UNIVERSITAT DE BARCELONA

An economic perspective on the challenges associated with tackling neglected diseases: from product development to implementation and adoption

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AN ECONOMIC PERSPECTIVE ON THE CHALLENGES ASSOCIATED WITH TACKLING NEGLECTED DISEASES: FROM PRODUCT DEVELOPMENT TO IMPLEMENTATION AND ADOPTION

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“The first wealth is health.”

Ralph Waldo Emerson

A mes grand-parents,

Pour leur soutien et amour inconditionel.

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Abbreviation and acronym list

AMC	Advance market commitment
CL	Cutaneous leishmaniasis
DALYs	Disability adjusted-life years
DD	Difference-in-differences
DDD	Difference-in-difference-in-differences
DNDi	Drugs for Neglected Diseases Initiatives
FDA	Food and Drug Administration
FIND	Foundation For Innovative New Diagnostics
Gavi	Global Alliance for Vaccines and Immunization
GBD	Global burden disease
GDP	Gross domestic product
GSK	GlaxoSmithKline
ICER	Incremental cost-effectiveness ratio
ICTPR	International Clinical Trials Registry Platform
ISGlobal	Barcelona Institute for Global Health
ITI	International trachoma Initiative
ITM	Institute of Tropical Medicine
LAMP	Loopamp™ detection kit
LF	Lymphatic filariasis
MDA	Mass drug administration
MoPH	Ministry of public health
NGOs	Non-governmental organization
NMB	Net monetary benefit
NMLCP	National malaria leishmaniasis control program
NTDs	Neglected tropical diseases
PCR	Polymerase chain reaction
PDPs	Product-development partnerships
PPPs	Public-private partnerships
PRV	Priority review voucher

QALYs	Quality adjusted-life years
R&D	Research and development
RDT	Rapid diagnostic test
REPEC	Research papers in Economics
SEM	Structural equation model
SSG	Sodium stibogluconate
STH	Soil-transmitted helminths
US	United States
USAID	The United States Agency for International Development
VBDs	Vector-borne disease
WHO	World Health Organization
WTP	Willingness-to-pay

Summary

Background

The World Health Organization (WHO) has identified over 20 neglected tropical diseases (NTDs), affecting 1.5 billion people worldwide (Uniting to combat neglected tropical diseases, 2017). While being all infectious diseases, many NTDs are chronic, with conditions that progressively become worse if undetected and untreated. Moreover, the damage they cause is often irreversible with important social and economic consequences (Sachs *et al.*, 2007; Lenk *et al.*, 2016). Such diseases are called neglected because they mainly affect the world's poorest populations, for whom there is no interest from the pharmaceutical industry to invest in research and development (R&D). As a result, most of the drugs currently used to treat NTDs are repurposed drugs that were originally developed for other indications (e.g. miltefosine for leishmaniasis was initially developed for cancer) (Pink *et al.*, 2005; Cheuka *et al.*, 2017; Weng, Chen and Wang, 2018). This is not without repercussions on their adequacy and efficacy, with various limitations including drug resistance, severe adverse-effects, lengthy treatment regimens, toxicity and complicated administration procedures (Cheuka *et al.*, 2017). While some NTDs such as leprosy, lymphatic filariasis (LF), trachoma, dracunculiasis can be eliminated using the currently available drugs, the remaining majority of NTDs truly need safe, effective, low-cost and short-course treatments (Weng, Chen and Wang, 2018). Given the many drawbacks of NTDs drugs, diagnostic tools that are accurate (i.e. good sensitivity and specificity) and field-amenable are particularly needed to decrease the number of untreated cases and ensure that patients are given the right treatment. Yet, since many of these diseases are zoonotic and/or vector-borne, control strategies based only on treating the infected human population are unlikely to be successful, thus leading to the concept of "one health" approach (Weng, Chen and Wang, 2018) (Okello *et al.*, 2011). It is generally agreed that vaccines are powerful and often cost-effective tools to reach elimination. However, vaccine development in the NTDs era has lagged behind: currently, licensed vaccines only exist for yellow fever, dengue and rabies (Hotez, 2018).

Unfortunately, the development of products for NTDs cannot rely upon the pharmaceutical industry alone. People affected by NTDs are mainly poor, live in countries with weak health systems that care for them, and will not be able to afford what the pharmaceutical industry will charge – resulting in the so-called market failure. As a result, in 2012, international organizations, partners from donor agencies and the pharmaceutical industry met in London to tackle the situation regarding NTDs and endorse the London Declaration, which specifically targeted the control or elimination of at least 10 NTDs by 2020 (Uniting to combat neglected tropical Diseases, 2012). To comply with this objective, a variety of push and pull mechanisms have been suggested; some of which have been implemented. These include, among others, R&D grants, priority review voucher (PRV) and advance market commitment (AMC). The rationale behind push and pull mechanisms is to delink the cost of research from the price of the product, so that the incentive to invest in the R&D of a particular NTD is not or less contingent on the price at which the product will be sold (Tuttle, 2016). Push mechanisms reduce the costs associated with R&D in advance of investment (ex-ante) whereas pull mechanisms offer rewards that are contingent on successful product discoveries (ex-post). Push and pull mechanisms are not mutually exclusively: they can be combined to form mixed mechanisms. Push, pull and mixed mechanisms provide avenues to public-private partnerships (PPPs) and more specifically to product-development partnerships (PDPs) .Partners of PDPs generally include non-governmental organizations (NGOs), academia, government and industry, with varying expertise that can be used at the appropriate stage to ensure a smooth development process. PDPs for NTDs have proliferated over the last two decades; in 2017, PDPs received 508$ million, accounting for 14% of all neglected disease basic research (Policy Cures Research, 2018). PDPs may focus on single disease and/or product type or alternatively, operate across multiple diseases and/or product types.

Yet, the challenges associated with NTDs are not limited to R&D market failure. A product that is developed may not be cost-effective for the country needing it. More precisely, the gain in effectiveness from a new product often comes at a cost, which affordability will depend on the country's available resources and often represented by the gross domestic product (GDP) per capita. Cost-

effectiveness analysis is a unique tool that allows to judge whether new products should be implemented in a country of interest. Yet, this is not a silver bullet: a product judged cost-effective and thus implemented may still not be accessible for diverse reasons, such as high prices, poor infrastructure, weak health systems and non-financial barriers (e.g. wrong beliefs, lack of knowledge and inaccurate perception of the infection's risk). Dwelling deeper into those non-financial barriers is even more crucial in the context of NTDs since most of these are vector-borne diseases (VBDs). For VBDs, individuals' demand/behavior about prevention plays a role in infection transmission. Furthermore, since the actual risk of infection is often uncertain, individuals' demand/behavior is influenced by their perception of the risk. A low risk perception, corresponding or not the actual risk, is likely to diminish the use of preventive measures (behavior). If risk perception is a good indicator of the actual risk of infection, then it has important implication in a context of disease elimination. However, as of now, very little empirical research has been conducted on the topic.

Therefore, as one can see, many barriers to the elimination of NTDs – from product development, to implementation and adoption – have economic components that warrant economic analyses. Accordingly, the general objective of this thesis is to improve our understanding of selected obstacles, from product development to their adoption at the individual level.

Methods

The work of this thesis was carried out at the Barcelona Institute for Global Health (ISGlobal) in collaboration with several institutions within and outside Europe. These included – but are not limited to – the Business school of Imperial College London, the Foundation for Innovative New Diagnostics (FIND), the Ministry of Public Health (MoPH) of Guyana and the University of Pompeu Fabra. This thesis presents four articles, of which three are published in peer-reviewed journals. Although these four articles all cover topics related to the challenges of neglected diseases, they look at the different angles (supply and demand) and process stages (product development, implementation and adoption). Moreover, they each make use of a different methodology.

More precisely, in the first one, a systematic review of the literature on PPPs for NTDs was conducted. In the second article, an econometric approach (i.e. difference-in-difference-in-differences (DDD)) was used to estimate the impact of a pull mechanism – the PRV – on stimulating R&D for neglected diseases. In the third article, the cost-effectiveness of novel diagnostic tools were estimated and compared with microscopy for a specific NTD (i.e. cutaneous leishmaniasis (CL)) in Afghanistan. Finally, in the fourth article, a structural equation model (SEM) was estimated to understand the role of non-financial barriers – more precisely, disease knowledge and risk perception – in shaping the demand for preventive measures for four selected vector-borne diseases (VBDs) among citizens of Guyana.

Main results

Systematic review of PPPs for NTDs

The literature on PPPs is very descriptive. Out of the 74 articles included, only 8 had an empirical research question that was addressed via a quantitative and/or qualitative analysis. Even more striking is that, among those 8 articles, not a single in depth impact evaluation of PPPs could be found. Instead, the literature is mainly focusing on anecdotal discussions of these models or reporting on their achievements. This is very much likely to be the result – as it is the case for the pharmaceutical industry – of a lack of transparency of PPPs, and more particularly of PDPs. Information on the funding received, investment made and clinical development should be made available to the public. Lastly, regarding what type of scheme PDPs should adopt, there seems to be a general consensus on mixed schemes. However the equilibrium between push and pull schemes is still to be defined. Additionally, there appears to be a clear dichotomy between development and access; products developed through PDPs should be manufactured, developed and distributed in the countries that need them the most.

The impact of the PRV on stimulating R&D

We found no effect of the PRV on stimulating R&D, which would suggest that the products developed for neglected diseases in the past decade would have been developed anyway, had the program not been implemented. More precisely,

according to the DDD approach, the marginal effect of the PRV was found not statistically significant (0.29) with less than one trial increase for the intended diseases in the US. Delayed effects of the policy on trial activity could not be found either. This lack of PRV's effect suggests that the voucher, whether used or sold, is not appealing to large pharmaceutical companies. Some of these companies have revenues exceeding dozens of billions of dollars and are unlikely to embark in risky projects for neglected diseases solely based on a voucher that has been valued as low as $67 million when the cost bringing a new product to the market is estimated at $2870 million (Dimasi, Grabowski and Hansen, 2016). Instead, the PRV may be better suited for products that are (i) developed through partnerships; (ii) known to be safe but not yet registered in the US; (iii) already somewhere in the development process; or (iv) for which new combinations or repurposed usages can be explored. These hypotheses stemming from the analysis are consistent with the outcome of 12 years of PRV implementation: 11 vouchers awarded to products that arose from new formulation combinations, in most cases, developed through a PDP. Moreover, when products were developed by pharmaceutical companies unilaterally, vouchers were often awarded to products already licensed outside the US.

The cost-effectiveness analysis of new diagnostic tools for cutaneous leishmaniasis in Afghanistan

In this study, we showed that novel tools for CL may not necessarily be cost-effective for an endemic country such as Afghanistan. More precisely, if the tools are compared at the National Malaria and Leishmaniasis Control Program (NMLCP) level in a period of low incidence, microscopy remains the preferred option. This being said, in a period of high incidence such as for instance during the CL peak season (i.e. winter), the Loopamp™ Leishmania Detection Kit (LAMP) becomes cost-effective if at least 35 tests can be performed at once. As for the CL Detect™ Rapid Test (RDT), it becomes cost-effective when implemented in peripheral health facilities so that transportation costs are being reduced for the patients. However, given its relatively low sensitivity, it is preferable that patients tested negative with RDT in peripheral centers get an additional diagnostic with either microscopy or LAMP at the reference (NMLCP) clinic in Kabul.

The role of disease knowledge and risk perception in shaping the demand for vector control measures in Guyana

This study is one of the few to show evidence of a bidirectional link between VBDs' risk perception and usage of vector control measures (i.e. preventive behavior). Indeed, a one-unit increase in risk perception translates into a 0.53 unit increase in self-reported preventive behavior for all diseases, while a one-unit increase in self-reported preventive behavior (i.e. the use of an additional measure) leads to a 0.46 unit decrease in risk perception for all diseases (except CL). This study also shows that higher education significantly improves knowledge and that better knowledge increases the take up of preventive measures if the risk perceived is high enough (i.e. for malaria and dengue). It is also worth saying that higher knowledge may increase preventive without affecting risk perception, which can be explained by a feeling of greater control (from using more vector control measures) over the infection. The type of region in which the individuals live also plays a key role on the adoption of vector control measures: although people living in the hinterland tend to have greater knowledge about the disease and an accurate risk perception, they use fewer preventive measures than people living in the coastal regions due mainly to geographic isolation. This finding thus stresses the paramount importance of promoting access to vector control measures when it comes to VBDs control and elimination, as otherwise it can undermine the responsiveness of behavior to risk.

Conclusions and recommendations

The literature on PPPs is majorly descriptive and misses thorough empirical analysis. This led us to point out the lack of PPP models' transparency. Although there is public money involved, there is no single database that routinely reports on the funding received, private investments made, R&D time frame and success rates. Nevertheless, in order to improve and perhaps maximize the potential of PPPs, one must evaluate their impact and how differences in their characteristics affect their performance. As a result, a key policy recommendation from this study is to promote greater transparency among PPPs, potentially through registration on a unique platform that would monitor their development and report the investments made.

With respect to the PRV, while it generated great enthusiasm at first sight, we can affirm that after a decade of implementation, the program has not succeeded in stimulating R&D for neglected diseases. Besides this, the PRV has been widely criticized for not promoting access to products and for granting vouchers to products that were already in use outside the US. While this should be corrected for ethical reasons mainly, it is unlikely be sufficient – as demonstrated by our study – to persuade pharmaceutical companies to embark alone on risky projects for neglected diseases. Perhaps, in order to stimulate investment from the pharma industry, the PRV may need to be supplemented with an additional pull mechanism such as the AMC to guarantee a minimum level of market profitability from the product awarded the voucher.

Although the novel tools developed for CL are not cost-effective in the base-case scenario, they can become cost-effective when tapping on their respective strengths. On the one hand, LAMP may be useful in boosting labor productivity in a context where laboratory expertise is lacking because of political instability and uncompetitive salaries. On the other hand, RDT may be valuable in remote parts of the country where there is no/low diagnostic capacities and expertise.

Finally, in Guyana, higher risk perception of a disease translates into greater demand for prevention while higher knowledge will translate into greater demand if the risk perceived is sufficiently high – as was the case for malaria and dengue fever. This finding has an important policy implication: in a context of elimination, for the government and population to act hand in hand, it is essential for the former to promote awareness of the risk to the latter to avoid a decrease in preventive behavior arising from a (correct) lower risk perception. This is all the more important for infections that are asymptomatic, as reaching elimination is likely to be further challenged by an underestimation of its actual risk of infection.

Resumen

Contexto

La Organización Mundial de la Salud (WHO, por sus siglas en inglés) ha identificado más de 20 enfermedades tropicales desatendidas (NTDs, por sus siglas en inglés) que afectan a 1.500 millones de personas en el mundo (Uniting to combat neglected tropical diseases, 2017). Aunque todas son enfermedades infecciosas, muchas NTDs son crónicas, con estados que empeoran progresivamente si no se detectan o tratan a tiempo. Además, los daños que causan son a menudo irreversibles y con importantes consecuencias sociales y económicas (Sachs *et al.*, 2007; Lenk *et al.*, 2016). Estas enfermedades se denominan desatendidas porque afectan principalmente a las poblaciones más pobres del mundo y, por lo tanto, la industria farmacéutica no tiene interés por invertir en su investigación y desarrollo (I+D). Como resultado, la mayoría de los fármacos que se utilizan actualmente para tratar las NTDs consisten en fármacos que han sido readaptados y que se desarrollaron originalmente para otras indicaciones. Por ejemplo, el fármaco miltefosina, que se usa contra la leishmaniasis, fue desarrollado inicialmente para el cáncer (Pink *et al.*, 2005; Cheuka *et al.*, 2017; Weng, Chen and Wang, 2018). Esto tiene repercusiones en su idoneidad y eficacia, teniendo varias limitaciones como el desarrollo de resistencias a los medicamentos, efectos adversos graves, regímenes de tratamiento prolongados, toxicidad y procedimientos de administración complicados (Cheuka *et al.*, 2017). Algunas NTDs como la lepra, la filariasis linfática (FL), el tracoma y la dracunculiasis podrían ser eliminadas con los fármacos actualmente disponibles. No obstante, para la mayoría de las NTDs, se necesitan urgentemente tratamientos seguros, eficaces, de bajo coste y de corta duración (Weng, Chen and Wang, 2018). Dadas las numerosas desventajas de los fármacos para las NTDs, se necesitan más técnicas de diagnóstico precisas (es decir, de alta sensibilidad y especificidad) y adecuadas para el terreno para disminuir el número de casos no tratados y garantizar que los pacientes reciban el tratamiento adecuado. Sin embargo, como muchas de estas enfermedades son zoonóticas y/o transmitidas por vectores, es poco probable que las estrategias de control basadas únicamente en el tratamiento de

la población humana infectada tengan éxito, lo que nos conduce al concepto de "one health" (Weng, Chen and Wang, 2018) (Okello *et al.*, 2011). Hay un acuerdo generalizado en considerar que las vacunas son herramientas potentes y a menudo rentables para alcanzar la eliminación de muchas NTDs. Sin embargo, el desarrollo de vacunas para las NTDs se ha quedado atrás: actualmente, solo existen vacunas autorizadas para la fiebre amarilla, el dengue y la rabia (Hotez, 2018).

Desafortunadamente, el desarrollo de productos para las NTDs no puede depender únicamente de la industria farmacéutica. Las personas afectadas por las NTDs son principalmente pobres, viven en países con sistemas de salud débiles y no pueden pagar lo que la industria farmacéutica les cobraría por los fármacos, lo que resulta en el llamado fracaso del mercado. Como resultado, en 2012 las organizaciones internacionales, los socios de los organismos donantes y la industria farmacéutica se reunieron en Londres para abordar la situación de las NTDs y aprobar la Declaración de Londres, la cual se centró en conseguir el control o la eliminación de al menos 10 NTDs en el 2020 (Uniting to combat neglected tropical Diseases, 2012). Para cumplir con este objetivo, se propusieron una serie de mecanismos de “push” y “pull”, algunos de los cuales ya fueron implementados en los años siguientes. Entre ellos se incluyen las subvenciones para I+D, el “priority review voucher” (PRV, por sus siglas en inglés) y el “advanced market commitment” (AMC, por sus siglas en inglés). El fundamento detrás de los mecanismos “push” y “pull” es desvincular el coste de la investigación del precio del producto, de manera que el incentivo para invertir en la investigación y el desarrollo de un determinado producto no dependa, o dependa en menor medida, del precio al cual se venderá (Tuttle, 2016). Los mecanismos “push” reducen los costes asociados con la I+D antes de la inversión (ex-ante), mientras que los “pull” ofrecen recompensas que dependen del éxito de los descubrimientos de productos (ex-post). Los mecanismos de “push” y “pull” no son mutuamente excluyentes: pueden combinarse para formar mecanismos mixtos. Los mecanismos “push”, “pull” y “mixed” ofrecen vías para las asociaciones público-privadas (PPPs, por sus siglas en inglés) y, más específicamente, para las asociaciones para el desarrollo de productos (PDPs, por sus siglas en inglés). Los socios de las PPPs generalmente incluyen organizaciones no gubernamentales (ONG), el mundo académico, el gobierno y

la industria. Cada uno de los socios tiene un conocimiento diferente que se puede usar en la etapa más apropiada para fomentar un desarrollo sin problemas. Las PDPs para las NTDs han proliferado en las dos últimas décadas; en 2017, las PDPs recibieron 508 millones de dólares, lo que representa el 14% de toda la investigación básica para NTDs (Policy Cures Research, 2018). Los PDPs pueden centrarse en una sola enfermedad y/o tipo de producto o, alternativamente, funcionar con múltiples enfermedades y/o tipos de productos.

Sin embargo, los desafíos asociados con las NTDs no solo se limitan a las deficiencias del mercado de la I+D. Un producto desarrollado puede no ser rentable para el país que lo necesita. Más concretamente, la ganancia obtenida por la eficacia de un nuevo producto suele tener un coste, cuya asequibilidad dependerá de los recursos disponibles del país y que a menudo está representada por el producto interior bruto (PIB) per cápita. El análisis de la eficacia en función de los costes es una herramienta única que permite juzgar si los nuevos productos deben ser implementados en un país de interés. Sin embargo, no se trata de una solución milagrosa: un producto que se considera rentable y, por consiguiente, se aplica, puede no ser accesible por diversas razones, tales como altos precios, una infraestructura deficiente, la debilidad de los sistemas de salud y otras barreras no financieras (por ejemplo, creencias equivocadas, falta de conocimiento o percepción inexacta del riesgo de infección). Profundizar en estas barreras no financieras es aún más importante en el contexto de las NTDs, ya que la mayoría de ellas son enfermedades transmitidas por vectores (VBDs, por sus siglas en inglés). En el caso de las VBDs, la demanda/comportamiento de los individuos en cuanto a la prevención juega un papel importante en la transmisión de la infección. Además, dado que el riesgo real de infección es a menudo incierto, el comportamiento de los individuos está influenciado por su percepción del riesgo. Una percepción de riesgo baja, que corresponda o no al riesgo real, es probable que disminuya el uso de medidas preventivas (comportamiento). Si la percepción del riesgo es un buen indicador del riesgo real de infección, entonces tiene una implicación importante en un contexto de eliminación de la enfermedad. Sin embargo, hasta ahora se ha realizado muy poca investigación empírica sobre el tema.

Por lo tanto, como se puede ver, muchas de las barreras para la eliminación de las NTDs –desde el desarrollo del producto, hasta su implementación y adopción– tienen componentes económicos que justifican los análisis económicos. Por consiguiente, el objetivo general de esta tesis es mejorar nuestra comprensión de los obstáculos seleccionados, desde el desarrollo del producto hasta su adopción a nivel individual.

Métodos

El trabajo de esta tesis se llevó a cabo en el Instituto de Salud Global de Barcelona (ISGlobal) en colaboración con varias instituciones dentro y fuera de Europa. Entre ellas se encuentran la Business School de la Imperial College London, la Fundación para Nuevos Diagnósticos Innovadores (FIND, por sus siglas en inglés), el Ministerio de Salud Pública de Guyana y la Universidad Pompeu Fabra. Esta tesis presenta cuatro artículos, de los cuales tres están publicados en revistas revisadas. Estos cuatro artículos analizan desde diferentes ángulos (oferta y demanda) las etapas del proceso (desarrollo, implementación y adopción de productos) hacia el control y la eliminación de las NTDs. Además, cada artículo utiliza una metodología diferente.

Más concretamente, en el primer artículo se realizó una revisión sistemática de la literatura sobre las PPPs para las enfermedades no transmisibles. En el segundo, se utilizó un enfoque econométrico (es decir, diferencia en diferencia en diferencias (DDD)) para estimar el impacto de un mecanismo “pull” –el PRV– en la estimulación de la I+D para las NTDs. En el tercer artículo, se estimó la rentabilidad de nuevos instrumentos de diagnóstico, comparado con la microscopía, para una NTD específica (es decir, la leishmaniosis cutánea (CL, por sus siglas en inglés)) en Afganistán. Finalmente, en el cuarto artículo, se estimó un modelo de ecuación estructural (SEM) para entender el papel de las barreras no financieras –más precisamente, el conocimiento de la enfermedad y su percepción del riesgo– en la demanda de medidas preventivas (comportamiento) para cuatro VBDs, entre ciudadanos de Guyana.

Principales resultados

Revisión sistemática de las PPPs para las NTDs

La literatura sobre las PPPs es muy descriptiva. De los 74 artículos incluidos, solo 8 tenían una pregunta de investigación empírica que fue abordada a través de un análisis cuantitativo y/o cualitativo. Aún más llamativo es que, entre estos 8 artículos, no se pudo encontrar ni una sola evaluación profunda del impacto de las PPPs. Por el contrario, la literatura se centra principalmente en discusiones anecdóticas de estos modelos o en informar sobre sus logros. Es muy probable que esto sea el resultado –como es el caso de la industria farmacéutica– de la falta de transparencia de las PPPs, y más particularmente de las PDPs. La información sobre la financiación recibida, la inversión realizada y el desarrollo clínico debe ponerse a disposición del público. Por último, en cuanto al tipo de esquema que deben adoptar las PDPs, parece existir un consenso general sobre los mecanismos “mixed”. Sin embargo, el equilibrio entre los sistemas de "push" y "pull" está aún por definir. Además, parece haber una clara dicotomía entre desarrollo y acceso; los productos desarrollados a través de los PDPs deberían ser fabricados, desarrollados y distribuidos en los países que más los necesitan.

El impacto del PRV en el estímulo de la I+D

No encontramos ningún efecto del PRV para estimular la I+D, lo que sugeriría que los productos desarrollados para enfermedades desatendidas en la última década se habrían desarrollado de todos modos si el programa no se hubiera implementado. Más precisamente, según el enfoque DDD, se encontró que el efecto marginal del PRV no era estadísticamente significativo (0.29) con menos de un ensayo para las enfermedades previstas en los Estados Unidos. Tampoco se pudieron encontrar efectos retrasados de la política en una actividad de ensayo clínico. Esta falta de efecto del PRV sugiere que el vale, ya sea usado o vendido, no es atractivo para las grandes compañías farmacéuticas. Algunas de estas compañías tienen ingresos que superan los cientos de miles de millones de dólares y es poco probable que se embarquen en proyectos arriesgados para enfermedades desatendidas únicamente basándose en un vale que se valoró a partir de 67 millones de dólares cuando el coste para llevar un nuevo producto al mercado se estima en 2.870 millones de dólares (Dimasi, Grabowski and Hansen, 2016). En cambio, el PRV puede ser más adecuado para productos que (i) se desarrollan a través de PPPs; (ii) se sabe que son seguros pero aún no están registrados en los Estados Unidos; (iii) ya están en algún punto del proceso

de desarrollo; o (iv) para los cuales se pueden explorar nuevas combinaciones o usos con nuevos propósitos. Estas hipótesis derivadas del análisis son consistentes con el resultado de 12 años de implementación de PRV: 11 vales otorgados a productos que surgieron de nuevas combinaciones de formulación, en la mayoría de los casos, desarrollados a través de un PDP. Asimismo, cuando los productos fueron desarrollados por compañías farmacéuticas unilateralmente, los vales a menudo se otorgaban a productos que ya tenían licencia fuera de los EE. UU.

El análisis coste-efectividad de las nuevas herramientas de diagnóstico para la leishmaniosis cutánea en Afganistán

En este estudio, mostramos que las herramientas novedosas para la CL no necesariamente son rentables para un país endémico como Afganistán. Más precisamente, si se comparan las herramientas a nivel del Programa Nacional de Control de la Malaria y la Leishmaniasis (NMLCP, por sus siglas en inglés) en un período de baja incidencia, la microscopía sigue siendo la opción preferida. Dicho esto, en un período de alta incidencia, como por ejemplo durante la temporada alta de CL (es decir, el invierno), el Loopamp™ Leishmania Detection Kit (LAMP, por sus siglas en inglés) se vuelve rentable si se pueden realizar al menos 35 pruebas a la vez. En cuanto a la prueba rápida de CL Detect™ (RDT, por sus siglas en inglés), se vuelve rentable cuando se implementa en instalaciones sanitarias periféricas, de modo que se reducen los costes de transporte para los pacientes. Sin embargo, dada su sensibilidad relativamente baja, es preferible que los pacientes con pruebas de RDT negativas en centros periféricos obtengan un diagnóstico adicional con microscopía o LAMP en la clínica de referencia (NMLCP) en Kabul.

El papel del conocimiento de la enfermedad y la percepción del riesgo en la demanda de medidas de control vectorial en Guyana

Este estudio es uno de los pocos que muestra evidencia de un vínculo bidireccional entre la percepción de riesgo de los VBDs y el uso de medidas de control de vectores (es decir, el comportamiento preventivo). De hecho, un aumento de una unidad en la percepción del riesgo se traduce en un aumento de 0,53 unidades en el comportamiento preventivo para todas las enfermedades,

mientras que un aumento de una unidad en el comportamiento preventivo auto-reportado (es decir, el uso de una medida adicional) conduce a una disminución de 0,46 unidades en la percepción del riesgo para todas las enfermedades (excepto la CL). Este estudio también muestra que la educación superior mejora significativamente el conocimiento y que un mejor conocimiento aumenta la adopción de medidas preventivas si el riesgo percibido es suficientemente alto (por ejemplo, para la malaria y el dengue). Es importante subrayar que un mayor conocimiento puede aumentar la prevención sin afectar a la percepción del riesgo, lo que puede explicarse por una sensación de mayor control (al utilizar más medidas de control vectorial) sobre la infección. El tipo de región en la que viven los individuos también juega un papel clave en la adopción de medidas de control de vectores: aunque las personas que viven en el interior tienden a tener un mayor conocimiento sobre la enfermedad y una percepción de riesgo precisa, utilizan menos medidas preventivas que las personas que viven en las regiones costeras debido principalmente al aislamiento geográfico. Así pues, este hallazgo subraya la importancia primordial de promover el acceso a las medidas de control de vectores cuando se trata del control y la eliminación de los VBD, ya que de lo contrario puede socavar la capacidad de respuesta del comportamiento ante el riesgo.

Conclusiones y recomendaciones

La literatura sobre las PPPs es mayormente descriptiva y no incluye un análisis empírico completo. Esto nos llevó a señalar la falta de transparencia de los modelos de PPPs. Aunque hay dinero público involucrado, no existe una base de datos única que informe de manera rutinaria sobre el financiamiento recibido, las inversiones privadas realizadas, el marco temporal de I+D y las tasas de éxito. Sin embargo, para mejorar y tal vez maximizar el potencial de las PPPs, es necesario evaluar su impacto y cómo las diferencias en sus características afectan su desempeño. Como resultado, una recomendación política clave que surge de este estudio es promover una mayor transparencia entre las PPPs, potencialmente a través del registro en una plataforma única que monitorearía su desarrollo e informaría sobre las inversiones realizadas.

Con respecto al PRV, si bien generó un gran entusiasmo a primera vista, podemos afirmar que después de una década de implementación, el programa

no ha logrado estimular la investigación y el desarrollo de las enfermedades desatendidas. Además, el PRV ha sido ampliamente criticado por no promover el acceso a los productos y por otorgar vales a productos que ya estaban en uso fuera de los Estados Unidos. Aunque esto debería corregirse principalmente por razones éticas, es poco probable que sea suficiente –como se demuestra en nuestro estudio– para persuadir a las compañías farmacéuticas a embarcarse solas en proyectos arriesgados para las enfermedades desatendidas. Quizás, para estimular la inversión de la industria farmacéutica, el PRV podría necesitar ser complementado con un mecanismo de atracción adicional como el AMC para garantizar un nivel mínimo de rentabilidad de mercado del producto al que se le otorgue el vale.

Aunque las novedosas herramientas desarrolladas para la CL no son rentables en el escenario base, aunque pueden llegar a serlo cuando se aprovechan sus respectivas ventajas. Por un lado, el LAMP puede ser útil para impulsar la productividad laboral en un contexto en el que se carece de experiencia en el laboratorio debido a la inestabilidad política y a los salarios poco competitivos. Por otro lado, el RDT puede ser valioso en partes remotas del país donde no hay o hay poca capacidad de diagnóstico y experiencia.

Finalmente, en Guyana la percepción de un mayor riesgo de una enfermedad se traduce en una mayor demanda de prevención, mientras que un mayor conocimiento se traducirá en una mayor demanda si el riesgo percibido es lo suficientemente alto, como fue el caso de la malaria y el dengue. Este hallazgo tiene una importante implicación política: en un contexto de eliminación, para que el gobierno y la población actúen de la mano, es esencial que el primero promueva la conciencia del riesgo al segundo para evitar una disminución de la conducta preventiva derivada de una (correcta) menor percepción del riesgo. Esto es aún más importante en el caso de las infecciones asintomáticas, ya que es probable que el logro de la eliminación se vea dificultado por una subestimación del riesgo real de infección.

I. Introduction

The neglected tropical diseases and their market failure

As of today, 20 neglected tropical disease (NTD) groups have been acknowledged by the world health organization (WHO) (Table 1). These infectious diseases are called neglected because they mainly affect the world's poorest populations living in tropical and subtropical conditions – those without access to safe water, sanitation, and basic health services, needed to protect against the infection from the different pathogens (i.e. bacteria, viruses, protozoa and helminth parasites). Some of these pathogens are carried and transmitted by a vector which can include, among others, mosquitoes, sandflies, tsetse flies and ticks. These diseases are commonly known as vector-borne diseases (VBDs). Not all NTDs are VBDs: other ways of transmission include rabid saliva, swimming in and drinking contaminated water, etc. Approximately 1 billion people are at risk of infection of at least one NTD, with another 1 billion people infected – thus representing a significant global mortality and morbidity burden (Hotez *et al.*, 2006). Many NTDs are chronic, with conditions that progressively become worse if undetected and untreated. Moreover, the damage they cause is often irreversible (e.g. onchocerciasis causes blindness; cutaneous leishmaniasis (CL) may lead to disfiguring scars; schistosomiasis leads to cognitive impairment particularly among children), with social and economic consequences (Sachs *et al.*, 2007) (Lenk *et al.*, 2016). To give a few examples: disfiguring scars with CL may lead – depending on the socio-cultural contexts – to social stigmatization, augmenting the probability of psychological disorders, isolation and decreased self-esteem (Kassi *et al.*, 2008); chronic lymphatic filariasis patients in India lose as much as 11 years of productivity (Ramaiah *et al.*, 2000); a child infected with soil-transmitted helminths (STH) has a 20% lower probability of school enrollment and a 40% reduction in subsequent adult wage income (Bleakley, 2007). Therefore, NTDs perpetuate the vicious cycle of poverty: they are a result of poverty and contribute to further poverty among those affected and their communities.

Despite being diverse, NTDs share common needs: the need for vaccines to prevent the infection and the need for diagnostic tools and drugs to detect and treat the infection when it could not be prevented in the first place. Vaccines are

severely lacking for NTDs: as of now, licensed vaccines only exist for yellow fever, dengue and rabies (Hotez, 2018). Vaccines are powerful tools in reaching elimination: vaccinated individuals become protected against the infection which results in an increase level of the population immunity, lowering the force of infection in the population and thus lowering the risk of infection among unvaccinated individuals (Smith, 2010). Accordingly, elimination may be achieved without having to vaccinate the entire population. However, as most NTDs are not vaccine preventable yet, safe, effective, low-cost and short-course treatment are essential. Having said that, only a few NTDs – e.g. leprosy, lymphatic filariasis (LF), trachoma, and dracunculiasis – can be eliminated using the current drugs available; for the remaining NTDs, the need persists (Weng, Chen and Wang, 2018). Here are a few case-specific examples: treatment for leishmaniasis relies on painful daily injection of sodium stibogluconate (SSG) – complemented with paramomycin in East Africa – but with associated drawbacks related to toxicity, administration, affordability and access (Drugs for Neglected Diseases Initiative, 2018b). Moreover, as the injections need to be administered by trained medical professionals and may require sometimes hospitalization, it puts an added burden to the patients and health systems. Treatment for the fungal form of mycetoma (i.e. eumycetoma) is only about 25% to 35% efficacious, and is neither safe nor affordable. As a consequence, amputation is often the only chance patients have to survive (Drugs for Neglected Diseases Initiative, 2018a). Treatment for Chagas disease consists of two drugs (benznidazole and nifurtimox) that were developed over 40 years ago and which present painful side-effects. Moreover, the chronic stage of the disease is deadly if left untreated but the treatment is poorly effective for patients in that disease's stage (Drugs for Neglected Diseases Initiative, 2018a). The many drawbacks of NTDs drugs thus further stress the need for good diagnostic tools: tools with high sensitivity and specificity that are affordable and field-amenable so that patients receive the right diagnostic and the ensuing right treatment. This is crucial as delays in diagnosis will not only increase the risk of morbidity and mortality but also the risk of transmission of infection to others.

Unfortunately, pharmaceutical products for these diseases cannot be developed through the traditional 'patent' system. The latter grants monopoly power to

pharmaceutical companies usually for a period of 20 years to prevent 'free-riding' and thus encourage investment in research and development (R&D). This implies that the patent holder will, during 20 years, be the only one allowed to produce, sell and make profit out of that product. The resulting lack of competition enables pharmaceutical companies to recover their R&D investment costs by setting a market price well above the marginal cost of production. That said, the lack of transparency on the true cost of R&D contributes to critiques that market pricing does not reflect the R&D investment and that pharmaceutical companies are simply charging what the market will bear. The pharmaceutical industry interest is mainly for drugs that are highly profitable, known as 'blockbuster' drugs. These drugs are usually taken over a long period (i.e. chronic diseases) and affect a large and stable market (e.g. heart diseases and depression) (Tuttle, 2016). It is thus evident that the patent system is not appropriate in the NTDs context: even if the people infected or at risk of infection are willing to pay a high price (given what they are capable of paying), it would still remain below the marginal cost of production. As a result, products for NTDs are simply not developed under the traditional patent system. This is well illustrated by the following widely cited figure: 5 new therapeutic products out of 850 (i.e. less than 1% market share) were approved for NTDs between 2000 and 2011 (Pedrique *et al.*, 2013). Instead, pharmaceutical companies have adopted a so-called 'opportunistic' or 'piggy-back' approach by repurposing drugs against NTDs that were historically developed for other indications (e.g. miltefosine for leishmaniasis was initially developed as an anti-cancer drug) (Pink *et al.*, 2005; Cheuka *et al.*, 2017; Weng, Chen and Wang, 2018). Nonetheless, this approach has important repercussions on the current drugs used against NTDs, with limitations ranging from drug resistance to severe adverse-effects, lengthy treatment regimens, toxicity and complicated drug administration procedures (Cheuka *et al.*, 2017).

The solutions to the research and development (R&D) market failure

Having said that, during the last decade, the situation regarding NTDs has started to change. In 2005, the first peer-reviewed papers using the term 'neglected tropical diseases' as a medical subject heading appeared in PubMed and other

scientific databases (P. J. Hotez, 2011). These publications also coincided with the establishment of a new Department of Neglected Tropical Diseases at the WHO, and shortly thereafter, the open-access journal *PLoS Neglected Tropical Diseases* (P. J. Hotez, 2011). An original list of 13 NTDs was established by the WHO – known as the WHO NTDs list – which enabled the gathering of different diseases under a single NTD 'brand' (Molyneux, Foster and Faal, 2013). In January 2012, the WHO published a roadmap that set new targets and associated milestones to enhance the control, prevention, and elimination of NTDs. A few days later, international organizations, partners from donor agencies and the pharmaceutical industry were meeting in London to endorse the London Declaration, that set as a target the control or elimination of at least 10 NTDs by 2020 (Uniting to combat neglected tropical Diseases, 2012). To reach this objective, a variety of push and pull mechanisms have been suggested; some of which have been put into practice. The theory underlying these different mechanisms is 'delinkage': delinking the cost of research from the price of the product. In other words, the incentive to invest in R&D of a particular disease must be independent of the price at which the product will be sold (Tuttle, 2016). Push and pull mechanisms reduce the investment required to develop a product – either ex-ante or ex-post of development – so that the incentive to enter the market is not (or less) contingent on the ability to charge high prices and recover costs through sales. Push mechanisms reduce upfront costs inherent to R&D activities through various grants and subsidies offered prior to product discoveries (i.e. ex-ante). A common push mechanism is 'R&D grants' in which governments or philanthropic institutions finance the clinical trial, usually conducted by a pharmaceutical company (Lewis, Reichman and So, 2007). Pull mechanisms, on the opposite, offer a reward that is contingent on successful product discoveries (i.e. ex-post). The most common pull schemes include advance market commitment (AMC) and the priority review voucher (PRV). Under AMC, pharmaceutical companies are guaranteed a market upon successful development of a product through the promise from a specific agency – e.g. Government bodies, financial entities or procurement agencies – to buy a certain quantity of the product at a pre-specified price. So far, the Global Alliance for Vaccines and Immunization (Gavi) has been the only one making use of this mechanism and which successfully led to the development of two pneumococcal

vaccines that are currently immunizing children against pneumonia in 58 countries (Gavi the Vaccine Alliance, 2017). With respect to the PRV, as for today, 32 vouchers have been awarded for neglected diseases; of which 12 for tropical (neglected) diseases. Under this mechanism, pharmaceutical companies are awarded a PRV by the Food and Drug Administration (FDA) upon successful development of a product for a disease that is eligible for the program. PRV-eligible diseases include tropical diseases and rare pediatric conditions. The voucher may then be used by the awarded company for a product in its pipeline – e.g. for a blockbusters drug – or sold to a third party, which selling price was initially estimated at about $300 million (Ridley, Grabowski and Moe, 2006).

Therefore, push and pull mechanisms offer avenues to public-private partnerships (PPPs) and more specifically to product-development partnerships (PDPs) – usually consisting of non-governmental organizations (NGOs), academia, government and industry – to tackle the situation of NTDs. Within PDPs, partners are able to contribute during the process stage at which they have the most expertise, promoting efficiency (Tuttle, 2016). PDPs may focus on a single disease and/or product type only or may work across multiple diseases and/or product types. A well-known PDP for drug development is the Drug for Neglected Diseases Initiative (DNDi) (https://www.dndi.org/). Since its creation in 2003, DNDi has brought 8 drugs to the market: 7 new drug combinations and 1 new chemical entity (fexinidazole) for the treatment of sleeping sickness. Its last approved drug – a pediatric formulation of the already existing drug benznidazole – was successfully developed from combining push and pull mechanisms to promote its development. The product was awarded a PRV in 2017 (pull), which R&D was financed through R&D grants (push).

The promotion of PDPs to advance R&D for NTDs was highlighted as one of the commitments of the London Declaration. In 2017, PDPs received 508$ million, accounting for 14% of all neglected disease basic research and product development funding, and 19% of all external investment (Policy Cures Research, 2018). While philanthropic foundations and aid agencies are usually the main funders of R&D, government agencies of high-income countries (HICs) became the major funders of PDPs in 2017 (Policy Cures Research, 2018). There is a growing recognition and reliance on PDPs to tackle the market failure of

neglected diseases, however, little is known about the way they operate, their pipeline, R&D timeline, and on their funding sources and amount. This brings us to the first two objectives of this thesis: investing on PDPs as well as on the underpinning push and pull mechanisms. More precisely, the first article of this thesis is about a systematic review of PPPs and inherently of the push/pull mechanisms, which was conducted mostly to appraise the scientific opinion on the topic and identify potential economic evaluations conducted on these models. The second article focuses on a particular type of pull mechanism: the PRV. In this article, we assessed whether the program has been effective at stimulating R&D for neglected diseases.

The other challenges associated with tackling neglected tropical diseases

The challenges associated with NTDs are not limited to R&D. A product may be developed but may not be implemented in the country for which it was intended because – among various other reasons – it is not cost-effective compared with existing products/current practices. Since resources are scarce, the use of resources in one way prevents their use in other ways – referring to the concept of opportunity cost. The opportunity cost of investing in a health intervention refers to the loss of health benefits that would have been avoided if the money had been invested in another intervention. Accordingly, to assess whether it is worth investing in an intervention, one should measure and compare the cost-effectiveness of each alternative. Ideally, effectiveness should be measured in terms of disability adjusted-life years (DALYs) or quality adjusted-life years (QALYS) because there is an agreed threshold set by the WHO for these indicators – although very much questioned in the recent years. That is, an intervention is cost-effective if the cost per DALYs averted/QALYs gained is lower than the GDP per capita of the country. This well-known type of analysis was used in this thesis to evaluate the cost-effectiveness of two new diagnostic tools for cutaneous leishmaniasis in Afghanistan (i.e. objective 4). The new tools were compared against microscopy, the gold standard strategy.

Notwithstanding, a product implemented and registered in a country may not automatically become accessible to the people who need it. Nowadays, access

is often facilitated through donation. For drugs, accessibility is often made through donation from large pharmaceutical companies that are delivered to the population by volunteers. These are called mass drug administration (MDA) programs. Well known examples of MDA programs include the Mectizan donation program for onchocerciasis and LF by Merck & Co and GlaxoSmithKline (GSK) (https://mectizan.org/); the International Trachoma Initiative (ITI) (https://www.trachoma.org/) by Pfizer; among others. Although these are generally claimed as successful, concerns regarding the sustainability of MDA programs have been raised due to a reliance on a donor that is profit-driven and on unpaid volunteers for distribution (Parker and Allen, 2011; Holt, Gillam and Ngondi, 2012). Furthermore, the effectiveness and sustainability of MDA will also be affected by changing political and economic contexts (Parker and Allen, 2011)(Hastings, 2016). In addition to this, there are also arguments against free distribution because (i) it can lower the willingness-to-pay (WTP) for the product in the long term and (ii) it may reduce the psychological effect of paying for a product, leading to its underuse or wastage – however this has been refuted in practice (Cohen and Dupas, 2010). Moreover, the principle behind MDA rests on the assumption that people (sick or not) will be willing to swallow the pill, however, this may not always be the case for numerous reasons (Hastings, 2016). So far, the success of most MDA are measured by treatment coverage but this translates into an incentive to distribute large quantities of drugs regardless of the actual need (Kabatereine *et al.*, 2010). Drug coverage and compliance are furthermore likely to decrease over time in a context of elimination where disease prevalence progressively decreases (Hauck, 2018). In the context of NTDs, because many infections are VBDs, individuals' behavior plays a role in infection transmission. This brings us to an important point of this thesis: demand for prevention and treatment will have an impact on infection transmission for many NTDs. Economic theory believes in a prevalence-elastic demand for products meaning that if the prevalence declines, individuals' demand for prevention will decrease more than proportionally. If this is the case, prevention is unlikely to lead to elimination and eradication unless appropriate government interventions take place (Hauck, 2018). Nevertheless, while the theory is clear, in reality, little has been shown on the role of prevalence (and risk perception) on behavior. This lack of empirical research on the topic brings us to the fifth objective of this thesis: understanding

the role of risk perception and disease knowledge in shaping the demand for preventive behavior for selected VBDs in Guyana – controlling for sociodemographic characteristics. The selected VBDs included malaria, dengue, Zika and CL.

Rationale of this thesis

One can see that the challenges associated with NTDs and neglected diseases generally are diverse and complex. I conducted this thesis with the primary objective of investigating on the economic aspects of some of the main challenges related to product development, implementation and adoption. More exactly, the thesis is divided into four chapters: the first two chapters relate to the 'development' side, while the third and fourth chapters respectively look at the 'implementation' and 'adoption' dimensions. For the first chapter, I conducted a systematic review of the literature on PPPs for NTDs to assess the scientific research and opinion on the topic. PPPs and more particularly PDPs are considered as 'the right' model but little is known about how cost-effective they are. Afterwards, I focused on a specific type of pull mechanism, the PRV, and try to evaluate the latter on its capacity to stimulate R&D (i.e. clinical trial registration) for the intended neglected diseases.

In the third chapter, I looked at the next step of successful R&D: whether developed products should be adopted in countries that need them. More specifically, I estimated the cost-effectiveness of two new diagnostic tools – the CL Detect ™ Rapid Test (RDT) and the Loopamp™ Leishmania Detection Kit (LAMP) – compared with microscopy for cutaneous leishmaniasis (CL) in Kabul, Afghanistan. The country has one of the highest prevalence in the world making it a particularly interesting context in which to conduct the study. In the last chapter, I looked at the very end of the R&D chain: adoption of preventive measures at the individual level in an endemic country. I attempted to quantify the role of disease knowledge and risk perception in shaping the demand for vector control measures (e.g. skin repellent, mosquito coils, windows screening). This study was carried out in 4 regions of Guyana: a country that has been neglected by research but which is endemic of several VBDs. Finally, although this is a thesis – broadly speaking – on neglected diseases, it has a particular

focus on NTDs and on leishmaniasis specifically since it was part of a Marie-Curie Innovative Training Networks consortium on leishmaniasis (http://www.euroleish.net/).

