push, pull and mixed schemes offer avenues for PPPs to overcome the barriers to the development of products for NTDs.

In 2011, half of the 34 new formulations for NTDs in clinical development – of which 85% were in Phase 2 or 3 – were sponsored through PPPs, charities, foundations and philanthropic institutions (8). PPPs, so far, have mainly used push schemes, with government (e.g. The United Kingdom Department for International Development) or philanthropic (e.g. Bill and Melinda Gates Foundation) bodies providing upfront financing for clinical trials. The role of PPPs mainly lies in product development (PDPs; e.g. The Drug for Neglected Disease Initiative (DNDi)) and in product delivery and uptake (Access PPPs; e.g. The Onchocerciasis Control Program (OCP)). Other types of PPPs include financing and coordinating partnerships (10). The different types of partnerships are not mutually exclusive: while it is more common for partnerships to dedicate themselves to one particular role, some use a hybrid model (10).

Tackling NTDs has become a major goal subscribed by the international community: the London Declaration – signed in 2012 – aims to reach the control or elimination of at least 10 NTDs by 2020 (11). Various PPPs, with differing models, have hence been put in place to achieve this objective (12). These have expanded over the past 20 years, and for some, the impacts are now measurable. Accordingly, we believe that it is now within researchers' reach to assess the effectiveness and impact of these alliances. We thus conducted this review to respectively: (i) assess the scientific opinion on the adequacy and viability of PPPs; (ii) identify potential best mechanism(s) between push, pull and mixed ones; (iii) map the different partnerships and analyze their role in reaching the globally set goal to control, eliminate or eradicate NTDs.

Study data and methods

Search strategy and selection criteria

A systematic literature search on PPPs for NTDs was performed over three databases: a general (Scopus), a bio-medical (PubMed) and an economic (IDEAS – Research Papers in Economics, REPEC) database. The search was conducted over three different databases to capture the multidisciplinary facets of PPPs. The REPEC database, for

instance, enabled us to capture the economic perspective – a crucial feature – of PPPs and hence of the push, pull and hybrid mechanisms. In order to not discard any initiatives (e.g. Onchocerciasis Control Program was launched in 1974), we searched for peer-reviewed articles published between – and as far as – January 1970 and August 2016 in English or French using the following search terms: (public-private partnership* OR public private partnership* OR PPP* OR product-development partnership* OR product development partnership* OR PDP*) AND (neglect* tropical disease* OR neglect* disease* OR each NTD of the WHO list). We first screened the "titles", "abstracts" and "keywords" of all extracted records. Next, we read the full text articles to evaluate them according to our inclusion criteria. The titles and abstracts of the extracted records were independently reviewed by two investigators (CA&TS). Records were excluded if, PPPs (i) were only mentioned in the conclusion or as a recommendation, (ii) focused on diseases that are not on the World Health Organization (WHO) NTDs list; (iii) considered NTDs of the WHO list but not for human species. Additionally, editorial material such as interviews, forum/symposium and round table discussion, comments and profile articles were excluded. All the remaining records were included in the review. If discordances occurred, they were resolved through discussions with a third investigator (ES); who would retrieve the full text in case of a doubt. The full text papers were then classified into three categories, based on the nature of their content:

i. Descriptive studies of PPPs context
ii. Descriptive studies of PPPs experiences
iii. Empirical studies

'Descriptive studies of PPPs context' review the weaknesses and strengths of the push, pull and mixed schemes. These were scrutinized tabulating the following features (cf. table V in appendix): scheme(s) or type(s) of partnership discussed; associated drawback(s); recommended scheme(s) or partnership(s); associated advantage(s); policy recommendation(s); and whether the paper mentions elimination. 'Descriptive studies of PPPs experience' report the existence, main characteristics, achievement and limitations of PPPs. These were analyzed tabulating the following aspects (cf. table VI in appendix): name of the PPP and year of creation; partners; disease(s); tool(s) used; what is the PPP resolving at; the outcome of the PPP; the limitation(s) of the PPP; and

whether the paper mentions elimination. 'Empirical studies' had a concise research purpose that was addressed via data-based analyses (qualitative and/or quantitative). These were examined tabulating the following features (cf. table VII in the appendix): research question; methodological approach; main finding(s); limitation(s) of the study; and whether the paper mentions elimination.

Results

The search resulted in 198 non-duplicate articles, among which 6 could not be accessed. After abstract screening and full-text review, 74 articles were assessed eligible (cf. Figure 1 for PRISMA diagram).