Table 1: The neglected tropical diseases and their global burden

	DALYs per 100,000 (2017)	Vector-borne disease
Buruli ulcer	NA	No
Chagas disease	3.04	Yes
Chikungunya	NA	Yes
Dengue	38.25	Yes
Dracunculiasis (guinea-worm disease)	0.0000072	No
Echinococcosis	1.31	No
Human African trypanosomiasis (sleeping sickness)	NA	Yes
leishmaniasis	10.13	Yes
Leprosy (Hansen's disease)	0.41	No
Lymphatic filiarasis	17.85	Yes
Mycetoma, chromoblastomycosis and other deep mycoses	NA	No
Onchocerciasis (river blindness)	17.58	Yes
Rabies	8.3	No
Scabies and other ectoparasites	59.27	Yes
Schistosomiasis	18.74	No
Snakebite envenoming	NA	No

Soil-transmitted helminthiases	NA	No
Taeniasis/cysitercosis	21.05	No
Trachoma	3.96	Yes
Yaws (Endemic treponematoses)	NA	No

Legend: NA "Not available"; DALYs "Disability adjusted-life years". NB: In parentheses are the non-scientific names of the diseases. The second column shows the burden per disease for the year 2017, using the number of DALYs per 100,000 inhabitants globally for both men and women across all ages. Source: (Institute of Health Metrics and Evaluation (IHME), 2017)

II. Hypotheses and Objectives

Hypotheses

The challenges associated with tackling neglected diseases are complex and touch upon various stages: product development, implementation and adoption. While all of these include economic aspects, few economic studies have dug into the topic. Identifying and quantifying the economic barriers across the above product stages is crucial to ensure that policy-making translates into cost-effective policies that will be able to control and eliminate those diseases.

Accordingly, the central hypothesis of this thesis is that challenges to be tackled in order to reach neglected diseases' elimination all embed economic aspects. This broad hypothesis can then be split into three specific hypotheses: (i) is the current gold standard model to develop products for neglected diseases – PPP – cost-effective? What about the various push and pull mechanisms that serve as avenues to PPP model? (ii) Are new products necessarily better than older ones? If not, can they improve depending on the context? (iii) What are the barriers (financial and non-financial) to the usage of effective preventive products?

General objective

The general objective of this thesis is to investigate the economic aspects underpinning the diverse challenges associated with tackling NTDs, ranging from product development, implementation and adoption at the regional level.

Specific objectives

The thesis is divided into 5 specific objectives, across three dimensions:

Development

1. To assess the evidence on the adequacy and viability of PPPs to tackle the market failure for NTDs
2. To map the PPPs across functionalities and diseases as well as describe their roles and limitations
3. To evaluate the impact of the PRV on stimulating R&D for tropical diseases

Implementation

4. To estimate and compare the cost-effectiveness of two new diagnostic tools with microscopy for cutaneous leishmaniasis in Afghanistan

Adoption

5. To understand the role of disease knowledge and risk perception in shaping the demand for preventive behavior for selected vector-borne diseases (malaria, dengue, Zika virus and cutaneous leishmaniasis) in Guyana

III. Materials and methods

This thesis is based on the work carried out at the ISGlobal in collaboration with the Swiss Tropical Health Institute (Swiss TPH) and the Institute of Tropical Medicine (ITM) for objective 1 and 2; the Business school of the Imperial College London for objective 3; the FIND and the MoPH of Afghanistan for objective 4; and lastly, with the Ministry of Public Health of Guyana, the University of Pompeu Fabra and the University Paris 1 Pantheon-Sorbonne for objective 5.

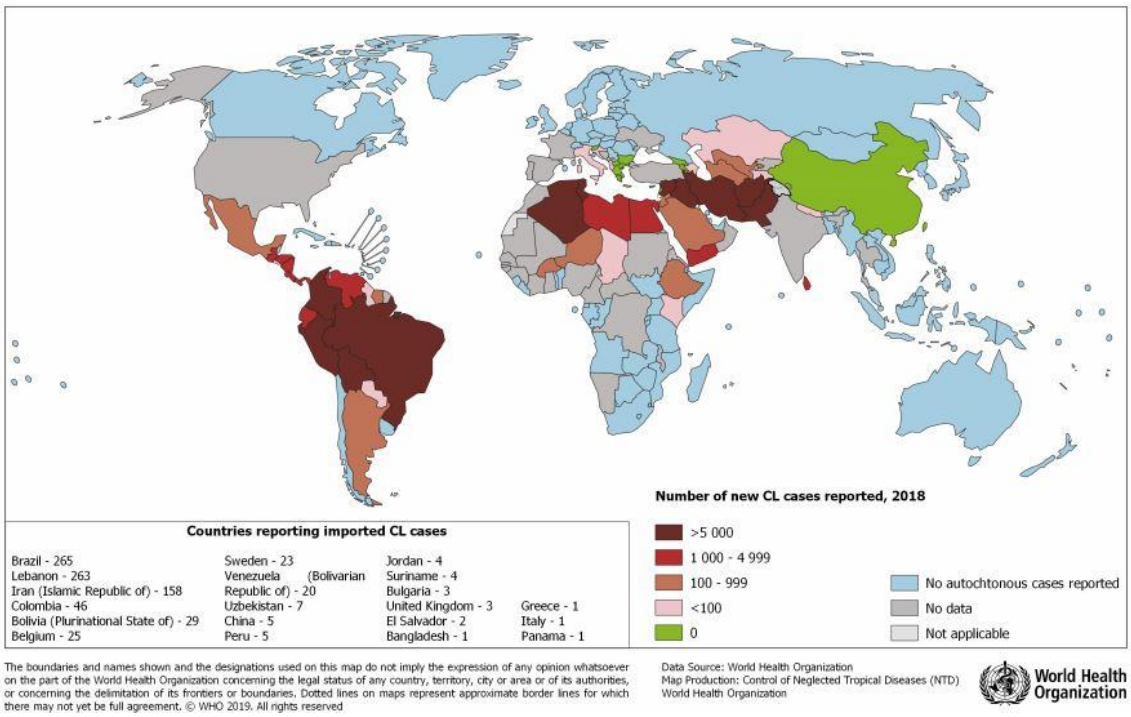
This project received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement Nº 642609. It also received additional funding from the United States Agency for International Development (USAID) for the fieldwork carried out in Guyana.

Study areas

The first three objectives are not specific to any study sites; they did not rely on primary data but used already existing data publicly available.

For objective 4, on the other hand, the analysis was conducted in Kabul, at the clinic of the National Malaria and Leishmaniasis Control (NMLCP) program, which belongs to the MoPH of Afghanistan. Data on the effectiveness of the tools (i.e. sensitivity and specificity) and on the costs associated with the diagnostics and treatments were collected at the NMLCP clinic. The study population consisted of individuals presenting themselves at the clinic with suggestive symptoms of CL. According to the MoPH, the NMLCP clinic is the biggest in the country and treats an estimated 5000-7000 CL cases yearly. Afghanistan is one of the countries with the highest burden of leishmaniasis – caused mainly by *leishmania tropica* – and particularly of the cutaneous form (Figure 1). As a consequence of decades of war, the country is suffering from a lack of health professionals and services as well as from insecurity and corruption, which has implications on the health system both at central and peripheral levels (Berry and Berrang-ford, 2016). New technologies that either save on laboratory expertise or laboratory facilities are hence needed.

Figure 1: Status of endemicity of cutaneous leishmaniasis worldwide (2018)

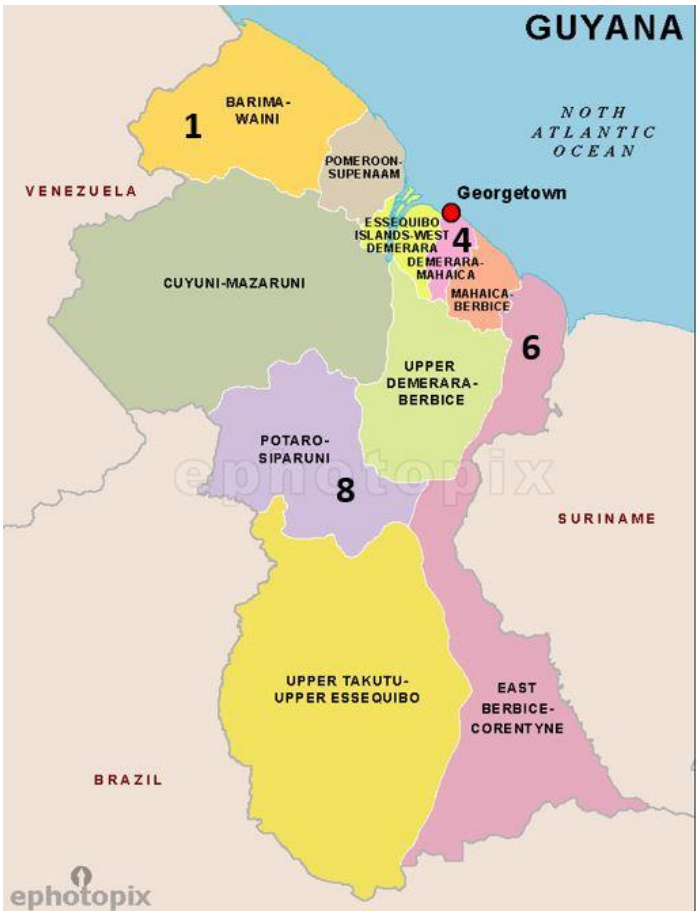


Source: (World Health Organization (WHO), 2018)

For objective 5, the study was conducted in selected regions of Guyana. Guyana lies between Suriname, Brazil and Venezuela, spanning over 216.000 square kilometers with a population of approximately 780.000 inhabitants. The country is divided into ten administrative regions that are categorized as either interior or coastal based on their geographical location, demographic characteristics, soil type, economic activities, and natural resources, among others (Ministry of Health Guyana, Guyana Responsible Parenthood Association (GRPA) and ORC Macro, 2004). The country's population is mainly distributed along the coast: almost half of the country's population lives in the capital city Georgetown, located in region 4. This region was selected in the study along with three other regions: regions 1, 6 and 8 (Figure 2). Regions 4 and 6 are coastal regions whereas regions 1 and 8 are categorized as hinterland. Those regions were selected to capture different endemic zones according to the disease. The four VBDs considered in this study included malaria, CL, dengue and Zika. The former two are endemic in the hinterland while the latter two are endemic in the coastal regions. Guyana provides an interesting context to study behavioral responses to VBDs transmission risk. It provides a strategic geographical location for promoting the

control and elimination of VBDs in the Northern coast of South America and in the Caribbean. Indeed, a regional cooperation between the Guianas (Guyana, Suriname and French Guyana) and Brazil has often been reported to be necessary (Carribean Public Health Agency, no date; Edward D, Bretas and Hiwat, 2018; Hiwat *et al.*, 2018). In addition to this, Guyana has been receiving an increasing number of migrants from Venezuela over the last years; which political situation has led to resurgence of VBDs transmission (Grillet *et al.*, 2019). Having said all of this, Guyana has until now been neglected by research of any type.

Figure 2. Map of Guyana and its regional division



Source: Mapsopensource. Available from: http://www.mapsopensource.com/guyana-political-map.html

Study methodology

The thesis is a compilation of four articles, divided into three main sections: product development, implementation and adoption. Three articles are published

in peer-reviewed journals while one is currently under review. Each article entails a distinctive methodology, as explained below.

Development

Systematic review of public-private partnerships for NTDs

The first article presents a systematic literature review, which searched articles on PPPs for NTDs in three different databases – Scopus, PubMed and in IDEAS (Research Papers in Economics, REPEC) – to capture the multidisciplinary facets of these models. The review included articles published between January 1970 and August 2016, either 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). The titles, abstracts and keywords of all extracted records were first screened. Afterwards, the full text articles were evaluated and included if fulfilling the inclusion criteria.

The impact of the priority review voucher on R&D for tropical diseases

This article evaluated the PRV program implemented by the US Congress in September 2007. Since the policy affects a specific group of diseases (neglected diseases) in a specific trial registry (ClinicalTrials.gov), we can evaluate the impact of the PRV using a DDD approach. More specifically, we employed a poisson fixed effects model with cluster-robust standard errors by disease-registry which enable us to control for a broad range of factors including exogenous yearly variations in R&D activity and unobserved time-invariant heterogeneity that are specific to trial registry and disease. To measure innovation in R&D, data on trial registration were retrieved from WHO International Clinical Trials Registry Platform (ICTRP), which gathers ongoing and completed clinical trials from 18 registries (http://apps.who.int/trialsearch/). More specifically, given the eligibility criteria of the program, non-inferior and interventional trials registered in phases 2 and 3, targeting either a drug, vaccine

or device were included in the analysis. Registration in ClinicalTrials.gov for both phases 2 and 3 is compulsory and must be documented to be granted a PRV.

Implementation

The cost-effectiveness analysis of new diagnostic tools for cutaneous leishmaniasis in Afghanistan

The third article evaluated the cost-effectiveness of new diagnostic tools for CL in Afghanistan. Data related to the cost and accuracy of these tools were collected at the clinic of the NMLCP in Kabul, Afghanistan. The effectiveness estimates were measured based on the tools' performance (using polymerase chain reaction (PCR) as a reference) but also indirectly using the disability-adjusted life years (DALYs). More precisely, as the sensitivity of a tool decreases, the chances of wrong diagnoses increase. If a sick patient is wrongly diagnosed, he/she will remain sick longer and carry the associated disease disability weight for a longer period of time. A decision tree was designed in TreeAge Healthcare Pro 2016 which incorporated a Markov model representing the natural history of CL. Cholesky decomposition among the parameters was performed so that the variance of each parameter and the variability within parameters (covariance) were kept constant through a multi-normal distribution. The results were analyzed using both deterministic and probabilistic (i.e. Monte Carlo simulations) analyses. Probabilistic analyses were exhibited using the cost-effectiveness plane (i.e. plotting the incremental cost and incremental effectiveness of each Monte Carlo simulation). Yet, given the similar effectiveness across the tools, we also rely on the net monetary benefit (NMB) curves to exhibit the probabilistic results.

Adoption

The role of risk perception and disease knowledge in shaping the demand for preventive measures for selected VDBs in Guyana

To assess the role of disease knowledge and risk perception in shaping preventive behavior, we collected data from 845 individuals between August and December 2017 in four regions of the country. For each disease, questions on disease knowledge, risk perception and use of preventative measures were asked. Keywords for describing the diseases and preventive tools were selected

based on discussions with the MoPH. Each time a keyword was cited, a box was ticked. We focused our analysis on data collected from private houses only (59% of the total sample) in order to control for individuals socioeconomic and demographic characteristics, which led to total sample size of 497 individuals. To analyze the data, a structural equation model (SEM) was estimated. This model is often advocated when dealing with different sources of endogeneity and when only cross-sectional data are available. These included – but are not limited to – omitted variables bias (e.g. whether the person already experienced the disease) and the bidirectional link between risk perception and behavior. In addition to this, SEM allows to control for measurement error by using latent variables as indicators of observed variables.

IV. Results

ARTICLE 1

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

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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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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: we could not find any impact evaluation analyses, while these are crucial to realize the full potential of PPPs and to progress further towards NTDs elimination.

1. 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 [5–7].

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

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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.

2. Study data and methods

2.1. 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. We then 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:

- Descriptive studies of PPPs context
- Descriptive studies of PPPs experiences
- 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.

3. 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. Fig. 1 for PRISMA diagram).

3.1. Descriptive studies of PPPs context

3.1.1. Push schemes

Push schemes have been heavily criticised 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 1.

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 beleive in 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

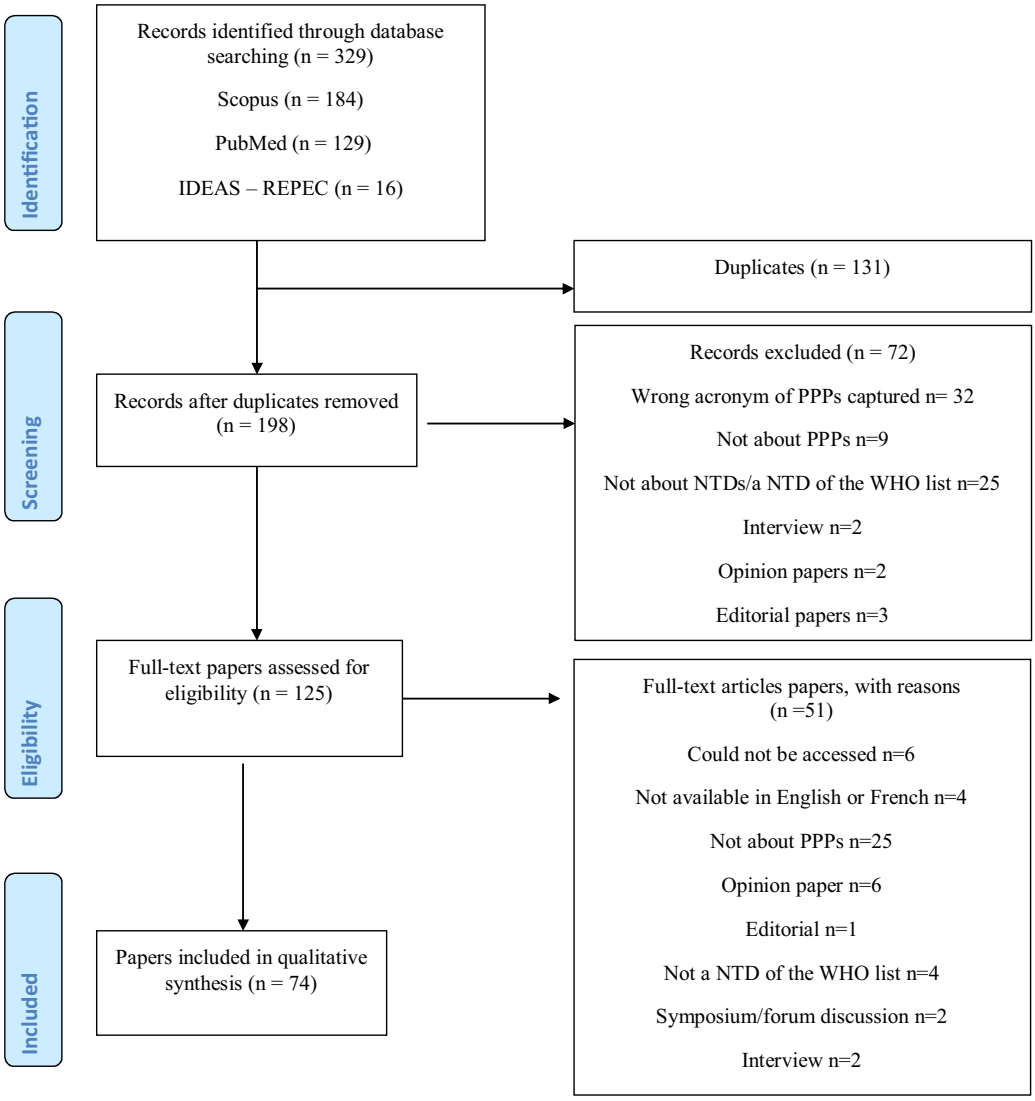

Fig. 1. PRISMA Flow Diagram.

Table 1
Push mechanisms: advantage(s) and disadvantage(s).

Push mechanisms	Advantage(s)	Disadvantage(s)
R&D grants: 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].

pull mechanisms are perhaps better suited to stimulate investment in R&D.

3.1.2. 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 2.

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

Table 2
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].

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].

3.1.3. Hybrid schemes

Mixed schemes use a combination of push and pull mechanisms; however examples are scarce. 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) [5,17,13]. 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 hand. There is a certain consensus that PDPs should adopt a mixed scheme strategy [6,13,18,15,19,28]. 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 2 and 3 [18,20,19].

3.2. 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 3.

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 Figs. 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.).

3.3. 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 drugs 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].

3.4. 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 4.

4. 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.

Table 3
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 Program	Social mobilization	After the program, the number of houses and schools with immature Ae. Aegypti had decreased [41]	[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 treat >86% of the cattle population to weaken the animal reservoir and reduce the 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 Tropical Disease (TDR)	PDP: Drug development (Miltefosine and Paramomycin)	NA	[47,50]
	DNDi	PDP: Drug development	NA	[21]
Leprosy	Novartis	Access PPP: Donation by Novartis of multidrug therapy packages (Dapsome, Rimactane and Lamprene)	NA	[22]
	The German Leprosy Relief Association (GLRA)	Various (e.g. staff training, provision of transport, etc.)	GLRA fills the gaps in existing national disease control programs in five South American countries and in seven Brazilian states [51]	[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 that cause LF [52]	[52,22,26,53]
	The Global Alliance for Elimination of Lymphatic Filariasis (GAELF)	Access PPPs	NA	[54]
	WIPO Re:Search consortium	Facilitate coordination for product development	NA	[38]

Table 3 (*Continued*)

NTDs of the WHO list	Partnership(s) or Organization leading the partnership	Tool(s)	Comment	Citation of the PPP
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 (OEPA)	Access PPP: drug donation of Ivermectin by Merck	By 2010, Colombia had interrupted transmission and stopped treatment. Several formerly endemic areas in Mexico, Guatemala and Venezuela have also stopped treatment [31]	[60,31,62,53]
	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) Human	PDP: vaccine development (Ov-103 and Ov-RAL-2 Necator)	The antigens are advancing through preclinical development [26]	[26]
	WIPO Re:Search consortium	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 Vaccine Institue and the Oswaldo Cruz Foundation (FIOCRUZ)	PDP: vaccine development (sm14)	Phase 2 trials were planned for 2005	[49,24,64,63,65,66]
	The Sabin Vaccine Institute with Baylor College of Medicine	PDP: vaccine development (Sm-TSP-2)	Phase 1 trial has been initiated in 2004	[26,63]
	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)	PDP: vaccine development (Na-GST-1 and Na-APR-1)	Both antigens are cur- rently in Phase 1 trials in Gabon and Brazil [26]	[49,24]
	The Human Hookworm Initiative (HHVI)	PDP: vaccine development (Na-ASP-2)	The Na-ASP-2 hookworm vaccine has undergone Phase 1 in the USA [68]	[68,69]
Taeniasis	No partnerships found			
Cysticercosis	WIPO Re:Search consortium	Facilitate coordination for product development	NA	[38]
	The Regional Network for Asian Schistosomiasis (RNAS)	Facilitate coordination for product development	NA	[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.

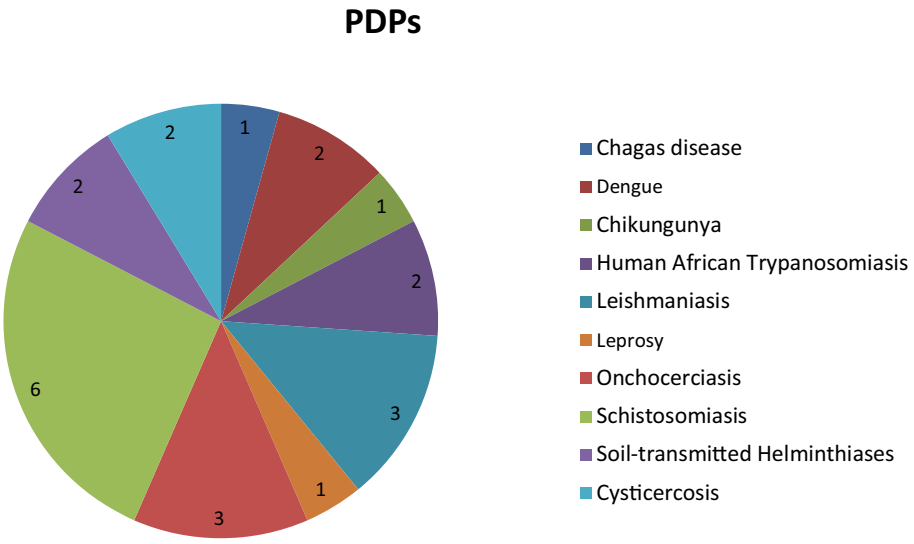

Fig. 2. Distribution of product-development partnerships(PDPs) across NTDs.

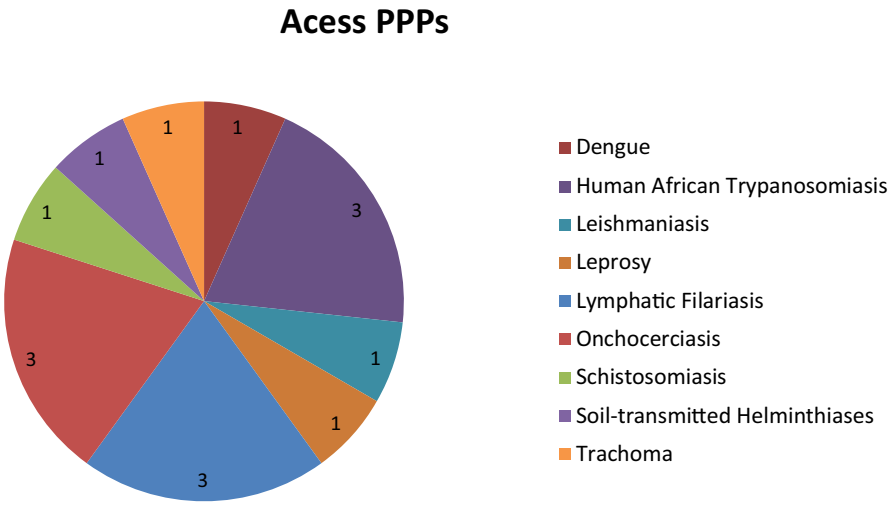

Fig. 3. Distribution of Access PPPs across NTDs.

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 [29,30]; 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 sin-

Table 4
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 2 trials, followed by AMC afterward) for the development of vaccines for neglected diseases.	Cost-effectiveness analysis. Estimates of costs associated with each model, timelines and transition probabilities from moving to one phase to the other were 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.	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.
[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 partnership process.	Systematic review over 12 databases.	10 of the 212 references initially extracted were included in the 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.

gle 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.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.healthpol.2017.05.005.

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Supplementary Material

Table V: Descriptions of PPPs context

NA= Not available

YEAR AND STUDY	(BORS *ET AL.*, 2015)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Research and development (R&D) grants 2. Prize funds 3. R&D treaty to finance and coordinate R&D grants and prize funds 4. Advance market commitment 5. Priority review vouchers (PRV) and tax credit. 6. Product development partnership (PDP) 7. Patent pools and open databases.
ASSOCIATED DRAWBACK(S)	1. R&D grants are subject to the changing will of the donor. Additionally, grant money may run out before the desired project is achieved. 2. Donors may not be perfectly aware of patient needs and as a result prize fund may seek for objectives of limited utility or that are not feasible. 3. Such treaty is very likely to be subject to political influence and hence would need to be carefully designed to ensure that it does not disadvantage low-income countries. 4. So far, there has only been one advance market commitment: the PneumoAMC, for the development of two pneumococcal vaccines. However critics have said that the PneumoAMC has neither accelerated the innovation cycle nor increased availability. Moreover, the PneumoAMC has been criticized for being expensive compared to other holistic approaches. 5. These methods have been poorly used. Only two PRVs have been awarded: one for an antimalarial drug and one for a tuberculosis medicine. 6. The overall impact of PDP is mixed. While TB Alliance has gathered the biggest portfolio of potential new TB drugs ever made, they have only produced one new TB drug (Bedaquiline). Concerning MMV, the partnership has succeeded more in

	terms of altering existing medicines for markets than creating new treatments. Other critics have argued that PDP are subject to high transaction costs, varying accountability and a lack of alignment with country priorities and systems. 7. The viability of patent pools to promote R&D is questionable since they have been very poorly used.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	NA
ASSOCIATED ADVANTAGE(S)	NA
POLICY RECOMMENDATION(S)	More funding should be directed at improving access to medicines, which will further require greater regulations of the pharmaceutical market place in low-income countries.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(BURROWS *ET AL.*, 2014)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	NA
ASSOCIATED DRAWBACK(S)	NA
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Product development partnership (PDP)
ASSOCIATED ADVANTAGE(S)	The PDP model presents specific advantages over the traditional pharmaceutical drug discovery process. Firstly, the financial cost and risk of developing drugs is typically shared across a number of partners. Secondly, since the PDP return on investment is lives saved and not money made, drugs will not fail on the basis of perceived or actual commercial viability. Thirdly, PDPs create extensive communication and research networks among academic and industrial laboratories that are uncomplicated by commercial concerns. Lastly, PDP have a sustained long-term focus on specific diseases for the discovery and delivery of new products, allowing them to build a comprehensive research and development (R&D) portfolio.

POLICY RECOMMENDATION(S)	Continued investment is needed to ensure that pipelines for neglected tropical diseases remain strong.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(CASTY AND WIEMAN, 2013)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	The pharmaceutical industry
ASSOCIATED DRAWBACK(S)	While the research and development (R&D) costs of pharmaceutical companies have increased, the return on investment has decreased.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Public-private partnerships (PPPs)
ASSOCIATED ADVANTAGE(S)	PPPs enable pharmaceutical companies to apply their experience and expertise, while achieving great efficiencies at the enterprise level, with marginal costs decreasing with each additional partnership. Advantages of PPPs are numerous and include: (i) decreasing costs associated with the partnerships, (ii) increased flexibility to take on multiple projects or shift resources quickly, (iii) accelerating drug development by sharing data and expertise, (iv) and amplified quality and value of product offerings. Additionally, PPPs enable small to medium-sized pharmaceutical companies that may be without in-house R&D facilities to engage into innovative drug development.
POLICY RECOMMENDATION(S)	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(CHAUDHURI, 2010)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Push incentives (direct public spending, research and development (R&D) grants and fiscal incentives) 2. Pull incentives (the patent system) in India
ASSOCIATED DRAWBACK(S)	1. The response to push incentives in India has been quite low. 2. Most of the pull incentives are not relevant to countries such as India because they assume that companies

	have the capacity and capability to undertake R&D.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Public-private partnership (PPP)
ASSOCIATED ADVANTAGE(S)	PPP makes better use of resources in India's public-funded institutions and are more oriented towards developing countries' needs.
POLICY RECOMMENDATION(S)	The cost of clinical trials is the largest cost of the drug development process (40%) and is much cheaper in developing countries. The authors suggest expanding regulatory approval in countries such as Brazil and China.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(PHD, DBA AND GUY NUYTS, NO DATE)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Push mechanisms (tax credit and direct funding) 2. Push-Pull (mixed) mechanism (orphan drug act (ODA)) 3. Pull mechanisms (Advance Market Commitment (AMC), Priority Review Voucher (PRV))
ASSOCIATED DRAWBACK(S)	1. Tax credit for the development of drugs for neglected disease has little impact because of low commercial value. With respect to direct funding, the issues are the following: if the innovator knows that all of the costs associated with product development are funded a priori, the incentive to deliver the product quickly is reduced. Moreover, assigning fund to a specific product or company discourages competition. 2. ODA combines push-pull mechanisms, but is not feasible for diseases that have very low commercial value prospect. 3. AMC are subject to the 'time-inconsistency' problem. The resulting value of PRV is hard to predict as it mainly depends on the kind of product the firm has for the developing world as well as on the potential 'blockbuster' product that could be sold in developed countries.

RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Mixed schemes that apply the 'risk-investment-incentive' model.
ASSOCIATED ADVANTAGE(S)	In the early stage, the authors advocate for push funding in order to support translational research and academic-industry initiatives and as soon as the 'proof-of-concept' has been established, pull mechanisms such as the AMC and PRV should be advocated for.
POLICY RECOMMENDATION(S)	Greater coordination among the health care systems at country level should be enhanced by National authorities.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(GRANVILLE AND TRUSHIN, NO DATE)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Advanced Market Commitment (APC) 2. Public-Private Partnership (PPP)
ASSOCIATED DRAWBACK(S)	1. Only large pharmaceutical companies may have enough cash to finance R&D in advance which may represent an issue as small firms play a crucial role in the development of new drugs 2. NA
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	A 2-stage procurement model of public-private partnership to provide better incentives for research and development (R&D) on neglected diseases which combines three ideas: (i) advance market commitment, (ii) subsidized clinical trials and (iii) rewards drugs based on their therapeutic effects through a prize screening mechanism.
ASSOCIATED ADVANTAGE(S)	It rewards quality of new drugs and shares the risks and costs of new drug development. Additionally, by giving a first pre-announced fixed prize it encourages small firms –which are more likely to be liquidity constrained - to take part in R&D for neglected diseases. Furthermore, the model also limits the issue of moral hazard: the first stage prize is set below the expected costs of the drug discovery to discourage entrance of applicants with low quality drugs.
POLICY RECOMMENDATION(S)	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(GRANVILLE AND TRUSHIN, 2015)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Push schemes: Subsidy schemes and public-private partnerships (PPPs) 2. Pull schemes: reward based on drug therapeutic effect; extending the duration of intellectual property rights (IPR); fast track approval in exchange for Neglected Tropical Disease (NTD) drugs: Advanced Market Commitment (AMC). 3. Mixed schemes: 'The Orphan Drug scheme'; Priority review voucher (PRV).
ASSOCIATED DRAWBACK(S)	Push, pull and mixed-schemes suffer from sustainable funding. 1. Subsidy schemes suffer from moral hazard and adverse selection as donors cannot perfectly monitor researchers. PPPs are seen as the best option among push schemes however they are not flawless. PPPs usually mainly work with drug candidates at advanced phases of development and only for diseases with a large potential commercial market (e.g. tuberculosis and malaria). PPPs also suffer from asymmetric information and hence may tolerate inefficient drug project. PPPs also lack of accountability and corporations participating in PPP may be driven by other motivations (e.g. marketing of public relations) than the development of the drug. 2. The main difficulty encountered in developing a model that rewards drug candidates based on their therapeutic effects is in estimating the global disease burden reduction. Extending patent protection in exchange for developing drugs for neglected disease is likely to create large distortions and dead-weight loss. As for AMC, since it is difficult to estimate the future costs and technological changes, the AMC prize is likely to be either too low or too high. Additionally, AMC can only benefit pharmaceutical companies which have the ability to finance R&D. 3. Orphan drug incentives are only effective for drugs that can be sold at a very high price, which is not the case

	for NTD. FDA priority voucher may not necessarily increase the number drugs that are therapeutically innovative but instead raise the number of 'me-too' drugs on the market.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Based on seventeen criteria grouped into four categories (efficiency, feasibility, fairness and sustainability), the best existing scheme for neglected diseases is the one proposed by Moran et al., (2005) with subsidies and grants channeled through a centralized PPP platform.
ASSOCIATED ADVANTAGE(S)	NA
POLICY RECOMMENDATION(S)	Among others, the drug discovery process should require long term R&D financing, with G20 countries allocating to NDs a 1% share of their current spending on public pharmaceutical R&D.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HOTEZ, BOTTAZZI AND STRYCH, 2015)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Pull funding instruments: Advance market commitment (AMC) and priority review voucher (PRV).
ASSOCIATED DRAWBACK(S)	These schemes assume that the pharmaceutical industry has the needed up-front fund to finance the initial vaccine manufacture and clinical development. However, this is very rarely the case for most of the product-development partnerships (PDP) or developing-country vaccine manufacturers.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	NA
ASSOCIATED ADVANTAGE(S)	NA
POLICY RECOMMENDATION(S)	In order for PDPs and developing-country vaccine manufacturers to survive, additional push mechanisms are urgently needed to provide the necessary up-front funds.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(JULIANO, 2013)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Public-Private Partnership (PPP)

ASSOCIATED DRAWBACK(S)	Although the success of PPPs is highlighted here (70% of the R&D for neglected diseases involved PPPs) it has still been criticized for adopting an unproductive 'layer cake' approach to drug development: that is, conducting initial early studies of biology that are disconnected from drug chemistry and from subsequent pharmaceutical work-up and clinical testing.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	A model of non-profit drug development corporations (NPDDCs) that would go further than PPPs by providing an integrated approach to early-stage drug discovery and development.
ASSOCIATED ADVANTAGE(S)	It would be based on free-standing, limited lifetime, not-for-profit R&D corporations built on partnerships between government, academic institutions and private industry.
POLICY RECOMMENDATION(S)	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(LE, 2014)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	None specifically; the author describes the "current situation"
ASSOCIATED DRAWBACK(S)	Funding towards neglected tropical diseases is mostly directed to innovation research – the "R" in research and development (R&D). Nevertheless, it is often the case that financial resources is then lacking to support product development – the "D" in R&D- once the discovery is made.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Public-private partnership (PPP)
ASSOCIATED ADVANTAGE(S)	PPPs are able to incentivize pharmaceutical companies to contribute to the development of treatments for neglected tropical diseases (NTD) – that are then perceived as public good – by sharing their technology and expertise. PPP first act as a push mechanism to encourage investments that are then pulled along by financial commitments of public and philanthropic funds.
POLICY RECOMMENDATION(S)	Policy directed towards the reduction of poverty must address health challenges like NTDs as well as other determinants of health (e.g. social inequality).

MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(LEXCHIN, 2010)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	The traditional pharmaceutical industry
ASSOCIATED DRAWBACK(S)	The presence of the patent system puts systematic barriers to the expansion of research capacity.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Public-private partnership (PPP)
ASSOCIATED ADVANTAGE(S)	Not explicitly mentioned. However the author does affirm that PPP is the most advanced alternative proposed by the usual method of researching and developing new drugs (47 out of the 63 new drugs for neglected diseases were being developed under a PPP).
POLICY RECOMMENDATION(S)	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(MACKEY AND LIANG, 2012)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Public-private partnership (PPP) for drug discovery solely.
ASSOCIATED DRAWBACK(S)	PPPs that exclusively focus on drug development may not recognize the diverse set of challenges posed by NTDs.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	The ‘One Health Initiative’: a multi-disciplinary PPP.
ASSOCIATED ADVANTAGE(S)	The main goal of the ‘One Health Initiative’ is to enhance connection and coordination among the human, animal, agricultural and environmental sectors. By emphasizing the interconnectedness of various sectors in disease eradication, the ‘One Health Initiative’ “advocate for integrative health risk management using knowledge sharing, education, and effective governance among these system participants to provide a comprehensive, strategic approach to future health challenges”.
POLICY RECOMMENDATION(S)	Tackling exclusively drug innovation is not enough.

MENTIONING ELIMINATION?	yes

YEAR AND STUDY	(MRAZEK AND MOSSIALOS, 2003)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Extended market exclusivity 2. “Roaming market exclusivity” (transfer a patent granted on a product for a neglected disease (ND) to any other product they preferred in developed countries) 3. Tax credits on R&D expenditure 4. Tax credit on sales 5. Advance market commitment (AMC)
ASSOCIATED DRAWBACK(S)	1. Extending market exclusivity for products for NDs is likely to increase prices which will hamper access. 2. “Roaming market exclusivity” raises the following problematic questions: (i) which product should be selected, (ii) for how long should they gain additional exclusivity and (iii) in which countries would this extended exclusivity apply. Additionally, this mechanism undermines competition and may not be judged fair by other industrial sectors. 3. Tax credit on R&D expenditure is already used to stimulate pharmaceutical R&D (e.g. US Orphan Drug Legislation). As a result, tax credit on R&D expenditure for NDs may need to be set very high in order to compete with the other tax credits already in place. 4. Without an AMC, a tax credit on sale is unlikely to have any impact on R&D. 5. This kind of mechanism may not provide enough security for firm to invest heavily in long-term projects (the approximate size of the amount needed for firm to be willing to invest is estimated at US$250 million).
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Public-private partnership (PPP)
ASSOCIATED ADVANTAGE(S)	PPPs provide a sustained support of basic research as well as subsidy at later stages of product development.
POLICY RECOMMENDATION(S)	Current issues related to PPPs such as transparency, accountability to the public interest, and a clear governance structure must

	be addressed. Moreover, authors argue that it is often the case that PPP's efforts are duplicated: due to a lack of effective communication among PPPs, these tend to target similar outcomes in parallel.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(MUNOZ *ET AL.*, 2014)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Push schemes 2. Pull schemes: Advance market commitment (AMC)
ASSOCIATED DRAWBACK(S)	1. Moral hazard. 2. Two crucial conditions for AMC are: (i) to set an adequate payment's size in order to attract participants and (ii) to specify the amount of commitment (doses, prices, ect.) that would be required to provide a sufficiently large market to overcome the barrier to R&D investment. However the size of the payment and the amount of commitment may be hard to specify in advance, especially given the lack of reliable estimates on the cost of R&D for the development of new medical products.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Product development partnership (PDP)
ASSOCIATED ADVANTAGE(S)	PDP leverage the resources and capabilities of a diverse network of public, philanthropic and private-sector partnership. They are able to bring innovation to address unmet medical needs with a final product that is either distributed freely or priced at a price close to the marginal cost of production to ensure a long-term health impact.
POLICY RECOMMENDATION(S)	The authors believe that "an agreement for increased global coordination of priority setting for R&D and resource allocation directed at neglected diseases, for instance, through the WHO, would serve to direct the work of PDPs in a more coherent and transparent manner".
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(NWAKA AND RIDLEY, 2003)

SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	“traditional” public-private partnership (PPP)
ASSOCIATED DRAWBACK(S)	Most PPPs so far have been based on the identification and screening of available compounds from other indication areas, followed by clinical development.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Building a virtual drug discovery and development model within PPPs.
ASSOCIATED ADVANTAGE(S)	A clear benefit of the virtual model is its flexibility. For instance, project can be developed in places where the needed intellectual capacity and expertise are already at disposal. This model also saves on equipment, other costly capital items and administrative costs since there are typically provided by the research partners. By working on several projects with several partners, long-term relationships with some partners can be used as a resource for other projects (e.g. a laboratory with expertise in drug testing against a specific parasite). This model has proved to be successful with the development of miltefosine, the first oral drug for the treatment of visceral leishmaniasis.
POLICY RECOMMENDATION(S)	There is a need to better involve disease-endemic countries into PPPs such that, in the future, these countries will be able to develop the drugs they need.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(PRATT AND LOFF, 2012)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Public-private partnership (PPP)
ASSOCIATED DRAWBACK(S)	Distribution and adoption of the developed products in developing countries are not obligatory features of PPP, nor is building research capacity in developing countries. Challenges still remain in ensuring that the drugs reach the people who need them.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	NA
ASSOCIATED ADVANTAGE(S)	NA
POLICY RECOMMENDATION(S)	Research funding must be more evenly allocated.

MENTIONING ELIMINATION?	No

YEAR AND STUDY	(SORENSON, 2009)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Push scheme: tax credits Pull scheme: Advance market commitment (AMC)
ASSOCIATED DRAWBACK(S)	The mechanisms have been ineffective, underused and not sufficiently pursued.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Product-development partnership (PDP)
ASSOCIATED ADVANTAGE(S)	PDPs provide a viable solution to the risk and uncertainty inherent to the drug development process. About 75% of neglected diseases (ND) drug projects are led by PDPs.
POLICY RECOMMENDATION(S)	Further multi-disciplinary analysis is required to accurately understand the dynamics underlying PDPs (e.g. governance)
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(TROUILLER *ET AL.*, 2002)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Public-private partnership (PPP)
ASSOCIATED DRAWBACK(S)	PPPs are likely to be insufficient “to meet the vast and increasing health needs of poor people in developing countries”. These partnerships are only feasible for diseases that represent a health threat to the developed world.
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	NA
ASSOCIATED ADVANTAGE(S)	NA
POLICY RECOMMENDATION(S)	Efforts should not only be put on developing a treatment but ensuring equitable access (e.g. equitable pricing policy worldwide) and sponsor agencies should do more to assist in drug procurement.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(WALT AND LUSH, 2001)

SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Public-private partnership (PPP)
ASSOCIATED DRAWBACK(S)	Firstly, not all partnerships include partners from developing countries, whereas these countries are more likely to know better what is needed. Secondly, within PPPs, partners' power relations are asymmetrical and have divergent goals and interests. Thirdly, there has been a considerable investment of time and energy into these partnerships but very little time and energy has been spent on getting to know their best practices or processes. Fourthly, the accountability of PPPs is questionable. Fifthly, it is not clear how far PPP replicate the work of public policy institutions such as the World Health Organization (WHO). Lastly, PPPs focus on very scattered issues (e.g. a majority of PPPs have focused on AIDS, Tuberculosis and Malaria).
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	NA
ASSOCIATED ADVANTAGE(S)	NA
POLICY RECOMMENDATION(S)	Efforts need to be pushed towards strengthening the health sector in developing countries.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(WEBBER AND KREMER, 2001)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	1. Push schemes 2. Pull scheme: transferable patent right
ASSOCIATED DRAWBACK(S)	1. The cost of research and development (R&D) itself is not a feasible explanation for the lack of R&D in neglected diseases. Instead, insufficient market attractiveness or viability, relative to the cost and risk level inherent in R&D is a more serious barrier. 2. Such action would place a burden (higher prices) on those patients in need of the medicine for which the patent has been extended.

RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	Tax credit for sales and advance market commitment (AMC)
ASSOCIATED ADVANTAGE(S)	Both schemes do not cost anything unless a viable product has been developed. AMC is judged cost-effective and has the potential to create a market that did not exist before. Moreover, access problems and market uncertainty are reduced as the number of doses and purchase prices are pre-specified.
POLICY RECOMMENDATION(S)	A mixture of push and pull schemes that could provide viable incentives to companies: e.g. between increased funding for public laboratories, larger purchases on underutilized existing medicines and vaccines and an AMC.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(WIDDUS, 2001)
SCHEME(S) OR TYPE(S) OF PARTNERSHIP DISCUSSED	Pull schemes: tax credit and building health service infrastructure Push schemes: public investment in basic research, sharing the costs of efficacy trials/production facilities, harmonizing international regulatory requirements and introducing tax credits for investment.
ASSOCIATED DRAWBACK(S)	NA
RECOMMENDED SCHEME(S) OR PARTNERSHIP(S)	The most cost-effective solution is to create a mix between push and pull interventions, facilitated by public-private partnerships.
ASSOCIATED ADVANTAGE(S)	These partnerships permit the different skills of the two sectors to be focused on the challenges specific to the diseases and their products.
POLICY RECOMMENDATION(S)	Efforts are needed to overcome health disparities in developing countries (e.g. better availability between and within countries).
MENTIONING ELIMINATION?	No

Table VI: Descriptions of PPPs experience

NA = Not available

YEAR AND STUDY	(AMAZIGO, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The African Program for Onchocerciasis Control (APOC) (1995)
PARTNERS	Merck
DISEASE(S)	Onchocerciasis
TOOL(S)	Community-directed treatment (CDT) with ivermectin
PPP RESOLVING AT	To eliminate human onchocerciasis from the African countries
OUTCOME	Using CDTI, APOC in 2006 provided treatment to over 46 million people in 15 countries
LIMITATION(S) OF THE PPP	Sustaining the CDTI when APOC ends in 2015
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(BARDOSH, 2015)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Stamp Out Sleeping Sickness (SOS) project (2006)
PARTNERS	Pharmaceutical company (Ceva Sante Animale – that doNAted the drug Vectocid), academic institutions (the University of Edinburgh and Makerere University), philanthropic institution (IK Aid and Relief Enterprise (IKARE)) and the UK department for International Development (DFID).
DISEASE(S)	Sleeping sickness (Human African Trypanosomiasis (HAT)).
TOOL(S)	Three rounds of mass chemotherapy in seven districts between 2006 and 2010.
PPP RESOLVING AT	Lack of awareness that HAT was associated with an animal reservoir.
OUTCOME	400,000 cattle were treated in Uganda.
LIMITATION(S) OF THE PPP	The project did not equate a “sustainable” HAT control, part of the problem was due to the limitations of the private sector itself, and the lack of public sector policies and capacities to enable the necessary infrastructure and outreach to rural farmers.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(BEAUMIER *ET AL.*, 2013)

NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. NA 2. The Sabin Vaccine Institute (Product-development partnership (PDP)) 3. The Infectious Disease Research Institute (IDRI) 4. NA 5. NA 6. a. Currently complementing the work of the Onchocerciasis Control Program, the African Program for Onchocerciasis Control, and the Onchocerciasis Elimination Program in the America. b. NA
PARTNERS	1. a. The National Institutes of Health (NIH) in collaboration with Johns Hopkins University b. The Walter Reed Army Institute of Research (WRAIR) with GlaxoSmith-Kline (GSK) c. Sanofi-Pasteur d. The Centers for Disease Control and Prevention in the United States 2. NA 3. NA 4. a. The Institut Pasteur in Lille b. The Oswaldo Cruz Foundation (FIOCRUZ) in collaboration with Financiadora Estudos e Projectos for Sm14 c. The Sabin Vaccine Institute (PDP) with Maryland University 5. The Sabin Vaccine Institute (PDP), Instituto Carlos Slim de la Salud (México), Laboratorio de Parasitologia, Universidad Autónoma de Yucatán (México), laboratorios de Biológicos y Reactivos de México (México), Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (México), Vector Molecular Biology Section, Laboratory of Malaria and Vector Research and the National Insitute of Allergy and infectious Diseases. 6. a. The EdnaMcConnel Clark Foundation b. The Sabin Vaccine Institute PDP with the New York Blood Center
DISEASE(S)	1. Dengue 2. Human Hookworm 3. Leishmaniasis 4. Schistosomiasis

	5. Chagas disease 6. Onchocerciasis
TOOL(S)	Vaccine
PPP RESOLVING AT	1. No available drugs to cure dengue infection. 2. Reinfection can occur within 6 months of treatment with the same burdens as those seen pre-treatment. 3. Individuals who have been infected and who recover from the infection tend to become resistant to later clinical infection. 4. The current available treatment for schistosomiasis (praziquantel) has several limitations such as high frequency of reinfection and increasing risk of developing drug resistant organisms. 5. The current treatments for Chagas disease are costly, require lengthy regimens, and present the risk of severe adverse events. Moreover, the treatments cannot be administered to pregnant women, which is problematic given the high rates of vertical transmission and congenital infection. 6. Vector and chemotherapy approaches for onchocerciasis control have been able to limit the extent and impact of this infection but these are not permanent solutions.
OUTCOME	1. a. Planning on beginning a phase 2 trial in Brazil (sponsored by Instituto Butantan) b. The vaccine has been tested and appeared to be safe in both naïve and immune volunteers. c. Sanofi-pasteur is the furthest in the development of a dengue vaccine. Phase 3 studies are currently on-going. d. Phase 1 trial in St. Louis Missouri has been completed and another phase 1 trial in Colombia was on-going. 2. Currently, the Sabin PDP is working on the development of two vaccines (NA-GST-1 and NA-APR-1). NA-GST-1 is undergoing phase 1 testing in healthy adults in both Washington, DC, and Brazil while NA-APR-1 was intended to enter phase 1 trials in 2013 in the United States in healthy adult volunteers and later in populations living in Brazil. 3. The potential candidate successfully made it to phase 2 clinical trials.