Descriptive studies of PPPs context

Push schemes

Push schemes have been heavily criticized in the literature. First, since push schemes subsidize research input and not research output, they may finance unsuccessful R&D activities (13). Second, they tend to suffer from a moral hazard and adverse selection problem (5)(14). Moral hazard arises due to asymmetric information between grant recipients and donors. Since donors know less than grant recipients about the success probability, cost and evolution of the project, they cannot perfectly monitor the activities of grant recipients. The effectiveness of the program can then be jeopardized if grant recipients have differing incentives from donors. Accordingly, donors are faced with the issue of picking the 'right' grant recipient. Common examples of push schemes are R&D grants, R&D tax credit and patent pools – which are described in table I.

So far, push mechanisms have been advocated to decrease the costs of R&D for NTDs: mostly to stimulate investment in early phases (i.e. basic research) providing a basis for later applied research. Nevertheless, some may argue that the cost of R&D per se does not explain the market failure attributed to these diseases. Pharmaceutical companies often make risky and expensive investment in products for which they trust having a market (15). Accordingly, the unviable market attractiveness of NTDs, relative to the

cost and risk of R&D investment, is a potentially more credible barrier than the cost of R&D per se (15). This would suggest that pull mechanisms are perhaps better suited to stimulate investment in R&D.

Pull schemes

Pull schemes guarantee a demand for the final product and hence ensure a positive return on R&D investment. Examples of such schemes include AMC, PRV and transferable intellectual property (IP) rights – as detailed in the table II.

Pull schemes also have their criticisms. AMC scheme is subject to the 'time-inconsistency' problem: once R&D investments are sunk, AMC donors may be tempted to renegotiate on their promise to obtain the lowest possible price (13). Moreover, AMC donors may encounter difficulties in setting the right 'AMC prize'; if too low, it will discourage companies' participation and if too high, it will lead to market inefficiency (15). Lastly, AMC assumes that companies have the necessary up-front fund to finance R&D, which may not necessarily be the case for the small ones (5). AMCs have resulted so far in two pneumococcal vaccines, which however have been criticised for neither accelerating the innovation cycle nor increasing availability. With respect to the PRV, there has been little evidence in the last decade that its benefits are going to where they were intended (16). To date, the FDA has awarded 4 PRVs to: an antimalarial drug (coartem), a multidrug resistant tuberculosis medicine (bedaquiline), an oral treatment for leishmaniasis (miltefosine) and a cholera vaccine (Vaxchora) (17). Among these 4 products, 3 were already developed and registered outside the United States (US) well before the voucher system was launched (17)(16). The PRV may inadvertently distorts incentives for developing novel and pioneering drugs by pushing through the development of close substitutes, known as me-too drugs (5).

Hybrid schemes

Mixed schemes use a combination of push and pull mechanisms; however examples are few. A well-known one is the orphan drug act (ODA) adopted in the US, Europe, Japan and Australia (5). The ODA offers an income tax credit equal to 50% of clinical trial expenses (push scheme) and extends patent rights with up to 7 years market exclusivity (pull scheme) (5) (18)(13). Although the ODA has proved to be successful in high-income countries (HICs), it is not applicable to NTDs. Market exclusivity is only

relevant for drugs that can be sold at a very high price affordable for health insurance systems in HICs (5). Mixed schemes however are not restricted to the ODA; different combinations are possible.

Push, pull and mixed schemes offer opportunities for PDPs but when it comes to Access PPPs, the incentive is left on the patent's holder concern. There is a certain consensus that PDPs should adopt a mixed scheme strategy (6)(13)(18)(15)(19)(20). That is, PDPs should first use push schemes to encourage investments in the earlier phases of R&D (e.g. R&D grants, prize mechanism, etc.) that would be then pulled along by financial commitments (e.g. AMC and PRV) from the public sector and philanthropic partners to encourage further investment in costly phase II and III (18) (20) (19).

Descriptive studies of PPPs experiences

The main motives behind PPPs are to respond to the lack of safe, affordable, easy-to-use and efficacious treatments (i.e. PDPs) (21) (22) and ensure delivery of products to populations affected by NTDs (i.e. Access PPPs) as illustrated in table III.

The most cited partnerships in the literature are the ones that include drug donations of Ivermectin by Merck & Co targeting onchocerciasis and lymphatic filariasis (i.e. OCP, APOC, OEPA, GPELF). PPPs are not equally distributed among NTDs: some NTDs could not be attributed any (e.g. dracunculiasis (guinea-worm disease), echinococcosis, endemic treponematoses, yaws, hansen disease, taeniasis) while others such as onchocerciasis, schistosomiasis and human African trypanosomiasis have 5 or more initiatives. The distribution of PDPs and Access PPPs across NTDs – i.e. the number of different initiatives found per NTD in the literature – is illustrated in Figure 2 and 3 respectively. The partnerships are mainly PDPs, followed closely by 'Access PPPs' (through mass drug administration (MDA)). Other types of partnership act as a coordination, awareness raiser, and provider of goods and services (e.g. transport, staff training, etc.).