	4. a. The Institut Pasteur in Lille has developed Bilhvax, which has recently completed phase 1 trials in healthy male adults. b. A phase 1 trial of another promising vaccine is currently on-going in Rio de Janeiro (no results are yet available) c. Although not yet in clinical trials, the potential vaccine has entered toxicology studies. The plan was to start phase 1 safety trials in 2013. 5. These partners are advancing a therapeutic vaccine from target selection through process development, scale up and manufacturing. 6. a. There have been many gains made in the field of vaccine development for onchocerciasis. b. The Sabin Vaccine Institute (PDP) has established a novel strategy of antigen selection. As a result, 8 top-ranking protective antigens have emerged.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(BOATIN, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Onchocerciasis Control Program in West Africa (OCP) (1975)
PARTNERS	Merck
DISEASE(S)	Onchocerciasis
TOOL(S)	Large-scale distribution of Mectizan
PPP RESOLVING AT	To eliminate human onchocerciasis from the program area
OUTCOME	By the end of 2002, the OPC covered 10 million people in 11 Western African countries.
LIMITATION(S) OF THE PPP	The adult O. volvulus has showed sub-optimal responses to Mectizan in former OCP area. To ensure the long-term viability of the drug, the effectiveness of Mectizan against microfilariae over time must be tracked.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(BOATIN AND RICHARDS, 2006)

NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Mectizan Donation Program (1987)
PARTNERS	NA
DISEASE(S)	Onchocerciasis (river blindness)
TOOL(S)	Drug
PPP RESOLVING AT	Before the 1980, only two drugs (suramin and diethylcarbamazine (DEC)) with severe drawbacks were available for the treatment of onchocerciasis. Suramin is toxic and requires repeated injection for several weeks whilst DEC has to be given over several days and produces severe side effects such as fever, headache, rash and oedema.
OUTCOME	In areas where large-scale ivermectin treatment has been applied twice annually for close to 13 years, transmission has been interrupted. However, in places where ivermectin has been the only means to control the disease, complete interruption has not been proven.
LIMITATION(S) OF THE PPP	The program has been successful in getting ivermectin to a huge amount of people, but it is not yet proven that the excellent geographic and therapeutic coverage achieved can be sustained over an indefinite period without external funding. There are also examples of population fatigue at the community level; people are tired of having to take the drug for years. Additionally, for such programmes to operate, government health system must support the community and its decisions pertaining to ivermectin distribution ideally through an integrated approach. Drug reporting, ordering, and supply are the most critical government function that must be strengthened and sustained.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(BOTTAZZI, 2015)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Sabin Vaccine Institute Product Development Partnership (Sabin PDP) (2000)
PARTNERS	The academia, private (Bill & Melinda Gates Foundation) and public (European Commission) sectors, governments of Brazil, of the Netherlands and of the European union.
DISEASE(S)	Hookworm
TOOL(S)	Vaccine

PPP RESOLVING AT	Before the Sabin PDP, the World Health Organization (WHO) control strategies relied on mass drug administration or preventive chemotherapy with a single annual table of either albendazole or mebendazole. However, the associated effectiveness of these treatments was questionable as reinfection in the treated individuals appears several months late after being treated.
OUTCOME	Clinical endpoints of the vaccine are being developed.
LIMITATION(S) OF THE PPP	Increased financing from major funders is critical to advance the vaccine development.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(BOTTAZZI AND BROWN, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Human Hookworm Vaccine Initiative (HHVI) (NA)
PARTNERS	The Sabin Institute, George Washington University, Queensland Institute of Medical Research, London School of Hygiene and Tropical Medicine, Oswaldo Cruz Foundation, Instituto Butantan, and Institute of Parasitic Diseases
DISEASE(S)	Human Hookworm
TOOL(S)	Vaccine
PPP RESOLVING AT	Develop vaccines that can protect against the larval stage and blood-feeding stage of hookworm infection.
OUTCOME	The NA-ASP-2 hookworm vaccine has undergone Phase I in the USA and is currently undergoing Phase I testing in Brazil.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(BOTTAZZI *ET AL.*, 2006)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Human Hookworm Vaccine Initiative (HHVI) (2000)
PARTNERS	The Sabin Vaccine Insitute, the George Washington University Medical Center (GWUMC) in collaboration with the Queensland Institute of Medical Research (QIMR), the René Rachou Research Center of the Oswaldo Cruz Foundation (FIOCRUZ), the London School of

	Hygiene and Tropical Medicine and the Instituto Butantan.
DISEASE(S)	The Human Hookworm
TOOL(S)	Vaccine
PPP RESOLVING AT	To develop a recombiNAnt protein hookworm vaccine.
OUTCOME	The PPP has successfully developed a vaccine (NA-ASP-2) to the point of clinical testing.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(BUSH AND HOPKINS, 2011)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Onchocerciasis Control Program (OPC)) (1974)
PARTNERS	United Nation bodies and a group of 20 donating countries and agencies
DISEASE(S)	Onchocerciasis
TOOL(S)	Drug (Mectizan)
PPP RESOLVING AT	Before the discovery of Mectizan, the only method to control the disease was to use a larvicide mostly distributed by aerial spraying of black fly breeding sites by helicopter.
OUTCOME	The program was a success, particularly in West Africa where onchocerciasis has been a major problem in the past; it enabled the treatment of over 60 million people in 2009 and has a final target of over 90 million.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(CHATELAIN AND IOSET, 2011)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Drugs for Neglected Diseases Initiative (DNDi)
PARTNERS	The Indian Council for Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI), the Malaysian Ministry of Health, the Oswaldo Cruz Foundation in Brazil, Médecins Sans Frontieres (MSF), the Institut Pasteur in France, and the Special Program for Research and Training in Tropical Diseases (TDR)
DISEASE(S)	Human African Trypanosomiasis, Chagas diseases, Visceral Leishmaniasis and Malaria
TOOL(S)	Drug

PPP RESOLVING AT	To respond to the need of safe, affordable, easy-to-use and efficacious treatments, as well as to tackle the lack of existing capacities and awareness about the need to develop new treatments in disease-endemic countries.
OUTCOME	In 2008, it launched its second product for Malaria and in 2009 it developed a combination treatment of nifurtimox and eflornithine (NECT) which is now recommended by the World Health Organization for the treatment of Human African Trypanosomiasis
LIMITATION(S) OF THE PPP	There is a need to strengthen the existing preclinical pipeline to cope with the attrition rate inherent to any R&D activity. There is also a need to increase awareness about NTDs in order to ensure the development of new treatments as well as to increase funding.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(COLATRELLA, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Mectizan donation program (MDP) (1987)
PARTNERS	Merck, the Mectizan Expert Committee (MEC), the Task Force for Child Survival and Development, the World Health Organization (WHO), the World Bank, the United Nations Children's Fund, National ministries of health, more than 35 non-governmental development organizations, and thousands of local community health workers.
DISEASE(S)	Onchocerciasis
TOOL(S)	Drug (Mectizan)
PPP RESOLVING AT	At the time of the discovery, the WHO's highly successful Onchocerciasis Control Program (OCP) was addressing the disease in West Africa, with aerial sprayings of insecticide.
OUTCOME	Merck has donated more than 1800 million tablets, with more than 530 million administered treatments for river blindness since 1987. The program currently reaches 68 million people in Africa, Latin America, and Yemen annually.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(DA VEIGA *ET AL.*, 2015)

NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. NA 2. NA 3. Novartis Institute of Tropical Disease (2002)
PARTNERS	1. The Walter Reed Army Institute of Research, GSK and the Oswaldo Cruz Foundation 2. Sanofi Pasteur 3. NA
DISEASE(S)	Dengue
TOOL(S)	Vaccine
PPP RESOLVING AT	Dengue is a considerable public health problem in many tropical and sub-tropical countries. Currently, there are no available dengue specific antiviral therapies.
OUTCOME	1. All three parties have contributed to preclinical and clinical R&D. The vaccine is in early Phase I trials in the US. 2. The vaccine has completed clinical testing. 3. Although the PPP has not yet led to the development of a clinical candidate, the experience gained during the past decade has provided a ratioNAl for the on-going effort to develop a dengue vaccine.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(DON AND CHATELAIN, 2009)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Drug for Neglected Diseases Initiative (DNDi) (2003)
PARTNERS	Médecins Sans Frontieres, the Oswaldo Cruz Foundation, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health in Malaysia, the Pasteur Institute in France, and the Special Program for Research and Training in Tropical Diseases (TDR).
DISEASE(S)	Human African trypanosomiasis (HAT), visceral leishmaniasis (VL), onchocerciasis (sleeping sickness) and Chagas disease.
TOOL(S)	Drug
PPP RESOLVING AT	Developing new drugs for neglected diseases. For instance, the current treatments for HAT are few and limited due to age, high toxicity, and loss of efficacy in several regions.

OUTCOME	DNDi has programs in phase II and III clinical trials for VL and sleeping sickness, and a strong network of clinical researchers and trial sites in disease-endemic regions.
LIMITATION(S) OF THE PPP	DNDi is aware of the high attrition rate associated with drug discovery and development. It attempts to maintain a full pipeline with longer-term lead optimization programs.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(DUMONTEIL *ET AL.*, 2013)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	NA
PARTNERS	Sabin Vaccine Institute, Texas Children's Hospital Center for Vaccine Development, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV), the center for research and advanced studies in Mexico City, Autonomous University of Yacutan, Laboratorios de Biológicos y Reactivos de México (Birmex), the Japanese company Eisai Co., Ltd, the Bernhard Nocht Institute for Tropical Medicine, University of Kansas, the PHICOR group of the University of Pittsburgh School of Medicine, and the Graduate School of Public Health (PA, USA).
DISEASE(S)	Chagas disease
TOOL(S)	Vaccine
PPP RESOLVING AT	Chagas disease affects approximately 10% of Latin America's 'bottom 100 million'. Based on disability-adjusted life-years (DALYs) the disease burden of Chagas disease is five times greater than malaria.
OUTCOME	The partnership has obtained the access for the testing and evaluation of a novel adjuvant, which has pioneered the development of the synthetic TLR4 agonist, E6020, as a vaccine adjuvant. Phase I clinical trials (for safety and immunogenicity) could start in healthy volunteers.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(GUSTAVSEN AND HANSON)

NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. Lymphatic filariasis elimination program (1998) 2. Mectizan donation Program (1987) 3. NA 4. Children without Worms program (2007) 5. International Trachoma Initiative (1998) 6. NA 7. NA 8. NA
PARTNERS	1. GSK, Merck and Co. Inc 2. Merck and Co.inc 3. Merck KGaA 4. Johnson & Johnson 5. Pfizer Inc 6. Norvatis 7. Sanofi and Bayer HealthCare 8. Bayer HealthCare
DISEASE(S)	1. Lymphatic filariasis 2. River blindness 3. Schistosomiasis 4. Parasitic Worm 5. Trachoma 6. Leprosy 7. Human African Trypanosomiasis 8. Chagas disease
TOOL(S)	1. Drug (Albendazole is co-administered with Mectizan) 2. Drug (Mectizan) 3. Drug (praziquantel) 4. Drug (mebendazole) 5. Antiobiotic (Zithromax) 6. Multidrug therapy package (dapsome, Rimactane and Lamprene) 7. Multidrug therapy package (pentamidine, melarsoprol and eflornithine) 8. Drug (lampit)
PPP RESOLVING AT OUTCOME	The lack of safe and efficacious treatments 1. NA 2. NA 3. NA 4. To donate up to fifty million doses 5. To support the elimination of blinding trachoma by 2020 6. To donate enough for all patients worldwide through 2010 7. Bayer has promised to donate 50,000 vials of the drug in 2008-2012 8. Bayer HealthCare has committed to donating 2.5 million tablets between 2007 and 2012

LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(GUSTAVSEN, HOPKINS AND SAUERBREY, 2011)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Onchocerciasis Elimination Program for the Americas (OEPA)
PARTNERS	Ministries of health from the six affected countries (Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela), the Bill and Melinda Gates foundation, the US Centers for Disease Control and Prevention, the Lions Clubs International Foundation, the Pan American Health Organization and others.
DISEASE(S)	Onchocerciasis (river blindness)
TOOL(S)	Drug (Mectizan)
PPP RESOLVING AT	To eliminate onchocerciasis morbidity from the Americas by 2007.
OUTCOME	At the end of 2010, Colombia had interrupted transmission and stopped the treatment. At a sub-national level, several formerly endemic areas in Mexico, Guatemala and Venezuela have also stopped the treatment. For the areas remaining under Mectizan treatment, the objective is to maintain coverage high.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(GUTTERIDGE, 2006)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Asta Medica/TDR development project (NA)
PARTNERS	Asta Medica, TDR
DISEASE(S)	Visceral leishmaniasis
TOOL(S)	drug
PPP RESOLVING AT	NA
OUTCOME	Despite difficulties encountered during the development process (see limitations) the drug miltefosine is now registered for the treatment of visceral leishmaniasis in India, Germany and Colombia.

LIMITATION(S) OF THE PPP	First, issues related to mergers and acquisitions: the R&D core of Asta Medica was spun off into a new pharmaceutical company, Zentaris, which few years later, was taken over by a Canadian pharmaceutical company. Second, the company would not proceed with the development of miltefosine for an antitumor indication. Fortunately, by then, most costs had been incurred, so the company pursued the preclinical studies and registered the miltefosine as a non-oncological product. Third, there were concerns about reprotoxicity.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HERRLING, 2007)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Novartis Institute for Tropical Diseases (NITD) (2003)
PARTNERS	Novartis and the Singapore Economic Development Board (EDB). For dengue fever, the partnership involves partners from the Genome Institute of Singapore, DSO National Laboratories of Singapore, Tang Tok Seng Hospital, Singapore and the Singapore Tissue Network.
DISEASE(S)	Tuberculosis, dengue fever and malaria
TOOL(S)	Drug
PPP RESOLVING AT	Lack of public awareness
OUTCOME	The objective of NITD is to have at least two compounds in clinical trials by 2008, and at least one novel and attractive compound on the market by 2012. Regarding dengue fever, the partnership has already resulted in the largest database of dengue virus genome.
LIMITATION(S) OF THE PPP	The author highlights the need to widen the network if one wants to make a substantial contribution to the problem of access to medicine in the poorest countries.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(HOERAUF, 2006)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. The African Program for Onchocerciasis Control (APOC) (1995) 2. The Global Alliance for Elimination of Lymphatic Filariasis (GAELF) (NA)
PARTNERS	1. Merck & Co. Inc.,

	2. More than 30 partners including the World Health Organization (WHO), World Bank and UNICEF
DISEASE(S)	1. Onchocerciasis 2. Lymphatic Filariasis
TOOL(S)	1. Distribution of microfilaricidal drug (ivermectin) for free and as long as needed. 2. The biggest mass drug administration program.
PPP RESOLVING AT	Lymphatic filariasis (LF) and onchorcerciasis affect 150 million people, while 1 billion living in endemic areas are at risk of infection.
OUTCOME	NA
LIMITATION(S) OF THE PPP	Even if the programs have been relatively successful, they have their limitations: coverage was too low; reappearance of infection by migration of infected people into controlled areas; targeting a stage that does not induce pathology in LF and thus lowers compliance and the potential development of drug resistance. In addition to that, the drugs used are not enough to stop transmission; there is a need for more efficient, complementary chemotherapeutical approaches that lead to long-lasting reduction of the pathology.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HOOPER *ET AL.*, 2009)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Global Program to Eliminate Lymphatic Filariasis (GPELF) (NA)
PARTNERS	Led by the World health organization (WHO) and two pharmaceutical companies: GlaxoSmithKline (GSK) and Merck & Co., Inc.,
DISEASE(S)	Lymphatic Filariasis (LF)
TOOL(S)	Drug donation (More than 1900 million antifilarial treatments in 48 countries: GSK donated > 745 million tablets of albendazole; Merck donated nearly 600 million tablets of ivermectin; WHO purchased more than 4500 million tablets of diethylcarbamzine)
PPP RESOLVING AT	NA
OUTCOME	The partnership has prevented the spread of an estimated 6.6 million newborns, stopped the progression to clinical morbidity in 9.5 million individuals already infected with the parasites that cause LF, and drastically decreased the burden of several co-infections.

LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HOPKINS, 2005)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Ivermectin donation programs (i.e. The onchocerciasis control program (OCP) and the African program for onchocerciasis control (APOC))
PARTNERS	Merck
DISEASE(S)	Onchocerciasis
TOOL(S)	Mass drug donation
PPP RESOLVING AT	To prevent blindness and suffering caused by onchocerciasis
OUTCOME	Ivermectin has had a considerable impact of relief of suffering both in blindness and skin disease. Fertile land that was deserted due to the diseases is now under cultivation in West Africa.
LIMITATION(S) OF THE PPP	One challenge of the donation programs is funding. Most programs are receiving little funding from the African program for onchocerciasis control (APOC) and non-governmental organizations from year 6 to year 8. Most governments are still not contributing to the program as planned. Other challenges include sustainability of the program and the working contexts (i.e. working in conflict areas). Lastly, a new medication that is able to the adult worm is essential to fully control onchocerciasis.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HOTEZ *ET AL.*, 2013)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. Sabin Vaccine Institute PDP (Chagas Vaccine Initiative) 2. NA 3. Sabin Vaccine Institute PDP (Human Hookworm Vaccine Initiative) 4. Infectious Diseases Research Institute (IDRI) 5. Sabin Vaccine Institute PDP (Schistosomiasis Vaccine Initiative) and FIOCRUZ
PARTNERS	Only industrial partners available here 1. Birmex and CINVESTAV 2. GSK, Merck & Co., Sanofi-Pasteur, Instituto Butantan

	3. FIOCRUZ-Bio-manguinhos, Aeras, Fraunhofer CMB 4. Instituto Butantan 5. Aeras, Instituto Butantan, Ouro Fino
DISEASE(S)	1. Chagas disease 2. Dengue 3. Hookworm infection 4. Leishmaniasis 5. Schistosomiasis
TOOL(S)	1. Vaccine 2. Vaccine 3. Vaccine 4. NA (“Human preventive, therapeutic, and veterinary) 5. Vaccine
PPP RESOLVING AT	NA
OUTCOME	1. Preclinical 2. Phase 1 and 2 3. Phase 1 4. Phase 1 and 2 and animal trials 5. cGMP manufacture
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(P. HOTEZ, 2011)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. Sabin Vaccine Institute (NA) 2. Infectious Disease Research Institute
PARTNERS	1. Public-sector vaccine manufacturers located in Brazil and Mexico. 2. Instituto Butantan, the Bill & Melinda Gates Foundation, the Carlos Slim Institute of Health, as well as other private bodies. From the public sector, the Dutch and Ministry of Foreign Affairs, the US National Institutes of Health and the Brazilian government have made major funding contributions.
DISEASE(S)	1. Various diseases (“human neglected diseases”) 2. Leishmaniasis
TOOL(S)	1. Vaccine 2. Vaccine
PPP RESOLVING AT	1. To develop vaccines for diseases for which major pharmaceutical companies do not have the mean or the will to produce. 2. NA

OUTCOME	1. The Sabin Vaccine Institute has produced new vaccines for hookworm infection and intestinal schistosomiasis. In addition, Sabin is starting to develop new vaccines for Chagas disease and Leishmaniasis together with the Autonomous University of Yucatan, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico NAcional, the US National Institutes of Health, and the public-sector vaccine manufacturer Birmex, for product and clinical development in Mexico. 2. Clinical testing is currently operating in Latin America.
LIMITATION(S) OF THE PPP	1. NA 2. NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HOTEZ AND BROWN, 2009)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Sabin Human Hookworm Vaccine Initiative (Sabin-HHVI) (2000)
PARTNERS	Brazil, the Bill & Melinda Gates Foundation, the department of Microbiology, Immunology, and Tropical Medicine of George Washington University Medical Centre (GWUMC)
DISEASE(S)	Hookworm
TOOL(S)	Vaccine
PPP RESOLVING AT	Mebendazole faced re-infection following treatment, which demanded repeated administrations of anthelminthic therapy that is not always sustainable in areas of extreme endemicity.
OUTCOME	The human hookworm vaccine under development is a “bivalent vaccine comprised of recombinant protein antigens from the infective larval stage of the parasite or from the adult blood-feeding stage of the parasite”.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(HOTEZ *ET AL.*, 2016)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Drug donation programs
PARTNERS	NA

DISEASE(S)	Lymphatic filariasis (LF) and onchocerciasis
TOOL(S)	Drugs
PPP RESOLVING AT	Drug donation programs have shown important decreases in global prevalence of LF and onchocerciasis. However since 1990, such decline is no longer observed. For onchocerciasis, it is believed that MDA alone is not sufficient to eliminate the disease. As a result, vaccines are needed.
OUTCOME	Through product development partnerships, a total of five human anthelmintic vaccines for human hookworm infection (two) and schistosomiasis (three) have advanced from discovery through manufacture and are now in Phase 1 clinical testing. Three additional antigens, two for onchocerciasis and one for schistosomiasis are also advancing through preclinical development.
LIMITATION(S) OF THE PPP	The absence of a pharma partner, uncertainties regarding how to introduce vaccines into health systems and the lack of innovative financing schemes.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(KABASA, 2007)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Stamp Out Sleeping Sickness (SOS) (2006)
PARTNERS	The (veterinary) pharmaceutical company CEVA Santé Animale, stakeholder Industri Kapital and a pan-Europe private-equity fund, Makere Univeristy, the University of Edinburgh, and the Coordinating Office for Control of Trypanosomiasis in Uganda (COCTU)
DISEASE(S)	Sleeping sickness
TOOL(S)	Drug (mass cattle treatment)
PPP RESOLVING AT	The situation regarding sleeping sickness has worsened in Uganda due to large movement of cattle in the 1980s from south-eastern Uganda to districts further north. These were likely to be asymptomatic carriers of human-infective Trypanosoma brucei rhodesiense. The disease was hence introduced in previously disease free districts. More worrying, is that the distance separating Trypanosoma brucei gambiense sleeping sickness from T. b. rhodesiense was decreasing, which would greatly complicate the diagnostic and treatment of sleeping sickness.

OUTCOME	During November and December 2006, approximately 200 000 cattle were treated with a trypanocidal drug for free. The aim is to treat > 86% of the cattle population which will weaken the animal reservoir and reduce transmission to humans. Phase I of the SOS campaign has been completed.
LIMITATION(S) OF THE PPP	"It is hoped that additional funding can be secured for a second phase to continue the campaign to achieve sustainable control of the T. b. rhodesiense"
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(KALK AND KONIG, 2002)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The German Leprosy Relief Association (GLRA) (NA)
PARTNERS	NA
DISEASE(S)	Leprosy
TOOL(S)	Various (e.g. staff training, provision of transport, etc.)
PPP RESOLVING AT	GLRA fills the gaps in existing National disease control programs in five South American countries (Argentina, Bolivia, Brazil, Colombia and Paraguay) and in seven Brazilian states.
OUTCOME	Argentina: GLRA facilitates staff training, provides the necessary transport and allowances Bolivia: leprosy control is mostly financed and executed by GLRA. Brazil: GLRA supports most of the on-going activities with limited resources. Its role in the execution of activities is limited to staff training, information, education and communication and the provision of necessary transport. Colombia: Apart from staff training, GLRA finances and executes the supervision of leprosy control and training in prevention of disability (POD). Furthermore it is financing the entire socio economic rehabilitation (SER) program. Paraguay: GLRA, along with other partners, shares the financial burden of all leprosy control activities.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	NA

YEAR AND STUDY	(KNIRSCH, 2007)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The International Trachoma Initiative (ITI) (1998)
PARTNERS	Pfizer and the McConnell Clark Foundation
DISEASE(S)	Trachoma
TOOL(S)	Drug (Zithromax)
PPP RESOLVING AT	The number of people visually impaired due to trachoma is estimated at 7.6 million, and an additional 84 million have active infections.
OUTCOME	To advance the WHO goal of eliminating blinding trachoma by the year 2020. ITI provides technical assistance and targeted financial support and conducts health education, communication, and resource development activities.
LIMITATION(S) OF THE PPP	“To achieve the GET2020 goals, it will require expanded partnerships, commitment, and research on program integration into evolving health systems”.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(LEE *ET AL.*, 2015)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	Drugs for Neglected Diseases Initiative (DNDi) (2000)
PARTNERS	Funders, academia, public sector research institutions and networks, pharmaceutical companies, non-governmental organizations and governments worldwide (including some 350 collaborations in 43 countries, 20 pharmaceutical and biotechnology companies, and 50 universities and research institutes).
DISEASE(S)	Various neglected diseases
TOOL(S)	Drug (either new drugs or combinations of existing drugs)
PPP RESOLVING AT	To fill the research and development (R&D) gaps for neglected diseases
OUTCOME	During the 10 years of activity, DNDi was able to deliver 6 new treatments for neglected diseases and establish a solid drug pipeline including 13 new chemical entities in pre-clinical and clinical development.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(LUNA *ET AL.*, 2004)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Dengue prevention program (1996)
PARTNERS	the Rotary Clubs of Bucaramanga-Chicamocha and San Juan (Puerto Rico), the Secretary of Health of Bucaramanga and the Division of Vector-Borne Infectious Diseases of the US Centers for Disease Control and Prevention (CDC)
DISEASE(S)	Dengue
TOOL(S)	Mass media communications, educational materials and equipment. The program focused on one day a week (i.e. Thursday) when residents were to seek and destroy the sites where the Aedes aegypti mosquito might occur.
PPP RESOLVING AT	To prevent dengue fever epidemics through educational and communication strategies
OUTCOME	27 % of the people recognized Thursday as Dengue Prevention Day and knew which actions to take to control for Ae. Aegypti breeding sites. After the program, the number of houses and schools with immature Ae. Aegypti was fewer.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(LUTUMBA *ET AL.*, 2005)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	NA (HAT control) (2001)
PARTNERS	World Health Organization (WHO), Sanofi-Aventis and Bayer AG
DISEASE(S)	Human African trypanosomiasis (HAT) (sleeping sickness)
TOOL(S)	Drug doNAtion (Sanofi-Aventis: difluoromethylornithine, melarsoprol, pentamidine; Bayer: suramin)
PPP RESOLVING AT	NA
OUTCOME	The alliance provided continued care for HAT patients and also released substantial financial resources that can be used in the future.
LIMITATION(S) OF THE PPP	The fact that the 3 main drugs used to treat HAT patients are produced and donated by a single company (i.e. Sanofi-Aventis) creates dependency. Care for HAT patients may be

	jeopardized if production or donation stopped for any reasons (e.g. Company takeover).
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(MAHOMOODALLY, 2013)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	PHYTOCHIK (2008)
PARTNERS	Laboratoire de Chimie des Substances Naturelle (LCSN laboratory), Faculté des Sciences et Technologies, Université de la Réunion (Reunion Island), the Malagasy Institute of Applied Research (IMRA) (Madagascar), Faculty of Science of the University of Mauritius, Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles du Centre National de la Recherche Scientifique (France), Laboratory for Virology and Chemotherapy, Rega Institute for Medical Research, Katholieke Universiteit Leuven (Belgium) and Unité des Virus Emergents, Faculté de Médecine, Marseille (France).
DISEASE(S)	Chikungunya
TOOL(S)	Bioprospection to develop drug candidates
PPP RESOLVING AT	To harness biodiversity in order to combat emerging viruses in the Indian Ocean with main goal as selection of natural drug candidates to fight the chikungunya.
OUTCOME	During the first 2 years of the PHYTOCHIK partnership, more than 1554 crude and filtered extracts, and 22 pure compounds were sent to France and Belgium partners for cytotoxicity and chikungunya evaluation.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(MAHONEY *ET AL.*, 2007)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Pediatric Dengue Vaccine Initiative (PDVI) (NA)
PARTNERS	NA
DISEASE(S)	Dengue
TOOL(S)	Vaccine
PPP RESOLVING AT	The disability adjusted life-years (DALY) is estimated at 1300 in dengue endemic countries of Asia and the Americas. Vaccines have been

	produced for other members of this virus family (e.g. yellow fever, Japanese encephalitis) while no dengue vaccine candidates have been evaluated yet in large clinical trials for efficacy and safety.
OUTCOME	The PDVI is focusing on developing diagnostics to (i) measure immune response to vaccines, (ii) detect acute infection, (iii) clinically evaluate vaccine candidates and (iv) promote vaccine access. Additionally, the PDVI is developing field sites that can be used for later-stage clinical trials including phase 4.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(MEREDITH, CROSS AND AMAZIGO, 2012)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. The Onchocerciasis Control Program (OCP) (1974) 2. The African program for Onchocerciasis Control (APOC) (1995)
PARTNERS	Merck & Co. Inc., WHO, the World Bank, National Ministries of Health, bilateral and multilateral donors, and NGOs.
DISEASE(S)	Onchocerciasis
TOOL(S)	1. Initially: Weekly aerial spraying with environmentally safe insecticides to control blackfly vectors. In 1988, the OCP supplemented aerial spraying with large-scale ivermectin treatment. 2. Extend mass distribution of ivermectin to 19 other endemic countries in Africa
PPP RESOLVING AT	The socioeconomic importance of blindness due to onchocerciasis was the main reason for the first multi-partner (the OCP).
OUTCOME	1. OCP successfully reduced the transmission, incidence and impact of blinding onchocerciasis in large areas of 11 countries. 2. APOC now treats over 90 million people annually in 19 countries, protecting at risk population of 15 million and preventing over 40,000 cases of blindness every year.
LIMITATION(S) OF THE PPP	1. The disease remained untargeted in other endemic countries in West, Central and Eastern Africa. The aerial spraying was not considered technically feasible or cost-effective due to the forested terrain.

	In 1987 Merck & Co. Inc decided to donate ivermectin for as long as needed. In 1988, the OCP introduced large scale ivermectin treatment to supplement aerial spraying.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(MERRIFIELD *ET AL.*, 2016)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	NA
PARTNERS	1. Institut Pasteur and INSERM 2. Sabin Vaccine Institute product development partnership, NIAID, NIH, Baylor College of Medicine Vaccine and Treatment Evaluation Unit 3. Oswaldo Cruz Foundation and Orofino
DISEASE(S)	Schistosomiasis
TOOL(S)	Vaccine
PPP RESOLVING AT OUTCOME	1. Bilhvax has completed Phase 2 and 3 in West Africa 2. Phase 1 trial had been initiated for Sm-TSP-2 in 2004 at Baylor College of Medicine 3. Phase 2 trials were planned in 2005 for Sm-14 in Brazil and Africa
LIMITATION(S) OF THE PPP	Further funding is crucial to advance these candidate vaccines
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(NEITZ *ET AL.*, 2015)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	NA
PARTNERS	The University of California in San Francisco, the Genomics Institute of the Novartis Research Foundation (GNF) and the National Institutes of Health (NIH)
DISEASE(S)	Chagas disease
TOOL(S)	Drug
PPP RESOLVING AT	The current treatments for Chagas disease are the drugs benznidazole and nifurtimox that were developed in the 1970s. Neither drug is approved by the Food and Drug Administration (FDA). Long treatment course (up to 180 days)

	and serious adverse effects are the major limitations of these two drugs.
OUTCOME	A new anti-T. cruzi scaffold derived from xanthine was identified.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(ODUOR *ET AL.*, 2011)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	NA
PARTNERS	World Health Organization Tropical Diseases Research division (WHO TDR), University of Washington (USA), University of Antwerp (Belgium), and Pfizer Global Research Development (UK).
DISEASE(S)	Human African trypanosomiasis (HAT)
TOOL(S)	Find novel leads – specific inhibitors of T.brucei using a target-based high throughput screening approach.
PPP RESOLVING AT	The lack of effective treatment for HAT constitutes a health concern in 36 countries of sub-Saharan Africa. Four drugs – Eflornithine, Suramin, Pentamidine and Melarsoprol – are registered as treatments for HAT. However, these are toxic and difficult to administer, limiting therapeutic choices.
OUTCOME	Identification potent and selective compounds representing potential attractive starting points for a drug discovery program.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(RAMAMOORTHI, GRAEF AND DENT, 2014)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	WIPO Re:Search consortium
PARTNERS	Initially (2011), WIPO, BIO Ventures for Global Health (BVGH) and eight pharmaceutical companies (Alnylam, AstraZeneca, Eisai, GlaxoSmithKline, MSD [Merck], Novartis, Pfizer, and Sanofi). Three years later it has expanded to over 90 for-profit, academic, non-profit, and government research organizations.

DISEASE(S)	Neurocysticercosis, Lymphatic Filariasis, Fungal disease, Buruli Ulcer, Onchocerciasis, Leishmaniasis, Human African trypanosomiasis, Diarrheal diseases, Dengue fever, Chagas disease, Soil-transmitted helminthiases, Schistosomiasis, Tuberculosis, Malaria and others (Drugs, vaccines and diagnostics)
TOOL(S)	Diverse but mostly drug
PPP RESOLVING AT	Re:Search consortium tackles the lack of safe and effective drugs, vaccines and diagnostics for NTDs by facilitating the sharing of biopharmaceutical companies' IP assets, knowledge and expertise, with academic and non-profit neglected disease researchers conducting novel product development projects.
OUTCOME	Up to 2014, WIPO Re:Search has facilitated over 70 research agreements between Consortium Members, including 11 collaborations focused on anthelmintic drug discovery.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(RIDLEY, 2003)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Special Program for Research and Training in Tropical Disease (TDR) (1975)
PARTNERS	The United Nations' Development Program, the World Bank and the World Health Organization (WHO)
DISEASE(S)	1. Malaria 2. Leishmaniasis 3. African trypanosomiasis 4. Onchocerciasis
TOOL(S)	1. Drug (artemisinin combinations) 2. Drug (miltefosine and paromomycin) 3. Drug (eflornithine) 4. Drug (ivermectin)
PPP RESOLVING AT	TDR has two specific goals: (i) to identify and develop new tools and methods to control tropical diseases and (ii) to develop research capacities in developing countries.
OUTCOME	Regarding leishmaniasis, the drug is being developed. For African trypanosomiasis, the developed drug is highly effective against the disease in its later stages. Regarding the drug Mectizan (developed by Merck), Onchocerciasis

	has shown enormous economic and welfare impact. More than 40 million people are now protected from the disease and over 25 million hectares of fertile riverside land have been made available for resettlement.
LIMITATION(S) OF THE PPP	The drug for human African trypanosomiasis is only active against one of the species that cause the disease which limits its use. Regarding Mectizan - the drug developed by Merck – only kills the pathology of 'river blindness' not the adult worms that can reside in the body for many years.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(SAUERBREY, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Onchocerciasis Elimination Program for the Americas (OEPA) (1992)
PARTNERS	The endemic countries, the Pan-American Health Organization (PAHO), the Carter Centers, Lions Clubs, the United States Centers for Disease Control and Prevention, the Bill and Melinda Gates Foundation, Merck & Co., Inc., and other partners.
DISEASE(S)	Human onchocerciasis (river blindness)
TOOL(S)	Drug donation
PPP RESOLVING AT	Human onchocerciasis occurs in 13 foci distributed among six countries in Latin America – Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela – were about 500,000 people are considered at risk.
OUTCOME	Significant progress has already been made in all six countries, each of which has active programs with treatment coverage exceeding the target of 85%. Onchocerciasis is estimated to be eliminated from most of the remaining foci in the Americas by 2012.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(SEKETELI *ET AL.*, 2002)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The African Program for Onchocerciasis Control (APOC) (1974)
PARTNERS	The member countries, NGDO, multi-lateral agencies, bilateral donors, the private sector, Merck & Co. Inc., and the scientific community.

DISEASE(S)	Onchocerciasis (river blindness)
TOOL(S)	Community-directed treatment with ivermectin (CDTI)
PPP RESOLVING AT	To prevent blindness – the most severe consequence of the disease – which may affect one third of the adult population of the most highly affected communities.
OUTCOME	Over 67 million of Mectizan tablets were distributed to 20 million people in the year 2000.
LIMITATION(S) OF THE PPP	The greatest challenge facing APOC is the sustainability of CDTI after the cessation of the program. There is a need to strengthen peripheral health system and integrate CDTI into the health service.
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(STURCHIO, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	The Mectizan donation Program for: 1. Onchocerciasis (1987) 2. Lymphatic filariasis (1998)
PARTNERS	Merck, the World Health Organization (WHO), the World Bank, the UNICEF, dozens of ministries of health, non-governmental development organizations and local communities
DISEASE(S)	1. Onchocerciasis (river blindness) 2. Lymphatic filariasis
TOOL(S)	Drug donation (Ivermectin)
PPP RESOLVING AT	1. River blindness is the leading cause of preventable blindness in the developing world 2. An estimated 300 million Africans are at risk, with 40 million already infected.
OUTCOME	1. More than 1.8 million tablets of Mectizan have been donated, with more than 530 million treatments approved since 1987. The program currently reaches more than 69 million people through river blindness programs in Africa, Latin America and the Middle East (Yemen) each year. In November 2007, public health officials announced that transmission of onchocerciasis has been halted in Colombia. 2. Currently more than 50 million treatments of Mectizan are approved each year for LF through the Global Alliance to Eliminate Lymphatic Filariasis.

LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(TENDLER AND SIMPSON, 2008)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	NA
PARTNERS	ALVOS (private company), the Oswaldo Cruz Foundation (FIOCRUZ) and a public Brazilian Financial Agency (FINEP)
DISEASE(S)	Schistosomiasis
TOOL(S)	Vaccine (Sm14)
PPP RESOLVING AT	The impact of schistosomiasis is potentially near to that of tuberculosis and malaria. Schistosomiasis cannot be eradicated solely with drugs. The development of a vaccine is therefore highly relevant.
OUTCOME	The vaccine is planning clinical trials.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(TAPIA-CONYER *ET AL.*, 2013)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. The Sabin Vaccine Institute (PDP) (NA) 2. NA
PARTNERS	1. Several multinational pharmaceutical companies, not-for-profit organizations such as PATH and Bill & Melinda Gates Foundation, universities and research institutes from Australia, Brazil, China, Mexico, the UK and the US. 2. The Carlos Slim Health Institute, Baylor College of Medicine, the Sabin Vaccine Institute, the Autonomous University of Yucatan and the Center for Research and Advanced Studies of Mexico.
DISEASE(S)	1. Hookworm, schistosomiasis, Chagas disease and others. 2. Leishmaniasis and Chagas diseases
TOOL(S)	Vaccine
PPP RESOLVING AT	The lack of available treatments for these diseases.
OUTCOME	1. The partnership has built a sustainable infrastructure and capacity for research,

	development, scale-up and mid-scale manufacturing, whilst operating primarily from academic institutions. 2. The partnership aims to develop vaccines from the discovery to scale-up stages and then transfer the technology at the large scale production stage.
LIMITATION(S) OF THE PPP	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(ZHOU, WAYLING AND BERGQUIST, 2010)
NAME OF THE PUBLIC-PRIVATE PARTNERSHIP (PPP) (YEAR)	1. The Regional Network for Asian Schistosomiasis (RNAS) (NA) 2. The Tropical Disease Research to foster Innovation & Knowledge Application (TropIKA.net) (NA) 3. The Chinese Network for Drugs and Diagnostics Innovation in tropical diseases (2009)
PARTNERS	1. Scientists from Cambodia, P.R China, Indonesia, Japan, Lao and the Philippines, World health organization (WHO), the Danish Centre for Experimental Parasitology (Denmark), the Swedish International Development Cooperation Agency (Sweden), the Queensland Institute of Medical Research (Australia) and the Swiss Tropical and Public Health Institute (Switzerland). 2. NA 3. 150 Chinese research leaders representing 52 institutions around the country
DISEASE(S)	1. Schistosomiasis and others (cysticercosis, clonorchiasis, opisthorciasis and fascioliasis) 2. Infectious diseases of poverty
TOOL(S)	1. Coordinate and secure support for research, encourage research on diagnostics, development of vaccines and new drugs, offer courses on methodology in health research, develop protocols for diagnostics and drug treatment, etc. 2. NA 3. NA
PPP RESOLVING AT	1. NA 2. It is designed to enhance access and to share essential knowledge with health

	researchers and policy makers dedicated to improving control of infectious diseases of poverty. 3. To exploit Chinese-led research in the development of infrastructure and scientific collaboration to leverage existing activities and deliver affordable new tools for the control of tropical diseases.
OUTCOME	1. The activities of the RNAS has worked out well (no more information) 2. So far users from 100 countries have accessed the TropIKA.net platform 3. A database of available regional knowledge of NTDs and other diseases of poverty, scholarly literature, funding information, research reports, etc is planned for 2010.
LIMITATION(S) OF THE PPP	1. The RNAS has worked better than expected, and is now in a situation where the means to control many of the different target diseases are becoming available, while the financial resources are not at hand 2. NA 3. NA
MENTIONING ELIMINATION?	Yes

Table VII: Empirical studies

NA = Not available

YEAR AND STUDY	(BUCKUP, 2008)
RESEARCH QUESTION	To measure the potential correlation between voting power (investor's ownership) and fiNAncial contributions among a sample of 17 global health initiatives (GHI)
METHODOLOGICAL APPROACH	Correlation aNAlysis
MAIN FINDINGS	There was no correlation between voting power and fiNAncial contribution for the private sector. However, public sector's contribution resulted in stronger representation, indicating a correlation.
LIMITATIONS	Authors highlight the need for further aNAlysis to confirm their findings. Deeper aNAlysis could look at the different stages of the partnerships' R&D process and the corresponding implications for goverNAnce structure.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(COHEN, STURGEON AND COHEN, 2014)
RESEARCH QUESTION	To assess the share of products approved for neglected diseases during 2009-2013 that were developed under a PPP.
METHODOLOGICAL APPROACH	They search was conducted across several databases – ClinicalTrial.gov, IMS R&D Focus and InvestigatioNAl Drug Database – as well as on drug regulatory websites.
MAIN FINDINGS	They found 20 new products, among which 57% had been developed through a PPP. The authors also found 18 products currently in phase III development.
LIMITATIONS	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(COHEN *ET AL.*, 2016)
RESEARCH QUESTION	To assess the progress of pharmaceutical companies in meeting the commitments on drug doNAtion set in the London Declaration
METHODOLOGICAL APPROACH	Peer-reviewed search followed by a survey to 10 company sigNAtories
MAIN FINDINGS	The survey respondents reported substantial progress in meeting the objectives of the London Declaration, with 17 doNAtion

	programs across 10 disease categories. However, none of the respondents disclosed information on whether the drug doNAtion programs were leading to a reduction in disease prevalence.
LIMITATIONS	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(DE PINHO CAMPOS, NORMAN AND JADAD, 2011)
RESEARCH QUESTION	To conduct a systematic review on PPPs
METHODOLOGICAL APPROACH	The systematic review was carried out over 12 databases between 1990 and 2010. The initial search led to 212 references, 50 of them were selected for full-text review and 10 were included in the fiNAl review.
MAIN FINDINGS	Seven major themes emerged from the aNAlysis and include the following: “win-win Agreements”, “Synergy of expertise”, “Stakeholder engagement”, “Local health capacity and infrastructure”, “The public and private sector’s perceptions regarding each other”, “Communication and knowledge exchange” and lastly, “Participatory maNAgement and organizatioNAl skills”.
LIMITATIONS	NA
MENTIONING ELIMINATION?	Yes

YEAR AND STUDY	(KOH JUN, 2012)
RESEARCH QUESTION	To assess how to optimally use the donor’s funding to incentivize research and development (R&D) for neglected diseases.
METHODOLOGICAL APPROACH	A cost-effectiveness aNAlysis comparing PPPs (categorized as a push incentive), advance market commitment (pull incentive) and hybrid mechanisms (mixed incentives) for the development of vaccines. Estimates of costs, timelines and transition probabilities were obtained from the literature. The health impact was measured using a base case of potential disability-adjusted life years (DALYs) averted per immunization for malaria (based on a WHO report). To obtain the total DALYs averted per year, the author multiplied it by the number of individuals vacciNAted annually.

MAIN FINDINGS	The results suggest that the hybrid mechanism is the most cost-effective option with the lowest cost per disability-adjusted life years (DALYs) averted. Although the PPP model is the cheapest, the number of DALYs was the lowest.
LIMITATIONS	Data on costs are obtained from DiMasi et al. (2002) who focused on drugs instead of vaccines.
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(MORAN *ET AL.*, 2010)
RESEARCH QUESTION	To examine the funding and expenditure patterns of product development partnerships (PDPs) for neglected diseases.
METHODOLOGICAL APPROACH	The authors used the Global Funding of Innovation for Neglected Diseases (G-FINDER) database.
MAIN FINDINGS	Expenditure pattern: In 2007, PPP spent US$262 million on R&D activities, with more or less 16% invested in their own laboratories and R&D staff and 88% distributed to exterNAl partners. Funding pattern: The Bill and Melinda Gates foundation remains the principal funder providing half of PPPs total funding. Followed by four public funders (28%) – the US Agency for InterNAtioNAl Development (USAID), the UK Department for InterNAtioNAl Development (DFID), the Dutch ministry of foreign affairs, and the Irish Aid.
LIMITATIONS	Issues related to reliance on the G-Finder database.
MENTIONING ELIMINATION?	yes

YEAR AND STUDY	(PETERS AND PHILLIPS, 2004)
RESEARCH QUESTION	To examine the evaluation of the Mectizan doNAtion program (MDP) from the participating partners
METHODOLOGICAL APPROACH	Semi-structured interviews
MAIN FINDINGS	They identified 34 individuals who participated in the MDP. The survey focused on four dimensions: benefits, costs, goverNAnce and maNAgement of the MDP. 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.
LIMITATIONS	NA
MENTIONING ELIMINATION?	No

YEAR AND STUDY	(PRATT AND LOFF, 2013)
RESEARCH QUESTION	To examine the progress of Medicine for Malaria Venture (MMV), Drugs for Neglected Diseases initiative (DNDi) and the One World Health (OWH) on their products availability, adoption, and affordability, and on their ability to strengthen research capacity in low- and middle-income countries (LMICs).
METHODOLOGICAL APPROACH	The authors relied on information derived from publicly available sources and used the framework developed by Frost and Reich (2008).
MAIN FINDINGS	Product availability and adoption: PDP products have been registered in most of the LMICs. Due to the limited information available on product distribution (aggregated data), it is difficult to assess whether distribution was adequate to countries' needs. Product affordability: the cost of most products is quite low but limited information is available on the selling cost. Research capacity strengthening: MMV allocate 2% of its annual research and development budget to strengthen research capacity in LMICs. In 2009, DNDi and MMV invested US $1.3 million and US $886,000 respectively.
LIMITATIONS	NA
MENTIONING ELIMINATION?	No

ARTICLE 2

The impact of the priority review voucher on research and development (R&D) for tropical diseases

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Under review

The impact of the priority review voucher on research and development (R&D) for tropical diseases

ABSTRACT

In 2007, the priority review voucher (PRV) was implemented in the United States to incentivize research and development (R&D) for tropical diseases. The PRV is issued by the Food and Drug Administration and grants a quicker review to manufacturers upon successful development of a product for a disease eligible for the program. This analysis assesses whether the PRV is encouraging R&D that would have not taken place in its absence. To do so, we use a difference-in-difference-in-differences strategy and rely on trial registration as a measure of R&D. Trials were retrieved from the World Health Organization International Clinical Trials Registry Platform for the years 2005-2019. Our results show that, so far, the PRV has not been able to stimulate trial registration for the intended tropical diseases, suggesting that the PRV program may need to be reconsidered and potentially supplemented with other mechanisms to generate market profitability.

1. INTRODUCTION

Research and development (R&D) is lengthy and costly. It takes more than a decade and costs around $2.6 billion to bring a new drug to the market (2013 USD) (Dimasi, Grabowski and Hansen, 2016). Failure in R&D is common: the overall probability that a drug entering clinical testing ends up being approved by the FDA is estimated to be 11.83%. Failure rates nonetheless vary across phases: they are estimated at around 45.9% for phase 1, 43.5% for phase 2, and 10.6% for phase 3/regulatory review (Dimasi, Grabowski and Hansen, 2016). Given the costly and risky nature of the R&D market, pharmaceutical companies have an interest in investing in diseases with a large and stable market in high-income countries (HICs). Consequently, infectious diseases that are mostly prevalent in low-income countries (LICs) such as leishmaniasis, sleeping sickness, dengue fever and Chagas disease, also referred to as tropical diseases, do not historically attract much interest. These diseases mainly affect the world's poorest populations with a purchasing power that is not high enough to generate a return on investment for the pharmaceutical industry. These diseases are, as a result, labelled as 'neglected diseases'. Between September 1999 and December 2011, 118,634 trials were registered in the United States (US) National Institutes of Health (NIH) registry – Clinicaltrials.gov – but only 1,541 (1%) were for neglected diseases (Pedrique *et al.*, 2013). While neglected diseases account for 12% of the global health burden, their R&D market share barely reaches 1%.

To tackle this market failure, the US congress established the priority review voucher (PRV) program in September 2007. The PRV was initially designed for tropical diseases but expanded to include rare pediatric conditions in 2012 and

medical countermeasures in 2016[1]. For tropical diseases, as opposed to rare pediatric conditions and medical countermeasures, the PRV includes a comprehensive list of eligible diseases (Exhibit1). The rationale behind the PRV is the following: the program rewards the development of successful products for one of the eligible diseases, by awarding the products' manufacturers a voucher that reduces the duration of a product review by the US Food and Drug Administration (FDA) from the usual 10 months to 6 months (Gaffney, Mezher and Brennan, 2019). The voucher thus grants faster review which can be used for any products of the PRV's holder choice either for earlier market launch or, although less likely, during more intermediate phases of R&D. Alternatively, the voucher can be sold to a third party for a value that has ranged from $67,5 million in 2014 to $338 million in 2015 (United States Government Accountability Office, 2020). The PRV is said to lead to a 'win-win' situation, with the social welfare gains to patients both in LICs and HICs and the net gains to manufacturers being greater than the cost of FDA review incurred by the government (Ridley, Grabowski and Moe, 2006; Régnier and Ridley, 2015; Ridley and Régnier, 2016).

However, more than a decade after its implementation, the supposed welfare gain of the PRV has arguably failed to materialize. The PRV has been criticized for rewarding products already in use/licensed outside the US and/or manufacturers that were not involved in any of the R&D (Doshi, 2014). Last but not least, the PRV is criticized for rewarding products that would have been developed anyway. This assumption is built upon the idea that a *potential* 4-

[1] Medical countermeasures are medical products intended to diagnose, prevent, or treat diseases or conditions associated with chemical, biological, radiological, and nuclear (CBRN) threats and emerging infectious diseases (Food and Drug Administration, 2018).

month early entry to the market is not sufficient to incentivize pharmaceutical companies to invest from scratch in risky projects for neglected diseases. The word ‘potential’ is important for two reasons: (i) R&D may not lead to successful product development and (ii) a voucher does not guarantee an earlier market launch since the FDA can decide to reject a product on which it conducted a priority review (e.g. the case of Novartis for its biological licensing application for Ilaris) (Mezher and Brennan, 2017). Additionally, the voucher’s uncertainty is not limited to its use but also extends to its sale: its market price has fluctuated significantly since the first voucher was sold in 2011, with a general depreciation since 2017. Selling the voucher rather than using it may appear more appealing to smaller pharmaceutical companies that do not have a blockbuster candidate in their pipeline on which to use the voucher.

The objective of this paper is to assess whether the PRV has been incentivizing R&D for the intended tropical diseases that would have not taken place in its absence. Until now, evidence of the PRV’s impact is limited; only three studies have attempted to look into it but their designs limits the extent to which causal inferences can be made. First, these studies use either before and after analyses (Jain *et al.*, 2017; Hwang *et al.*, 2019) or differences-in-differences (DD) methodology (Kerr, Henry and Miller, 2018) to identify the impact of the PRV. Before and after analyses are very descriptive in nature and not suitable for causal inference as they fail to control for several time cofounders that might drive the observed effect of the PRV. While widely used in policy evaluation studies, DD methodology delivers biased estimates of interventions in the presence of time-varying confounders that affect treatment and control groups differently, violating the common trends assumption required for such analyses. These

cofounders exist in the PRV setting and include policy (e.g. funding) shocks to specific diseases, as was the case with the endorsement of the London Declaration in 2012 (Uniting to combat neglected tropical Diseases, 2012). Second, the scope of these studies is limited. They focus on an incomplete (i.e. left-censored) measure of innovation by looking at phase 1 trials only (Jain *et al.*, 2017; Hwang *et al.*, 2019). Phase 1 trial registration, as opposed to phases 2 and 3, is not compulsory to be later granted a PRV. If any effect is expected to be observed, it is more likely to be during later phases of the R&D process when compounds have successfully demonstrated safety and/or efficacy. Moreover, many therapies for neglected diseases are a combination of existing drugs or rely on a drug that has been repurposed for a new indication, different from the one it first targeted. In these cases, such therapies may not need to undergo phase 1 trial to demonstrate safety. By focusing on one type of clinical phase, these studies suffer from small sample sizes (between 31 and 54 observations) making it difficult to control for all the disease and year fixed effects, thus raising the issue of potential time invariant cofounders. Third, they all rely on commercial database, which may not provide a totally comprehensive picture of the R&D landscape due to a tendency to over represent successful projects and omit the ones from academia and not-for-profit organizations.

Therefore, while our contribution relates to these studies, we build on them in three different ways. First, by employing a difference-in-difference-in-differences (DDD) approach, we are able to exploit variation across time, disease eligibility and across the different registries to identify the causal impact of the PRV. Indeed, since the policy targets specific diseases (Exhibit 1) from a specific regulatory body/trial registry (i.e. the FDA/Clinicaltrials.gov), we can use two

control groups: the diseases that are not targeted by the PRV (non-eligible diseases) and the registries that are not affected by the PRV (any other registries than ClinicalTrials.gov that belongs to the WHO International Clinical Trials Registry Platform (ICTPR) (Exhibit A2 in Appendix)). Second, we focus our analysis on a more complete and relevant measure of innovation. Instead of focusing on phase 1 only, we focus on trial registration for phase 2 and phase 3, which registration is compulsory for being granted a voucher. Moreover, since the PRV may be used for earlier market launch or faster review during more intermediate R&D phases, we believe that focusing on trial registration in phases 2 and 3 gives a more adequate and broader measure of the possible PRV impact. The visualization of earlier market launch will indirectly stimulate earlier R&D phases. Third, we believe that our study relies on a more comprehensive database by relying on the WHO ICTRP. The latter aims to ensure a complete view of research by gathering clinical trials from numerous registries across the world. This was made possible when in 2005 the International Committee of Medical Journal Editors (ICMJE) made it compulsory to prospectively register clinical trials to later publish the results (The International Committee of Medical Journal Editors, 2004).

2. THE PRIORITY REVIEW VOUCHER (PRV) PROGRAM

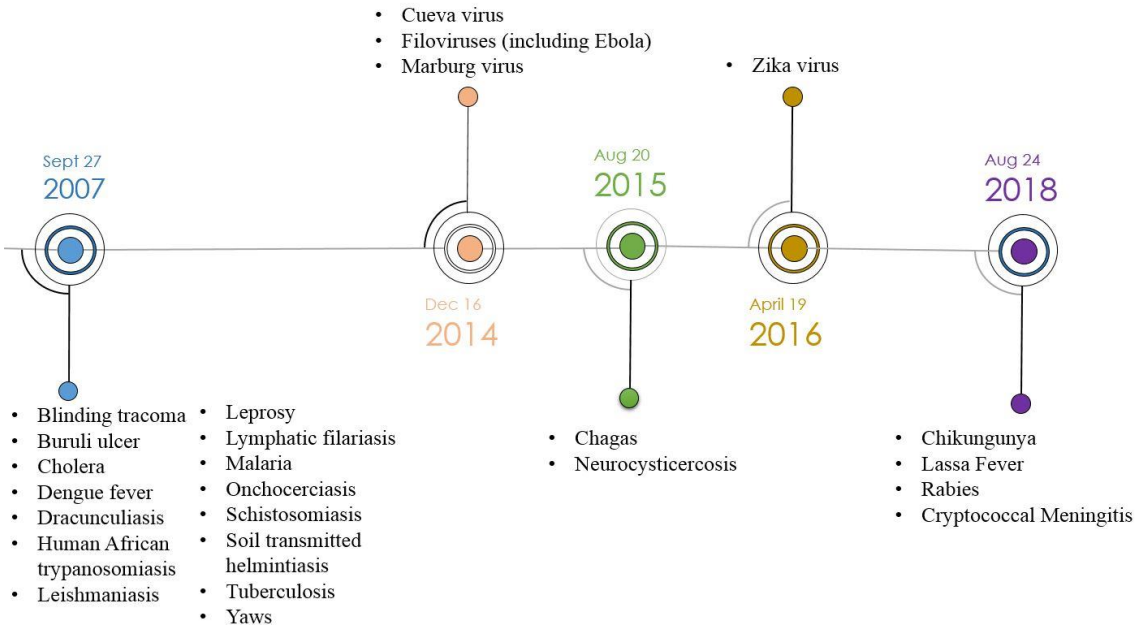
The PRV program was proposed in 2006 by Ridley et al., in a publication in Health Affairs (Ridley, Grabowski and Moe, 2006) and was implemented by the US congress a year later, in September 2007 (U.S. government, 2007). For tropical diseases, the PRV policy includes a specific list of eligible diseases that is presented in Exhibit 1. The policy was implemented in a staggered way: most tropical diseases became eligible as of September 2007, while a few became eligible in 2014, 2015, 2016 and 2018 (Exhibit 1). Products (drugs, vaccines and devices) for those eligible diseases must also meet specific requirements. They must (i) be submitted to the FDA and approved after the PRV program start date (ii) contain no active ingredient that has been approved in any other application (though combination products with at least one new active moiety are eligible), and (iii) be clinically superior to existing products. Accordingly, eligible clinical trials are trials other than phase 1 that are non-inferior, interventional, and registered on ClinicalTrials.gov within 21 days of enrolling the first patient. Furthermore, trials must either have been initiated after the 27th of September 2007, or, on or before that date if they were still ongoing as of the 26th of December 2007. For diseases eligible in 2014, 2015 and 2016, trials should have been initiated after their date of implementation. The voucher is granted at the time of marketing approval which takes place after phase 3 completion.

2.1 Structural changes of the priority review voucher (PRV) program

The program faced structural changes since its implementation. Initially, companies that were granted (or that bought) the voucher and wanted to use it had to notify the FDA 365 days in advance but as this was limiting the usefulness of the voucher it was changed to a 90-day notice in 2014. In that same year, it

was decided that the voucher could be sold an unlimited number of times as opposed to once before. These two changes are captured as part of the PRV effect. Additionally, since 2011, a fee has to be paid to the FDA to compensate the incurred added cost of conducting a priority review. This fee varies annually – from $2.32 million in 2014 up to $5.28 million in 2012 – and is also controlled for in our analysis (Food and Drug Administration, 2008).

Exhibit 1 (Figure): Timeline of PRV-eligible diseases



Source: Our elaboration on U.S. Food & Drug Administration data (U.S. Food & Drug Administration, 2018)

3. STUDY DATA AND METHODOLOGY

Data on clinical trials were retrieved from the WHO ICTRP, which gathers ongoing, completed or terminated clinical trials from 18 registries (Exhibit A2 in the Appendix) (http://apps.who.int/trialsearch/) and whose objective is to ultimately improving research transparency and provides a comprehensive database on clinical trial activity (World health organization (WHO), 2005). Since its creation in 2005, registries have progressively entered the platform conditional on fulfilling specific requirements. To enter the WHO ICTRP, Registries must fulfilled the ICMJE rule (i.e. prospective registration of trials) and meet the WHO Registry Criteria (World Health Organization (WHO), 2012). All diseases were separately entered in the ICTRP search portal to retrieve the data. Since the disease eligibility requirement of the PRV is to be an infectious disease for which there is no market in HICs, our control group is made up of the contrary: non-communicable diseases (NCDs) with a significant market in HICs. To do so, we chose the NDCs that account for the biggest number of disability adjusted-life years (DALYs) in HICs according to the Global Burden of Disease website (Institute for Health Metrics and Evaluation (IHME), 2018): Ischemic heart disease, diabetes, lung cancer and stroke. In this way, we can assure that the diseases in the control group have no chance of becoming eligible for the policy. Given the profitability of these diseases, six times more trials were found for those four diseases than for all the eligible diseases combined. Similarly, more trials were found in ClinicalTrials.gov than in all the other WHO ICTPR registries combined (Exhibit A3 in the Appendix).

Eligible clinical trials are trials other than phase 1 that are non-inferior, interventional, and registered on ClinicalTrials.gov within 21 days of enrolling the

first patient. As a result, only interventional and non-inferior trials from phase 2 to 3 targeting either a drug, vaccine or device were kept. We focused our analysis on trial activity from 2005 to 2019 included. Data on trial registration before 2005 are incomplete because before then it was not compulsory to register a trial to later publish its result (Viergever and Li, 2015).We also restrict eligibility to the diseases that are recorded on the PRV list (Exhibit 1) because until now, not a single voucher has been awarded to a disease that fulfills the definition of eligibility but that does not appear on the list. Hence, our analysis includes 15,288 trials, which are tabulated Exhibit 2 across disease groups as well as before and after becoming eligible. The database was then organized as follow: for each disease and each registry, we counted the number of starting clinical trials per year. Therefore, our dependent variable is the yearly number of starting clinical trials per registry and disease – resulting in a yearly panel of disease_registry (e.g. *ClinicalTrials.gov_malaria*).

Exhibit 2: Descriptive statistics of trial activity per disease group and registry, before and after becoming eligible for the PRV program

	Eligible					**Control**	**Total**
	2007	**2014**	**2015**	**2016**	**2018**		
Before	276	41	31	0	212	2,043	2,603
After	1,264	44	16	4	30	11,327	12,685

Notes: Before period includes all trials registered before 2007, 2014, 2015, 2016 and 2018 depending on the diseases. After period includes all trials registered after the above years.

The data being particularly skewed to the left due to a significant number of zeros (Exhibit A4 and A5 in the Appendix), we employed a poisson fixed effects model with cluster-robust standard errors by disease-registry. Although the evidence of overdispersion would suggest the use of negative binomial, we employed the latter as it generates more robust estimates (Wooldridge, 1999). The DDD model estimation is provided in the Appendix (Empirical Model). The outcome variable of the model is the number of starting clinical trials per registry, disease and year. Trials included are non-inferior interventional trials either in phase 2 or 3 (i.e. phase 1/2; phase 2; phase 2/3; phase 3; phase 3/4) and registered between 2005 and 2019. The model includes, in addition to the policy variable, two covariates, registry per disease fixed effects as well as year fixed effects. The first covariate captures the yearly share of total DALYs per disease in upper middle- and high-income countries according to the world bank definition (Institute for Health Metrics and Evaluation (IHME), 2018). This measure is used as a proxy for the yearly "market size/potential": the higher the DALYs' share in those countries, the greater is the potential return on investment. The other covariates includes the imposed fee since 2011 by the FDA for performing a faster review, which may act as a turn off and be against the PRV's interest, particularly for smaller companies with lower profit margins. Lastly, the model includes registry fixed effects per disease fixed effects to control for disease registry specific time invariant cofounders. Example of confounders include increased funding to target a disease or a specific group of diseases (e.g. London Declaration; Ebola outbreak) as well as different regulatory requirements across national registries. The model also includes year fixed effects to control for time varying cofounders

that impact R&D activity across registries and diseases[2]. Therefore, by estimating a two-way error component model, we were able to control for a broad range of factors including exogenous yearly variations in R&D activity and unobserved time-invariant heterogeneity that are specific to trial registry and disease.

To look into the dynamics effect of the PRV policy effect, we considered two further specifications of the model. Since R&D is a lengthy process, we believe it is relevant to look how the policy effect varied over time, that is, if different periods post PRV program show a different effect. In models 2 (M2) and 3 (M3), we bundle the lags together by blocks of 2 years. The first block includes the policy year and the year after, the second block includes the second and third years post policy implementation, etc. Model 3 thus shows the results of the parallel trends assumption. The parallel trend assumption is a prerequisite for DD and DDD analyses and relies on the assumption that trials for eligible and non-eligible diseases would follow the same path, in the treated and control registries, had the policy not been implemented. Following the literature (Autor, 2003; Angrist and Pischke, 2008), we test it by including leads to our most complete specification (i.e. M2).

In the sensitivity analysis section, we present the results of two sensitivity tests. The first one looks at the policy effect when moving ahead the policy introduction one year ahead. We do so to test for an anticipatory effect of the policy that could exist given the lag between announcement and implementation dates. Indeed, the policy was disclosed to the public in 2006 but implemented in 2007. In the second sensitivity test, we look into additional lagged effect of the user fee

[2] Given the variation in our dependent variable, we were unable to control for those fixed effects separately in addition to them jointly.

implemented in 2011. R&D activity is a lengthy process and is thus unlikely to be capable of immediately responding (e.g. by switching to another product in the pipeline) to a changing user fee. The latter is likely to have a lagged effect (of one year or more) on R&D activity. All analyses were undertaken in Stata 16 software.

4. RESULTS

The marginal effects from the Poisson regressions, along with their standard errors and 95% confidence intervals (CIs), are represented in Exhibit 3 for the 3 models. The overall marginal effect of the policy (M1) is 0.29 (95% CI -0.648; 1.221) indicating an increase in trial registration – although not statistically significant – by 0.3 trial per annum for the eligible diseases in the US registry. When looking into potential delays of the policy (M2 and M3), regardless of the post policy period, the PRV has had no effect on stimulating trials registration for the intended diseases. All the marginal effects have a 95% CI that crosses the zero line. Moreover, it is worth adding that when including phase 1 trials in the main analysis, the results show no effect neither. The results of the parallel trends assumption can be seen in M3, which shows that the assumption is not violated since the 95% CI crosses the zero line for the year prior to the policy introduction (i.e. t-1).

4.2 Sensitivity analysis

4.2.1 Changing the year of policy introduction

Given that the policy came out to the public a year before its implementation, we hereby test for a potential anticipatory effect of the policy. In addition to this, the policy starting date cannot be fully clear-cut from the data available. More specifically, we do not know whether trials registered before September 2007

were still ongoing as of 26th of December 2007. As a result, we made the restrictive assumption in the main analysis that trials registered in 2006 or before were no longer ongoing at the end of 2007 and thus were not considered as part of the 'after' period. Likewise for the diseases that became eligible in 2014, 2015, 2016 and 2018. Therefore, we simulated the policy to have taken place one year earlier than its true year of introduction (i.e. 2006 instead of 2007, 2013 instead of 2014, etc.) but which did not affect qualitatively the results. The PRV remains ineffective at stimulating trial activity thereby confirming the robustness of our findings.

4.2.2 Testing for lagged effect of the user fee on trials registration

In the analysis, we have assumed a one-year lagged effect of the covariate user fee on trial registration. To relax this assumption, we ran the model and tested for a potential longer delayed effect of the variable of up to 4 years. A four-year delayed effect would imply that the user fee's value in 2011 would affect trial registration in 2015. However considering delayed effect of the user fee on trial activity did not affect the results. This would suggest that the value chosen and imposed by the FDA is not responsible for the PRV's lack of effect.

Exhibit 3: Triple-differences and parallel trend results

	M1		*M2*		*M3*	
	Marginal effects (Std. Err)	95% CI	Marginal effects (Std. Err)	95% CI	Marginal effects (Std. Err)	95%CI
After*Eligible*ClinicalTrials.gov	.287 (.477)	(-.648; 1.221)				

Lead1 *Eligible*Clinical Trials.gov				.411 (.529)	(-.626; 1.449)
Lag0-1 *Eligible*Clinical Trials.gov		.566 (.58)	(-.572; 1.703)	.652 (.605)	(-.534; 1.837)
Lag2-3*Eligible*ClinicalTrials.gov		.647 (.704)	(-.732; 2.026)	.747 (.704)	(-.633; 2.127)
Lag4-5 *Eligible*Clinical Trials.gov		.062 (1.037)	(-1.971; 2.094)	.140 (1.020)	(-1.858; 2.139)
Lag6-7 *Eligible*Clinical Trials.gov		.222 (.676)	(-1.103; 1.546)	.3 (.67)	(-1.013; 1.614)
Lag8-9* Eligible*Clinical Trials.gov		.146 (.83)	(-1.481; 1.773)	.246 (.824	(-1.369; 1.862)
Lag10-11 *Eligible*Clinical Trials.gov		-.044 (.795)	(-1.603; 1.515)	.036 (.797)	(-1.527; 1.598)
No. of observations	2,973	2,973		2,973	

Notes: All regressions include the control variables, as well as registry_disease and year fixed effects (Poisson model). 95% CI= confidence interval; Std. Err= standard errors. In model 2, only lags are included (i.e. no leads). In model 3, lead and lags are included where lead2 is the reference group. This model (M3) thus represents the parallel trend test. In both models 2 and 3, lags are bundled together by blocks of 2 years. The first block (Lag0-1) includes the policy year and the year after, the second block (Lag2-3) includes year's 2 and 3 post policy implementation, etc.

5. DISCUSSION

The PRV was implemented by the US congress in 2007 to encourage pharmaceutical investment in R&D for diseases of the poor. Given the specificities of the program, we were able to employ a DDD strategy to assess the PRV's impact on trial activity. Our findings show that the program has been ineffective at stimulating the number of trials for new products. We found a non-statistically significant increase in trial registration of less than half a trial per year for the intended neglected diseases in the US registry. Delayed effects of the policy could not be found either, with the 95% CIs systematically crossing the zero line. The user fee imposed by the FDA since 2011 to perform a priority review does not seem to be a reason for the policy's lack of effect. Therefore, our findings suggest that the reward of the PRV – a four-month anticipated review – whether used or sold, is not sufficient to generate R&D incentives for neglected diseases. Indeed, it seems reasonable to believe that large pharmaceutical companies, some with yearly revenues exceeding $50 billion, are unlikely to shift or expand their portfolio towards risky projects for tropical diseases based solely on a voucher that can be sold for as low as $68 million. Furthermore, even if sold at its highest price – $338 million – it would not be sufficient to cover the total cost of developing and launching a new product. While it is true that large pharmaceutical companies may have a greater interest in using the voucher rather than selling it (as they are more likely to have a blockbuster product in their pipeline): the benefit of a 4-month earlier entry on the market is not a sufficient compensation. Accordingly, if pharmaceutical companies are involved in such diseases projects, it is more likely to be within product-development partnerships (PDPs). Consequently, the PRV may not actually act as a real 'pull' mechanism

but instead, as a recompense for doing it right. In line with this, the PRV may be better suited at incentivizing the continuation or take up of projects (i) that are already somewhere in the development process; (ii) that are known to be safe but not yet registered in the US or (iii) for which new combinations or repurposed usage can be explored. Those products may not need to go through the entire trial cycle but may be approved on a pivotal phase 2/3 combined. These hypothesis stemming from our analysis are consistent with the outcomes of 12 years of PRV implementation (Exhibit A1 in the Appendix). That is, 33 vouchers awarded so far, of which, 11 were for tropical diseases but for products that arose from new formulation combinations, and in most cases, developed through a PDP. When products were not developed by PDPs but unilaterally by pharmaceutical companies, the vouchers were often awarded to products already licensed outside the US. While we believe this study is the first ever to thoroughly evaluate the PRV, we must highlight its various limitations, which mainly relate to the quality of the data. Each of the caveat is explained in the Appendix (c.f. Caveats of the analysis). To summarize the limitations, they mainly touch upon (i) missing trials in the WHO ICTRP platform; (ii) multi-centered trials being registered in more than one registry and (iii) and the capacity to only consider eligible trials for products that “contain no active ingredient that has been approved in any other application”.

6. CONCLUSION

To finish with, in order to incentivize and reward products that are closer to true innovations, policy recommendations drawn from this study would need to address and correct the main flaw of the program.That is, it should require a minimum level of novelty: a product cannot be granted a voucher if it was already

licensed outside the US. Doing so would restrict the number of awarded vouchers (i.e. the supply) and slow down the ongoing depreciation of its market value. Nonetheless, while this is important for ethical reasons, it is unlikely to strengthen the program's appeal among pharmaceutical companies. Accordingly, if one wants to encourage not only publicly-funded basic research but also industry-funded research, the PRV may need to be supplemented with other types of mechanisms, such as advance market commitment (AMC), to guarantee a minimum level of market profitability and accessibility on products for tropical diseases. While the ICTPR search portal is a great initiative to improve R&D data transparency, evaluations of policies like the PRV would greatly benefit if such a database was able to group trials into projects. As a first step, the establishment of a universal trial number (UTN)[3] should be made compulsory across all trial registries. Once universally compulsory, the trial sponsor/principal investigator should be asked, when submitting a new trial, to indicate all previously-linked trials (with their UTN).

[3] The UTN was launched by the WHO in 2009 but is not yet compulsory. The main idea behind the UTN is to unambiguously identify a trial by linking multiple records on the same trial through the ICTRP search portal.

Appendix

Exhibit A1: Vouchers awarded for neglected diseases

Year	Disease/ product	Manufacturer	Price	User/ voucher used for	Comment
2009	Malaria/ Coartem (artemether/ lumefantrine)	Novartis	Unsuccessfully used	Novartis/ Ilaris (canakinumab)	The drug was already licensed outside the US
2012	Tuberculosis/ Sirturo (bedaquiline)	Janssen	Successfully used	Janssen/ Tremfya (guselkumab)	
2014	Leishmaniasis/ Impavido (miltefosine)	Knight	Sold for $125 million	Gilead/ Odefsey	Initially developed through a PDP The drug was already licensed outside the US
2016	Cholera/ Vaxchora	PaxVax	Sold for 290 millions	Gilead/ Biktarvy	
2017	Chagas/ Benznidazole	Chemo Research	Selling price undisclosed	Novo Nordisk Inc./ Rybelsus	Developed through a PDP New formulation (pediatric)
2018	Onchocerciasis/ Moxidectin	Medicines development	Selling price undisclosed	Novo Nordisk Inc/ semaglutide	Developed through a PDP
2018	Malaria/	GlaxoSmithKline (GSK)	Successfully used	GSK/Dovato (dolutegravir	Developed through a PDP

	Krintafel (tafenoquine)			and lamivudine)	
2019	Fasciolasis/ Egaten (triclabendazole)	Novartis	Succesfully used	Novartis/ ofatumumab	The drug was already registered and used outside the US
2019	Dengue/Dengvaxia	Sanofi	Unused		
2019	Tuberculosis/ Pretomanid tablets in combination with bedaquiline and linezolid*	Global Alliance for TB drug development	Unused		Developed through a PDP New formulation combination
2019	Ebola/ Ervebo	Merck	Unused		

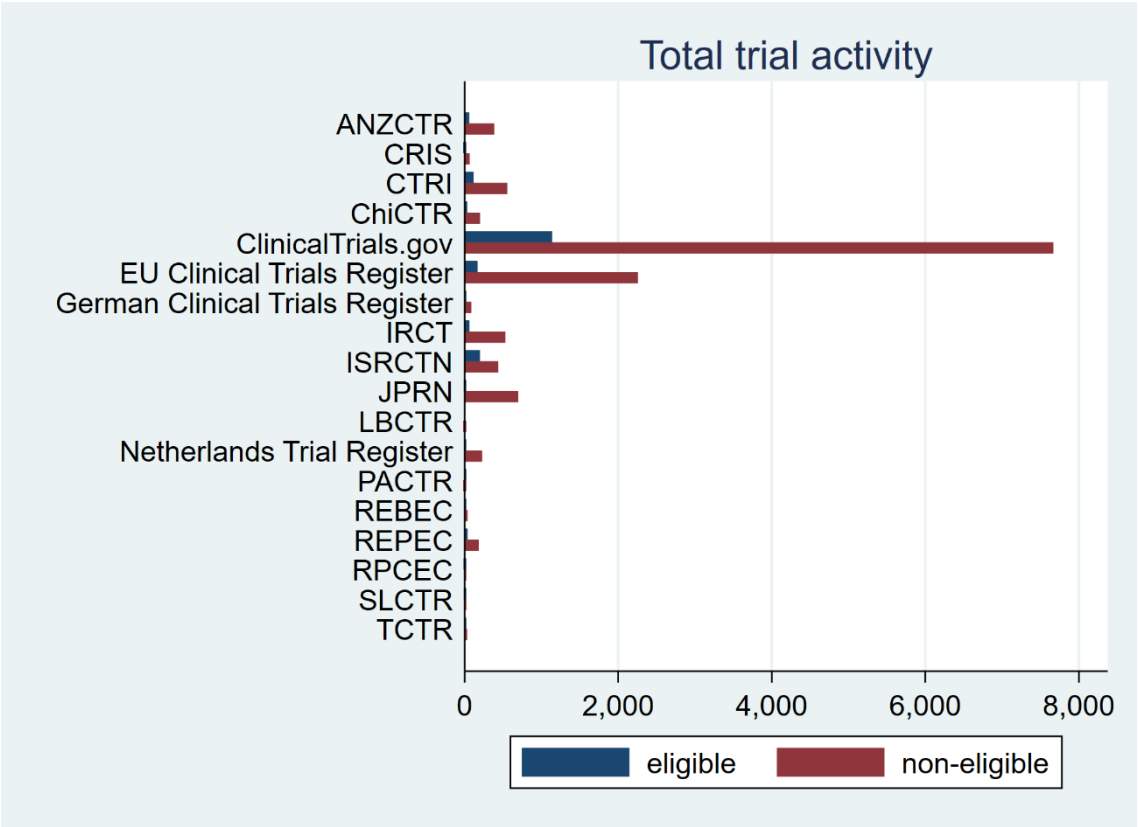
PDP=Product-development partnership
*Pretomanid tablets in combination with bedaquiline and linezolid is for the treatment of a specific type of highly treatment-resistant tuberculosis of the lungs. Source:(United States Government Accountability Office, 2020)

Exhibit A2: List of registries

	Registry	Acronym
Treated registry	The United States Clinical Trials	ClinicalTrials.gov
Control registries	Australian New Zealand Clinical Trials Registry	ANZCTR
	Clinical Research Information Service (Korea)	CRIS
	Clinical Trials Registry	CTRI
	Chinese Clinical Trial Registry	ChiCTR
	EU Clinical Trials Register	EU-CTR
	German Clinical Trials Register	DRKS
	Iranian Registry of Clinical Trials	IRCT
	International Standard Randomised Controlled Trial Number	ISRCTN
	Japan Primary Registries Network	JPRN
	Lebanese Clinical Trials Registry	LBCTR
	The Netherlands National Trial Register	NTR
	Pan African Clinical Trial Registry	PACTR
	Brazilian Clinical Trials Registry	ReBec
	Peruvian Clinical Trial Registry	REPEC

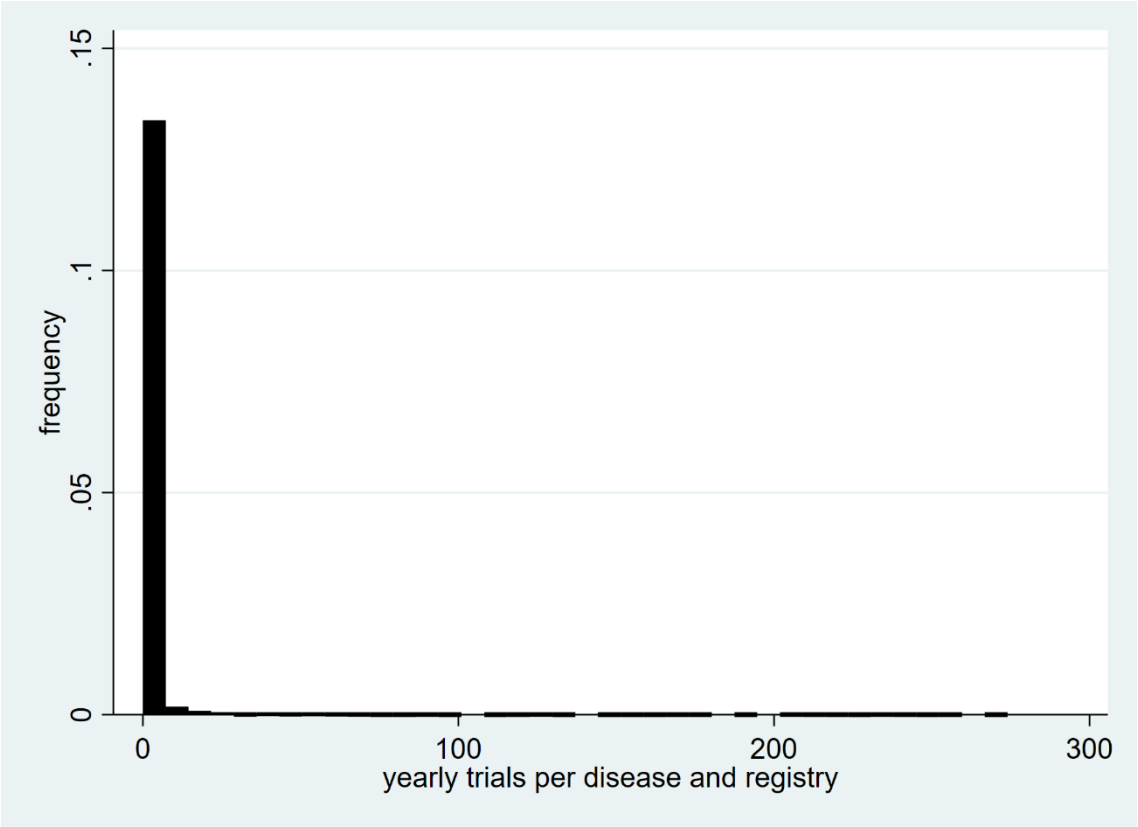
Cuban Public Registry of Clinical Trials	RPCEC
Sri Lanka Clinical Trials Registry	SLCTR
Thai Clinical Trials Registry	TCTR

Exhibit A3: yearly number of trials for each registry of the WHO International Clinical Trials Registry Platform (ICTRP) across eligible diseases (2005-2018)



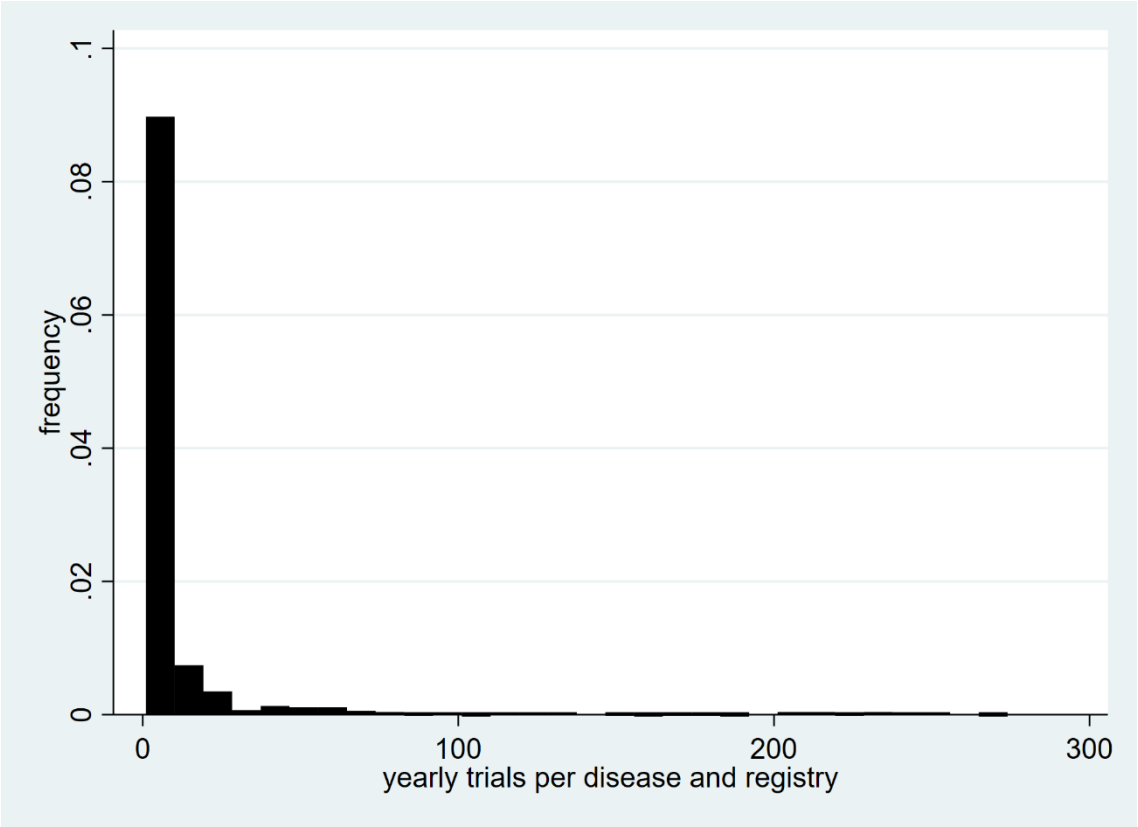
Legend: ANZCTR= Australian New Zealand Clinical Trials Registry; CRIS= Clinical Research Information Service; CTRI= Clinical Trials Registry – India; ChiCTR= Chinese Clinical Trial Registry; ClinicalTrials.gov= United States registry; EU-CTR= EU Clinical Trials Register; DRKS= German Clinical Trials Register; IRCT= Iranian Registry of Clinical Trials; ISRCTN= International Standard Randomised Controlled Trial Number; JPRN= Japan Primary Registries Network; LBCTR= Lebanese Clinical Trials Registry; NTR= The Netherlands National Trial Register; PACTR= Pan African Clinical Trial Registry; REBEC= Brazilian Clinical Trials Registry; REPEC= Peruvian Clinical Trial Registry; RPCEC= Cuban Public Registry of Clinical Trials; SLCTR= Sri Lanka Clinical Trials Registry; TCTR= Thai Clinical Trials Registry

Exhibit A4: Histogram of trials (0 included)



Legend: This bar chart exhibits the frequency of yearly trials registered per disease and registry. For a significant number of disease, registry and year, the number of trials registered is zero. In a few cases, we have a hundred or more observations. For instance, 365 trials were registered in ClinicalTrials.gov for diabetes in 2012.

Exhibit A5: Histogram of trials (0 excluded)



Legend: This graph is the same as of Exhibit A4 except that observations with 0 trials are excluded.

Empirical Model

The PRV quasi experimental design and selective introduction allow us to isolate its impact using a DDD approach. DDD allows to control both for registry (e.g. different regulatory requirements) and disease confounders (e.g. funding/policy shocks) in addition to time-varying fixed effects. The DDD model is estimated as follow:

$$E[y_{jit} | X_{jit}] = \exp(\beta_1 after_{it} + \beta_2 after_{it} * eligible_i + \beta_3 after_{it} * ClinicalTrials.gov + \beta_4 after_{it} * eligible_i * ClinicalTrials.gov + \beta_5 DALYs_{it} + \beta_6 User\_fee_{jit-1} + \alpha_j * \delta_i + \gamma_t)$$

The dependent variable y_{jit}, is the number of starting clinical trials per registry (*j*), disease (*i*) and year (*t*). Trials included are non-inferior interventional trials either in phase 2 or 3 (i.e. phase 1/2; phase 2; phase 2/3; phase 3; phase 3/4) and registered between 2005 and 2019. The variable *after* equals 1 from the year the disease became eligible of the PRV (i.e. 2007, 2014, 2015, 2016 and 2018 depending on the disease) and 0 otherwise. The variable *eligible* equals 1 if the disease is eligible of the PRV and 0 otherwise. The variable *ClinicalTrials.gov* equals 1 if the trial is registered in that registry and 0 otherwise. The coefficient β_4 is thus the DDD coefficient and compares the change in trial registration for the eligible diseases with the non-eligible diseases, in both the treated and control registries, before and after the policy. The coefficient β_2 is the DD coefficient and picks up any diseases and year specific effects that are correlated with the policy. We would expect this coefficient to be insignificant in the DDD specification. Similarly, the coefficient β_3 picks up any registry and year specific effects that are correlated with the policy. The variable *DALYs_share* captures the yearly share of total DALYs per disease in upper middle- and high-income countries according to the world bank definition (Institute for Health Metrics and Evaluation (IHME), 2018). This measure is used as a proxy for the yearly "market size/potential": the higher the DALYs' share in those countries, the greater is the potential return on investment. Since DALY estimates are not yet available for the years 2018 and 2019, estimates for these two years were computed by multiplying the DALYs for the year 2017 by the average annual change since 2000. The variable *User_fee* is used to capture the imposed fee since 2011 by the FDA for performing a faster

review. The fee may act as a turn off and be against the PRV's interest, particularly for smaller companies with lower profit margins. The variable $User\_fee$ takes a non-zero value only for trials targeting eligible diseases and registered in ClinicalTrials.gov from 2011 onwards. The fee has been increasing over the years and as it is unlikely to have an immediate impact on trial registration, we considered potential lagged effects. More precisely, in the main specification we assumed a one-year lag effect of the user fee value on trial activity (e.g. the user fee of the fiscal year 2014 is assumed to affect trial registration in 2015, etc.) but which we extended to further lags in the robustness section. It is worth highlighting that we do not control for the market value of the PRV, which has been depreciating since 2017, as this would dilute the effect of the PRV. In other words, the PRV market value is a channel through which the policy may have impacted on R&D activity. The model includes registry fixed effects per disease fixed effects ($\alpha_j * \delta_i$) to control for disease_registry specific time invariant cofounders. Example of confounders include increased funding to target a disease or a specific group of diseases (e.g. London Declaration; Ebola outbreak) as well as different regulatory requirements across national registries. The model also includes year fixed effects (γ_t) to control for time varying cofounders that impact R&D activity across registries and diseases[4]. Therefore, by estimating a two-way error component model, we were able to control for a broad range of factors including exogenous yearly variations in R&D activity and unobserved time-invariant heterogeneity that are specific to trial registry and disease.

[4] Given the variation in our dependent variable, we were unable to control for those fixed effects separately in addition to them jointly: $\alpha_j * \delta_i + \alpha_j + \delta_i$.

Caveats of the analysis

The study present various limitation that mainly arise due to the quality of the data. First, trials may be missing in the WHO platform. This is an issue if the reason behind missing trials is a confounder of the analysis that that affects differently treatment and control groups. However, since registration for trials other than phase 1 within the first days of patient enrollment is now compulsory for publication, we believe this issue to be minor. Second, there is the issue of multi-centered trials: trials may take place in different countries/regions simultaneously and end up being registered in more than one registry. In such cases, the ICTRP shows more than one record and bridges those into a single trial (and only the oldest trial will appear when downloading the data). Nevertheless, it seems that multiple records are few (e.g. 279 records for 273 trials were found for leishmaniasis which implies 6 multi-centered trials) and if this occurs equally for the eligible and non-eligible diseases, then the issue no longer stands from using a DDD approach. Third, even though the PRV is only valid for products that “contain no active ingredient that has been approved in any other application”, we were not able, given the data available, to exclude those that fail to meet this requirement. This problem is nonetheless counterbalanced by the fact that drug combinations – usually very common for neglected diseases – with at least one new active moiety are eligible for the voucher.

ARTICLE 3

Cost Effectiveness of New Diagnostic Tools for Cutaneous Leishmaniasis in Afghanistan

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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of New Diagnostic Tools for Cutaneous Leishmaniasis in Afghanistan

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Abstract

Background and Objectives Cutaneous leishmaniasis is responsible for chronic and disfiguring skin lesions resulting in morbidity and social stigma. The gold standard to diagnose cutaneous leishmaniasis is microscopy but has a variable sensitivity and requires trained personnel. Using four scenarios, the objective of this study is to compare the cost effectiveness of microscopy with two new tools: Loopamp™ *Leishmania* Detection Kit (LAMP) and CL Detect™ Rapid Test (RDT).

Methods Data related to the cost and accuracy of these tools were collected at the clinic of the National Malaria and Leishmaniasis Control Program in Kabul, Afghanistan. The effectiveness estimates were measured based on the tools' performance but also indirectly, using the disability-adjusted life years. A decision tree was designed in TreeAge Healthcare Pro 2016, combined with a Markov model representing the natural history of cutaneous leishmaniasis. In addition to a deterministic analysis, univariate sensitivity and probabilistic analyses were performed to test the robustness of the results.

Results If the tools are compared at the National Malaria and Leishmaniasis Control Program level in a period of low incidence, microscopy remains the preferred option. LAMP becomes more appropriate during cutaneous leishmaniasis seasons or outbreaks when its capacity to process several tests (e.g. up to 48) at a time can be maximised. RDT has a cost similar to microscopy when used at the reference clinic but as it is relatively easy to use, it could be implemented at the peripheral level, which would become cheaper than employing microscopy at the reference clinic. Moreover, combining RDT with microscopy or LAMP at the reference clinic for the negative suspects is economically more interesting than directly performing LAMP or microscopy respectively on all cutaneous leishmaniasis suspects at the reference clinic.

Conclusions When taking advantage of their respective strengths, LAMP and RDT can prove to be cost-effective alternatives to using microscopy alone at the reference clinic.

Key Points for Decision Makers

If the diagnoses are to be made at a reference clinic in a period of low incidence, it is not worth replacing microscopy with the novel tools.

The Loopamp™ *Leishmania* Detection Kit (LAMP) is particularly relevant during cutaneous leishmaniasis seasons or outbreaks when its capacity to process several tests at a time is used (i.e. minimum of 35 tests).

The characteristics of the CL Detect™ Rapid Test (RDT) make its implementation feasible in peripheral health centers. A primary screening with RDT in peripheral centers followed by LAMP or microscopy at the reference clinic for the negative suspects is more cost effective than screening all suspects at the reference clinic directly with LAMP or microscopy respectively. This is conditional on the fact that follow-up treatments are carried out in peripheral centers as well.

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1 Introduction

The leishmaniases are a group of infections caused by protozoan parasites of the *Leishmania* genus that are transmitted to humans through the bites of infected female phlebotomine sandflies. There are three main forms of leishmaniasis: visceral, mucocutaneous and cutaneous. Cutaneous leishmaniasis (CL) is the most common form of the disease and produces lesions on exposed parts of the body [1]. Although not fatal, it is responsible for chronic and disfiguring skin lesions resulting in high morbidity and social stigma [2, 3]. More than 100,000 new cases of CL are reported annually to the World Health Organization in the Eastern Mediterranean Region. Nevertheless, the incidence is estimated to be three to five times higher as most cases are either undiagnosed or not reported to health authorities [4].

Afghanistan is one of the countries with the highest prevalence of CL, caused by *Leishmania major* and *Leishmania tropica* [5]. The latter is the most prevalent and is related to anthroponotic urban transmission. It can evolve into cutaneous leishmaniasis recidivans (CLR) characterised by papular lesions appearing around the scar of a healed lesion months to years after a clinical cure, which may last for many years [4, 6]. Although efforts have been made to rebuild the Afghan healthcare system after the fall of the Taliban regime in 2001, the country is struggling with insecurity, corruption, low-quality health services and accessibility to health services [6]. Accordingly, cost-effective solutions to tackle public health priorities are needed, and as for leishmaniasis specifically, significant improvements in the diagnostic and treatment strategies are necessary.