Are PPPs capable of reaching NTDs elimination?

PDPs and 'Access PPPs' provide an opportunity to reach NTDs elimination (23). So far, NTDs control and elimination strategies have mainly relied on MDA with drug donated by large pharmaceutical companies and repeatedly administered to populations (i.e. Access PPPs) (24). This approach has been named as "preventive chemotherapy" by the WHO for diseases like lymphatic filariasis (i.e. GPELF) and trachoma (i.e. ITI) because it is leading to the interruption of transmission and disease elimination (25). However, for most NTDs such as onchocerciasis, hookworm, schistosomiasis, dengue, leishmaniasis, and Chagas disease, new molecular entities (NMEs) as well as additional control tools are truly needed (23)(25)(26). In 2011, the funding gap for drug alone was estimated at $222 million USD (27). The needed control tools include preventive vaccines and easy-to-use, reliable and low-cost diagnostics to identify infected patients; monitor the impact of MDA programs; and survey disease re-emergence (20).

Empirical studies of PPPs

Only 8 out of the 74 papers assessed eligible, attempted to address a specific research purpose using either quantitative and/or qualitative methods. Although using research methods, the types of analysis remain particularly descriptive (e.g. assess the number of drugs developed under a PPP over 2009-2013; examine the funding patterns of PPPs; etc.) Not a single in-depth impact evaluation analysis of PPPs could be found despite their critical role in assessing PPPs efficiency. Only one economic evaluation – a cost-effectiveness analysis – was found, and revealed that the PDP model is not the most cost-effective approach if it acts as a push scheme through R&D grants (18). Each study is summarized in table IV.

Discussion

The scientific literature on PPPs for NTDs is predominantly descriptive. An important part of the literature focuses on narrative descriptions of specific partnerships. A smaller but still significant share of the literature describes the different schemes – push, pull and mixed schemes – that can be used in a partnership. The striking point, however, is

the small number of empirical studies: only 8 studies out of 74 had a research objective that was assessed through empirical investigation.

PDPs are loosely defined and the decision regarding which scheme to adopt is not unanimous. Nevertheless, it seems that overall mixed schemes should be applied to PDPs but the equilibrium between push and pull incentives is still to be defined in the context of NTDs, as it was done for rare diseases (i.e. ODA). PDPs are also subject to various criticisms that need to be addressed. These include, among others: (i) their lack of transparency, accountability, clear government structure, and alignment with country priorities and systems (28)(14)(29); (ii) their tendency to alter existing medicines rather than creating new ones (30)(29); and the lack of coordination between sectors and partners resulting in duplicated efforts (28). PDPs' generalized lack of transparency, for instance, is a potential reason for the dearth of empirical research conducted on the topic. Without transparency, pharmaceutical companies are not forced to report on donations received, private investments made, R&D time frame and success rates. With respect to Access PPPs, the criticisms are fewer and mainly highlight the need for greater epidemiologic surveillance following the end of a partnership (31)(32). Lastly, PDPs and Access PPPs have distinctive roles but – as underlined in the literature – these should not be mutually exclusive (33)(34). The fact that large-scale manufacturing, adoption and distribution of developed products in low income countries are not a compulsory requirement of PDPs, reveals a dichotomy between the two (34). Hence, schemes should be revised and designed in a way that not only encourages investment in R&D but also in product delivery and uptake. Greater harmony between the development and delivery processes within PPPs is crucial to reach NTDs elimination (29).

To conclude, PPPs present numerous advantages over the traditional pharmaceutical industry development process. Thanks to their flexibility, PPPs have the ability to tap on each of the participants' comparative advantage(s). PDPs and Access PPPs, together, provide a great opportunity to tackle the challenges posed by NTDs. However, in order to make the best of these alliances, one must evaluate their impact; analyze how differences in their characteristics affect their performance. The research on PPPs for NTDs is hindered by the limited availability of standard, consistent, and routinely collected measures of progress in pharmaceutical innovation (35). As pointed out by

Daniel et al., "no single routinely updated, publicly available database exists to evaluate pharmaceutical innovation" (35). There is one database, called G-FINDER, which reports on the public, philanthropic and private funding to partnerships but not on their specific characteristics and scientific progress. To deal with this lack of transparency and ensuing shortage of data, one could require partnerships to register on a single platform, on which partners would have to declare all funding received; investments made; starting and ending dates of each clinical step; etc. This incentive to the public provision of information on partnership could be enhanced by a scheme, as suggested in the literature: "transparency in exchange for public funds" (5). In addition to the lack of data, the research is challenged by the absence of a counterfactual to which PPPs for NTDs could be compared; as it is unlikely to see non-PPP models for diseases that mainly affect the poor. However, assessing how different characteristics of PPPs – such as geographic coverage, stakeholders involved, funding and governance structure – affect the desired outcome would already provide good insights into how the model could be optimized; shedding light on the drivers of their success or failure.