The main diagnostic tools for CL are microscopy and polymerase chain reaction (PCR) but both have their respective drawbacks. Microscopy, considered as the mainstay diagnosis method, requires trained personnel and has a low and variable sensitivity, which, in many cases, leads clinicians to neglect its use and reach a diagnosis based on clinical judgements [7]. However, the broad variety of CL manifestations complicates its clinical diagnosis and its identification among other infectious and non-infectious diseases such as psoriasis, blastomycosis, chromoblastomycosis, sarcoidosis, and cutaneous tuberculosis in the Eastern Mediterranean Region. Additionally, in long-lasting lesions, the lesion may expand but the parasite load decreases over time, which makes its detection more difficult. In such cases, molecular diagnosis (i.e. PCR) has shown to be far more sensitive than microscopy [8, 9]. Nevertheless, this tool requires well-equipped laboratory facilities and experienced laboratory staff, as well as sufficient financial resources, which prevents its use outside well-equipped laboratories [10].

Thus, there is a need to move towards user-friendly, cost-effective and field-amenable diagnostic options. This need is further heightened by the current treatment options for CL. Treatment regimens are not standardised; the first-line treatment in Afghanistan is based on injectable pentavalent antimony, which is usually intra-lesional but may require systemic (intramuscular) administration in complicated cases such as CLR. The daily intramuscular injections impose significant travel costs and commuting time to the patients. Although effective, these injections can be toxic and cause serious side effects [11, 12]. Accordingly, accurate diagnosis will ensure that only those infected will be given treatment, avoiding unnecessary and unpleasant treatment, the misuse of available drugs and the emergence of drug resistance.

In a context such as Afghanistan where skilled health workers are lacking, improving technology can help increasing labour productivity and the quality of CL detection. Two point-of-care diagnostic tools have been recently developed: Loopamp™ *Leishmania* Detection Kit (LAMP) [Eiken Chemical Co., Japan] and CL Detect™ Rapid Test (RDT) [InBios International Inc., USA] (a detailed description of these tools is given in the Electronic Supplementary Material [ESM]). On the one hand, LAMP is able to perform as well as PCR in terms of sensitivity and specificity but the reagents come in a ready-to-use dry format that is stable at ambient temperature. The results are obtained faster and can be visualised directly using simple detection methods [13]. Additionally, LAMP can process several tests at a time, from 8 to 48 or more, depending on the machine. On the other hand, RDT is fast and easy to use, does not require any machine as opposed to LAMP and microscopy, and has a close to perfect specificity [14].

To our knowledge, there is no cost-effectiveness study comparing the available diagnostic tools for CL; the available cost-effectiveness studies on CL tend to focus on treatment strategies instead [15–19]. To fill this gap, the objective of this study is to compare the cost effectiveness of RDT and LAMP with that of microscopy, using PCR as a reference [20–22]. We use four hypothetical scenarios. Scenario 1 compares the above tools in a reference clinic, the National Malaria and Leishmaniasis Control Program (NMLCP), assuming one test is performed at a time, whereas scenario 2 compares the same tools in the same clinic but assumes a high incidence of CL (e.g. winter season) where the assumed full capacity of the LAMP is being used (48 tests processed at a time). Scenario 3 attempts to capture the benefit of implementing RDT in remote healthcare facilities compared to the implementation of LAMP and microscopy in the reference clinic. In this scenario, treatment is administered in remote facilities, thus diminishing the associated treatment costs to the patient by reducing commuting times and expenses. Last, scenario 4 relies on the same assumptions, except that negative RDT suspects are tested again at the NMLCP with microscopy or LAMP.

2 Data and Methods

2.1 Study Population and Diagnosis

The new diagnostic tools were evaluated among 274 individuals presenting themselves with suggestive signs of CL at the leishmaniasis clinic of the NMLCP in Kabul; a department of the Ministry of Public Health. The clinic is the CL reference clinic in Kabul treating 5000–7000 new CL cases per year. To be enrolled in the study, inclusion criteria were: (1) older than 2 years of age; (2) consenting to participate; and (3) not receiving treatment for CL at the time of enrolment. Samples from participants were subject to the four diagnostic tests: microscopy, LAMP, RDT and PCR (see details in the ESM). A logistic regression was performed to assess whether individual-level characteristics, age and sex were significantly associated with being positive for CL (when presenting skin lesions). The recruitment period spanned from April to June 2016.

2.2 Cost-Effectiveness Model Structure

We developed a decision tree designed in TreeAge Healthcare Pro 2016 (TreeAge Software, Williamstown, MA, USA), which was combined with a Markov model representing the natural history of CL due to *L. tropica* (see Figs. 1 and 2), as all patients have shown to be infected with this *Leishmania* species. The model is based on a static cohort of 10,000 individuals and runs for 80 annual cycles. Individuals enter the model at the age of 6 years: the youngest age observed in the study population. To follow the cohort over a life-long span, the individual entering the model encounters an annual probability of dying, which is independent of CL and varies across age groups and sex. The Markov model is composed of seven mutually exclusive health states and starts with "no skin lesion", "skin lesion(s)" and "death" states to translate this health facility-based study into a community-based study and to capture the risk of infection in an endemic area. The remaining health states include the "No CL", "CL", "cure" and the "CLR" states (see Fig. 2).

Each annual cycle, the individual either stays in the same health state or moves to another one according to transition probabilities (see Table 4). If the individual is healthy and does not have skin lesions, he/she can: (1) remain healthy; (2) develop skin lesion(s); or (3) die for reasons independent of CL. If the individual presents with skin lesion(s), the lesions might be due to: (1) CL, which is equal to the percentage of confirmed CL cases observed at the health facility or (2) other diseases (i.e. "No CL"). Alternatively, the individual may die for unrelated reasons. Whether the CL-positive cases are detected will not only depend on the sensitivity of the tools but also on the likelihood that infected people seek a diagnosis. What follows after a true-positive or a false-negative case is best explained in Fig. A1 in the ESM.

If a patient is infected by *L. tropica* and develops CL, he/she can either: (1) remain infected for another year; [4, 10] (2) become cured; or (3) die. If a patient is not infected with *L. tropica* (i.e. "No CL"), he/she can either: (1) stay uninfected for another cycle; (2) become infected and develop CL according to the incidence rate; (3) or die. Once the patient has cured from a CL infection (i.e. "Cure"), he/she can: (1) stay cured; (2) develop CLR ("CLR" state) [23]; or (3) die. Patients infected with CLR can: (1) stay infected with CLR for up to 10 years; [4] (2) become cured; or (3) die. Nonetheless, it is worth highlighting that no cases of CLR were recorded among the study population.

2.3 Cost Estimates

Data on costs were collected through three tailor-made questionnaires capturing both the patient and the health system perspective. Costs figures were initially collected in local currency (i.e. Afghan Afghani) and were then translated into US dollars using the exchange rate for the year 2016 (i.e. 0.015). First, the 'patient cost questionnaire' (see questionnaire I in the ESM) was administered to a subset ($n = 111$) of the 274 individuals enrolled in the study, regardless of their diagnostic results. The first half of the questionnaire was completed on the day of the diagnosis and the remaining half was completed at the end of the treatment period by positive patients only, with the help of a fieldworker. This questionnaire gathers information related to direct (i.e. transportation) and indirect (i.e. wage loss during travelling and incapacity to work during illness period) costs associated with a potential CL episode. Patient costs were controlled for individual-level characteristics (i.e. age, sex and occupation) by matching cost estimates obtained from this questionnaire to a patient folder that collected information on individual characteristics such as occupation and family income. This led to a reduced subset of 85 individuals. Second, the 'laboratory and medical staff' questionnaire (see questionnaire II in the ESM) captures cost estimates among medical staff running CL diagnostics. These include the time spent on average per diagnostic; the types of medical staff required and their salaries; and the equipment required to run the diagnostic. The market price of the kits and the cost of the machines/instrument (i.e. incubator/thermocycler in the case of LAMP) were also included. The cost of the instruments was calculated over 80 years, the cohort life expectancy, assuming a life span of 5 years. DNA extraction cost was included for LAMP. Last, an additional questionnaire was administered to medical staff: the 'drug and treatment' questionnaire (see questionnaire III in the ESM), which collected information mainly related to costs of intra-lesional and intramuscular treatment. Treatment cost is based on the

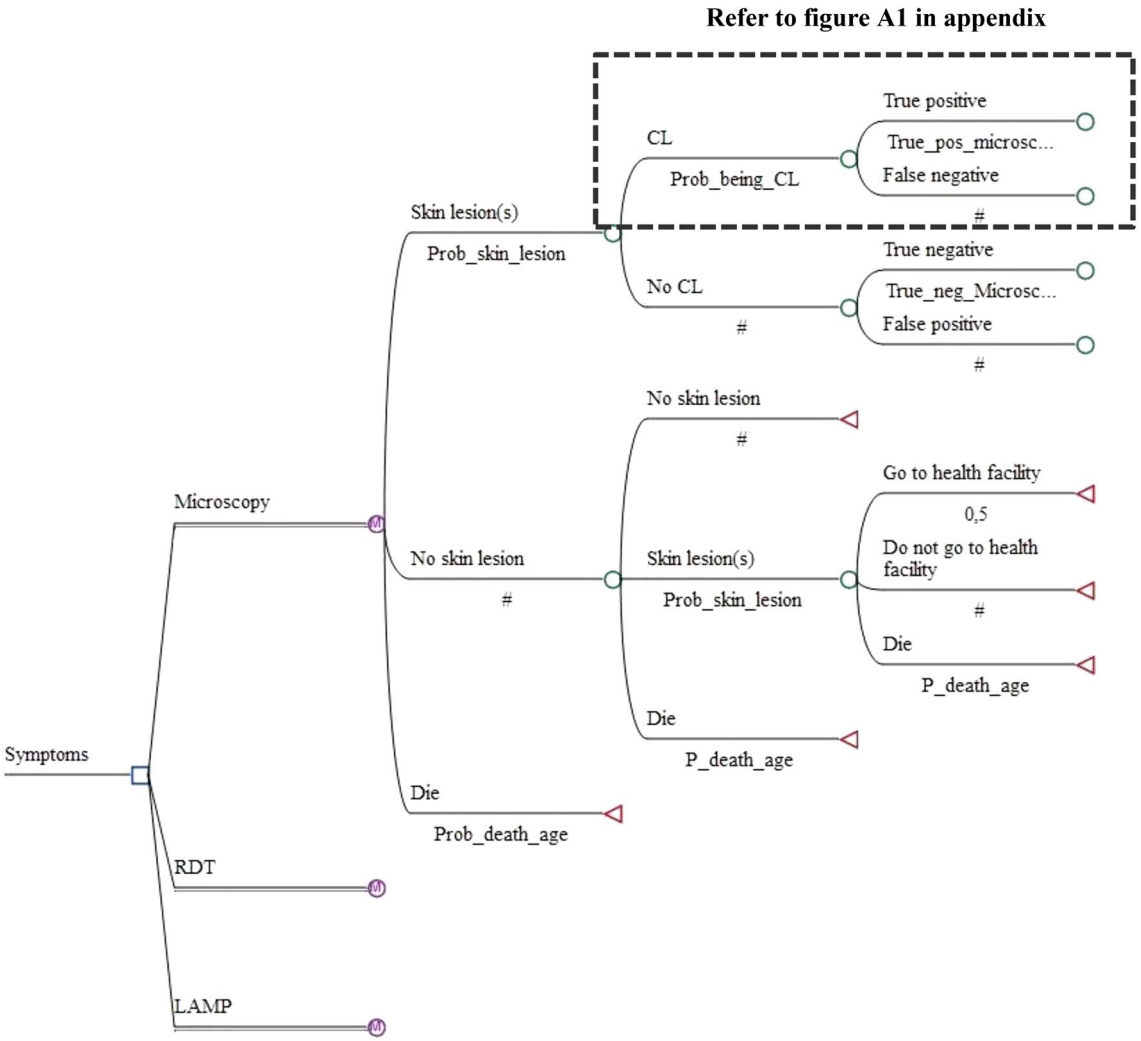


Fig. 1 Decision tree: comparative strategies. *CL* cutaneous leishmaniasis, *LAMP* Loopamp™ *Leishmania* Detection Kit, *RDT* CL Detect™ Rapid Test

generic price of Pentostam®, which is donated by the World Health Organization in Afghanistan [24]. Patients pay out-of-pocket-associated travel expenses and incur a wage loss from travelling and waiting to receive the daily injections. If treatment was intra-lesional, patients would have to receive 3–5 injections, whereas if treatment was intramuscular, patients would have to receive 14–21 injections implying considerable travel expenses. Lastly, all cost parameters were discounted at 3% per annum as recommended by World Health Organization guidelines [25].

2.4 Effectiveness Estimates

In the economic model, the effectiveness estimates were estimated directly through the sensitivity and specificity of the tools, as presented in Table 1, but also indirectly through an indicator of disease burden: the disability-adjusted life years (DALYs). The DALYs were estimated per annual cycle and because CL is not lethal these are an estimation of years lived with disability. To better understand and capture the impact of a CL episode on a patient's quality of life, the standardised 'Dermatology Life Quality Index' (DLQI) questionnaire was administered to individuals enrolled in the study and used as an indicator of social stigmatisation [26] (see questionnaire IV in the ESM). Information collected through the DLQI informed the calculation of DALYs: more precisely, the percentage of CL-positive people (based on PCR) who reported "A little", "A lot" or "Very much" embarrassment and/or social stigmatisation in question 2 were attributed a higher disability weight of 0.067. This disability weight is coded as disfigurement level 2 in the Global Burden of Diseases study and is defined as follows: "has a visible physical deformity that causes others to stare and comment" [27]. The remainder of the cohort was attributed

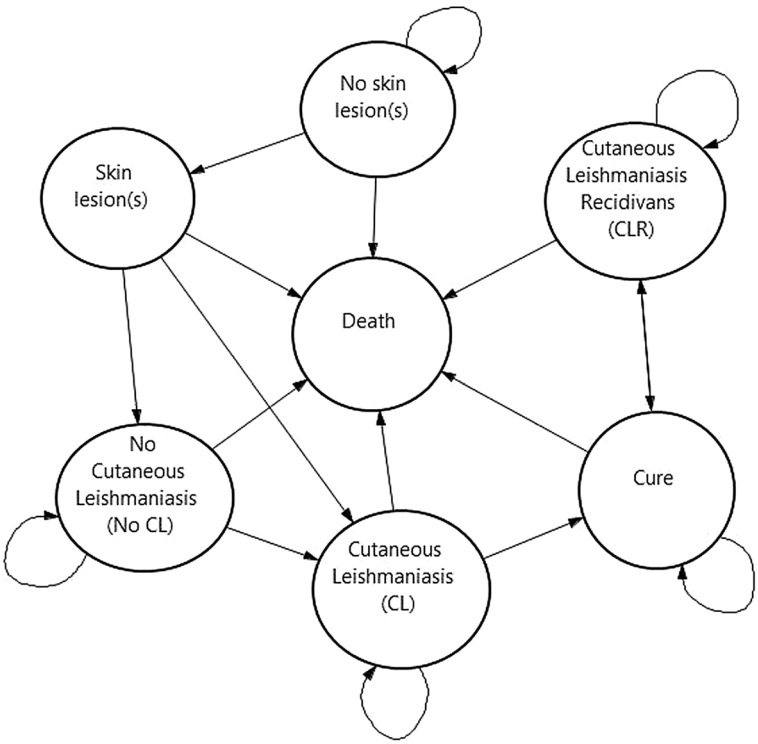


Fig. 2 Natural history of *Leishmania tropica*

Table 1 Sensitivity and specificity of the tools using polymerase chain reaction as a reference

Tools	Diagnostic performance (%)	95%CI
Microscopy	Se = 78.97	73.74–84.20
	Sp = 77.27	57.49–97.06
RDT	Se = 66.27	60.23–72.31
	Sp = 95.45	84.48–100
LAMP	Se = 89.68	85.73–93.64
	Sp = 63.64	41.26–86.01

CI confidence interval, *LAMP* Loopamp™ *Leishmania* Detection Kit, *RDT* CL Detect™ Rapid Test, *Se* sensitivity, *Sp* specificity

Source: [29]

a disability weight of 0.011, which is coded as disfigurement level 1 and defined as "a slight, visible physical deformity that others notice, which causes some worry and discomfort" [27].

As no age weighting and discounting were taken into account in the DALY formulation, DALYs for CL and CLR are simply a weighted average of disfigurement level 1 and 2, which can be accumulated for up to 2 and 10 years, respectively [28]. However, although no discounting was taken into account in the DALY formulation, a discount rate of 3% per annum was applied in the decision tree as DALYs have a bigger impact in younger ages.

2.5 Scenarios

To capture the inherent benefit of the tools, four scenarios were studied. Scenario 1 compared microscopy, LAMP and RDT at the NMCLP level, assuming that the full capacity of the LAMP is irrelevant such that one test at a time is being processed. This is a rather conservative approach but feasible outside the CL incidence peak (i.e. outside the winter season). Scenario 2 compared the tools at the NMLCP level but assuming here that the capacity of the LAMP to process several samples at a time is used fully. To do so, the labour cost spent on LAMP is divided by 48, its assumed maximum capacity. The maximum capacity of the LAMP can vary and hence a sensitivity analysis was conducted on this parameter. Scenario 3 compared microscopy and LAMP at the NMLCP level but RDT at the peripheral level, that is, in remote health facilities. To capture the benefit of implementing the RDT in peripheral facilities, the associated treatment costs to the patient were diminished by half, which are independent of the treatment cost per se, as treatment is provided by the NMLCP, but instead include transportation costs and wage loss as a result of commuting and waiting to receive the daily injections. As halving the treatment-associated costs when RDT is implemented at peripheral levels is rather arbitrary, we conducted a sensitivity analysis on this parameter to look for any potential threshold value(s) that would alter the order of the strategies. Finally, as the sensitivity of RDT is relatively low (i.e.

a high proportion of false negatives), a fourth scenario was studied in which RDT is implemented at the peripheral level but negative patients are sent to the NMLCP to be tested again with microscopy or LAMP. In scenario 4 (and as in scenario 3), we assumed that treatment would be administered at the peripheral level.

2.6 Data Analysis

2.6.1 Measurement of Cost Effectiveness

An intervention is judged cost effective if the incremental cost-effectiveness ratio (ICER) between two competing strategies is below the country's gross domestic product per capita (US$561) [30]. If the incremental effectiveness between strategies is close to 0, the net monetary benefit (NMB) can also be used for comparing strategies, NMB = threshold* effectiveness—cost, where the weight is put on costs. The strategy with the highest NMB is the one preferred—that is, often the one reporting the lowest cost.

2.6.2 Model Estimate and Sensitivity Analysis

The model was estimated by applying deterministic and probabilistic analyses. A deterministic analysis was performed using the mean or median value for each parameter, depending on distribution skewness. Univariate sensitivity was applied to scenario 1 by varying the mean or the median values of all parameters by both − 50% and + 50% or to the minimum or maximum feasible values (i.e. 0 or 1 if parameters are probabilities). For the same scenario, threshold analyses were carried out on selected parameters for which a change (i.e. up to ± 50%) affects the chosen strategy in terms of their respective costs. Probabilistic analysis was performed through Monte Carlo simulations; the number of iterations needed to produce stable results was based on the graphical representation of the average of the cumulative NMB. Different probabilistic distributions were assigned to parameters following indications from the literature and are listed in Table 4 [31]. To account for uncertainty among individual-level cost data, we regressed the logarithm of the cost of being diagnosed on individual-level characteristics: age, sex and occupation. Occupation was divided into four categories: (1) no earnings: "students" and "jobless"; (2) unsecured jobs: "farmers" and "housekeepers"; (3) secured jobs: "army officer", "government official"; and last (4) unknown occupations. Cholesky decomposition among the parameters was performed so that the variance of each parameters and the variability within the parameters (covariance) is kept constant through a multi-normal distribution.

For the sensitivity and specificity of the tools, the difference between the upper and lower limit from the 95% confidence interval, based on a t Student distribution, was used to calculate the standard deviations. If the difference between the upper and lower limit was too wide to yield positive alpha and beta values, it was reduced until positive parameters were reached. For variables obtained from the literature or at the health facility level, a standard deviation of 20% was chosen. [32] Results of the probabilistic analyses were graphically presented through the cost-effectiveness plane and acceptability curves. The cost-effectiveness plane plots all Monte Carlo simulations for the two best strategies, with respect to the incremental cost and effectiveness. Acceptability curves are generated using the NMB and show

Table 2 Deterministic results

Scenarios	Strategies	Average per person		ICER	Outcome	NMB
		Cost (2016 US$)	DALYs	US$ per DALY averted		
1	Microscopy	53.79	0.0486	–	Undominated	− 81.03
	RDT	53.91	0.049	–	Dominated	− 81.38
	LAMP	60.18	0.0482	18614.89	Undominated	− 87.23
2	Microscopy	c.f. 1	c.f. 1	–	Dominated	c.f. 1
	RDT	c.f. 1	c.f. 1	–	c.f. 1	c.f. 1
	LAMP (full capacity)	53.73	c.f. 1	–	Undominated	− 80.79
3	Microscopy	c.f. 1	c.f. 1	18325.54	c.f. 1	c.f. 1
	RDT (peripheral)	46.32	c.f. 1	–	Undominated	− 73.79
	LAMP	c.f. 1	c.f. 1	18457.92	c.f. 1	c.f. 1
4	Microscopy	c.f. 1	c.f. 1	586.24	c.f. 1	c.f. 1
	RDT (peripheral) + microscopy	52.27	0.0511	–	Undominated	− 80.96
	LAMP	c.f. 1	c.f. 1	2699.6	c.f. 1	c.f. 1
	RDT (peripheral) + LAMP	54.59	0.051	–	Dominated	− 83.2

c.f. 1 refer to scenario 1, *DALYs* disability-adjusted life years, *ICER* incremental cost-effectiveness ratio, *LAMP* Loopamp™ *Leishmania* Detection Kit, *NMB* net monetary benefit, *RDT* CL Detect™ Rapid Test

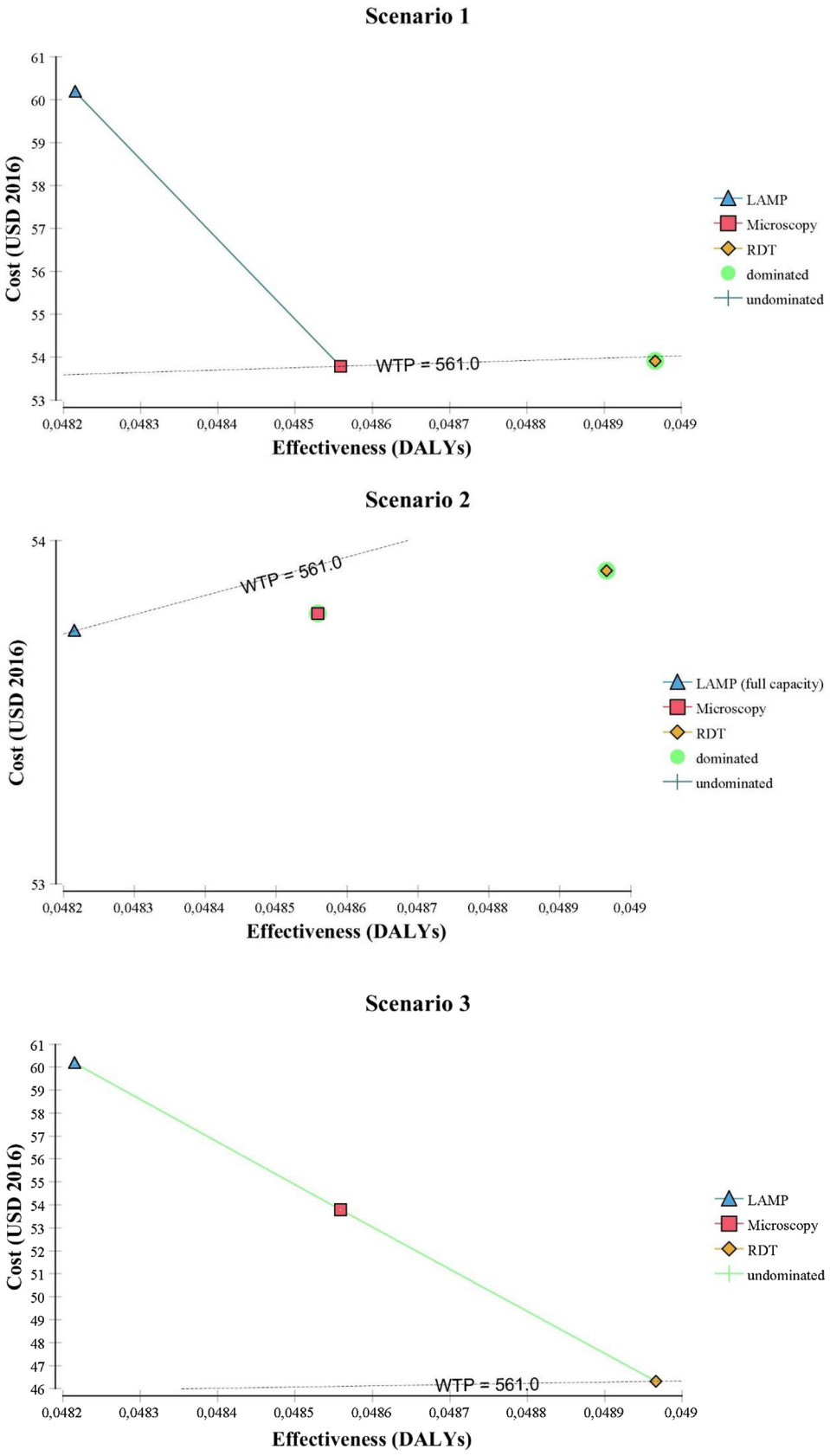
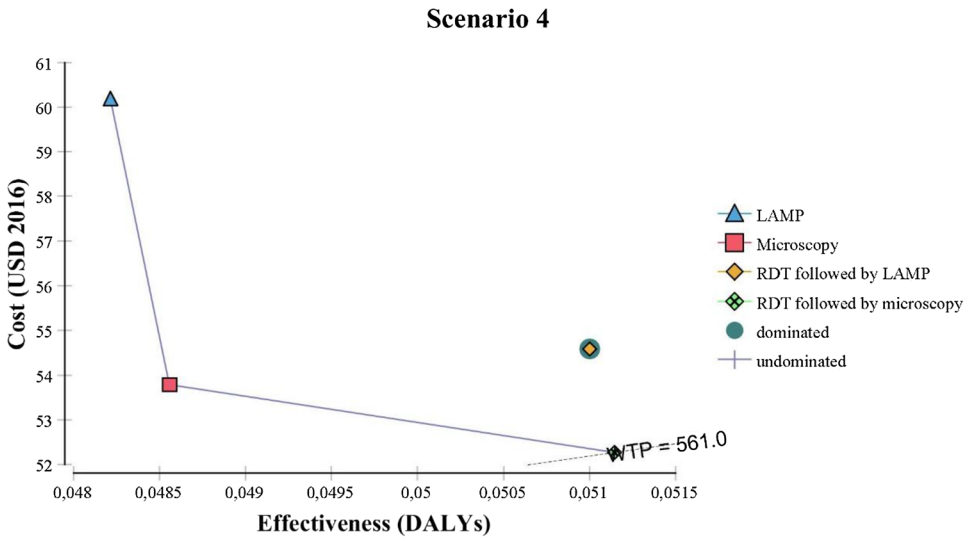


Fig. 3 Cost-effectiveness graph with willingness-to-pay (WTP) line. *DALYs* disability-adjusted life-years, *LAMP* Loopamp™ *Leishmania* Detection Kit, *RDT* CL Detect™ Rapid Test

Fig. 3 (continued)



the probability of the tools to be cost effective according to different willingness-to-pay (WTP) values.

3 Results

From the logistic regression, it became clear that CL positivity was not significantly correlated with age and sex (refer to Table A1 in the ESM). Hence, the analyses were not stratified across these two demographic variables.

3.1 Cost

The predicted mean cost incurred by patients to be tested reaches US$1—controlling for individual-level characteristics—and include transportation costs and indirect costs related to wage lost during the clinic visits and the illness period. The results of the regression analyses as well as tests of linear assumptions are presented in Table A2 and Fig. A2 of the ESM. While age and sex are not significantly associated with patients' costs, occupation types are: people with low social security jobs (e.g. house keepers and farmers) experience a 99% cost increase per CL episode when compared with the reference group: people without any earnings (students and jobless). In contrast, occupations with more social security (e.g. retail workers, tailors) experience a cost increase of 53% per episode compared with people without earnings. Cost of treatment, borne by the health system, is higher for intramuscular treatment than for intra-lesional treatment, US$41 vs. US$13, but 80% of the patients are treated with the latter. Travel expenses for the patients are also higher for intramuscular treatment than for intra-lesional treatment, US$18 vs. US$4. Microscopy and RDT have identical labour costs, which approximates to US$14 per person tested. LAMP is slightly more costly with approximately $US20 per person tested; however, this is using a conservative approach where one test is processed at a time.

3.2 Disability-Adjusted Life-Years

Based on the DLQI questionnaire, 60% of the cohort reported embarrassment and/or social stigmatisation as a result of CL and were attributed a higher disability weight of 0.067. The remaining 40% was attributed a lower disability weight of 0.011. Hence, on average, one episode of CL or CLR was associated with 0.0446 DALY annually, which could be accumulated for up to 2 years for patients infected with CL and 10 years for patients infected with CLR.

3.3 Cost Effectiveness

Results of the deterministic analyses are represented in Table 2 for each scenario but also graphically in Fig. 3.

Microscopy and LAMP are the two undominated strategies in scenario 1: the first has the lowest associated cost while the latter has the highest associated effectiveness (i.e. fewer associated DALYs) but as the incremental effectiveness between the two is close to 0, the ICER tends to infinity. Looking at the NMB, it is almost identical for microscopy

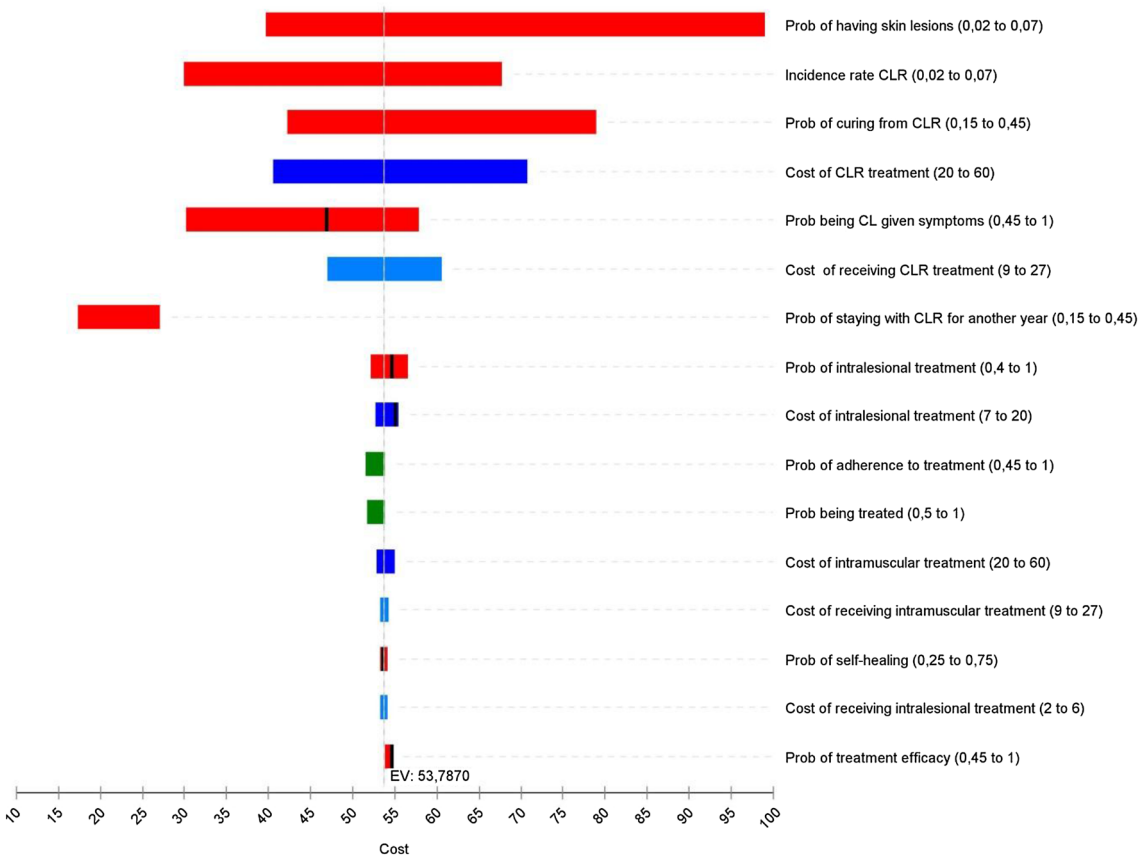


Fig. 4 Tornado diagram. Parameter categories are grouped by color: dark blue represents costs borne by the health system; light blue represents costs borne by the suspects/patients with cutaneous leishmaniasis (CL); red represents transition rates; and green represents patient/clinician behaviours. The values in the parentheses stand for the lower and higher range over which the parameter was varied. The vertical line represents the expected value of the microscopy cost. A segmented bar indicates a change in the cost threshold: CL Detect™ Rapid Test becomes cheaper than microscopy. *CLR* cutaneous leishmaniasis recidivans, EV, *Prob* probability

and RDT but lower for LAMP. In scenario 2, when the assumed full capacity of the LAMP (48 tests at once) is used, LAMP has the lowest cost and the highest effectiveness: it dominates microscopy and RDT with the highest NMB. The sensitivity analysis on the capacity of the LAMP to process several tests at once has shown that: for LAMP to be the cheapest option, 35 tests should be processed at once and for LAMP to have the greater NMB, 17 tests should be processed at once. In scenario 3, RDT has the lowest associated cost and the highest NMB. In other words, if implemented in peripheral health centers, RDT is preferred over microscopy and LAMP used in the reference center. The assumption behind scenario 3 is that if RDT is implemented in remote facilities, the ensuing treatment regimens will be administered in the remote facilities, thereby decreasing the treatment-related costs to the patient. Sensitivity analyses of the cost of treatment, both intra-lesional and intramuscular, are presented in Fig. A3 of the ESM and shows that a decrease of at least 5% in the intramuscular treatment cost for patients when RDT is chosen over microscopy or LAMP. When it comes to scenario 4, sending the RDT negatives to the reference clinic to be tested with microscopy or LAMP is naturally more costly than using RDT alone but cheaper than using direct microscopy or LAMP at the NMLCP on all CL suspects. RDT followed by microscopy is cheaper and leads to higher NMB than RDT followed by LAMP.

Figure 3 provides a visual representation of the results where undominated strategies are connected by a line (which does not show in scenario 2 as LAMP dominates both RDT and microscopy). The gradient of this line is the ICER: the steeper the line, the bigger the ICER. A strategy should be chosen if positioned on the ICER line and crossing the WTP

Table 3 Monte Carlo simulation results

Scenarios	Strategies	Average per person					
		Cost (2016 $US)	DALYs	Differences		ICER	Outcome
		Mean [95% CI]	Mean [95% CI]	Cost (2016 US$)	DALYs	US$ per DALY averted	
1	Microscopy	56.67 [54.48–58.86]	0.0513 [0.0493–0.0533]	–	–	–	Undom.
	RDT	56.75 [54.55–58.94]	0.0517 [0.0497–0.0537]	0.081	0.0004	–	Dom.
	LAMP	62.86 [60.53–65.18]	0.051 [0.049–0.053]	6.19	− 0.0003	∞	Undom.
2	Microscopy	c.f. 1	c.f. 1	0.1286	0.0003	–	Dom.
	RDT	c.f. 1	c.f. 1	0.21	0.0007	–	Dom.
	LAMP (full capacity)	56.54 [54.35–58.73]	0.051 [0.049–0.053]	–	–	–	Undom.
3	Microscopy	c.f. 1	c.f. 1	8.143	− 0.0004	6924.40	Undom.
	RDT (peripheral)	48.53 [46.67–50.38]	0.0517 [0.0497–0.0537]	–	–	–	Undom.
	LAMP	c.f. 1	c.f. 1	14.33	− 0.0007	19797.76	Undom.
4	Microscopy	c.f. 1	c.f. 1	2.20	− 0.003	∞	Undom.
	RDT (peripheral) + microscopy	54.46 [52.51–56.42]	0.0539 [0.0519–0.0559]	–	–	–	Undom.
	RDT (peripheral) + LAMP	56.74 [54.73–58.76]	0.0538 [0.0518–0.0558]	2.29	− 0.0001	–	Dom.
	LAMP	c.f. 1	c.f. 1	8.389	− 0.0029	∞	Undom.

c.f. 1 refer to scenario 1, *CI* confidence interval, *DALYs* disability-adjusted life-years, *Dom.* dominated, *LAMP* Loopamp™ *Leishmania* Detection Kit, *RDT* CL Detect™ Rapid Test, *Undom.* undominated

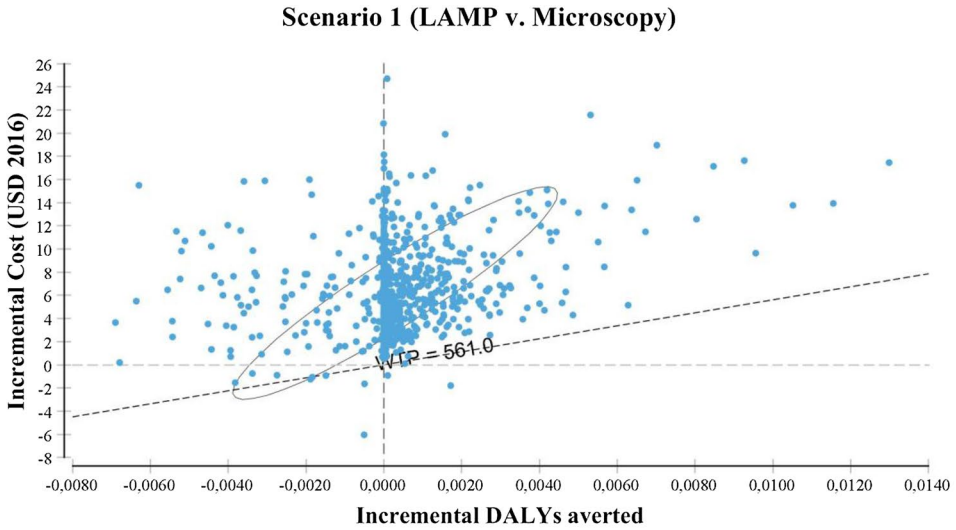
slope. Accordingly, microscopy should be chosen in scenario 1, LAMP in scenario 2, RDT in scenario 3 and RDT followed by microscopy in scenario 4.

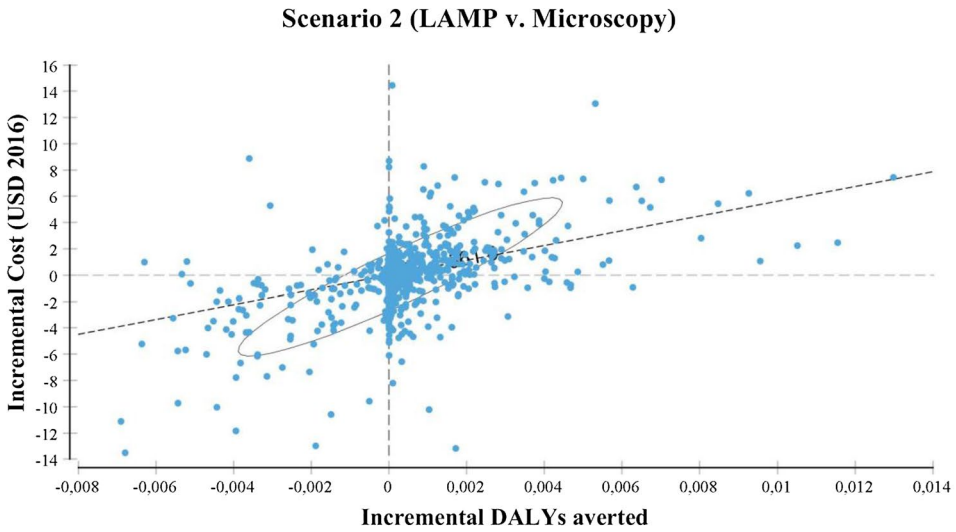
3.4 Sensitivity Analysis

The one-way sensitivity analysis on the expected value of the cost of microscopy vs. RDT and LAMP (with the assumption of scenario 1) is illustrated by the tornado diagram in Fig. 4. To start with transition rate parameters, an increase in the prevalence of skin lesions within the population significantly increases the expected cost of the tools. If the probability of the skin lesions being due to CL ("Prob being CL given symptoms") decreases below 78%, the expected cost of RDT becomes a slightly lower than microscopy (see Fig. A4 in the ESM). The same applies to the incidence rate of CLR. On the contrary, the greater the annual curing rate the lower the expected cost of the tools and vice versa (i.e. probability of staying with CLR for another year). When lowering the probability of intra-lesional treatment from 80% to below 70%, RDT becomes cheaper than microscopy (see Fig. A4 in the ESM). The same applies to the probability of treatment efficacy or self-healing: if the former is lower than 45% or the latter higher than 62%, RDT becomes the cheapest option (see Figs A6 and A7 in the ESM). As with cost parameters, it is obvious that any increase in one of these will result in higher expected costs of the tools. Only one cost parameter can affect the order of the tools when judging on their respective expected costs: the cost of intra-lesional treatment. If increasing above $US18 per treatment regimen, RDT becomes less costly than microscopy. Finally, as the probability of being treated and the adherence to treatment increase, the cost of the tools increases.

In the probabilistic analysis, about 1000 random iterations of the cost-effectiveness model were required to achieve stable results. Compared with the deterministic results, both the mean cost and mean effectiveness parameters have increased. The mean ICER in most of the scenarios is now tending towards infinity because for many simulations its denominator, the difference in DALYs, is close to zero (see Table 3).

Monte Carlo simulations are represented through the cost-effective plane in Fig. 5 and the cost-effectiveness acceptability curves (CEACs) in Fig. 6, in which the former is generated using the incremental cost and effectiveness and the latter using the NMB. The cost-effectiveness plane compares both the incremental cost and effectiveness of the undominated, or the two best strategies for each scenario. In scenario 1, almost all of the simulations are located above the WTP threshold, suggesting than LAMP is not preferred





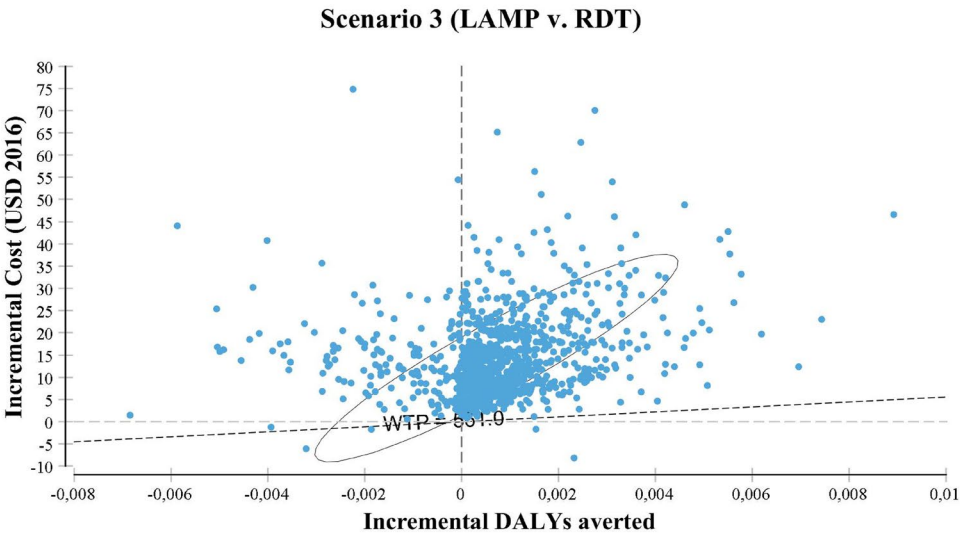
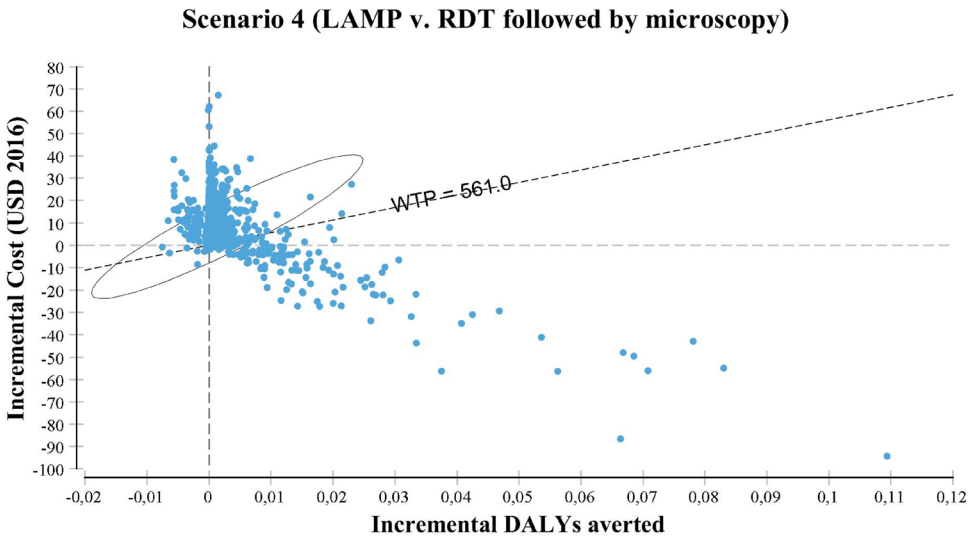


Fig. 5 Cost-effectiveness plane. The circle represents the 95% ellipse (the 95% credible interval); the willingness-to-pay (WTP) line represents the WTP threshold that is equal to the one time gross domestic product per capita. *DALYs* disability-adjusted life-years, *LAMP* Loopamp™ *Leishmania* Detection Kit, *RDT* CL Detect™ Rapid Test

Fig. 5 (continued)



over microscopy. In scenario 2, LAMP becomes more competitive: about half of the simulations are located on or below the WTP threshold. The cost-effectiveness plane in scenario 3 suggests that RDT is significantly preferred over LAMP with nearly all simulations above the WTP threshold. Last, in scenario 4, most of the simulations are located above or on the WTP threshold: it appears more cost effective to first use RDT in the peripheral centers and perform microscopy on the negative patients at the reference clinic than directly performing LAMP (or microscopy) on all suspects at the reference clinic. However, as shown by the credible interval, the uncertainty regarding the cost effectiveness of this combined strategy is large.

With respect to the CEACs, as the effectiveness is close to 0, different WTP values have little impact on modifying the probability of the tools to be cost effective and this further implies that for the tools to offer higher NMB, their respective costs must be reduced. In Scenario 1, where all tools are compared at the NMLCP level, RDT has a higher probability of being cost effective up to a WTP of a US$1000 per DALY averted, which at first seems to contradict the finding in Table 3 that RDT is dominated. However, because the CEAC is based on the NMB of each option, it is possible for an option to have a higher net benefit without dominating another option [33]. The probability of RDT to be cost effective is even greater when employed at the peripheral level (i.e. scenario 3): regardless of the WTP value it has a 95% probability to be cost effective. In scenario 2, when the LAMP capacity is maximised, the latter becomes more likely to be cost effective than RDT (at the reference clinic) above a WTP threshold of around US$400 per DALY averted. In scenario 4, RDT performed at the peripheral level followed by microcopy is the strategy that is most likely to be cost effective irrespective of the WTP value (Table 4).

4 Discussion

This article discusses four hypothetical scenarios for microscopy, RDT and LAMP. That is, (1) the tools are implemented at the referral clinic (NMLCP), assuming the conservative approach that one test is performed at a time with LAMP; (2) the tools are used at the NMLCP but assuming the full capacity of the LAMP is reached (e.g. 48 tests processed at once); (3) microscopy and LAMP are implemented as in scenario 1 but RDT is implemented at peripheral levels, which translates into lower associated treatment costs to the patients; and (4) the tools are implemented as in scenario 3, except that the CL suspects tested negative with RDT are sent to the reference clinic to be tested a second time with either microscopy or LAMP. In this last scenario, we assumed (as in scenario 3) that treatment is administered at the peripheral level. Such scenarios have been designed to capture the inherent benefits of the tools: the capacity of LAMP to process multiple samples at a time and the low level of expertise required for RDT, making its use possible in centers with no or low diagnostic capacities. However, its variable sensitivity may require a combined strategy with microscopy or LAMP, as illustrated in scenario 4.