Ethical issues: There are no ethical issues.

Conflict of interest: There is no conflict of interest

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Figure 1: PRISMA Flow Diagram

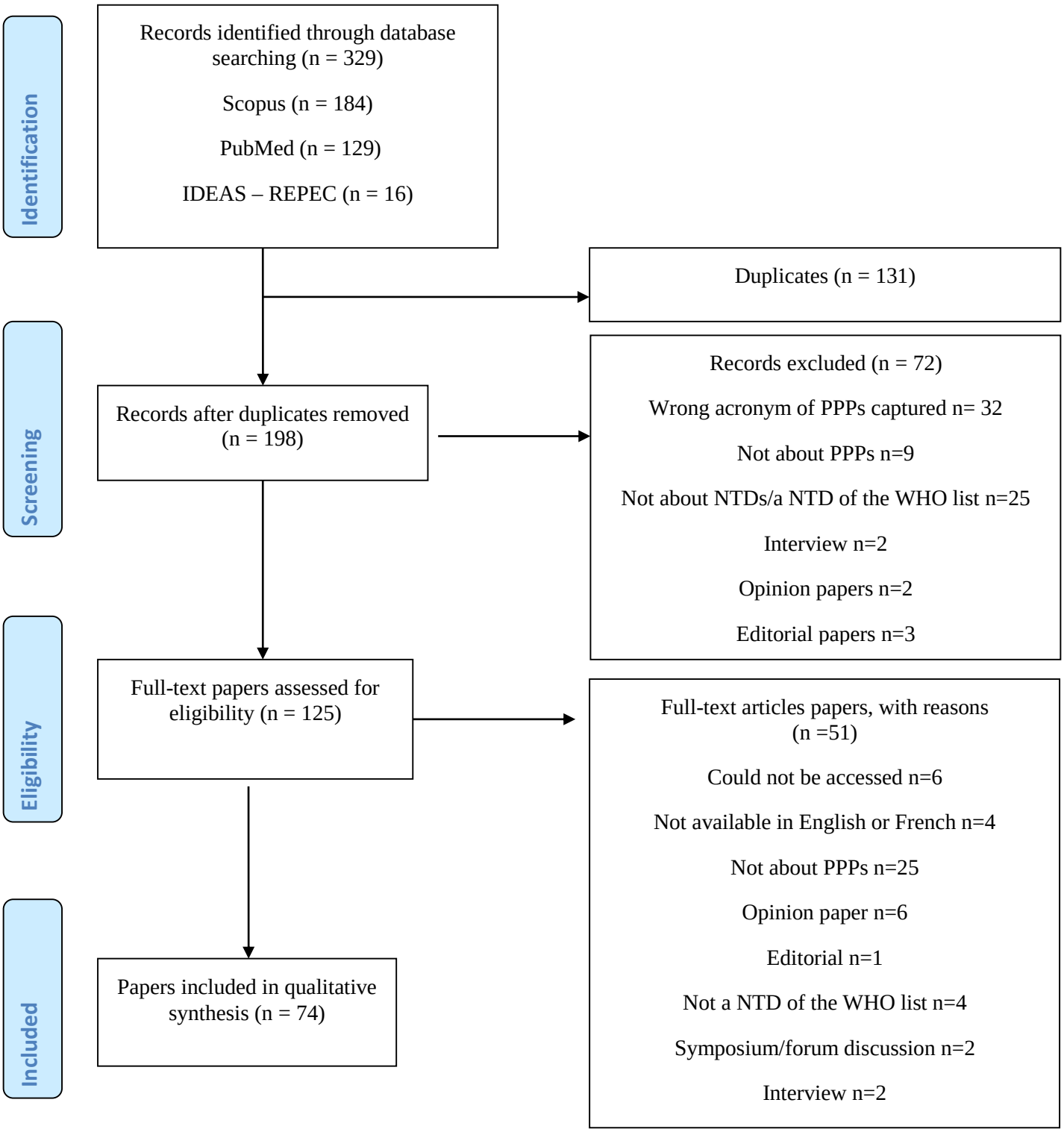


Figure 2: Distribution of product-development partnerships(PDPs) across NTDs

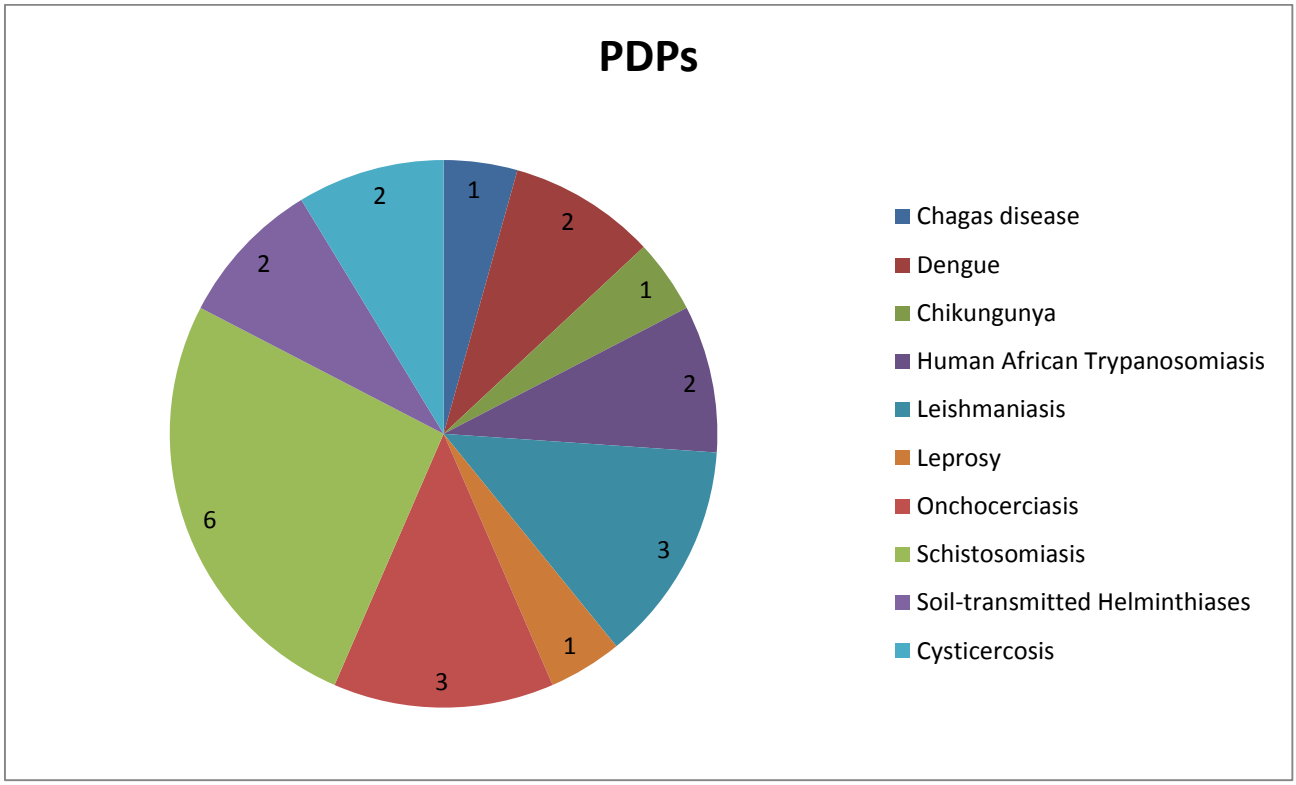
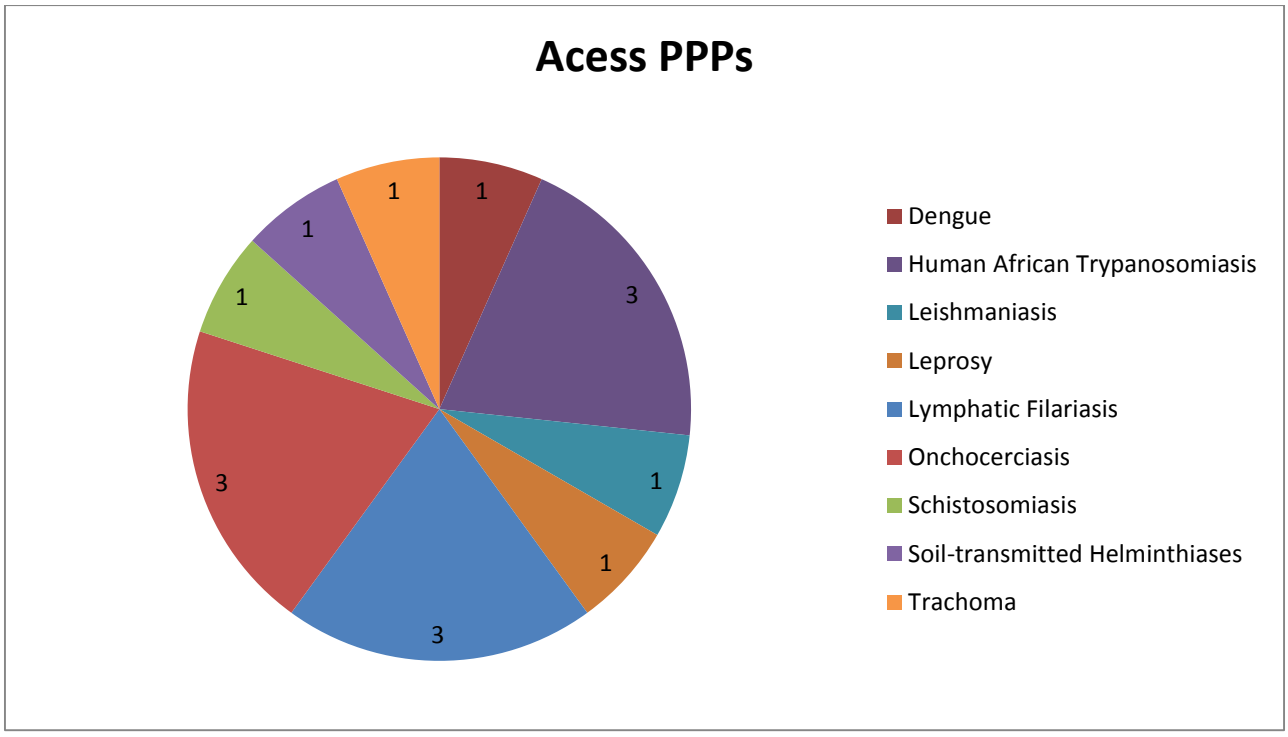


Figure 3: Distribution of Access PPPs across NTDs



Exhibits

Table I: Push mechanisms: advantage(s) and disadvantage(s)

Push mechanisms	**Advantage(s)**	**Disadvantage(s)**
R&D grant: these grants are provided to innovators in advance of drug discovery.	They encourage small companies with less capital to step in (18).	Moral hazard and adverse selection problem: companies may exaggerate the R&D cost in order to receive more funding (18)(5).
R&D tax credit: companies investing in R&D for NTDs are eligible for reduced taxation.	Widely used to stimulate research in a specific area (15).	Tax credit can only benefit companies with large tax burden (i.e. income earning ones). Hence it is not relevant to smaller companies whom generally play a crucial role in the product development process (18)(5)(15).
Patent pools (i.e. open-source R&D): invite patent owners to cross-license their patents, either between each other or to third parties, which can subsequently be used for further research.	Patent pools avoid negotiation with each patent holder (36).	The viability of patent pools is questionable as these have been poorly used (29). There is also a risk of anti-competitive behavior due to cartel formation (18).

Table II: Pull mechanisms: advantage(s) and disadvantage(s)

Pull scheme	Advantage(s)	Disadvantage(s)
Advance market commitment (AMC): donors make a prospective commitment to purchase a successful product at a pre-specified price for a fixed quantity.	The reward is only granted once a viable product has been developed (15).	Time-inconsistency problem (13); Difficulty is setting the right AMC prize (15); may not be appealing to small pharmaceutical companies (5).
Priority review voucher (PRV): Pharmaceutical companies are granted by the food and drug administration (FDA) a priority review voucher (i.e. review within 6 months) upon successful development of a product for a NTD. The voucher can be sold to a third party and may be valued at about US$300 million or more by a company with a potential blockbuster drug candidate (5).	PRV encourages R&D for NTDs while promoting welfare gains from earlier market access in high income countries (HICs).	PRV may not necessarily reward the true innovators (37).
Transferable IP rights: pharmaceutical companies are awarded an IP extension for a product of their choice conditional on successfully bringing a NTD product on the market.	This scheme is potentially very attractive to big pharmaceutical companies (15).	IP extension translates into high prices for a prolonged period, imposing a burden on patients whom are in need of the product for which the patent has been extended (15).

Table III: Public-private partnership(s) per disease

NTDs of the WHO list	Partnership(s) or Organization leading the partnership	Tool(s)	Comment	Citation of the PPP
Buruli Ulcer	WIPO Re:Search consortium	NA	NA	(38)
Chagas disease	Drugs for Neglected Diseases Initiative (DNDi)	PDP: Drug development	NA	(21) (39)
Dengue	Novartis Institute of Tropical Disease	PDP: Vaccine and drug development	The PDP has not yet led to a vaccine candidate but has resulted in the largest database of dengue virus genome (40)	(42)(40)
	The Pediatric Dengue Vaccine Initiative (PDVI)	Developing diagnostics to measure immune response to vaccines, detect acute infection, clinically evaluating vaccine candidates, and promoting vaccine access.	NA	(43)
	The Dengue Prevention	Social mobilization	After the program, the number of	(41)