In scenario 1, LAMP has a slightly higher effectiveness (i.e. lower associated DALYs) but the cost increase in using this tool compared with microscopy is around US$6 per person tested. This higher cost implies lower NMB and would point to the use of microscopy as demonstrated by the Monte

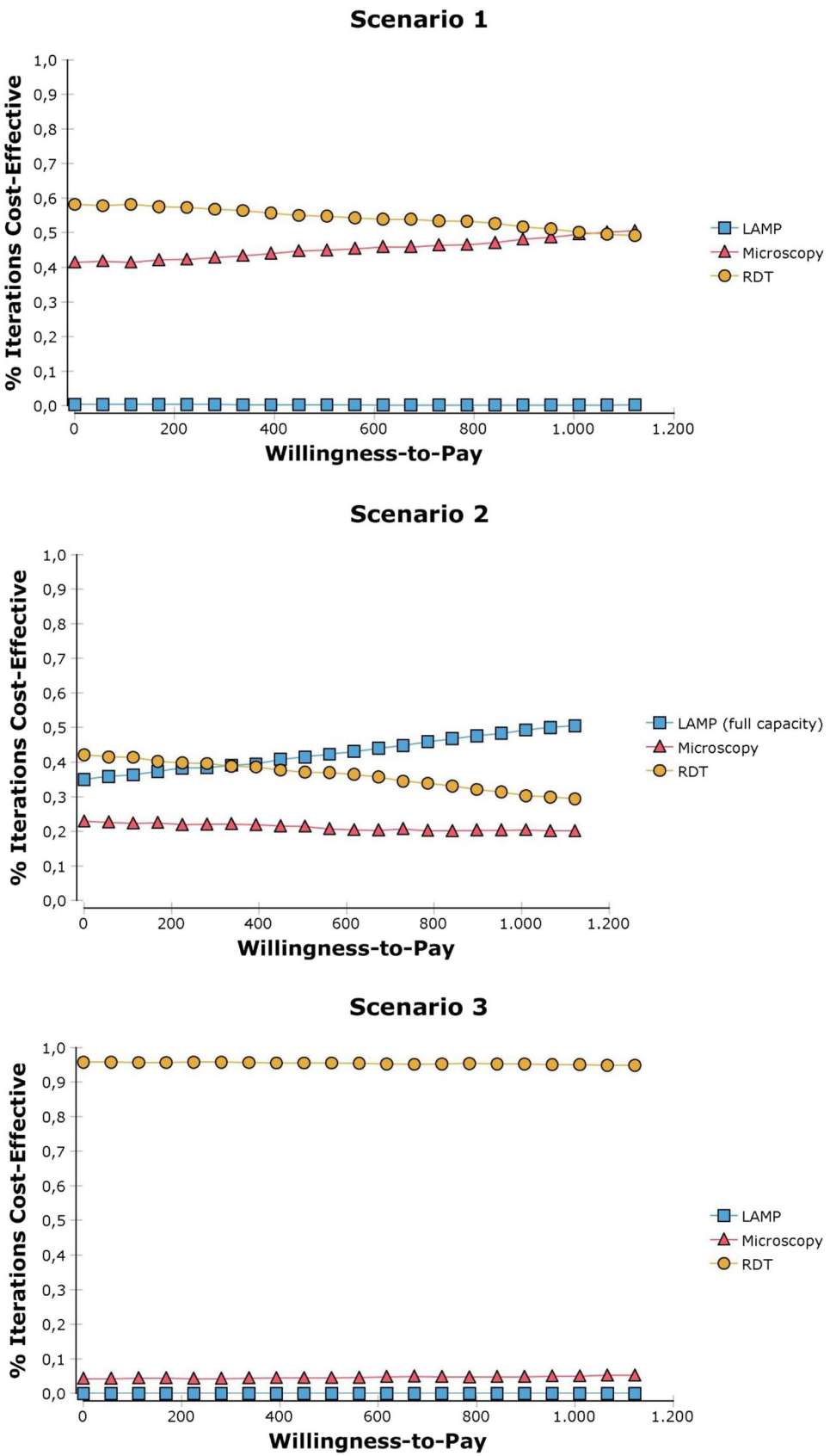
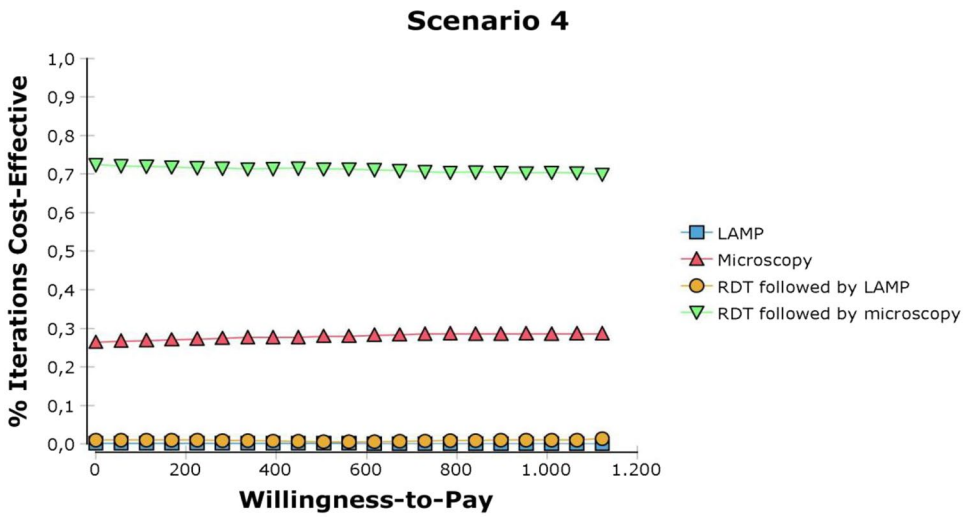


Fig. 6 Cost-effectiveness acceptability curves. The *y-axis* represents the probability of the tools being cost effective while the *x-axis* represents different willingness-to-pay values. *LAMP* Loopamp™ *Leishmania* Detection Kit, *RDT* CL Detect™ Rapid Test

Fig. 6 (continued)



Carlo simulations. RDT has a very similar cost and effectiveness to microscopy, with crossing CEACs. In scenario 2, when dividing the labour cost on LAMP by 48, its associated cost per person tested becomes slightly cheaper than that of RDT and microscopy. This scenario is plausible during the peak of the CL season or during an outbreak [34]. It also makes sense if LAMP is used simultaneously for other diseases than CL (e.g. malaria and/or tuberculosis). In such cases, LAMP potentially becomes a cost-effective solution but the uncertainty regarding the cost effectiveness of the latter vs. microscopy is significant, as demonstrated by the cost-effectiveness plane in Fig. 5.

In scenario 3, the associated treatment costs incurred by the patients, which exclusively include travel costs and wage losses associated with commuting and waiting times (as diagnosis and treatment is provided free of charge), were halved. The sensitivity analysis on this parameter shows that even if decreased by just 5%, RDT becomes cheaper than any other strategy. We believe this is very likely to happen if the tool is implemented outside the reference clinic. However, one potential factor to consider if implementing the RDT in remote facilities is awareness-raising costs. As highlighted by the Ministry of Health, although the population may be aware that diagnostic and treatment options are provided in remote facilities, there is a general tendency to go to the reference clinic (NMLCP) even if it implies hours or days of travelling. Another feature to consider is the proportion of false negatives among CL individuals tested with RDT (i.e. sensitivity of 66.75%).

This is considered in scenario 4, where RDT negative suspects (i.e. false positive and true negative) are tested at the reference clinic with LAMP or microscopy. RDT followed by LAMP is slightly more costly than RDT followed by microscopy and the difference in effectiveness between the two is negligible. This being said, it remains preferable to perform a primary screening of CL suspects remotely with RDT followed by microscopy or LAMP for the negative suspects, rather than testing all suspects directly with microscopy or LAMP (respectively) at the NMLCP. This is indeed illustrated by the CEACs in scenario 4: RDT followed by microscopy is on average 45–50% more likely to be cost effective than microscopy alone.

To conclude, the novel tools are promising and have their respective advantages. On the one hand, LAMP may be particularly relevant in a reference clinic during high endemic periods. Furthermore, in a context where laboratory expertise is lacking because of political instability and uncompetitive salaries, improving technology can significantly boost labour productivity. On the other hand, RDT may be particularly suitable in parts of the country where there is no/low diagnostic capacities. Such usage of RDT could be combined with additional testing at the reference clinic using other strategies with higher sensitivity. Nevertheless, even though this study attempts to capture the particularity of the tools with four different scenarios, one must keep in mind that estimates were collected from a single site, the NMLCP, which may not be representative of the whole country and which further implies that results may not be generalisable at the national level. Additionally, the results of this study are challenged by a very small incremental effectiveness across tools, questioning the use of DALYs when representing the burden associated with a disease such as CL. DALYs estimates based on the Global Burden of Diseases report may not capture the full burden, such as social stigmatisation and emotional burden that may be particularly important for women of young ages, and would suggest that, perhaps, the

Table 4 Model parameters

	Base-case value	PSA distribution	PSA parameters	Description	Source
Variable					
Age	Age + _startAge	NA	NA	Age of individuals. Individuals enter at age 6 year; each year they become 1 year older (until they reach 86 year)	Patient folder
Probabilities					
Incidence rate CL	0.00179	Beta	$\alpha = 24.95$; $\beta = 13915.52$	Incidence rate of CL in Afghanistan	[4]
Incidence rate CLR	0.05	Beta	$\alpha = 23.7$; $\beta = 450.3$	Probability of developing CLR (given that the patient had CL before)	[23]
Probability of being treated	0.97	Beta	$\alpha = 2.03$; $\beta = 0.06$	Probability of being treated if tested positive	Questionnaire III in the ESM
Probability of adherence to treatment	0.97	Beta	$\alpha = 2.03$; $\beta = 0.06$	Probability of being adherent	Questionnaire III in the ESM
Probability of being CL given symptoms	0.92	Beta	$\alpha = 1.15$; $\beta = 0.1$	Prevalence of people with suggestive signs of CL, being tested positive based on PCR and microscopy combined	Questionnaire III in the ESM
Probability of treatment efficacy	0.90	Beta	$\alpha = 2.30$; $\beta = 0.33$	Probability of curing within 1 y if treated (treatment efficacy[a] probability of being adherent[a] probability of being treated)	Questionnaire III in the ESM
Probability of self-healing	0.5	Beta	$\alpha = 12$; $\beta = 12$	Probability of self-healing	[35, 36]
Probability of curing from CLR	0.30	Beta	$\alpha = 17.2$; $\beta = 40.13$	Probability of being cured from CLR each year and if treated	NMLCP
Probability of intra-lesional treatment	0.80	Beta	$\alpha = 4.2$; $\beta = 1.05$	Probability of receiving intra-lesional treatment if treated	NMLCP
Probability of intramuscular treatment	0.20	Beta	$\alpha = 19.80$; $\beta = 79.2$	Probability of receiving intramuscular treatment if treated	NMLCP
Probability of death	Age dependent	NA	NA	Probability of dying for unrelated reasons to CL (across age groups and average by 50% between men and women)	[37]
Probability of skin lesion(s)	0.029	Beta	$\alpha = 3.3$; $\beta = 110.52$	Probability of having skin lesion(s) at the community level	[8]
Discount rate	0.03	Triangular	Minimum = 0; maximum = 0.05; likeliest = 0.03	Annual discount rate applied to cost and DALY parameters as recommended by WHO guidelines	[25]
Cost estimates (US$ 2016)[a]					
Cost of being diagnosed	1	Multi-normal	Cholesky table	The median (direct and indirect) cost incurred by patients to get diagnosed	Questionnaire I in the ESM
Cost of receiving intra-lesional treatment	4	Gamma	$\alpha = 25$; $\lambda = 6.25$	The median cost incurred by patients with intra-lesional treatments (one injection per day between 3 and 5 days)	Questionnaire III in the ESM

Table 4 (continued)

	Base-case value	PSA distribution	PSA parameters	Description	Source
Cost of receiving intramuscular treatment	18	Gamma	$\alpha=25; \lambda=1.39$	The median cost incurred by patients with intramuscular treatment (one injection per day during 14–21 days)	Questionnaire III in the ESM
Cost of receiving CLR treatment	18	Gamma	$\alpha=25; \lambda=1.39$	The median cost incurred by patients with CLR (usually these are treated intramuscularly)	Questionnaire III in the ESM
Labour cost of RDT	13.60	Gamma	$\alpha=25; \lambda=1.84$	The average labour cost when using RDT	Questionnaire II in the ESM
Labour cost of LAMP	20.94	Gamma	$\alpha=25; \lambda=1.19$	The average labour cost when using LAMP	Questionnaire II in the ESM
Cost of intra-lesional treatment	13.21	Gamma	$\alpha=0.48; \lambda=0.04$	The average cost of intra-lesional treatment (Pentostam®) until lesion(s) is (are) healed	[24]
Cost of intramuscular treatment	41.28	Gamma	$\alpha=0.48; \lambda=0.16$	The average cost of intramuscular treatment based on a person weighing 35 kg	[24]
Cost of CLR treatment	41.28	Gamma	$\alpha=0.48; \lambda=0.16$	The average cost of treating CLR (intramuscular treatment) based on a person weighing 35 kg	[24]
Market price of RDT	US$5	Gamma	$\alpha=0.69; \lambda=0.14$	The market price of RDT	InBios International Inc. (personal communication, estimated)
Market price of LAMP	US$7	Gamma	$\alpha=25; \lambda=4.5$	The market price of LAMP. Because the price of LAMP for leishmaniasis has not been negotiated yet, we based it on the average between the price of LAMP for malaria and tuberculosis	[39]
Market price of microscopy	2	Gamma	$\alpha=25; \lambda=12.49$	Market price of microscopy	NLMCP
Labour cost of microscopy	13.60	Gamma	$\alpha=25; \lambda=1.84$	The average labour cost when using microscopy	NLMCP
Cost of LAMP incubator/thermocycler	6.33	Gamma	$\alpha=25; \lambda=3.95$	Cost of the LAMP incubator/thermocycler	HPRO
Cost of microscope	1.19	Gamma	$\alpha=25; \lambda=21$	Cost of the microscope	NLMCP
DNA extraction cost	3	Gamma	$\alpha=25; \lambda=8.33$	Cost of DNA extraction required with LAMP	Foundation for Innovative Diagnostics (FIND)
DALY estimates					
DALY CL/CLR	0.0446	Gamma	$\alpha=25; \lambda=560.53$	DALYs associated with one episode of CL/CLR	[40] Questionnaire IV in the ESM
Sensitivity and specificity (%)					
True-positive microscopy	78.97	Beta	$\alpha=0.67; \beta=0.3$	True-positive rate of microscopy	[9]
True-negative microscopy	77.27	Beta	$\alpha=0.08; \beta=0.02$	True-negative rate of microscopy	[29]
True-positive RDT	66.27	Beta	$\alpha=3.62; \beta=1.84$	True-positive rate of RDT	[29]
True-negative RDT	95.45	Beta	$\alpha=0.082; \beta=0.004$	True-negative rate of RDT	[29]

Table 4 (continued)

	Base-case value	PSA distribution	PSA parameters	Description	Source
True-positive LAMP	89.68	Beta	$\alpha = 0.03; \beta = 0.01$	True-positive rate of LAMP	[29]
True-negative LAMP	63.64	Beta	$\alpha = 0.28; \beta = 0.16$	True-negative rate of LAMP	[29]

AMC Academic Medical Center, *CL* cutaneous leishmaniasis, *CLR* cutaneous leishmaniasis recidivans, *DALYs* disability-adjusted life-years, *ESM* Electronic Supplementary Material, *HPRO* Health Protection and Research Organization, *LAMP* Loopamp™ *Leishmania* Detection Kit, *NA*, *NLMCP* National Malaria and Leishmaniasis Control Program, *PCR* polymerase chain reaction, *PSA*, *RDT* CL Detect™ Rapid Test, *WHO* World Health Organization

[a]For cost figures to be converted in 2016 international dollars, figures should be converted back to Afghan Afghani currency and then divided by the Purchasing Power Parity conversion factor for the year 2016 (19.613)

burden of CL should be measured in a more qualitative way, as attempted with the DLQI questionnaire.

Compliance with Ethical Standards

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Conflict of Interest Céline Aerts, Martijn Vink, Sayed Jalal Pashtoon, Sami Nahzat, Albert Picado, Israel Cruz and Elisa Sicuri have no conflicts of interest that are directly relevant to the contents of this article.

Ethics Approval The study was carried out in accordance with the Helsinki Declaration, and approved by the Institutional Review Board of the National Public Health Institute, Ministry of Public Health, Islamic Republic of Afghanistan (Approval No. 361549).

Consent to Participate The participants provided written informed consent in a one-on-one session with a member of the study. For illiterate individuals, the informed consent process was conducted in the presence of an impartial witness and for minors, the consent from a parent or guardian had to be obtained to be enrolled in the study.

Data Availability The datasets generated during and/or analysed during the current study are available in the figshare repository at https://doi.org/10.6084/m9.figshare.6949043.

Author Contributions IC, SP and SN provided the study concept and design, acquisition of data, analysis and interpretation, and study supervision. CA and ES contributed to the model design, data analysis and interpretation. CA, ES, IC, AP and MV contributed to the revision of the manuscript.

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Appendix

Diagnostic tools for cutaneous leishmaniasis: further description

Two new point-of-care tests have been developed for cutaneous leishmaniasis: the Loopamp™ *Leishmania* Detection Kit (LAMP) and CL Detect ™ Rapid Test (RDT). LAMP is a simpler molecular method than the Polymerase chain reaction (PCR). It amplifies DNA from human blood and tissue sample with high efficiency, specificity and rapidity under isothermal conditions (Notomi *et al.*, 2000). Simple visual detection is possible with the LAMP since it produces a remarkable amount of amplified products. The CL Detect™ Rapid Test (RDT) (InBios International Inc., USA) is a qualitative, in vitro immunochromatographic assay for the rapid detection of Leishmania species antigen in ulcerative skin lesions. A sample from the skin lesion is collected with a dental broach and placed in a lysis buffer. The lysed sample is applied to the test strip and reacts with the dye conjugate. Once a reaction is obtained, a red line indicates a positive result whereas its absence indicates a negative result.

Sample collection

Samples from participants were first analyzed by microscopy and RDT at the NMLCP clinic whereas LAMP was performed in the facilities of the Health Protection and Research Organization (HPRO) which provides laboratory support to the NMLCP. PCR was conducted at the Academic Medical Center (AMC) in Amsterdam, Netherlands (Vink *et al.*, 2018).

$$Y_{Positive,i} = \propto_i + \boldsymbol{\beta}_{\mathbf{female,i}} + \boldsymbol{\gamma}_{age,i} + \boldsymbol{\mu}_i$$

Table A1: determinants of CL positive cases

Be positive of CL	Odds Ratio (st. error)
Female	1,58 (1.212)
age	0,996 (0,013)
constant	12,05 (5,23)

$$Y_{cost,i} = \propto_i + \beta_{female,i} + \gamma_{age,i} + \delta_{occupation,i} + \mu_i$$

Table A2: Determinants of costs from the patient's perspective

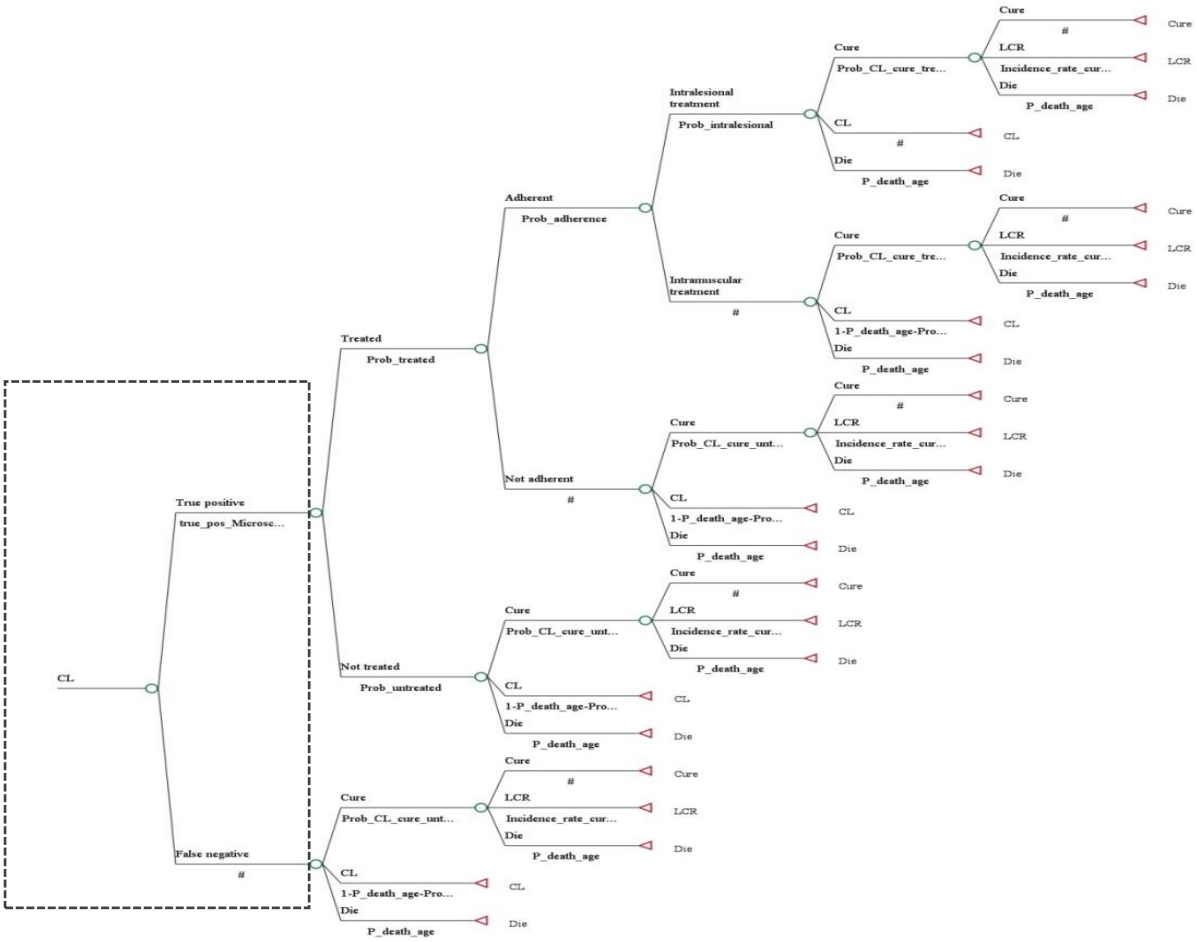
Log cost of being tested (N=85)	**Coeff. (St. Error)**
age	-0,004
	(0,007)
female	-0,037
	(0,302)
Occupation	
2 (unsecured occupation)	0,999***
	(0,262)
3 (secured occupation)	0,527*
	(.295)
4(unknown occupation)	0,906**
	(0,406)
Constant (ref. group)	0,397
	(0,353)

***p< 0,1; **p<0,05; ***p<0,001**

With regards to occupation, the reference group consists of people without any earnings, that is, "jobless" and "students". Unsecured occupations include "housekeepers" and "farmers" for which we suppose there is no associated social security. Secured occupations include people working in a shop or running a

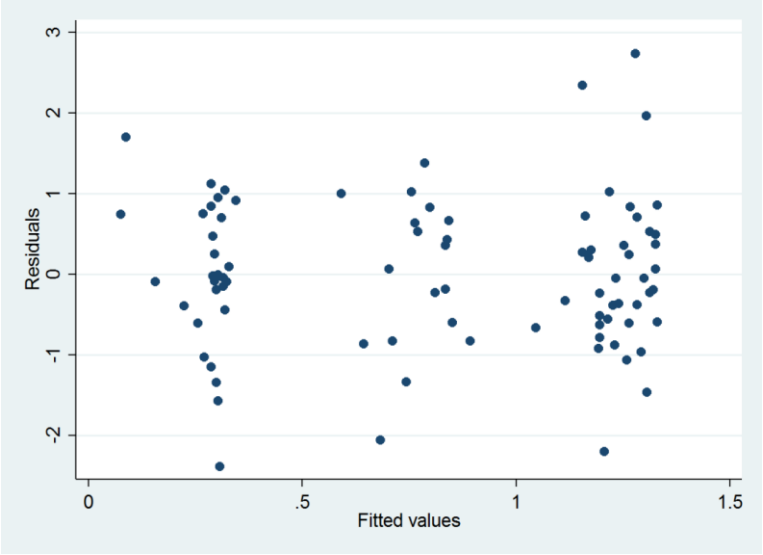
small business: e.g. “tailoring”, “shoe makers”, “taxi driver”, etc. The last category consists of individuals for whom the occupation is unknown.

Figure A1: The natural history of cutaneous leishmaniasis infection



Legend: Each year, the individual is at risk of developing skin lesion(s). If the individual develops skin lesion(s), the probability that it is due to CL is equal to the percentage of confirmed CL cases observed at the clinic. We assume that 50% of the population with skin lesions comparable to CL will go to the health facility to seek a diagnostic. If the patient is diagnosed positive of CL, he/she can either be a true positive or a false positive case. In both cases, most of the patients will be treated which is unnecessary in the case of a false positive. If the patient is diagnosed negative of CL, it can either be a true negative or a false negative case. If the patient is a true negative case, each year, he remains at risk of infection. On the other hand, if the patient is a false negative case and does not self-heal within one year, we assumed he/she would seek for a diagnosis again in the next year thereby imposing a “cost punishment” to tools with low sensitivity.

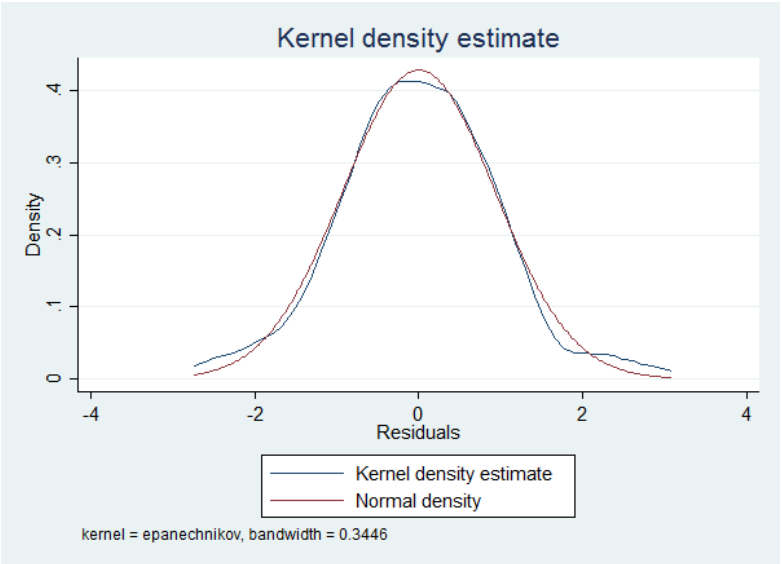
Figure A2: Heteroskedasticity and normality test




```
Breusch-Pagan / Cook-Weisberg test for heteroskedasticity
         Ho: Constant variance
         Variables: fitted values of logcDiagnostic

         chi2(1)      =     0.03
         Prob > chi2  =   0.8709
```

The p-value is above 0,05 so we cannot reject the H0 of a constant variance. In other words, there is no issue of heteroskedasticity.



The kernel density estimate is very close to the normal density which indicates that the variable follows a normal distribution.

Figure A3: Sensitivity analysis on the cost of receiving treatment for RDT

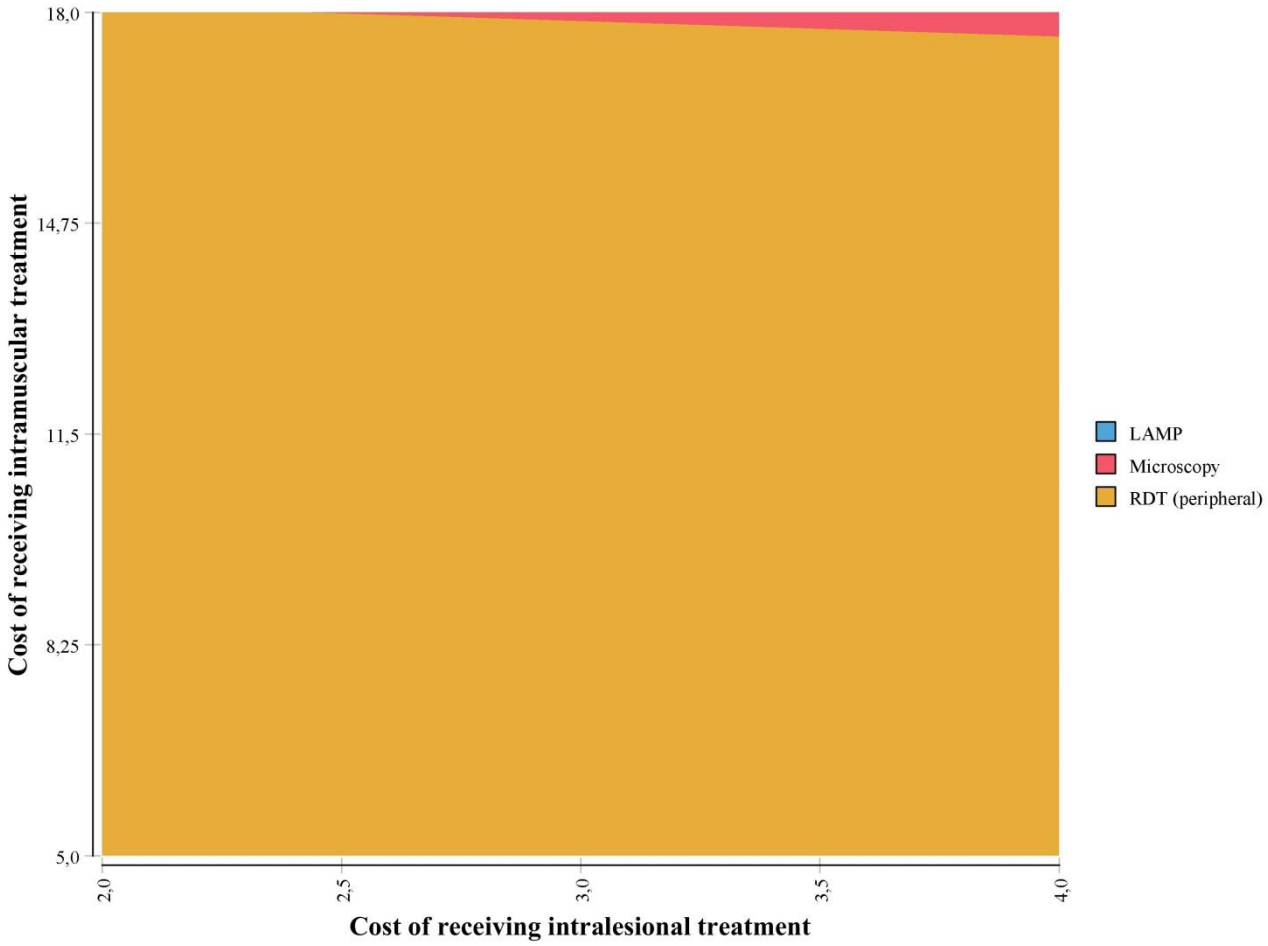
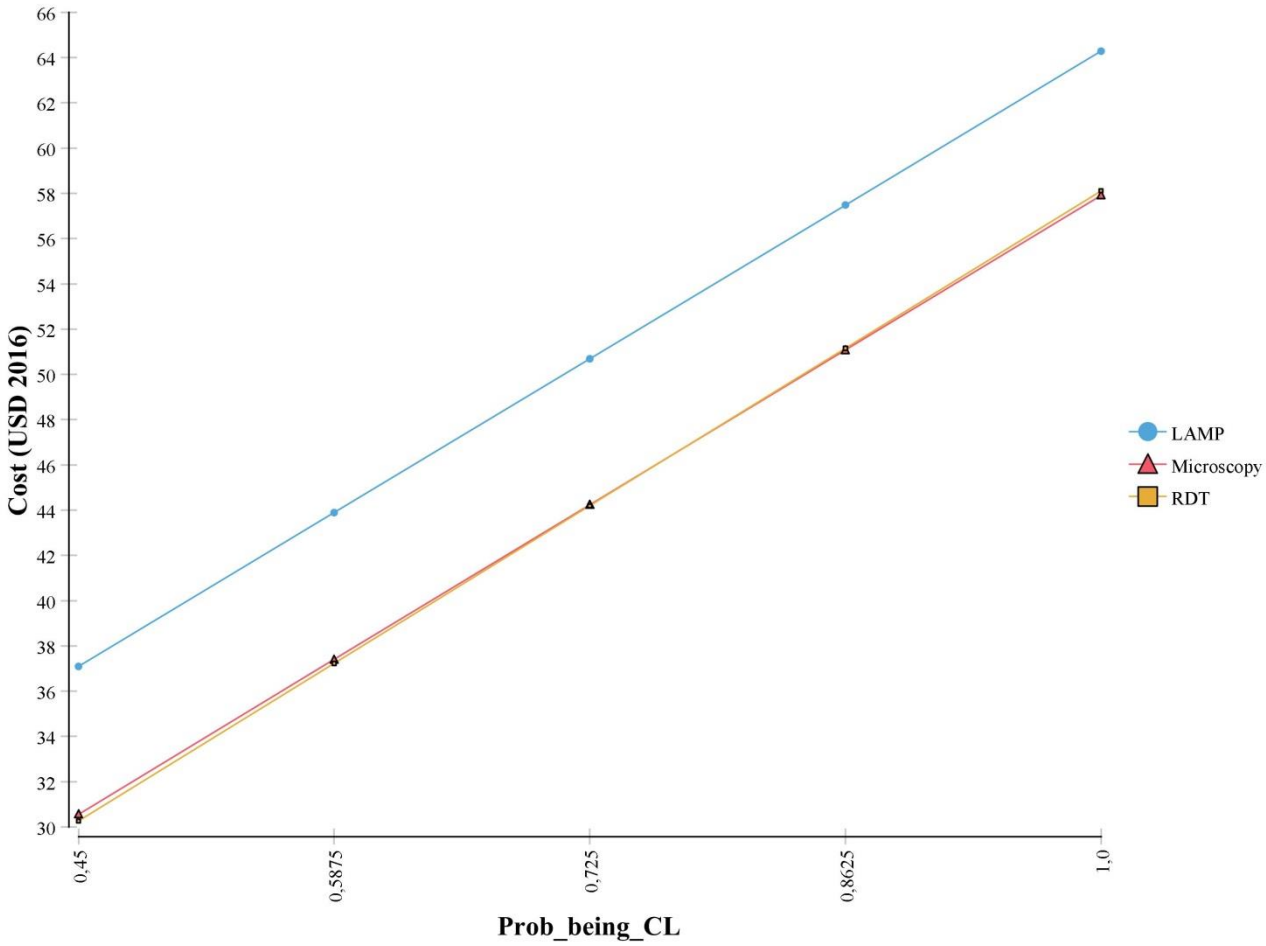
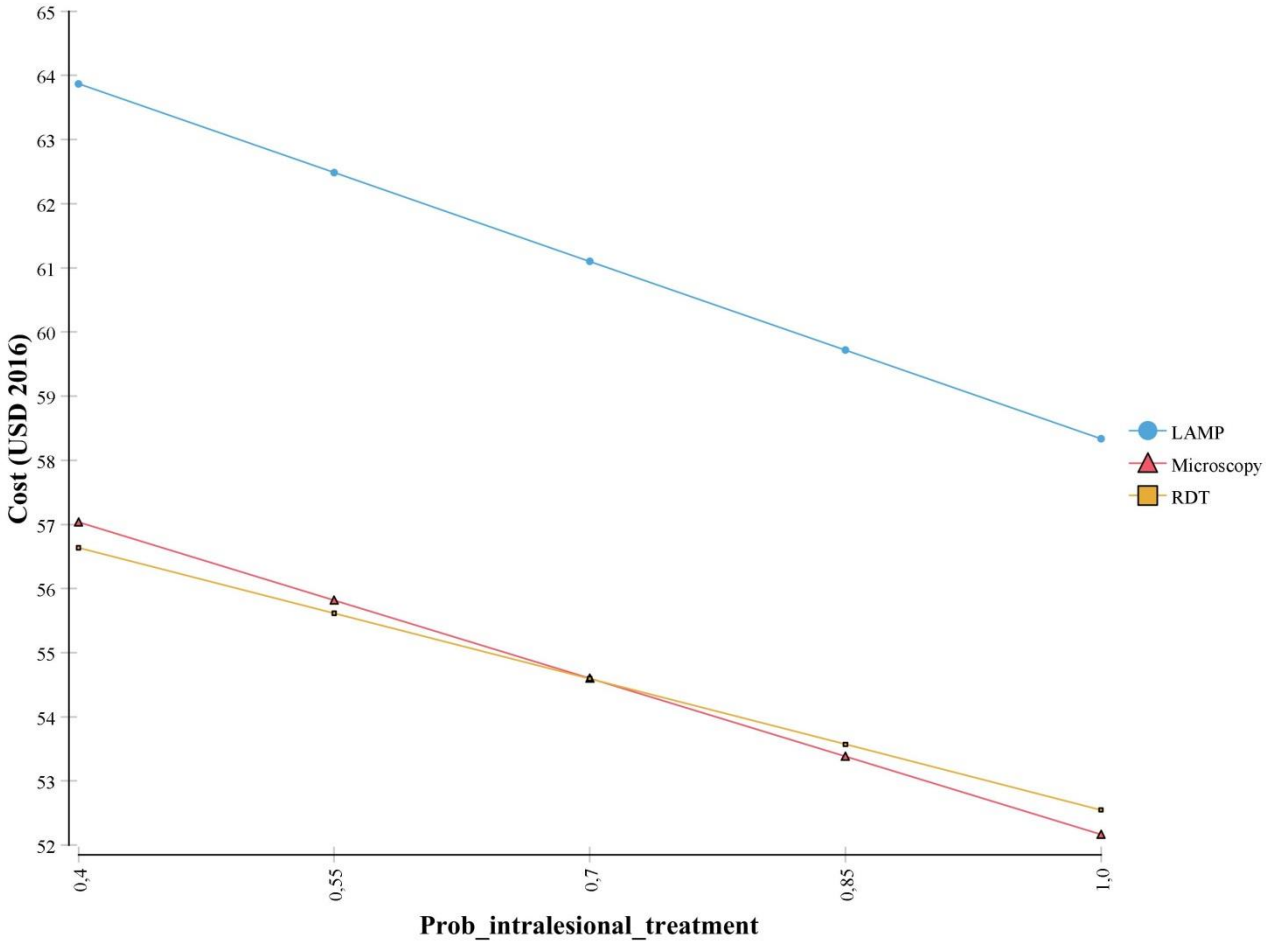


Figure A4: Threshold analysis – Probability of being CL given skin lesions



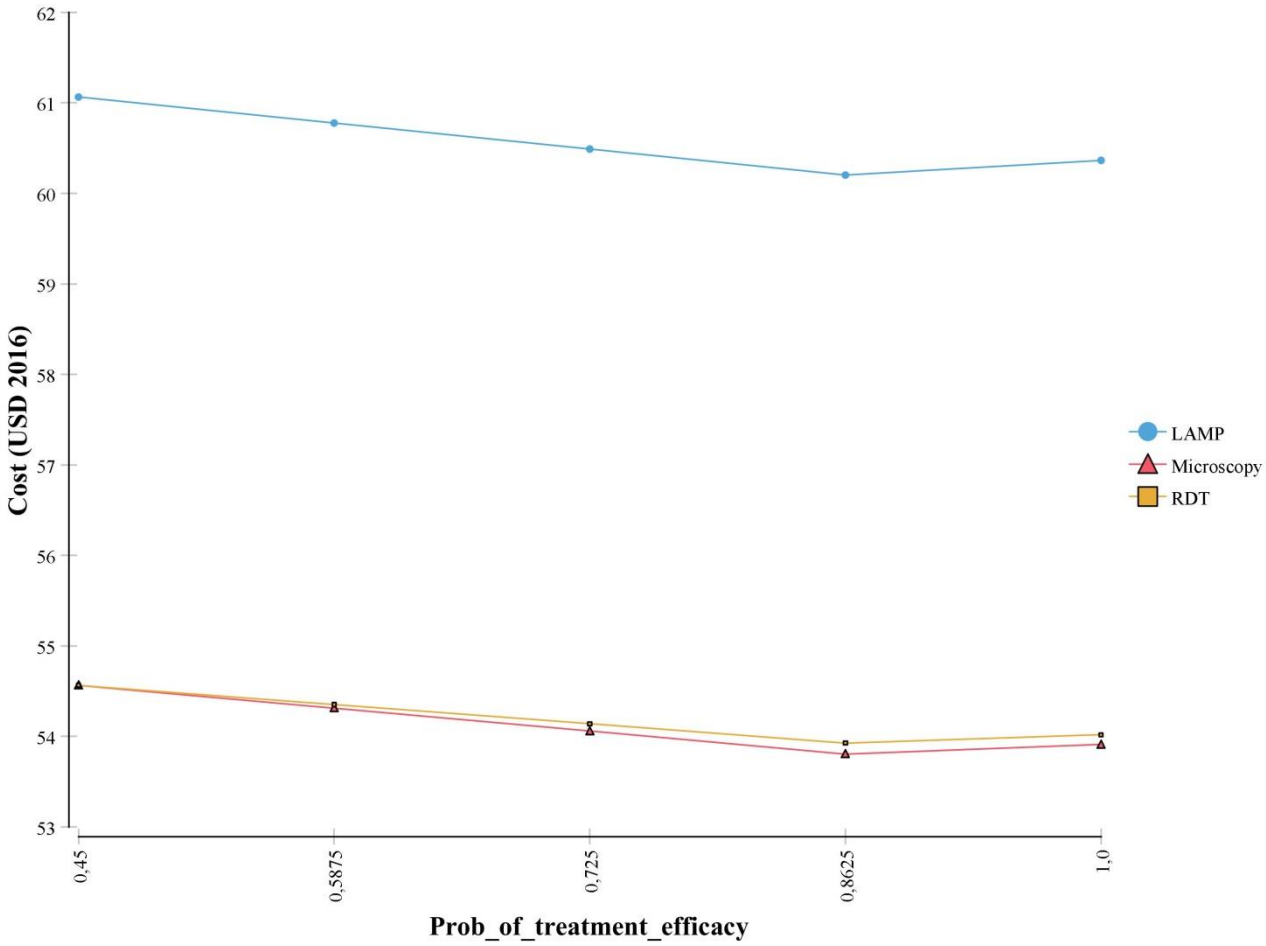
Legend: As the percentage of people with CL increases, it implies more people being diagnosed and treated with increase the associated costs of the tools. The current probability of being CL given skin lesions is equal to the ratio of confirmed cases (91,7 %). Although there is a threshold percentage in the probability of CL below which RDT becomes cheaper, the difference in cost between the two is minor.

Figure A5: Threshold analysis –Probability of administering intralesional treatment



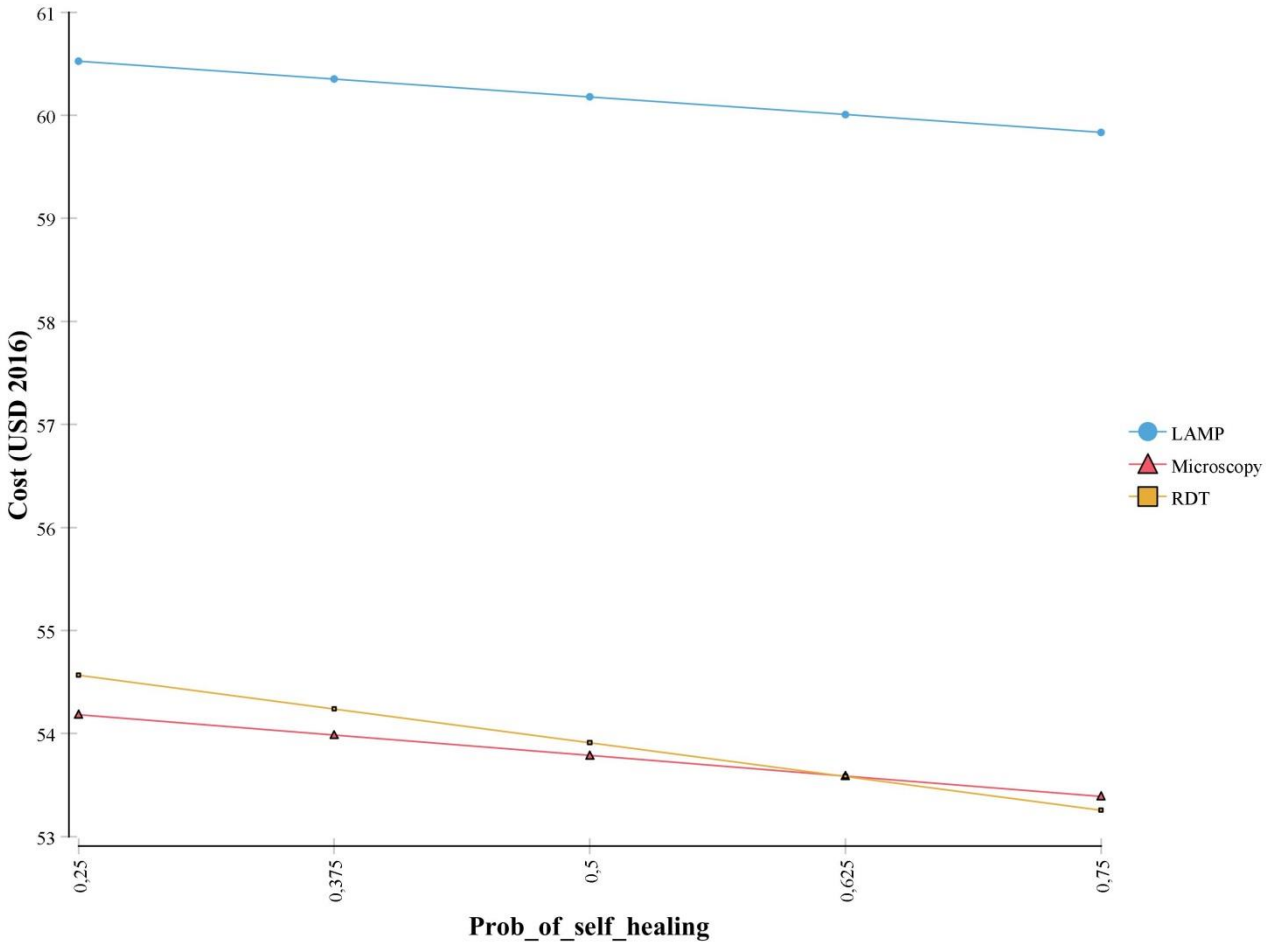
Legend: The probability of administering intralesional versus intramuscular treatment depends on the severity of the disease. If multiple lesions for instance, intramuscular treatment will be administered which has a higher cost. Accordingly, increasing the probability of intralesional treatment decreases the costs of the tools. As the sensitivity of microscopy is higher than of RDT, more people will be detected sick and hence treated and therefore the cost decrease will be proportionally higher for microscopy.

Figure A6: Threshold analysis – Probability of treatment efficacy



Legend: The probability of treatment efficacy is set at 87% in the model. If below 45 %, RDT becomes cheaper than microscopy. Lower treatment efficacy suggests that more people will stay with CL for another year, which implies additional costs.

Figure A7: Threshold analysis – Probability of self-healing



Legend: The probability of self-healing is put at 50% in the model. If increasing, it implies that fewer sick people will be put under treatment, lowering the cost of the tools.