	Program		houses and schools with immature Ae. Aegypti had decreased (41)	
Chikungunya	PHYTOCHIK	PDP: Bioprospection to develop drug candidates	During the first 2 years: 22 pure compounds were evaluated for chikungunya (44)	(44)
Dracunculiasis (guinea-worm disease)	No partnerships found			
Echinococcosis	No partnerships found			
Endemic treponematoses	No partnerships found			
Yaws	No partnerships found			
Human African trypanosomiasis (HAT) (sleeping sickness)	Stamp Out Sleeping Sickness (SOS)	Access PPP: Mass cattle treatment with drug donation by Ceva Sante Animale	The objective is to threat > 86% of the cattle population which will weaken the animal reservoir and reduce transmission to humans (45)	(48)(45)
	DNDi	PDP: Drug development (A combination treatment of nifurtimox and eflornithine (NECT))	NECT was developed in 2009 and is now recommended by the WHO (21)	(21)

	HAT control program	Access PPP: Drug donation by Sanofi-Aventis (difluoromethylornithine, melarsoprol, pentamidine) and Bayer (suramin)	The donation of drugs released substantial financial resources and provided continued care for HAT patient (46)	(46)
	The Special Program for Research and Training in Tropical Disease (TDR)	PDP: Drug development (eflornithine)	The drug is highly effective for the disease in its later stages (47)	(47)
	WIPO Re:Search consortium	Facilitate coordination for product development	NA	(38)
Leishmaniasis	The Infectious Disease Research Institute (IDRI)	PDP: Vaccine development	The candidate made it to phase 2 clinical trials (49)	(49) (24)
	WIPO Re:Search consortium	Facilitate coordination for product development	NA	(38)
	The Special Program for Research and Training in	PDP: Drug development (Miltefosine and Paramomycin)	NA	(47)(50)

	Tropical Disease (TDR) DNDi	 PDP: Drug development	 NA	 (21)
Leprosy	Novartis The German Leprosy Relief Association (GLRA)	Access PPP: Donation by Novartis of multidrug therapy packages (Dapsome, Rimactane and Lamprene) Various (e.g. staff training, provision of transport, etc.)	NA GLRA fills the gaps in existing national disease control programmes in five South American countries and in seven Brazilian states (51)	(22) (51)
Hansen disease	No partnerships found			
Lymphatic Filariasis (LF)	The Global Program to Eliminate Lymphatic Filariasis (GPELF)	Access PPPs: drug donation of Albendazole by GlaxoSmithKline and Ivermectin by Merck	GPELF has stopped the progression to clinical morbidity in 9.5 million individuals already infected with the parasites	(52)(22)(26)(53)

		Access PPPs	that cause LF (52)	
	The Global Alliance for Elimination of Lymphatic Filariasis (GAELF)		NA	(54)
	WIPO Re:Search consortium	Facilitate coordination for product development	NA	(38)
Onchocerciasis (river blindness)	The African Program for Onchocerciasis Control (APOC)	Access PPP: community-directed treatment with Ivermectin (donated by Merck)	In 2012, the program was treating over 90 million people annually in 19 countries (55)	(56)(54)(55)(57)(53)
	The Onchocerciasis Control Program (OCP)	Access PPP: drug donation of Ivermectin by Merck	OCP successfully reduced the transmission, incidence and impact of onchocerciasis in large areas of 11 countries (55)	(58)(59)(27)(60) (61)(55)(57)(53)
	The Onchocerciasis Elimination Program for the Americas	Access PPP: drug donation of Ivermectin by Merck	By 2010, Colombia had interrupted transmission and stopped treatment. Several formerly	(60)(31)(62)(53)

	(OEPA)		endemic areas in Mexico, Guatemala and Venezuela have also stopped treatment (31)	
	The Sabin Vaccine Institute with the New York Blood Center	PDP: vaccine development (establish a novel strategy of antigen selection)	8 top-ranking protective antigens have emerged (49)	(49)
	DNDi	PDP: drug development	DNDi has drug candidates in phase 2 and 3 (39)	(39)
	TOVA (The Onchocerciasis Vaccine for Africa)	PDP: vaccine development (Ov-103 and Ov-RAL-2	The antigens are advancing through preclinical development (26)	(26)
	Human WIPO Re:Search consortium	Necator) Facilitate coordination for product development	NA	(38)
Rabies	No partnerships found			
Schistosomiasis	Institut Pasteur in Lille	PDP: vaccine development (Bilhvax)	Bilhvax has completed phase 2 and phase 3	(49)(63)
	The Sabin	PDP: vaccine	Phase 2 trials were	(49)(24)(64)(6