Questionnaire I: patient cost questionnaire

CLeishPOCECO study: costs incurred by patients with CL in AFGHANISTAN, Kabul (NMLCP)
This questionnaire is addressed to patients or to carers of patients (for patients < 18 years of age) receiving a diagnosis of CL (primary diagnosis) at one of the health facilities included in the study. **Inclusion criteria for administering the questionnaire:** - Having been diagnosed positive for CL - Individuals more than two years old - Individuals are consenting to participate - Patients must not be receiving treatment at the time of enrolment ***/!\ Questions 1 to 13 should be filled in <u>on the day of receiving the diagnostic result</u>*** ***/!\ Questions 14 to 21 should be filled in <u>at the end of treatment</u>***
PATIENT ID:

1. Date in which the result of the test is received (dd / mm / yyyy, Gregorian)

   |__|__|-|__|__|-|__|__|__|__|

2. At which health facility is the interview taking place?

   |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

DEMOGRAPHIC DATA

3. Education Level |__|

   1= No education; 2= Completed primary education; 3= Completed secondary school; 4= Completed college/university; 5= other (specify)

   |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

4. Education Level of the Head of Household |__|

   1= No education; 2= Completed primary education; 3= Completed secondary school; 4= Completed college/university; 5= other (specify)

   |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

   Who is the Head of Household in relation to you?

   Specify: ________________________________

5. What is the average family income per month?

Local currency |__|__|__|__|__|__|__|__|__|__|__|__|__|

6. Are you (the patient) covered by health insurance? |__|

(**1=**Yes **2**=No **3**=Don't Know)

If **Yes**, would your health insurance cover all your expenses related to this CL episode? |__|

(**1=**Yes **2**=No **3**=Don't Know)

If **No**, how much will be covered? |__|

(**1**=<25%, **2**=25-50%, **3**=50-75%, **4**=>75%)

TRAVEL COSTS ON THE DAY OF GETTING TESTED

7. How did you travel to this health facility from home and how much did it cost?

(i) By walking |__|

(ii) By bus |__| Local currency
|__|__|__|__|__|

(iii) Bicycle |__| Local currency
|__|__|__|__|__|

(iv) Your own Car |__| Local currency
|__|__|__|__|__|

(v) Taxi |__| Local currency
|__|__|__|__|__|

(vi) Other, specify: _____Local currency
|__|__|__|__|__|

8. How long did it take you to get here from your home?
Days |__|__| Hours |__|__| Minutes |__|__|

TIME AND TRAVEL COST RELATED TO GETTING THE RESULT OF THE TEST

9. How much time did you have to wait at the health facility to get the result of the test

Days |__|__| hours |__|__| minutes |__|__|

10. Where did you stay during that time? |__|

(**1**= health facility; **2**=home; **3**=relative; **4**=hotel; **5**=other)

If other, specify: _____

11. How did you travel from the place selected in question 10 to the health facility and how much did it cost?

(i) By walking |__|

(ii) By bus |__| Local currency
|__|__|__|__|__|

(iii) Bicycle |__| Local currency
|__|__|__|__|__|

(iv) Your own Car |__| Local currency
|__|__|__|__|__|

(v) Taxi |__| Local currency
|__|__|__|__|__|

(vi) Other, specify: _____Local currency
|__|__|__|__|__|

INDIRECT COSTS

12. Did you have to stop any of your occupations due to your illness?

|__| Farmer months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Stockbreeder months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Housekeeper months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Student months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Seasonal worker months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Health worker months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Tourist months|__|__|weeks|__|__| days |__|__| hours |__|__|

|__| Other, specify: _____ months|__|__|weeks|__|__| days |__|__| hours |__|__|

13. Did anyone have to do your activities while you were sick?
|__|
(1=yes, 2=no, 3=don't know)

If **yes**,

Did you have to pay that person?

|__| (1=yes, 2=no, 3=don't know)

If **yes**,

What was that person salary per day Local currency |__|__|__|__|__|

How long did you employ the person for? Weeks |__|__| days |__|__| hours |__|__|

/!\ Questions 14 to 21 should be filled in <u>at the end of treatment</u>

COST IN THE HEALTH FACILITY AT THE END OF TREATMENT

14. Date of interview at the end of treatment (dd/ mm/ yyyy, Gregorian)
|__|__|-|__|__|-|__|__|__|__|

15. How did you travel today to this health facility and how much did it cost?

(i) By walking |__|

(ii) By bus |__| Local currency
|__|__|__|__|__|

(iii) Bicycle |__| Local currency
|__|__|__|__|__|

(iv) Your own Car |__| Local currency
|__|__|__|__|__|

(v) Taxi |__| Local currency
|__|__|__|__|__|

(vi) Other, specify: _____Local currency
|__|__|__|__|__|

16. How long did it take you to get here today?

Days |__|__| Hours |__|__| Minutes |__|__|

17. How much time have you spent in total today at this health facility?

Days|__|__|Hours |__|__| Minutes|__|__|

18. How much have you spent at the health facility over the treatment period?

- Drugs: |__| Local currency
  |__|__|__|__|__|
- Laboratory tests: |__| Local currency
  |__|__|__|__|__|
- Consultation/outpatient fees: |__| Local currency
  |__|__|__|__|__|
- Other, specify: _____ Local currency
  |__|__|__|__|__|

INDIRECT COSTS AT THE END OF TREATMENT

19. Since you are ill, did you have to stop any of your occupations due to your illness?

|__| Farmer months|__|__|weeks|__|__| days |__|__|

|__| Stockbreeder months|__|__|weeks|__|__| days |__|__|

|__| Housekeeper months|__|__|weeks|__|__| days |__|__|

|__| Student months|__|__|weeks|__|__| days |__|__|

|__| Seasonal worker months|__|__|weeks|__|__| days |__|__|

|__| Health worker months|__|__|weeks|__|__| days |__|__|

|__| Tourist months|__|__|weeks|__|__| days |__|__|

|__| Other, specify: _____ months|__|__|weeks|__|__| days |__|__|

20. Did someone have to do your activities while you were sick?

|__|

(1=yes, 2=no, 3=don't know)

If **yes**,

Did you have to pay that person?

|__|

(1=yes, 2=no, 3=don't know)

If **yes**, what was that person salary per day? Local currency

|__|__|__|__|__|

How long did you employ that person for? Weeks |__|__| days

|__|__| hours|__|__|

21. Did have secondary effects due to treatment?

|__|

(1=yes, 2=no)

If **yes**, specify:

_____

Questionnaire II: Laboratory and medical staff questionnaire

Questionnaire: diagnostic tools for cutaneous leishmaniasis
Health facility **NMLCP, Kabul Afghanistan**
This questionnaire is addressed to the medical doctor/PI running diagnoses for cutaneous leishmaniasis at one of the health facilities included in the study.
Date Day |__|__| Month |__|__|

22. Diagnostic tool: |__|

(1=smear; 2=LAMP-UV; 3=LAMP-RT; 4=CL Detect RDT)

Questions 3 to 5 are related to the diagnostic tool selected

23. The average time required to run the diagnostic test:

Hours |__|__| Minutes |__|__|

The minimum time required to run the diagnostic test

Hours |__|__| Minutes |__|__|

The maximum time require to run the diagnostic test

Hours |__|__| Minutes |__|__|

24. How many people are involved in the diagnostic test? |__|

What is their respective occupation; monthly salary* and; average time spent on the test?

**gross salary based on a 40 hours working week*

- (1= medical nurse; 2= medical doctor; 3= lab staff; 4=other, specify below) |__|

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- Salary Local currency |__|__|__|__|__|
- Average time spent on the test Hours |__|__| Minutes |__|__|

- (1= medical nurse; 2= medical doctor; 3= lab staff; 4=other, specify below) |__|

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- Salary Local currency |__|__|__|__|__|

- Average time spent on the test Hours |__|__| Minutes |__|__|

- (1= medical nurse; 2= medical doctor; 3= lab staff; 4=other, specify below) |__|

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- Salary Local currency |__|__|__|__|__|
- Average time spent on the test Hours |__|__| Minutes |__|__|

- (1= medical nurse; 2= medical doctor; 3= lab staff; 4=other, specify below) |__|

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- Salary Local currency |__|__|__|__|__|
- Average time spent on the test Hours |__|__| Minutes |__|__|

- (1= medical nurse; 2= medical doctor; 3= lab staff; 4=other, specify below) |__|

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- Salary Local currency |__|__|__|__|__|
- Average time spent on the test Hours |__|__| Minutes |__|__|

- (1= medical nurse; 2= medical doctor; 3= lab staff; 4=other, specify below) |__|

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- Salary Local currency |__|__|__|__|__|
- Average time spent on the test Hours |__|__| Minutes |__|__|

25. What kind of material is used for this specific diagnostic test? Please specify the name and the quantity:

Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__| quantity |__|__|__|__|

Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__| quantity |__|__|__|__|

Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__| quantity |__|__|__|__|

Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__| quantity |__|__|__|__|

Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__| quantity |__|__|__|__|

26. What is the yearly average associated costs with the diagnostic method method? (e.g. recurring cost such as maintenance of microscope, quality control of the lab, etc.)

Local currency |__|__|__|__|__|__|__|__|__|__|__|

27. How many suspected cases of CL does the health facility detect per year (approximately)?

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

28. How many microscopy tests does the health facility run per year (approximately) for CL and other diseases?

|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Questionnaire III: The drug and treatment questionnaire

Health facility **NMLCP, Kabul Afghanistan**
This questionnaire is addressed to the medical doctor/PI running diagnoses for cutaneous leishmaniasis.
This questionnaire is part of the costs study related to each of the participating clinics. And together to the *laboratory and medical staff questionnaire* it will provide information on the costs related to diagnosis and treatment of cutaneous leishmaniasis (CL).
Only one questionnaire per participating clinic is needed.
Date Day |__|__| Month |__|__|

1. Are the drugs for CL treatment always available at the clinic? Yes |_| No |_|

If NO, please explain why?:

2. Who does provide the drug for CL treatment to the clinic?

|_| Government |_| WHO |_| NGO (indicate which NGO):

|_| Other (indicate):

3. Which drugs are used at the clinic to treat CL?

4. Do the patients have to pay for the drugs? Yes |_| No |_|

If YES, what is the average cost (in local currency) for:

- Intralesional treatment per dose_____ and complete treatment _____
- Systemic treatment per dose_____ and complete treatment _____

5. If drugs are not available at the clinic, does the patient buys them at the private sector or black market? Yes |_| No |_|

If YES, do you know the approximate cost of the drug in the private sector or black market?, please indicate:

6. Are there additional costs for the patient with regard to treatment administration?

Yes |_| No |_|

If YES, please indicate the nature of the additional costs and its value per dose and/or per complete treatment:

7. Who administers treatment at the clinic?: |_|

(1= medical doctor; 2= nurse; 3=other, specify) Other:

What is her/his monthly salary* and average time spent on treatment application?

*(in local currency; gross salary based on a 40 hours working week)

- Salary Local currency |__|__|__|__|__|
- Average time spent on the treatment application in: Hours|__|__| Minutes|__|__|

8. On which basis is the decision to apply intralesional or systemic treatment taken?

9. What is the usual treatment regime at the clinic (describe for intralesional and/or systemic treatment)?

- Localized cutaneous Leishmaniasis (CL):
- Mucosal or mucocutaneous leishmaniasis (MCL):
- Diffuse cutaneous leishmaniasis (DCL):
- Cutaneous leishmaniasis recidivans (CLR):
- Other forms (describe form):

10. What is the average treatment duration at the clinic, for intralesional and systemic treatment according to the different clinical forms (please, describe)?

11. What are the usual secondary effects observed at the clinic? Please describe below according to treatment regime (drug and intralesional or systemic treatment), and clinical form (LCL, ML, DCL, CLR).

12. At the clinic, what is the approximate treatment efficacy rate (%)?

13. At the clinic, what is the approximate % of CL patients that do not receive treatment because its administration is not judged necessary? |___%|

14. What is the (approximate) percentage of patients that complete treatment? |___%|

In case you know, what are the main reasons for treatment withdrawal?

15. At the clinic, what is the proportion (%) of each of the CL clinical forms?

LCL |___|, MCL |___|, DCL |___|, CLR|___|, Other (describe) |___|:

16. In your country, what is the prevalence of CL? And could you please provide data by age (<5 yrs, 5-15 yrs, 16-30 yrs, 31-50yrs; >50yrs) and sex?

17. In your country, what are the estimated number of patients evolving from LCL to any of the complicated forms of CL (MCL, DCL, CLR)?

Questionnaire IV: The Dermatology Life Quality Index questionnaire

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes □ No □ Not relevant □
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot □ A little □ Not at all □
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
9.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much □ A lot □ A little □ Not at all □ Not relevant □

Please check you have answered EVERY question. Thank you.

ARTICLE 4

Understanding the role of disease knowledge and risk perception in shaping preventive behavior for selected vector-borne diseases in Guyana

Céline Aerts, Mélanie Revilla, Laetitia Duval, Krijn Paaijman, Javin Chandrabose, Horace Cox, Elisa Sicuri

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PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Understanding the role of disease knowledge and risk perception in shaping preventive behavior for selected vector-borne diseases in Guyana

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Abstract

Background

Individual behavior, particularly choices about prevention, plays a key role in infection transmission of vector-borne diseases (VBDs). Since the actual risk of infection is often uncertain, individual behavior is influenced by the perceived risk. A low risk perception is likely to diminish the use of preventive measures (behavior). If risk perception is a good indicator of the actual risk, then it has important implications in a context of disease elimination. However, more research is needed to improve our understanding of the role of human behavior in disease transmission. The objective of this study is to explore whether preventive behavior is responsive to risk perception, taking into account the links with disease knowledge and controlling for individuals' socioeconomic and demographic characteristics. More specifically, the study focuses on malaria, dengue fever, Zika and cutaneous leishmaniasis (CL), using primary data collected in Guyana–a key country for the control and/or elimination of VBDs, given its geographic location.

Methods and findings

The data were collected between August and December 2017 in four regions of the country. Questions on disease knowledge, risk perception and self-reported use of preventive measures were asked to each participant for the four diseases. A structural equation model was estimated. It focused on data collected from private households only in order to control for individuals' socioeconomic and demographic characteristics, which led to a sample size of 497 participants. The findings showed evidence of a bidirectional association between risk perception and behavior. A one-unit increase in risk perception translated into a 0.53 unit

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increase in self-reported preventive behavior for all diseases, while a one-unit increase in self-reported preventive behavior (i.e. the use of an additional measure) led to a 0.46 unit decrease in risk perception for all diseases (except CL). This study also showed that higher education significantly improves knowledge and that better knowledge increases the take up of preventive measures for malaria and dengue, without affecting risk perception.

Conclusions

In trying to reach elimination, it appears crucial to promote awareness of the risks and facilitate access to preventive measures, so that lower risk perception does not translate into lower preventive behavior.

Author summary

In the context of Guyana, people's self-reported behavior (i.e. use of vector control tools) is based on their risk perception and on their knowledge of the disease if the risk perception is high enough (i.e. for malaria and dengue fever). Measures donated by the government, such as bed nets, are widely reported to be used and their use is less likely to be contingent on the perceived risk. In other words, because those measures are donated, they are more likely to be used regardless of the risk perception. The type of region in which individuals live also plays a key role on the adoption of vector control measures: although people living in the hinterland tend to have greater knowledge about the disease and an accurate risk perception, they use fewer preventive measures than people living in the coastal regions–thus pointing to the importance of promoting access to preventive measures in the hinterland. Therefore, in trying to reach the elimination of vector-borne diseases, it is essential for the government to promote awareness of the risks and facilitate (i.e. donate) access to preventive measure to avoid a reduced usage of vector control measures arising from a lower risk perception.

Introduction

According to the World Health Organization (WHO), vector-borne diseases (VBDs) represent 17% of all infectious diseases and cause more than 700,000 deaths annually, with 80% of the world's population at risk [1,2]. VBDs are caused by pathogens transmitted through vectors, most of them being bloodsucking insects such as mosquitoes or sandflies. Since 2014, major outbreaks of VBDs such as malaria, dengue fever, Zika and chikungunya have spread to previously unaffected areas of Latin America, overwhelming the health system of many countries [1,3–6]. Individual behavior–particularly choices about prevention–plays a role in infection transmission, and is thus a topic of interest in both the public health and social science (e.g. economic) disciplines. Yet, more research is needed to improve our understanding of the role of human behavior in disease transmission so that policy-making translates into decreased morbidity and saved lives [7–9].

In the public health discipline, behavioral practice is often studied together with knowledge and risk perception through 'knowledge, attitude, and practice' (KAP) surveys. Although KAP studies are informative, they are generally descriptive and do not dig in the complex links between knowledge, risk perception and behavioral practices. No KAP studies have been

previously carried out in Guyana on VBDs but several have been carried out in other contexts. Keeping in mind that these contexts are different from Guyana, the results of such studies–among others (i.e. mixed method and qualitative studies)–are inconclusive regarding the association between knowledge and behavior: some find a positive association [10–15], whereas other find a negative [16] or no association [17–22]. This diversity in the findings suggests that the results are context specific and cannot be generalized across different areas/regions and diseases. The most similar context in which a KAP study has been conducted was in French Guyana, and it shows that an increased understanding of transmission led to better dengue prevention practices [11]. Moreover, while KAP studies do not shed light on the association between risk perception and behavior, other quantitative studies generally report a lack of association between the two. For instance, a recent study conducted by Chan et al. shows that (using the Granger causality test) there is no association between risk perception and protective behavior against Zika in the United States (US) [23]. Similarly, through a confirmatory factor analysis, Castro et al. find no association between greater risk perception and dengue related practices in Cuba [12].

In the economic discipline, behavior is usually modelled as the demand for prevention, which is assumed responsive to risk perception. More precisely, when purchasing preventive measures, individuals estimate the costs of prevention against the benefits of avoiding the infection in the future. As the actual risk, expressed in terms of prevalence or incidence, is often uncertain–if not completely unknown by the population at risk–prevention decisions are affected by the individual's risk perception and preferences [8]. Risk-averse individuals will face a 'risk-elastic demand for prevention': a percentage increase in the risk will lead to a greater percentage increase in self-protective behavior. The demand is also more likely to be 'risk-elastic' when vaccines are inexistent; and yet more if treatment options are lacking, inadequate or unaffordable [24]. Quantifying the elasticity of the demand to the risk perception is essential for effective prevention programs because it will predict the effect of changes in the risk perception on individual choices. Elastic demand to risk perception makes it harder to eradicate a disease: as the transmission of the infection decreases, risk perception should decrease and even more so should the demand for prevention [8]. Risk-elastic demand is supported by theoretical economic models but in reality, few empirical studies have looked into it. A majority focus on HIV [8,25–28] but few on VBDs. For malaria, a reference study is the one by Picone et al., which looked at the elasticity of bed nets usage for malaria across nine countries in sub-Saharan Africa and finds a coefficient that is positive but lower than one, suggesting an inelastic relationship [29]. Two main factors can explain the scarcity of quantitative research on the topic: the (i) challenges in measuring behavior and (ii) reverse relationship between behavior and risk perception [8]. Behavior is often self-reported as it is difficult to observe and measure [30]; self-reported behavior tends to overestimate actual behavior due to–among others–social desirability bias [31]. The second issue affecting quantitative/statistical modelling is the reverse relationship between behavior and risk perception: more precisely, it is difficult to estimate the impact of risk perception on preventive behavior if the same behavior in the past has contributed to today's risk perception [8]. Unless using appropriate research designs or statistical methods, the response of behavior to risk is likely to be biased upward [32]. A common way to deal with endogeneity is using an instrumental variable approach but finding a robust instrument may be challenging. Another way suggested to overcome this statistical challenge is using a structural equation model (SEM), which is able to control for over-reporting of preventive behavior and isolate the impact of risk perception on behavior and vice versa.

The objective of this study is to assess whether preventive behavior is responsive to risk perception and whether it differs across diseases, taking into account the role of disease

knowledge on behavior and risk perception, and controlling for individuals' socioeconomic and demographic characteristics. The innovative character of this study lies in its focus on four diseases (malaria, dengue, Zika and cutaneous leishmaniasis (CL)) and in its reliance on primary data collected in Guyana, where practically no research has ever been conducted on the topic. Moreover, these four VBDs are responsible for a significant morbidity and mortality burden worldwide [1,33–35]. The measure of the burden for these diseases (except for malaria) is limited in Guyana due to a deficient surveillance system. Nonetheless, according to the Ministry of Public Health (MoPH), they are responsible for a substantial morbidity burden. Despite the country's small population, the number of malaria cases in Guyana accounts for 3% of the total estimated cases in America, with incidence levels in specific areas of the hinterland (i.e. mining areas) that are above many sub-Saharan African countries [36].

Material and methods

Ethics statement

The study protocol with the reference number 265 was reviewed and approved by the Institutional Review Board (IRB) of the Ministry of Public Health of Guyana. All adult subjects provided written informed consent prior to participating to the study.

Study setting and population

Guyana lies between Suriname, Brazil and Venezuela, spanning over 216,000 square kilometers with a total population of approximately 780,000 inhabitants [37]. It is divided into ten administrative regions, which are either categorized as so-called hinterland or coastal based on their geographical location, demographic characteristics, soil type, economic activities, and natural resources, among others. Coastal regions are more densely populated and include the capital city Georgetown (region 4), where nearly half of the country's population live [38]. While some infectious diseases are more prevalent in the coastal regions and others in the hinterland, a surveillance system reporting the exact distribution and number of cases across the country is only available for malaria. The number of malaria cases have increased for the two most recent figures, with 11,108 reported cases in 2016 and 13,936 cases in 2017. Figures available for dengue report 230 laboratory-confirmed cases in 2019, 286 cases in 2018, while up to 863 cases in 2014 [39,40]. As for Zika, 52 cases have been reported in 2015, 339 in 2016 while none in 2017 [41]. One figure is available for CL in 2017, which reports 21 confirmed cases per 100,000 inhabitants; its incidence rate varies greatly across the country and is classified as 'intense' in the hinterland [42]. The data collected by the MoPH suggest that Zika and dengue are more prevalent in the coastal regions whereas CL and malaria are more prevalent in the hinterland, where mining areas are the hot spot of infection. Overall, infectious and parasitic diseases are estimated to be responsible for 11% of the deaths in the country [40]. Importantly, Guyana is a strategic country given its geographic location for promoting the control and elimination of VBDs in the Northern coast of South America and the Caribbean. A regional cooperation between the Guianas (Guyana, Suriname and French Guyana) and Brazil has often been reported to be necessary [43–45]. Moreover, Guyana shares the border with Venezuela, which is facing a difficult political situation and experiencing an overwhelming resurgence of VBDs transmission [6].

Data collection and analysis

In Guyana, not all regions are endemic or equally endemic. Therefore, the data were collected in four regions of the country, two in the hinterland (regions 1 and 8) and two along the coast

(regions 4 and 6) to capture endemic and non-endemic areas depending on the disease. In the coastal regions (4 and 6, populated and urban areas), 15 villages per region were randomly selected (among preselected villages by the MoPH for their reachability by foot or public transports) based on 'selection proportional to size'. This method randomly selected villages based on (i) the chosen number of villages per region and on (ii) the number of inhabitants per village. Within those 15 villages, the number of questionnaires administered was also proportional to size: the most populated village had the highest number of questionnaires assigned and vice versa (cf. S2 File). In the hinterland regions (1 and 8), given the very low number of inhabitants, 'selection proportional to size' was not applied. Instead, villages with the highest population density (that include the main health facilities, our starting point for data collection) were selected to participate and questionnaires were administered until the target size was reached. This being said, in all regions and within all selected villages, data collectors selected houses starting from the health facility and moving forward while applying the 'spinning bottle' rule [46].

Given the available resources, the targeted sample size was set to above 800 in total: 210 questionnaires per region. Accordingly, between 209 and 215 participants (over 18 years old) were interviewed in each region (Fig 1). Before conducting the interviews, a training of the fieldworkers (data collectors) was organized, followed by a piloting of the questionnaire in each region. The questionnaire was then refined based on fieldworkers' feedback. Face-to-face interviews were performed using tablets and conducted from August 2017 to December 2017. These were conducted in private house (59%), workplaces (30%), schools (5%), restaurants (4%), and in hospitals/health centers (2%). In private houses, as opposed to the other places, a set of indicators such as assets and livestock ownership, education and occupation was gathered (cf. S1 File). We focused our analysis on data collected from private houses only (59%) to

Fig 1. Map of data collection. Each dot contains the number of individuals interviewed in that specific area. Note that while region 1 may appear as coastal, it is classified as hinterland by the government given its economic activity and topography. Source: the map was created from the data we collected using the KoBoToolbox.

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be able to control for the individuals' socioeconomic and demographic characteristics (N = 497). In order to capture disease knowledge, risk perception and behavior for the four diseases separately, the following questions were asked to each of the participants:

- "Do you know disease X?"

If the respondent answered 'yes', he/she was asked:

"Can you briefly describe what you know about disease X?"

- "How much do you think you and the people in this place are at risk of disease X on a scale from 0 to 10 (0 –no risk; 10 –very high risk)?"
- "What do you do to avoid disease X?"

Keywords for describing the diseases and preventive tools were selected based on discussions with the MoPH. As participants were describing the diseases or reporting their behavioral practices, a box was ticked for each keyword mentioned. The possible answers for behavioral practices were mainly related to the use of preventive tools (cf. S1 File).

The data were uploaded in an online (secured) reporting platform that guaranteed anonymity of the data. The analysis was conducted in Stata software (StataCorpLP, http://www.stata.com) to obtain the correlation matrices that were then inputted in LISREL (http://www.ssicentral.com/lisrel/) to estimate the SEM [47] (cf. S1 Text).

Descriptive data

Descriptive statistics of the respondents across regions are presented in Table 1. The socioeconomic status (SES) consists in a wealth index that was obtained by applying multiple correspondence analysis (MCA) to asset and livestock ownerships. A wealth index per region was initially computed since asset and livestock ownerships may have different meanings to wealth

Table 1. Descriptive statistics of the respondents interviewed in private houses.

	Hinterland		Coastal regions	
	Region 1 N (freq.)	Region 8 N (freq.)	Region 4 N (freq.)	Region 6 N (freq.)
Wealth index				
1st quintile (poorest)	36 (24.49%)	28 (24.35%)	16 (12.21%)	20 (19.23%)
2nd quintile	37 (25.17%)	16 (13.91%)	29 (22.14%)	17 (16.35%)
3rd quintile	17 (11.56%)	19 (16.52%)	36 (27.48%)	30 (28.84%)
4th quintile	28 (19.05%)	22 (19.13%)	26 (19.85%)	22 (21.15%)
5th quintile (richest)	29 (19.73%)	30 (26.09%)	24 (18.32%)	15 (14.42%)
Education				
No formal education	8 (5.44%)	3 (2.61%)	0	0
Primary	47 (31.97%)	45 (39.13%)	28 (21.37%)	25 (24.04%)
Secondary	82 (55.78%)	64 (55.65%)	99 (75.57%)	67 (64.42%)
University	10 (6.80%)	3 (2.61%)	4 (3.05%)	12 (11.54%)
Sex				
Female	99 (67.35%)	93 (80.87%)	109 (83.21%)	76 (73.08%)
Male	48 (32.65%)	22 (19.13%)	22 (16.79%)	28 (26.92%)
Sample size (N)	147	115	131	104

Legend: freq = frequency.

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across regions. For instance, livestock ownership may be a sign of richness in the hinterland (i.e. regions 1 and 8) while the opposite in the capital city (i.e. region 4). S1 Fig shows the dimension 1 and 2 of the MCA per region. Dimension 1 is interpreted as wealth: modalities with negative coordinates can be seen as indicators of 'richness' whereas positive coordinates are indicators of 'poorness'. For instance, for region 4, not having electricity, a color-television and/or a refrigerator is clearly a sign of low economic status (cf. S1 Fig). The four wealth indices were then pooled into one index. If looking across regions, there is a higher proportion of people belonging to the first quintile (i.e. the poorest) of the wealth index in regions 1 and 8, the hinterland. As expected, regions that recorded the highest proportion of its population in the first quintile also experienced the highest rate of 'no formal education'. Lastly, a significant majority of the participants consisted of female for interviews conducted in private houses.

The model

SEM offers several advantages: it can (i) deal with omitted variable bias [48]; (ii) account for measurement error by using latent variables as indicators of observed variables [49]; (iii) solve for reverse relationship if the model is empirically identified; and (iv) compare models in terms of their best fit as well as perform multiple group analysis [50,51] (cf. S3 Text) Our SEM model is presented in Fig 2 and is built assuming a linear structure of relationships using the maximum likelihood estimator (MLE) for participants interviewed in private houses. It was developed based on findings from the literature, mainly from KAP studies. The variable knowledge is a categorical variable, which is equal to 0 if the person does not know the disease;

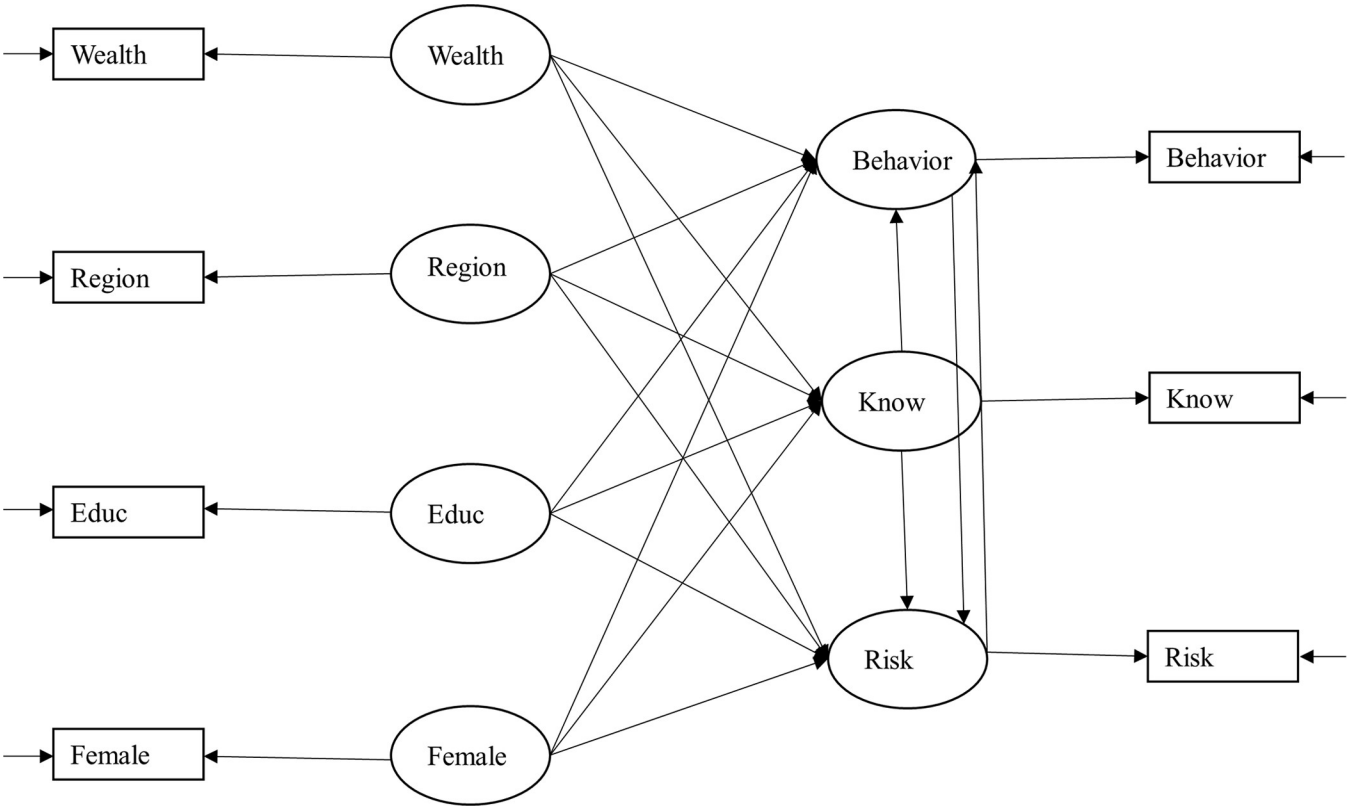

Fig 2. Path diagram of the system of simultaneous equations. Circled variables are the latent ones and boxed variables are the observed ones. The arrow from the circled variables to the boxed variables indicates the quality coefficient.

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1 if the person cited one keyword; 2 if the person cited two keywords; etc. People who reported absolutely no knowledge of the disease were removed from the analysis since we cannot obtain an unbiased estimate of their risk perception and behavior. We nonetheless included in S3 File a probit estimation to assess the determinants of knowledge across the four diseases. The variable behavior is also categorical, measured as the reported number of vector control strategies used by the respondent. In this analysis, behavior embeds two types of tools: 'personal protection tools' (e.g. mosquito coils and repellent) and 'vector control tools' (e.g. fogging and IRS). It nevertheless does not look at 'vector reduction behavior' such as water holding container management. In coding behavior, we distinguished between 'passive' and 'active' behavior, where the former captures usage only and the latter captures demand. More precisely, 'passive' behavior refers to using measures that were provided free of charge by the MoPH while 'active' behavior refers to using measures that were purchased. Accordingly, 'passive' behavior includes bed nets (treated with 55mg/m^2 deltamethrin), indoor residual spraying (IRS) and fogging (all provided by the MoPH in Guyana) and 'active' behavior includes tools such as mosquito coils, skin repellent, screened windows–among others. Hence, the variable behavior is equal to 0 if the person reports to use nothing (although the person knows about the disease); 1 if the person 'uses' only one or all of the measures provided by government (a bed net and/or IRS and/or fogging); 2 if the person uses one other measure than the ones provided by the government; 3 if the person uses two other measures than the ones provided by the government; etc. Usage of measures such as fogging or IRS should be interpreted as acceptation of invasive but necessary interventions inside and around the house. Nevertheless, in order to test the robustness of our definition of 'positive' behavior, we ran the model with an alternative definition in which bed net use is considered as active and not passive, even if not purchased but received free of charge from the government. In that case, the dichotomy between active and passive behavior is not based on the measures being purchased/donated but on them requiring an active usage versus a passive one. Accordingly, the variable behavior is equal to 0 if the person reports to use nothing; 1 if the person 'uses' IRS and/or fogging; 2 if the person uses another measure than IRS and/or fogging; etc. The variable risk is a measure of self-reported risk perception and ranges from 0 to 10, with 0 meaning 'no risk' and 10 meaning 'very high risk' as indicated by the question. As for the exogenous variables, the variable wealth consists of a wealth index. The variable educ stands for education and ranges from no formal education to university degree–'no formal education', 'primary', 'secondary', and 'university'. The variable region is a dummy variable taking the value of 1 if the person lives in the hinterland (regions 1 or 8), and 0 if the person lives in a coastal region (4 or 6). The variable female is equal to 1 if the respondent is a female and 0 otherwise.

Where the algebraic representation of the SEM is as follow:

$$\text{Behavior} = \beta_1\text{knowledge} + \beta_2\text{risk} + \beta_3\text{wealth} + \beta_4\text{region} + \beta_5\text{educ} + \beta_6\text{female} + \varepsilon_B \quad (1)$$

$$\text{Knowledge} = \gamma_1\text{wealth} + \gamma_2\text{region} + \gamma_3\text{educ} + \gamma_4\text{female} + \varepsilon_K \quad (2)$$

$$\text{Risk} = \delta_1\text{knowledge} + \delta_2\text{behavior} + \delta_3\text{wealth} + \delta_4\text{region} + \delta_5\text{educ} + \delta_6\text{female} + \varepsilon_R \quad (3)$$

For which $E(\varepsilon_B, \varepsilon_K, \varepsilon_R) = 0$.

Eq (1): As mentioned in the introduction, the findings on the association between knowledge and behavior cannot be generalized across diseases and contexts, while for risk perception, economic models believe it to increase behavior but few empirical studies have proved so. As for wealth, it is expected to have a positive effect on behavior through greater purchasing power [52]. Higher level of education also tends to increase the demand for preventive tools

[16,52,53] and women have a tendency to adopt a greater range of vector control practices than men [16,53].

Eq (2): Disease knowledge is believed to be determined primarily by education and higher wealth from increased access to information through multiple channels such as television, radio and social media [10,12,17,52,54]. Sex also tends to play a role on knowledge: a study demonstrated that women had 63% higher odds of being able to correctly cite at least three dengue symptoms [17].

Eq (3): Higher knowledge is likely to be associated with greater risk perception [18] [23] although some studies found otherwise [11] [13]. Safer behavior is supposed to decrease risk perception from a feeling of control over the infection [7]. People with a higher economic status are more likely to have a more accurate perception of the risk, potentially through higher education and knowledge [55]. As for the sociodemographic variables educ and *female*, they tend to play a role in risk perception but findings are mixed [10,17,55].

Lastly–as for the other socioeconomic and demographic variables–the variable region is included in each equation. Preventive behavior, knowledge and risk perception are all likely to vary depending on the geographic proximity to the diseases' vectors but also on other characteristics that are specific to the region (e.g. education system, health system, transportation services, etc.) [22] [53].

Measurement error and testing of the model

Measurement errors in data collected through surveys can be significant, implying a significant margin between the variable that one wishes to measure and the one that is truly measured [56,57]. As a result, measurement was considered for the self-reported variables: behavior, knowledge and risk perception using the Survey Quality Predictor program (http://sqp.upf.edu/) [58]. To test the model's fit, a postestimation tool for the SEM–Jrule–was used in addition to the usual chi-square test to identify potential local misspecifications [59–61] (cf. S4 Text).

Results

Descriptive results

Disease knowledge. As seen in Table 2, almost 80% of the population did not know about CL, whereas this figure was about 54% for Zika, 33% for dengue and 12% for malaria. The determinants of knowledge–obtained through a probit model–varied across diseases (cf. S3 File). Yet, a significant determinant of knowledge across diseases was the variable region: people living in the hinterland (regions 1 and 8) had a higher probability of knowledge for malaria

Table 2. Knowledge level per disease.

Do you know about the disease? If yes, can you please describe what you know about the disease?				
	Malaria	**Dengue fever**	**Zika**	**Cutaneous leishmaniasis**
Does not know	**11.87%**	**32.60%**	**53.52%**	**77.46%**
At least 1 keyword cited	88.13%	67.40%	46.48%	22.54%
At least 2 keywords cited	70.82%	32.19%	23.54%	4.43%
At least 3 keywords cited	50.50%	3.22%	10.66%	
At least 4 keywords cited	29.78%		3.82%	
At least 5 keywords cited	16.10%			
At least 6 keywords cited	11.07%			

Legend: for each disease, the number of keywords cited was summed up.

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and CL. Furthermore, people living in region 1 had a higher probability of knowledge not only for malaria and CL but for Zika and dengue as well. In addition to this, a higher education level increased the probability of knowledge for Zika and malaria but did not significantly affect CL or dengue; being a male increased the likelihood of knowing about malaria and dengue; and pertaining to a higher quintile of the wealth index increased the probability of knowing about Zika and CL but not about dengue and malaria.

Afterwards, for the individuals who reported a minimum knowledge of the diseases, their level of knowledge–based on the number of keywords cited regarding the diseases' causes and symptoms–was measured. From Table 2, one can see that up to 6 keywords could be cited for malaria while only two for CL. Knowledge of CL (called 'bush yaws' by the population) was low, potentially because the disease mainly affects a subsample of the population which are gold miners. For a description of the keywords cited, refer to S1 Table.

Risk perception

Fig 3 shows the cumulative frequency of self-reported risk perception per disease. Depending on the disease, between 12% and 18% of the respondents believed the risk of infection to be zero while between 3% and 14% believed the risk to be 10. Risk perception and knowledge seemed to follow the same path: the median risk perception is the highest for malaria, followed by dengue, Zika and CL.

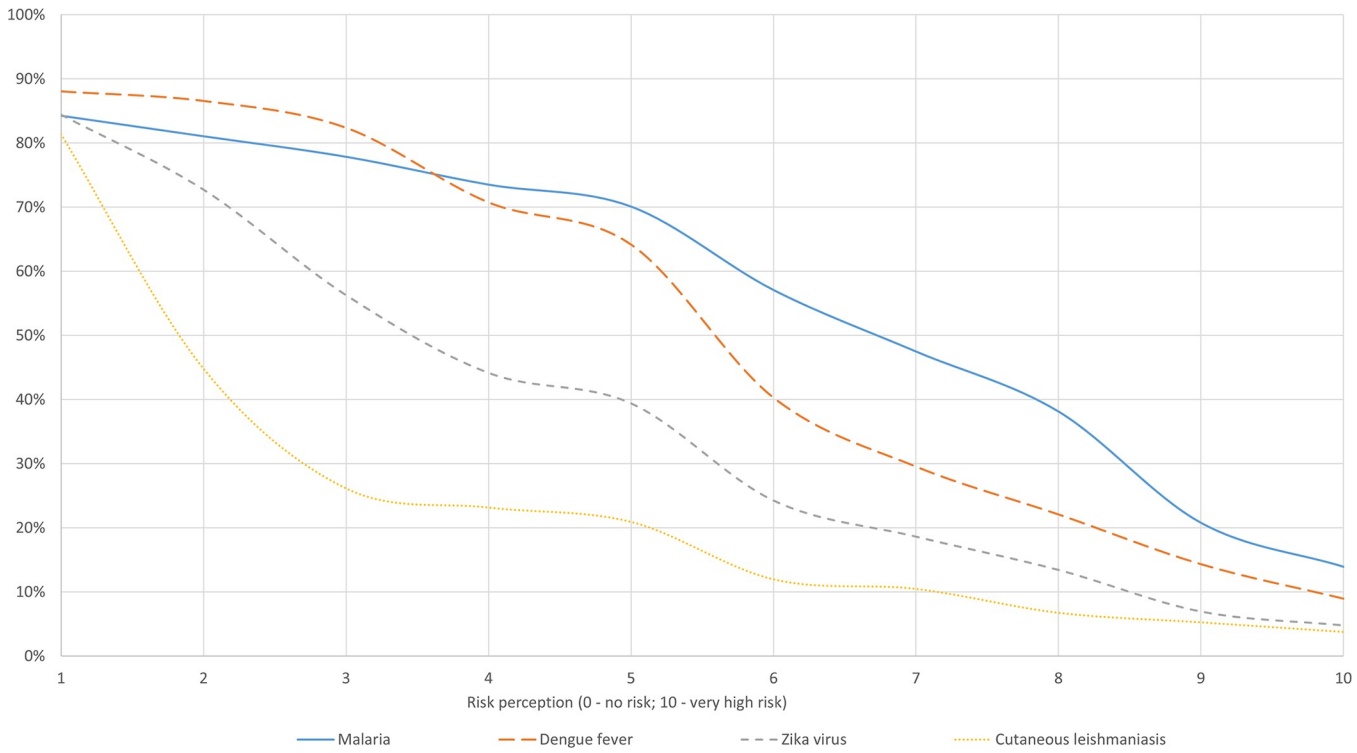

Fig 3. Cumulative frequency of self-reported risk perception across diseases. As this graph shows the cumulative frequency of risk perception, we start by including the people who had a risk perception of at least 1 (on a scale from 0 to 10). The percentage of people who had a risk perception of 0 can be computed for each disease by subtracting to the sample the proportion of people who perceived a risk of at least 1. For instance, for malaria, 100%-84% = 16% of the sample believed the risk to be 0 (although knowing about the disease).

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Table 3. Self-reported vector control practices.

What do you do to avoid disease x?					
First definition of behavior (i.e. bed net use is passive)					
		Malaria	**Dengue fever**	**Zika**	**Cutaneous leishmaniasis**
	Nothing	3.88%	7.16%	3.46%	54.48%
Passive	Bed net and/or IRS and/or fogging only	45.43%	57.01%	39.39%	29.85%
Active	Use 1 other measure than a bed net/IRS/fogging	34.02%	29.85%	47.62%	12.69%%
	Use 2 other measures than a bed net/IRS/fogging	14.38%	5.67%	8.23%	2.99%
	Use 3 other measures than a bed net/IRS/fogging	2.28%	0.3%	1.30%	
Second definition of behavior (i.e. bed net use is active)					
	Nothing	3.88%	7.16%	3.46%	54.48%
Passive	IRS and/or fogging only	4.34%	19.19%	9.96%	18.66%
Active	Use 1 other measure than a IRS/fogging	44.29%	42.69%	49.35%	14.18%
	Use 2 other measures than a IRS/fogging	31.28%	25.37%	30.74%	9.70%
	Use 3 other measures than IRS/fogging	14.38%	5.67%	5.63%	2.99%
	Use 4 other measures than IRS/fogging	1.83%		0.87%	

Legend: IRS = Indoor residual spraying.

In the first definition of behavior, passive behavior includes all measures that are donated by the government (IRS, fogging and bed nets). In the second definition of behavior, passive behavior only includes IRS and fogging but not bed nets since it can be seen as requiring an 'active' usage.

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Disease practices

Self-reported usage of vector control tools for each disease is tabulated in Table 3. When people know about the disease, they tend to protect themselves–except for CL,for which almost 55% of the population reported to do nothing to protect against the vector. Measures provided by the government were highly used among the population. About 94% for malaria, 90% for dengue and 81% for Zika of the respondents reported to use at least one measure offered by the government (i.e. a bed net and/or IRS and/or fogging). For the individuals who only used the measures donated by the government, bed net seemed the most common one. For the remaining individuals, overall, they used a maximum of three additional measures–or two in the case of CL–than the ones provided by the government. Among these, skin repellent and mosquito coils were the most commonly purchased ones (cf. S2 Table).

SEM results

Standardized estimates of the structural model are reported in Table 4 and the final LISREL input is provided in S2 Text. A quality coefficient of 0.728, 0.744 and 0.752 was estimated for behavior, knowledge and risk respectively, implying a measurement error of approximately 25%. The process that led to those measurement errors can be traced in the SQP database under the study name of 'repuls'. Following Jrule postestimation results, the effect of region on risk perception was let free to vary across the four diseases. Other parameters were let free to vary but for some specific diseases only, such as knowledge on behavior for CL and Zika; knowledge on risk perception for CL; etc. This led to a model with a chi-square of 31.99, 24 degrees of freedom and an associated p-value of 0.12714, which combined with a Root Mean Square Error of Approximation (RMSEA) of 0.034, suggested that the model fits well the data.

The results showed that behavior was significantly responsive to the level of risk perception: a one-unit increase in risk perception (on a scale from 0 to 10) increased the demand for prevention by 0.53 unit for all diseases. Behavior also seemed to be responsive to the level of knowledge but for malaria and dengue only since for CL and Zika, the coefficient lacked

Table 4. Results of the structural model.

		Malaria	Dengue fever	Cutaneous leishmaniasis	Zika
Dependent variable	**Explanatory variables**	**St. Coeff (Std. Error)**	**St. Coeff (Std. Error)**	**St. Coeff (Std. Error)**	**St. Coeff (Std. Error)**
Eq 1					
Behavior	Knowledge	0.841*** (0.106)	=	0.747 (0.554)	0.203 (0.189)
	Risk	0.530** (0.232)	=	=	=
	Wealth	0.0117** (0.057)	-0.121 (0.080)	=	=
	Region	-0.841*** (0.169)	=	-0.172 (0.338)	-0.119 (0.147)
	Educ	0.006 (0.052)	=	=	=
	Female	0.010 (0.045)	=	=	=
Eq 2					
Knowledge	Wealth	0.001 (0.045)	=	-0.177** (0.085)	0.177** (0.077)
	Region	0.639*** (0.059)	0.380*** (0.066)	-0.589*** (0.095)	0.568*** (0.077)
	Educ	0.256*** (0.040)	=	0.051 (0.066)	=
	Female	0.019 (0.033)	=	=	=
Eq 3					
Risk	Knowledge	0.28 (0.185)	=	1.503 (1.089)	=
	Behavior	-0.463** (0.212)	=	-0.010 (0.876)	=
	Wealth	0.123* (0.064)	-0.099 (0.085)	=	-0.007 (0.104)
	Region	0.695*** (0.106)	0.211 (0.153)	=	-0.194 (0.146)
	Educ	0.056 (0.052)	0.056 (0.052)	=	-0.015 (0.106)
	Female	0.009 (0.040)	=	=	=
N		438	335	134	231

Chi-Squared (df) = 31.99 (24); p-value = 0.12714

RMSEA = 0.034

Legend: '=' implies that coefficients are equal to the ones estimated for the malaria model (model 1);

**significant at 5% significance level;

*** significant at 1% significance level; St. Coeff = standardized coefficient; Std. Error = Standard error; N = sample size; df = degrees of freedom; RMSEA = Root Mean Square Error of Approximation. Region is a dummy variable equal to 1 if the respondent lives in the hinterland and 0 otherwise.