	Vaccine Institue and the Oswaldo Cruz Foundation (FIOCRUZ)	development (sm14)	planned for 2005	3)(65)(66)
	The Sabin Vaccine Institute with Baylor College of Medicine	PDP: vaccine development (Sm-TSP-2)	Phase I trial has been initiated in 2004	(63)(26)
	WIPO Re:Search consortium	Facilitate coordination for product development	NA	(38)
	No partnership name available	Access PPPs: Drug donation by Merck (Praziquantel)	NA	(22)
	No partnership name available	PDP: Vaccine development (Sm-TSP-2, Sh28GST and Sm-p80)	Currently in Clinical trials	(26)
	The Regional Network for Asian Schistosomiasis (RNAS)	Facilitate coordination for product development	NA	(67)
Soil-transmitted Helminthiases	WIPO Re:Search consortium	WIPO Re:Search consortium	NA	(38)

	The Human Hookworm Initiative (HHVI) The Human Hookworm Initiative (HHVI)	PDP: vaccine development (Na-GST-1 and Na-APR-1) PDP: vaccine development (Na-ASP-2)	Both antigens are cur- rently in Phase 1 trials in Gabon and Brazil (26) The Na-ASP-2 hookworm vaccine has undergone Phase I in the USA(68)	(49)(49)(24) (68)(69)
Taeniasis	No partnerships found			
Cysticercosis	WIPO Re:Search consortium The Regional Network for Asian Schistosomiasis (RNAS)	Facilitate coordination for product development Facilitate coordination for product development	NA NA	(38) (67)
Trachoma	The International Trachoma Initiative (ITI)	Access PPP: Drug donation of Zithromax by Pfizer	ITI is working on the WHO goal of eliminating blinding trachoma by the year 2020	(32)(22)

NA = not available

Table IV: Empirical studies

Study	Research question	Methodology and Data sources	Main findings
(70)	To measure progress in neglected diseases drug development.	Assess the number of drugs approved that were developed under a PPP between 2009 and 2013 according to ClinicalTrials.gov, IMS R&D Focus, Investigational Drugs database and regulatory agency websites.	57% of the 20 newly approved products for neglected diseases were developed under a PPP but 60% of these were for HIV and malaria.
(71)	To assess the contribution of Medicine for Malaria Venture (MMV), DNDi and the One World Health (OWH) on their products' availability, affordability and adoption in LICs.	The framework developed by Frost and Reich (2008) (72) using publicly available sources.	To various extents, these partnerships have successfully ensured products' registration, distribution and adoption into national treatment policies in LICs, but ensuring broad and equitable access still remains an issue.
(18)	To compare the cost-effectiveness of the PDP (categorized as push scheme) with the advance market commitment scheme (pull scheme) and mixed schemes (PDP until phase II trials,	Cost-effectiveness analysis. Estimates of costs associated with each model, timelines and transition probabilities from reaching one phase to the other were	Although the PDP scheme was the cheapest option, the number of disability adjusted-life years (DALYs) averted was much lower than for the mixed scheme and advance market commitment scheme. Mixed scheme is the most cost-effective.

	followed by AMC afterward) for vaccines' development for neglected diseases.	obtained from the literature. The health impact was measured using a baseline case from a WHO report of potential disability-adjusted life years (DALYs) averted per immunization for malaria.	
(73)	To examine the role of PDP in R&D for neglected diseases	To examine the funding pattern of 14 PDPs for neglected diseases during the year 2007 using the Global Funding of Innovation for Neglected Diseases (G-FINDER) database	The Bill and Melinda Gates foundation remains the principal funder of PPPs (50% of annual income), followed by four public funders: the US Agency for International Development (USAID), the UK Department for International Development (DFID), the Dutch ministry of foreign affairs, and the Irish Aid (collectively contributing to 28% of annual income).
(74)	To measure the correlation between partner's voting power and financial contribution among global health initiatives	Correlation analysis among 17 global health initiatives using Official statements of PPPs and the Initiative on Public-Private Partnerships for Health (IPPPH) database.	For the public sector – whilst not for the private sector – this correlation exists and is positive.
(75)	To understand crucial elements in the	Systematic review over 12 databases	10 of the 212 references initially extracted were included in the

	partnership process		final review. The development stage requires: share goals and values; equality of power relation; exchange of expertise and resources; stakeholder engagement; and assessment of the local health capacity while the management stage requires: transparency; communication; and engaged decision-making amongst partners.
(76)	To assess the progress of pharmaceutical companies in meeting the commitments on drug donations set at the London Declaration in 2012	Medline and LexisNexis searches of peer-reviewed publications and trade journals as well as surveys administered to 10 company signatories.	Substantial progress has been reported, with 17 donation programs across 10 disease categories.
(77)	To examine the evaluation of the Mectizan donation program (MDP) from the participating partners	Semi-structured interviews of 25 partners	Overall, the program was rated highly beneficial. However the two main pitfalls were: that the activities may not reach the primary constituency of the partner's program and the effort of the individual organization may not be recognized.