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statistical significance. That is, a one-unit increase in disease knowledge (i.e. one more keyword cited) increased the demand for prevention by 0.84 unit for malaria and dengue. The association between wealth and behavior was statistically significant but close to zero (or not statistically significant in the case of dengue) indicating that low purchasing power did not act as a considerable barrier to the adoption of additional measures. Overall, people in the hinterland seemed to demand less for prevention than in coastal regions: more precisely, they

demanded 0.84 unit less for malaria and dengue and between 0.12 and 0.17 unit less (although not significant) for Zika and CL respectively. As for education and sex, they showed to have no influence on the demand for prevention.

Regarding the degree of disease knowledge, it varied depending on the respondent's level of education and the region in which he/she lived. More exactly, people living in the hinterland had greater knowledge about malaria, dengue and Zika (i.e. from 0.38 to 0.64 unit increase) but lower knowledge about CL (i.e. a 0.59 unit decrease). While for education, moving to the next level (e.g. from primary to secondary) increased the level of knowledge by 0.26 unit for all diseases, except for CL, for which the coefficient lacked statistical significance.

With respect to the determinants of risk perception, (i) vector control practices (i.e. behavior), (ii) socio-economic status and (iii) the geographic location seemed key. To be more specific: (i) an additional measure used to protect against the disease decreased risk perception by 0.46 unit for malaria, dengue and Zika but did not affect risk perception for CL; (ii) a higher economic status translated into an increased risk perception (by 0.12 unit) for malaria and CL; and (iii) people living in the hinterland had a higher risk perception for malaria and CL (by 0.70 unit), which, based on the MoPH estimations, would imply that the perceived risk reflected the actual risk of infection. Education and sex had no influence on risk perception for any of the four diseases.

A robustness check on the definition of behavior–where bed net usage is no longer considered passive but active–supported our initial finding of a positive association between risk perception an behavior (cf. S4 File). Furthermore, as expected, the coefficient was smaller in this case: a one-unit increase in risk perception increased the demand for prevention by 0.27 unit, as opposed to 0.53 unit before. This is because considering bed nets use as active in a context in which they are donated diminishes the effect of risk perception on behavior. In other words, because bed nets are donated, they more are likely to be used regardless of the risk perception. This also applies to the reverse relationship–the effect of behavior on risk. Using an additional measure–which can now include bed net–than IRS and/or fogging was no longer statistically significantly associated with a decrease in risk perception. If bed nets are used regardless of the perceived risk, their use are less likely to decrease risk perception. Lastly, while overall our results are similar across the two definitions of behavior, according to the Chi2 test, the model fitted better the data when bed nets use was considered as passive and not active (which seems reasonable in a context in which they are donated).

Discussion

This study is one of the few empirical ones to show evidence of a circular link between risk perception and preventive behavior [8]. Higher risk perception translates into the take up of more preventive measures–the more people fear, the more they protect themselves–which in turn decreases risk perception. Measures subsidized by the government (specifically bed nets) were highly used showing that–as claimed by Dupas' work–heavy subsidization of health products promotes their usage [62,63]. Furthermore, as shown by our second definition of behavior, measures that are provided free of charge (i.e. bed nets) were more likely to be used regardless of the perceived risk. This study also demonstrated that, in Guyana, better knowledge increases the take up of personal preventive measures for malaria and dengue without affecting risk perception. This can be explained by the following: the more people know about the diseases, the more measures they will use, the more in control they will feel, and the less affected is their risk perception [7]. As for Zika and CL, better knowledge did not increase the take up of preventive measures, which may be explained by a general low risk perception. As seen in Fig 3, the risk perception was much lower for Zika and CL than for malaria and dengue. This would

suggest that if the overall risk perception of a disease is low, greater knowledge is not sufficient to trigger a behavioral change. Therefore, behavior is determined by knowledge if risk perception is high enough. Nevertheless, risk and knowledge were not the only factors to affect behavior. The type of region–hinterland or coastal–in which the respondent lives played an important role. Indeed, throughout the analysis the variable region played a key role in explaining (i) behavior, (ii) knowledge and (iii) risk perception. That is, people in the hinterland (i) used fewer vector control measures but (ii) had a higher knowledge levels for all diseases, except of CL. More specifically, among the people who had a minimum knowledge of the diseases, the level of knowledge (i.e. number of keywords cited) was likely to be higher for all diseases (except CL) for those living in the hinterland. And as seen from the probit estimation, in the hinterland, people were more likely to know about malaria and CL. This overall higher knowledge in the hinterland was the result of greater awareness raising, particularly for malaria, carried out by the MoH to respond to the distance between health facilities and where infection is contracted (i.e. hours/days of travelling) and by gold mining companies to keep their workers healthy and productive. Higher knowledge for dengue and Zika in the hinterland suggested the existence of positive spillover effects of malaria on other VBDs. Nonetheless, we see that this does not apply to CL–of which knowledge was lower in the hinterland–but which could be explained by the bias in our sample: CL is mostly prevalent amongst men working in gold mining camps, while our sample mainly included women. Lastly, people in the hinterland (iii) had a higher risk perception for malaria and CL, where those diseases are actually endemic, thereby indicating that the variable region is a good proxy for the actual prevalence and that the risk perception is consistent with the actual risk of infection. Furthermore, the combination of these three findings–people in the hinterland having a higher knowledge, an accurate perception of the risk but demanding fewer vector control measures–suggested that the variable region was not only a proxy for the disease's prevalence but captured other features that are specific to the region, such as accessibility. Accessibility to preventive measures is indeed more complicated in the hinterland, and may actually represents a bigger obstacle than wealth to the demand for prevention, which showed to have little effect. Similarly, the variables educ and sex showed to have no influence on the model, except for the effect of education on knowledge. This being said, the lack of statistical significance of the variable sex is likely to be due to an over-representation of women (i.e. 76%) in our sample.

This brings us to the limitations of the study. More than 70% of our sample is made of women simply because they were more likely to be found at home. This over-representation of women in our sample is likely to bias the results–for instance, by lowering the disease knowledge and perceived risk for malaria and CL, which population mostly at risk consists of male gold miners. Another limitation is that we do not know the exact prevalence of dengue, Zika and CL in Guyana, which prevents us from making a direct association between risk perception and the actual risk of being infected. However, we can confirm from the data available that the risk perception for malaria is much greater in regions where the incidence rates are higher. Understanding whether risk perception reflects the true risk of infection is an important line of research that merits further investigation. Additionally, our reliance on cross-sectional data–instead of longitudinal data–implies that we are unable to control for time-invariant characteristics–such as risk preferences–that may influence behavior. Lastly, given the debate on the actual capacity of the SEM to identify causation, we took a conservative position and kept our results to associations rather than causal effects. Beyond this debate, we find SEM as a very useful model when complex and/or circular relationships among variables have to be studied (particularly when cross-sectional data are only available). It also has the advantage of being intuitive and easy to replicate.

To conclude, unpacking the direct and mediating effects of positive behavior against VBDs, we could observe that the perceived risk and the level of knowledge (if the perceived risk is high enough) were key, which were jointly influenced by the geographical location, and individually influenced by current behavior practices and education respectively. Last but not least, it appeared that easier access to preventive measures was also essential to the adoption of vector control measures, which can otherwise undermine the behavioral responsiveness to risk. Thus, accounting for the reverse relationship of behavior on risk perception, we can say that, in the context of Guyana, people act according to the risk they perceived and to their knowledge–if the risk perception is high enough for knowledge to trigger a behavioral change. This finding has important implications for health policy-making, as it can help modelling the impact of outbreaks as well as of public health interventions. Although from this analysis we cannot speak about the elasticity of the demand for prevention to risk, we can confirm that, by providing the population with an accurate estimation of the infection's risk, the population will respond through greater protection against the vector. Moreover, providing information about the causes and symptoms of the diseases is also likely to increase the take up of preventive measures, especially if the perceived risk is high. While these findings are specific to Guyana, we believe that they can be generalized to some neighboring countries/areas: more specifically, to Suriname, French Guyana and Roraima state in Brazil (which borders region 8 of Guyana that is included in the study).

Consequently, in a context of elimination such as for malaria, one key recommendation from this study is effective communication with the population at risk, particularly during the so-called 'last mile'. In such a context, for the government and population to act hand in hand, it is essential for the former to promote awareness of the risk to the latter to avoid a decrease in preventive behavior arising from a lower risk perception. This is all the more important for diseases that are asymptomatic or that face common symptoms such of fever and headaches but which lack routine surveillance (e.g. dengue or Zika), as reaching their control and/or elimination is likely to be further challenged by an underestimation of the actual risk of infection. Moreover, as seen in this study, the donation of measures by the government will also considerably help on that matter.

Supporting information

S1 File. Questionnaire.
(PDF)

S2 File. Sample selection method.
(DOCX)

S3 File. The determinants of knowledge. A probit regression to assess the determinants of knowing versus not knowing at all about a disease x.
(DOCX)

S4 File. Robustness checks using another definition of positive behavior. A second definition of behavior where bed net use is considered as active and not passive.
(DOCX)

S1 Text. Data management and analysis.
(DOCX)

S2 Text. Input from LISREL. Input used to run the structural equation model in LISREL.
(DOCX)

S3 Text. Structural equation model (SEM). This section details the several advantages of using SEM.
(DOCX)

S4 Text. Measurement error and testing of the model.
(DOCX)

S1 Fig. Multiple correspondence analysis per region.
(DOCX)

S1 Table. Keywords cited per disease. The table exhibits all the cited keywords per disease.
(DOCX)

S2 Table. Vector control measures used per disease. The table exhibits all the measures used per disease.
(DOCX)

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Supplementary file

Vector Control Services - Repuls Project

1. GPS coordinates

latitude (x.y °)

longitude (x.y °)

altitude (m)

précision (m)

2. a. Region

- ◯ Region 1
- ◯ Region 4
- ◯ Region 6
- ◯ Region 8

2. b. Questionnaire serial number

3. Interviewee ID

Enter a 6-digit number after 'abc'

abc

4. Date of interview

Today's date

yyyy-mm-dd

5. Place of interview

- ◯ Private house
- ◯ Workplace
- ◯ Restaurant
- ◯ Hospital/Health centre
- ◯ School

6. Position of interviewee within the place in Question 5

- ◯ Husband
- ◯ Wife
- ◯ Workplace owner
- ◯ Workplace worker
- ◯ Hospital director
- ◯ Hospital worker
- ◯ School director
- ◯ School teacher

7. Nationality

- ◯ Guyanese
- ◯ Brazilian
- ◯ Venezuelan
- ◯ Cuban
- ◯ Other

7. b. Other nationality

_____

8. Town / Village name

_____

9. Sex

- ◯ Male
- ◯ Female

10. Date of birth

yyyy-mm-dd

11. What ethnic group do you belong to?

- ◯ Amerindian
- ◯ European
- ◯ African
- ◯ East Indian
- ◯ Portuguese
- ◯ Chinese
- ◯ Mixed

12. What is your martial status?

- ◯ Common law
- ◯ Married
- ◯ Separated/Divorced
- ◯ Widow/Widower
- ◯ Single

13. What is your highest level of education?

- ◯ Never been to school
- ◯ Primary
- ◯ Secondary
- ◯ Undergraduate studies
- ◯ Postgraduate studies

14. What is your occupation?

- ◯ Farmer
- ◯ Miner
- ◯ Fisherman
- ◯ Office employer
- ◯ Shop trade
- ◯ Other

14. b. Other occupation

15. What is your main source of drinking water?

- Piped water - Piped into dwellinger
- Piped water - Piped to yard/plot
- Piped water - Public tap/standpipe
- Piped water - Tube well or borehole
- Rainwater
- Tanker truck
- Cart with small tank
- Surface water (river/dam/lake/pond/stream/canal/irrigation channel)
- Bottled water
- Dug well
- Protected well
- Unprotected well
- Water from spring - Protected spring
- Water from spring - Unprotected spring

16. What kind of toilet facility do you use?

- No facility/bush/field
- Flush to piped sewer system
- Flush to septic tank
- Flush to pit (latrine)
- Flush to somewhere else
- Flush, don't know where
- Ventinlated improved pit latrine
- Pit latrine with slab
- Open pit
- Composting toilet
- Bucket toilet
- Hanging toilet / hanging latrine

17. Do you have:

- [ ] Electricity
- [ ] A radio
- [ ] A cell phone
- [ ] A land-line phone
- [ ] A refrigerator
- [ ] A clock
- [ ] A black/white television
- [ ] A color television
- [ ] A freezer
- [ ] An electric generator
- [ ] A fan
- [ ] An air-conditioner
- [ ] A fan
- [ ] An air-conditioner
- [ ] Washing machine
- [ ] Computer
- [ ] Digital photo-camera
- [ ] Non-digital photo-camera
- [ ] A VHS player
- [ ] A DVD player
- [ ] A bed
- [ ] A vanity
- [ ] A wall divider
- [ ] A watch
- [ ] A bicycle
- [ ] A motorbicycle
- [ ] A motorbicycle or motor scooter
- [ ] An animal-drawn cart
- [ ] A car, truck or mini-van
- [ ] A boat with a motor
- [ ] A boat without a motor

18. What type of fuel do you mainly use for cooking?

- [ ] Electricity
- [ ] LGP
- [ ] Natural gas
- [ ] Biogas
- [ ] Kerosene
- [ ] Coal, Lignite
- [ ] Charcoal
- [ ] Wood
- [ ] Straw/Shrubs/Grass
- [ ] Agricultrual crop
- [ ] Animal dung
- [ ] No food cooked in household

19. Does any member of this household own any agricultural land?

- ( ) Yes
- ( ) No

20. Which of the following animals does this household own?

- [ ] Milk cows or bulls
- [ ] Horses, donkeys or mules
- [ ] Goats
- [ ] Sheep
- [ ] Chicken or other poultry
- [ ] None of the above

20. a. How many cows?

_____

20. b. How many horses, donkeys or mules?

_____

20. c. How many goats?

_____

20. d. How many sheep?

_____

20. e. How many chickens or other poultry?

_____

21. Main material of floor

- Natural - Earth/Sand
- Natural - Dung
- Rudimentary - Wood planks
- Rudimentary - Palm/bamboo
- Finished - Parquet or polished wood
- Finished - Vinyl or asphalt strips
- Finished - Ceramic tiles
- Finished - Cement
- Finished - Carpet
- Other

21. b. Other material of floor

_____

22. Main material of roof

- No roof
- Natural - Thatch/palm leaf
- Natural - Sod
- Rudimentary - Rustic mat
- Rudimentary - Palm/bamboo
- Rudimentary - Wood planks
- Rudimentary - Cardboard
- Finished - Metal (including zinc)
- Finished - Wood
- Finished - Calamine/cement fiber
- Finished - Ceramic tiles
- Finished - Cement
- Finished - Roofing shingles
- Other

22. b. Other material of roof

_____

23. Main material of exterior walls

- No walls
- Natural - No walls
- Natural - Cane/palm/trunks
- Natural - Dirt
- Rudimentary - Bamboo with mud
- Rudimentary - Stone with mud
- Rudimentary - Uncovered adobe
- Rudimentary - Plywood
- Rudimentary - Cardboard
- Rudimentary - Reused wood
- Finished walls - Cement
- Finished walls - Stone with lime/cement
- Finished walls - Bricks
- Finished walls - Cement blocks
- Finished walls - Covere adobe
- Finished walls - Wood planks/shingles
- Other

23. b. Other material of exterior walls

24. Does any member of your household live outside of Guyana?

- Yes
- No

24. b. Where?

24. c. What is your relation to the person(s) living outside Guyana?

- [ ] Spouse
- [ ] Son/Daughter
- [ ] Brother/Sister
- [ ] Mother/Father
- [ ] Uncle/Aunt
- [ ] Cousin
- [ ] Friend
- [ ] Other

24. d. Other relation

_____

25. How many workers in total work in this place (including temporaray workers)?

_____

26. What are the main activities of the place?

- [ ] Sugar
- [ ] Gold
- [ ] Bauxite
- [ ] Agriculture
- [ ] Restaurant
- [ ] Shop
- [ ] Other

26. b. Other main activity

_____

27. Type of school

- ( ) Kindergarten
- ( ) Primary
- ( ) Secondary
- ( ) University
- ( ) Other

28. How many students are there in this institution?

_____

29. Type of health facility

- Dispensary/Health Post
- Health Centre
- Hospital
- Private clinic

30. How many outpatients visits do you have on an ordinary day in total?

_____

31. How many beds are there in the hospital?

_____

32. Which is the disease you fear the most?

_____

33. Do you know what the Zika virus is?

- Yes
- No

33. a. Can you briefly describe what you know about the Zika virus?

- Mosquito(es)
- Fever
- Skin rash
- Pregnancy
- Microcephaly
- Paralisis

34. Do you know what Dengue fever is?

- Yes
- No

34. b. Can you briefly describe what you know about Dengue fever?

- Mosquito(es)
- Fever
- Skin rash

35. Do you know what Malaria is?

- Yes
- No

35. b. Can you briefly describe what you know about Malaria?

- [ ] Mosquito(es)
- [ ] Fever
- [ ] Headache
- [ ] Cold sweat
- [ ] Vivax
- [ ] Falciparum

36. Do you know what Bush Yaws (Leishmaniasis) is?

- ◯ Yes
- ◯ No

36. a. Can you briefly describe what you know about Bush Yaws (Leishmaniasis)?

- [ ] Sandfly
- [ ] Skin lesion
- [ ] Dog

37. How much do you think you and the people in this place are at risk of Zika virus on a scale from 0 to 10 (0 - risk; 10 - very high risk)?

_____

38. How much do you think you and the people in this place are at risk of Dengue on a scale from 0 to 10 (0 - risk; 10 - very high risk)?

_____

39. How much do you think you and the people in this place are at risk of Malaria on a scale from 0 to 10 (0 - risk; 10 - very high risk)?

_____

40. How much do you think you and the people in this place are at risk of Bush Yaws (Leishmaniasis) on a scale from 0 to 10 (0 - risk; 10 - very high risk)?

_____

	Decrease	Remain the same	Increase	Don't know
41. In 5 years, what impact do you think the Zika virus will have on the health of the people of this community?				
Zika virus	◯	◯	◯	◯
42. In 5 years, what impact do you think the Dengue fever will have on the health of the people of this community?	Decrease	Remain the same	Increase	Don't know
Dengue fever	◯	◯	◯	◯
43. In 5 years, what impact do you think Malaria will have on the health of the people of this community?	Decrease	Remain the same	Increase	Don't know

Malaria	◯	◯	◯	◯
44. In 5 years, what impact do you think Bush Yaws (Leishmaniasis) will have on the health of the people of this community?	Decrease	Remain the same	Increase	Don't know
Bush Yaws (Leishmaniasis)	◯	◯	◯	◯

45. What would you do to avoid the Zika virus? (Multiple replies allowed)

- ☐ Nothing
- ☐ Screened windows
- ☐ Skin repellent
- ☐ Mosquito zapper racket
- ☐ Beeper mosquito
- ☐ Fogging
- ☐ Indoor residual spray
- ☐ Mosquito coils
- ☐ Bed nets
- ☐ Bracelets
- ☐ Sitting next to a fire

45. What would you do to avoid the Dengue fever? (Multiple replies allowed)

- ☐ Nothing
- ☐ Screened windows
- ☐ Skin repellent
- ☐ Mosquito zapper racket
- ☐ Beeper mosquito
- ☐ Fogging
- ☐ Indoor residual spray
- ☐ Mosquito coils
- ☐ Bed nets
- ☐ Bracelets
- ☐ Sitting next to a fire

45. What would you do to avoid Malaria? (Multiple replies allowed)

- [ ] Nothing
- [ ] Screened windows
- [ ] Skin repellent
- [ ] Mosquito zapper racket
- [ ] Beeper mosquito
- [ ] Fogging
- [ ] Indoor residual spray
- [ ] Mosquito coils
- [ ] Bed nets
- [ ] Bracelets
- [ ] Sitting next to a fire

45. What would you do to avoid Bush Yaws (Leishmaniasis? (Multiple replies allowed)

- [ ] Nothing
- [ ] Screened windows
- [ ] Skin repellent
- [ ] Mosquito zapper racket
- [ ] Beeper mosquito
- [ ] Fogging
- [ ] Indoor residual spray
- [ ] Mosquito coils
- [ ] Bed nets
- [ ] Bracelets
- [ ] Sitting next to a fire

46. How effective do you perceive the preventative measures you would use on a scale from 0 to 10?

_____

SHOW INTERVIEWEE EMB1 PICTURE

Click here to upload file. (< 5MB)

SHOWINTERVIEWEE EMB2 PICTURE

Click here to upload file. (< 5MB)

SHOW INTERVIEWEE EMB3 PICTURE

Click here to upload file. (< 5MB)

SWITCH TO THE RANDOM NUMBER GENERATOR APP TO GET A NUMBER FROM 1 TO 13

Enter the number you would have generated

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ 11
- ◯ 12
- ◯ 13

SHOW THE CORRESPONDING PICTURE NUMBER TO THE NUMBER YOU GENERATED

Click here to upload file. (< 5MB)

47. a. In your opinion, which of the three options described do you think is best?

- ◯ EMB1
- ◯ EMB2
- ◯ EMB3

47. b. Taking into account your circumstances, which one of the options would you take?

- ◯ EMB1
- ◯ EMB2
- ◯ EMB3
- ◯ None

S2. Sample selection method

Sample size was strongly determined by the availability of resources: our sampling approach was therefore exploratory. Within this context, we aimed at representing both coastal and hinterland regions: the two categories of regions summarize substantial within-country variability across a number of relevant dimensions for this study. Coastal regions are more populated with a high concentration of the main country towns (Georgetown, the country capital, and New Amsterdam). In the coastal regions, there is a higher burden of *Aedes* mosquitos transmitted parasite infections (such as dengue and zika viruses) and access to health care services is much easier than in the hinterland. Hinterland regions have an unusual low population density, with nearly the totality of its inhabitants concentrated in a few small towns. The economy in the hinterland is mostly based on extraction activities (mainly of gold, diamonds and bauxite) and logging. The access to healthcare is poor and the burden of vector borne diseases is mainly determined by parasites transmission though *Anopheles* mosquitos (malaria). Given our resources constraints, we chose two coastal and two hinterland regions. Coastal regions include regions 4 and 6, the former includes the capital city Georgetown which concentrates 30% of the national population while the latter includes the second largest city, New Amsterdam. Interior regions consisted of regions 1 and 8, which are geographically vast but with a very low population density, and where we conducted our survey around two main towns: Mabaruma and Mahdia respectively.

Again, given the limited resources available, we collected about 800 questionnaires in total, which we equally divided across the 4 regions (i.e. a sample size per region of 200). We obtained information from the Bureau of Statistics of Guyana on the number of inhabitants in each region, split by lower administrative units (called villages) – most recent population data were from the 2012 national census. Based on that information, a subset of villages were selected by the Ministry of Public Health based on their proximity to the starting point and their accessibility by walking distance or public transport. More precisely, 49 villages out of 198 villages were ‘preselected’ for region 4 and 22 out of 190 villages for region 6. Among these villages, 15 villages in regions 4 and 6 were randomly chosen applying sampling proportional to size (World health organization (WHO), no date). In each of the selected 15 neighborhoods, the

number of questionnaires was also assigned based on population's size, with more questionnaires assigned to more populated neighborhoods (Table S2). We assigned 210 questionnaires to account for potential attrition[5]. A starting point was chosen by data collectors within each neighborhood who then applied the "spinning bottle" rule (Bostoen and Chalabi, 2006). In the interior of the country, since most villages are small, far away from each other and poorly connected, we decided to focus our research around the main centers of Mabaruma in region 1 and Mahdia in region 8, which have a total population of about 2,000 inhabitants each. For those two towns, selection proportional to size was not applied. Instead, data collectors selected houses starting from the health center and then moved forward applying the "spinning bottle" rule.

Table S2: Selection proportional to size (regions 4 and 6)

Names (or abbreviations) of your primary sampling units	Estimated size of sampling units	Probability of inclusion	Number of quesitonnaires
Region 4			
Cummings Lodge	7246	1	21
Kitty	6789	1	20
Turkeyen	6599	0,978557447	19
Campbellville	5031	0,74604069	18
Pattensen	5013	0,743371493	17
West Ruimveldt	4206	0,623702473	16
Albouystown	3838	0,569132214	15
Sophia	3687	0,546740613	14
Liliandaal	3100	0,459695118	13
Werk En Rust	2760	0,409276944	12
Albertown	2357	0,349516579	11
East La Penitence	1984	0,294204876	10
Ogle	1391	0,206269648	9
Prashad Nagar	1013	0,150216502	8

[5] The study is currently proceeding with 2 additional data collection rounds among the same cohort of individuals.

Lamaha Gardens	638	0,094608221	7
Region 6			
Cumberland	3875	1	21
Mount Sinai	3861	1	20
Canefield	3268	1	19
Rose Hall	3067	1	18
Stanleytown	3049	1	17
Glasgow	1868	0,94448377	16
Adelphi	1303	0,658812822	15
Little Bleyendaal	1214	0,613813328	14
Sheet Anchor	1114	0,563252098	13
Edinburg	1069	0,540499545	12
Reliance	921	0,465668925	11
Ordnance Fort Canje	883	0,446455658	10
Overwinning	873	0,441399535	9
Vrymans Erven	802	0,405501062	8
Palmyra or No. 4	540	0,27303064	7

NB: 210 questionnaires were aimed in each region to account for dropouts in the following rounds of data collection

S3. The determinants of knowledge:

$Knowledge\_malaria_i = \beta_0 + \beta_1 Education_i + \beta_2 Sex_i + \beta_3 Wealth\_index_i + \beta_4 Region_i + \varepsilon_i$

$Knowledge\_dengue_i = \beta_0 + \beta_1 Education_i + \beta_2 Sex_i + \beta_3 Wealth\_index_i + \beta_4 Region_i + \varepsilon_i$

$Knowledge\_zika_i = \beta_0 + \beta_1 Education_i + \beta_2 Sex_i + \beta_3 Wealth\_index_i + \beta_4 Region_i + \varepsilon_i$

$Knowledge\_leishmaniasis_i = \beta_0 + \beta_1 Education_i + \beta_2 Sex_i + \beta_3 Wealth\_index_i + \beta_4 Region_i + \varepsilon_i$

Where i=individual 1 to 497

Table S3: The determinants of knowledge (probit regression)

	Malaria	Dengue fever	Zika virus	Cutaneous leishmaniasis
	Coef. (St. Err)	Coef. (St. Err)	Coef. (St. Err)	Coef. (St. Err)
Education				
No formal education (base)	(empty)			
Primary education	-1.329**	-0.382	0.918	0.196
	(0.540)	(0.710)	(0.587)	(0.469)
Secondary education	-0.836	-0.106	1.449**	0.373
	(0.518)	(0.710)	(0.588)	(0.471)
University	(base)	-0.324	1.617**	0.349
		(0.768)	(0.635)	(0.542)
Sex				
Female (base)				
Male	0.558**	0.407**	0.0320	0.0812
	(0.247)	(0.169)	(0.147)	(0.154)
Wealth index				
1st quantile of the wealth index (base)				
2nd quantile of the wealth index	0.340	-0.285	0.342*	0.282
	(0.288)	(0.219)	(0.198)	(0.226)
3rd quantile of the wealth index	0.260	-0.123	0.640***	0.627***
	(0.269)	(0.211)	(0.201)	(0.226)
4rth quantile of the wealth index	0.107	-0.180	0.666***	0.882***
	(0.281)	(0.217)	(0.204)	(0.223)
5th quantile of the wealth	0.370	-0.0828	0.706***	0.649***

index				
	(0.306)	(0.223)	(0.203)	(0.223)
Region				
region 4 (base)				
region 6	-0.630***	-0.751***	-0.303*	-0.470**
	(0.194)	(0.173)	(0.171)	(0.226)
region 8	0.988***	-0.0800	-0.764***	0.557***
	(0.280)	(0.171)	(0.179)	(0.185)
region 1	(empty)	1.586***	0.584***	0.962***
		(0.252)	(0.168)	(0.177)
Constant	1.639***	0.620	-1.794***	-1.850***
	(0.584)	(0.713)	(0.589)	(0.472)
Observations	347	497	497	497

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

The coefficient cells are empty for the categories *No education* and *region 1* in the malaria estimation reducing the sample size to 347 individuals. This is because there were no people with no education who had no knowledge of malaria and there were no people living in region 1 who did not know about malaria. As “no formal education” is empty in the malaria equation, “University” becomes the reference category for education.

S4. Robustness check by using another definition of positive behavior

In this case, behavior is equal to 0 if the respondent uses nothing, 1 if the respondent uses IRS and/or fogging, 2 if the respondent uses one other measure than IRS and/or fogging, 3 if the respondent uses two other measures than IRS and/or fogging, etc. Accordingly, as opposed to the definition used in the manuscript, bed net use is no longer considered passive but active. Results of the SEM are provided in the below Table S4.

Table S4: Robustness check. Results of the structural model with the other definition of behavior

		Malaria	**Dengue fever**	**Cutaneous leishmaniasis**	**Zika virus**
Dependent variable	**Explanatory variables**	St. Coeff (Std. Error)	St. Coeff (Std. Error)	St. Coeff (Std. Error)	St. Coeff (Std. Error)
Equation 1					
Behavior	Knowledge	0.924*** (0.096)	0.382*** (0.116)	0.999*** (0.301)	-0.627 (0.403)
	Risk	0.267* (0.135)	=	=	=
	Wealth	0.155*** (0.055)	-0.217*** (0.073)	=	=
	Region	-0.563*** (0.109)	=	-0.219 (0.199)	0.178 (0.252)
	Educ	0.038 (0.047)	=	-0.127* (0.073)	=
	Female	0.041 (0.035)	=	=	=
Equation 2					
Knowledge	Wealth	0.017 (0.045)	=	-0.226** (0.085)	0.208** (0.075)
	Region	0.630*** (0.059)	0.359*** (0.068)	-0.523*** (0.104)	0.569*** (0.078)
	Educ	0.168*** (0.036)	=	=	=
	Female	0.011 (0.032)	=	=	=
Equation 3					
Risk	Knowledge	-0.110 (0.120)	0.094 (6.873)	-0.114 (0.769)	=
	Behavior	-0.071 (0.138)	=	1.481** (0.607)	=
	Wealth	0.030 (0.049)	-0.027 (0.144)	=	=
	Region	0.924***	0.366	=	0.019

		(0.078)	(2.470)		(0.130)
	Educ	0.088	-0.077	=	0.035
		(0.058)	(1.155)		(0.095)
	Female	-0.007	=	=	=
		(0.043)			
N		438	335	134	231
Chi-Squared (df)=34.70 (23); p-value=0.05566					
RMSEA=0.042					

Legend: '=' implies that coefficients are equal to the ones estimated for the malaria model (model 1); **significant at 5% significance level; *** significant at 1% significance level; St. Coeff= standardized coefficient; Std. Error= Standard error; N=sample size; df= degrees of freedom; RMSEA= Root Mean Square Error of Approximation.

S1 Text. Data management and analysis

The data collected were uploaded either instantaneously or at the end of the day (depending on the availability of the network facilities) in an online reporting platform (https://www.kobotoolbox.org/) that could only be accessed with a password. All questionnaires were coded with a unique serial number and each interviewee was identified with a unique code to ensure anonymity of the data. Data were primarily exported into Microsoft Excel and afterward exported to Stata software (StataCorpLP, http://www.stata.com) to obtain the correlation matrices, which were then inputted into LISREL (http://www.ssicentral.com/lisrel/) for estimating the SEM using the below input.

S2 Text. Input from LISREL

```
Group1 Malaria
data ng=4 ni=7 no=438 ma=km

km
1.0000
0.3508   1.0000
0.0194   0.2140   1.0000
0.2073   0.0227  -0.1048   1.0000
0.1900  -0.0093  -0.0083   0.2797   1.0000
0.0455   0.4351   0.6193  -0.2331  -0.0350   1.0000
0.0386  -0.0834  -0.0195   0.0605   0.0995  -0.0365   1.0000

labels
Behavior Know Risk Educ Wealth Region Female

se
Behavior Know Risk Wealth Region Educ Female /

model ny=3 nx=4 ne=3 nk=4 lx=fu,fi ly=fu,fi te=fu,fi td=fu,fi be=fu,fi ga=fu,fi
ph=sy,fr ps=sy,fi

le
Behavior Know Risk

lk
Wealth Region Educ Female

!measurement error
va 0.728 ly 1 1
va 0.747 ly 2  2
va 0.752 ly 3 3

!fix variance of errors terms to 1-q2
va .47 te 1 1
va  .4420 te 2 2
va  .4345 te 3 3

!effects between the eta
fr be 1 2 be 3 2 be 1 3 be 3 1

!effects between eta and ksi
fr ga 1 1 ga 1 2 ga 2 2 ga 3 2 ga 2 3 ga 1 3 ga 3 3 ga 2 1 ga 1 4 ga 2 4  ga 3 4
ga 3 1

!measurement perfect for the x
va 1 lx 1 1
va 1 lx 2 2
va 1 lx 3 3
va 1 lx 4 4
```

```
!free variances for the eta
fr ps 1 1 ps 2 2 ps 3 3

out mi AD=OFF it=500

Group2 Dengue

data ni=7 no=335 ma=km

km
1.0000
0.2047   1.0000
-0.0239   0.0888   1.0000
0.1397   0.1663  -0.0972   1.0000
-0.0248   0.0819  -0.0382   0.3201   1.0000
-0.2223   0.2440   0.3305  -0.1692  -0.0500   1.0000
0.0233   0.0211  -0.0239   0.0616   0.1396  -0.0674   1.0000

labels
Behavior Know Risk Educ Wealth Region Female

se
Behavior Know Risk Wealth Region Educ Female /

model ny=3 nx=4 ne=3 nk=4 lx=fu,fi ly=fu,fi te=fu,fi td=fu,fi be=in ga=in ph=sy,fr
ps=in

va 0.728 ly 1 1
va 0.747 ly 2  2
va 0.752 ly 3 3

va .47 te 1 1
va  .4420 te 2 2
va  .4345 te 3 3

va 1 lx 1 1
va 1 lx 2 2
va 1 lx 3 3
va 1 lx 4 4

fr ga 3 2 ga 3 1 ga 2 2 ga 1 1
fr ps 2 1 ps 3 1 ps 3 3

out mi AD=OFF it=500

Group3 leishmaniasis
data ni=7 no=134 ma=km

km
```

```
1.0000
0.4425   1.0000
0.1499   0.3525   1.0000
0.0890   0.0265   0.1042   1.0000
-0.1540  -0.1572  -0.0027   0.3275   1.0000
-0.5240  -0.4257  -0.1796  -0.0830   0.1078   1.0000
0.0384   0.0732   0.1299   0.1081   0.0947  -0.0759   1.0000

labels
Behavior Know Risk Educ Wealth Region Female

se
Behavior Know Risk Wealth Region Educ Female /

model ny=3 nx=4 ne=3 nk=4 lx=fu,fi ly=fu,fi te=fu,fi td=fu,fi be=in ga=in ph=sy,fr
ps=in

va 0.728 ly 1 1
va 0.747 ly 2  2
va 0.752 ly 3 3

va .47 te 1 1
va  .4420 te 2 2
va  .4345 te 3 3

va 1 lx 1 1
va 1 lx 2 2
va 1 lx 3 3
va 1 lx 4 4

fr be 1  2 be 3 1 be 3 2
fr ga 2 1 ga 2 2 ga 1 2 ga 2 3
fr ps 2 1 ps 3 1 ps 2 2 ps 3 2

out mi AD=OFF it=500

Group4 zika
data ni=7 no=231 ma=km

km
1.0000
0.0928   1.0000
0.0290  -0.0633   1.0000
0.0271   0.2371   0.0329   1.0000
0.0370   0.2188   0.0171   0.1344   1.0000
-0.0047   0.4272  -0.0238  -0.0655   0.1270   1.0000
-0.0121   0.0728  -0.0442  -0.0489   0.0713  -0.0993   1.0000

labels
Behavior Know Risk Educ Wealth Region Female
```

```
se
Behavior Know Risk Wealth Region Educ Female /

model ny=3 nx=4 ne=3 nk=4 lx=fu,fi ly=fu,fi te=fu,fi td=fu,fi be=in ga=in ph=sy,fr
ps=in

va 0.728 ly 1 1
va 0.747 ly 2  2
va 0.752 ly 3 3

va .47 te 1 1
va  .4420 te 2 2
va  .4345 te 3 3

va 1 lx 1 1
va 1 lx 2 2
va 1 lx 3 3
va 1 lx 4 4

fr be 1 2
fr ga 2 1 ga 1 2 ga 2 2 ga 3 2 ga 3 3 ga 3 1
fr ps 1 1 ps 2 2 ps 3 2 ps 3 3

pd

out mi AD=OFF it=500
```

S3 Text. Structural equation model (SEM)

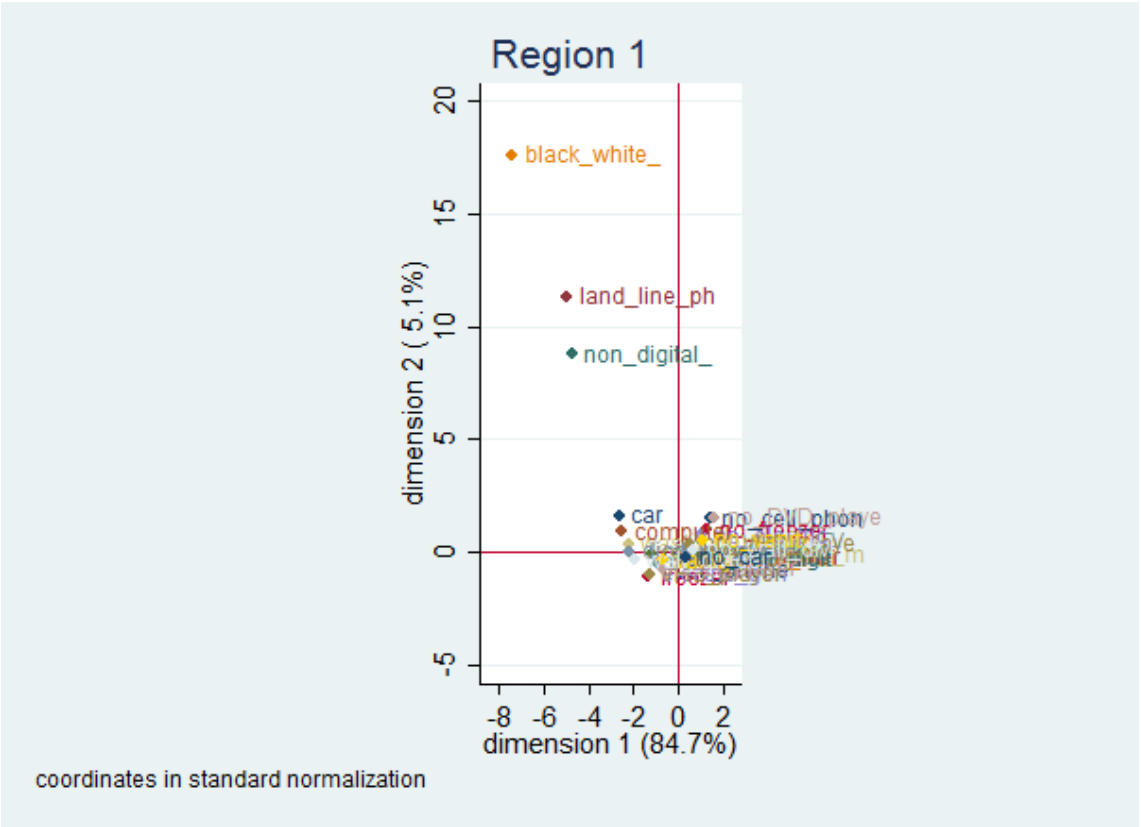
SEM has been widely used in social sciences, initially among quantitative scientists in sociology and psychology (Tarka, 2018) and later became one of the causal models for health-sciences research (Greenland and Brumback, 2002). Despite the causality debate surrounding the use of SEM (Bollen and Pearl, 2013), this model has often been suggested to deal with the different sources of endogeneity without requiring longitudinal data. First, it is capable of dealing with omitted variable bias (as long as these do not play a crucial role in the analysis) by allowing correlation between the error terms (Tarka, 2018). An example of omitted variable in here is whether the individual experienced a previous episode of the disease, which is likely to be correlated with the error term of *knowledge*, *risk* perception and *behavior*. Second, SEM is able to account for measurement error by using latent variables as indicators of observed variables. Indeed, measurement error can be significant when using reported measures and particularly when related to health (Butler *et al.*, 2018). Third, this model may be capable of solving for reverse relationship, which is conditional on being empirically identified (i.e. from having at least as many exogenous variables than endogenous ones). Fourth, SEM allows for comparing models in terms of their best fit with the data – the so-called 'confirmatory analysis' (Borghi *et al.*, 2018). Lastly, another feature of SEM is that it allows for multiple group analysis so that statistical differences between groups (i.e. diseases) can be assessed (Rosa, 2002). Hence, we are able to test whether the responsiveness of preventive behavior to risk differs across diseases.

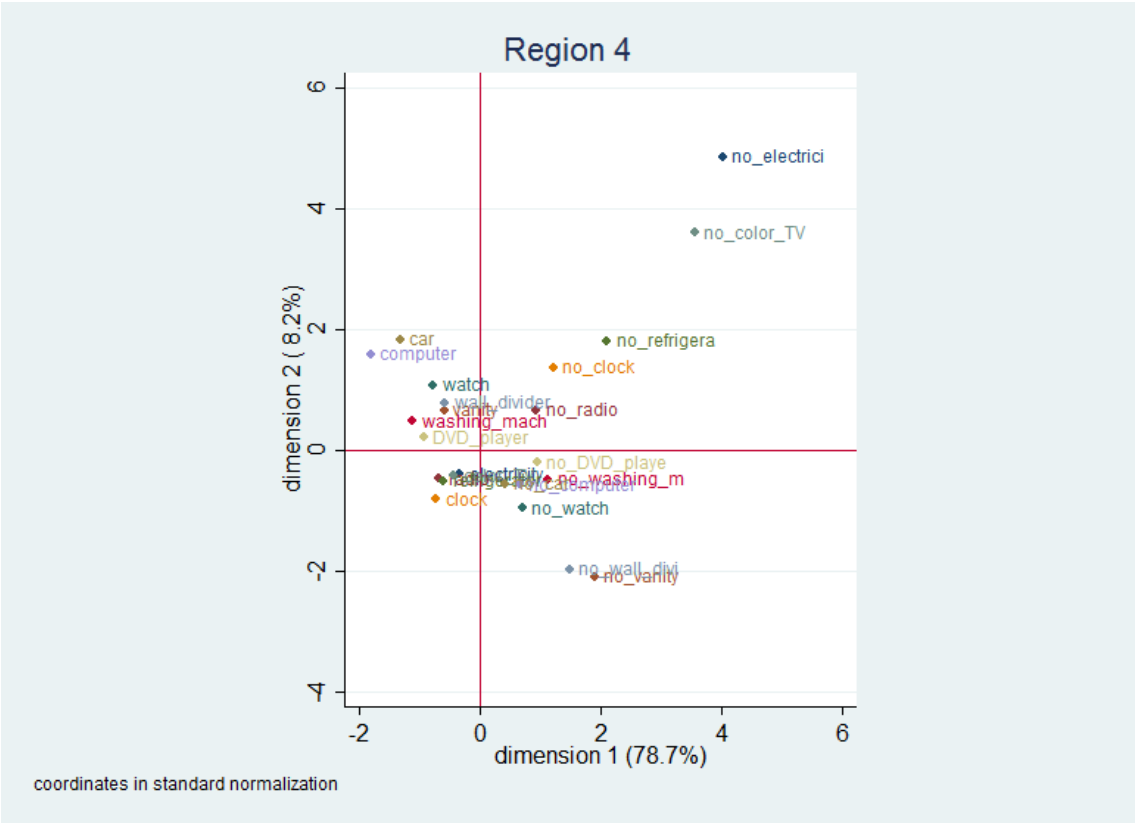
S4 Text. Measurement error and testing of the model

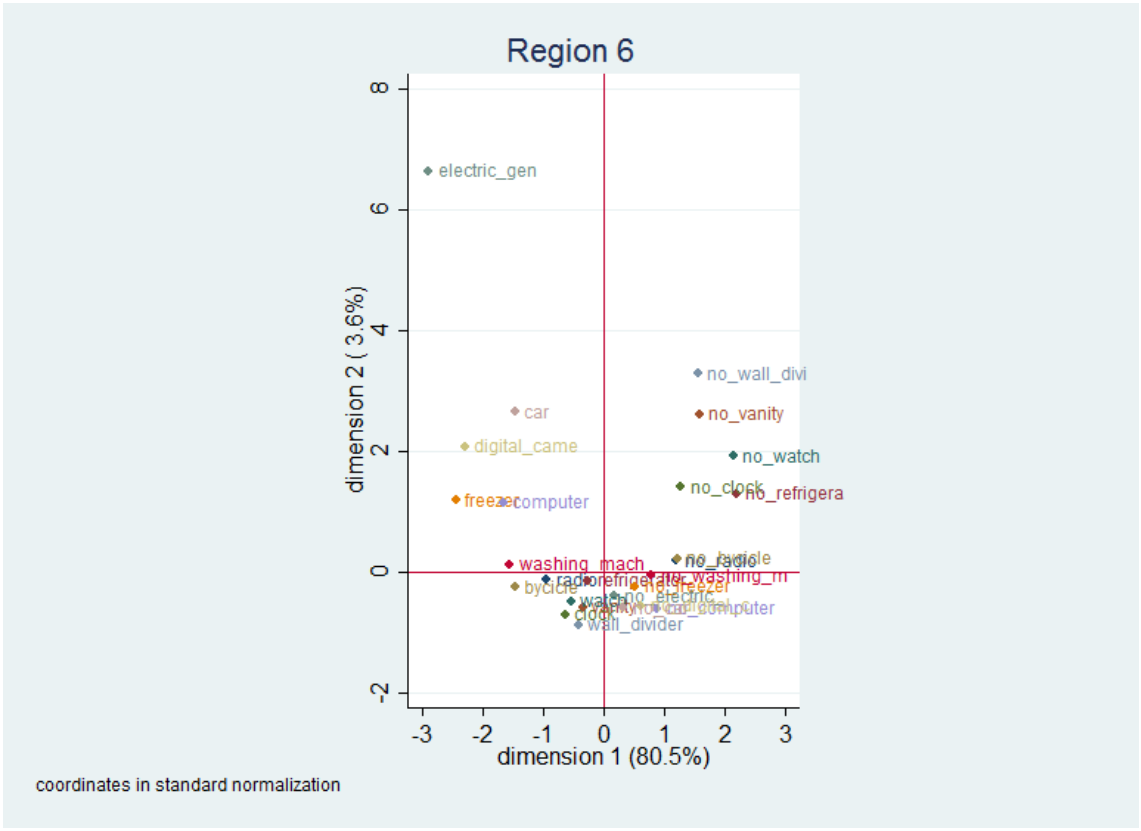
Since measurement error can be significant for survey measures, it was considered for the self-reported variables: *behavior*, *knowledge* and *risk* perception using the Survey Quality Predictor program (http://sqp.upf.edu/) (Senik, 2005; van de Mortel, 2008; Saris, 2013). Furthermore, since SEM is better at dealing with continuous variables rather than categorical ones, correcting for measurement error also takes into account that while the latent variable is continuous the observed variable behind may be categorical. For the exogenous variables – *wealth*, *education*, *region*, and *female* – it is not possible to correct for measurement error using the SQP program and hence it was assumed a perfect measurement, implying a quality coefficient of 1. Nonetheless, this is not believed to be a major issue as these variables do not embed subjectivity.

Regarding the testing of the model, parameters of the equations were first assumed equal across diseases (i.e. group analysis) in LISREL. Afterward, based on Jrule suggestions – a postestimation tool for the SEM command that indicates local misspecifications based on the modification index (MI), the power of the MI and the expected parameter change (EPC) (van der Veld, Saris and Satorra, 2008; Van Der Veld, Saris and Satorra, 2008; Aichholzer, 2018) – parameters that were found to differ across diseases were let free to vary. Jrule was used in addition to the usual chi-square test to assess the model's fit because – as opposed to the latter – it is able to detect the size of the misspecification and is not influenced by sample size (Saris, Satorra and van der Veld, 2009).

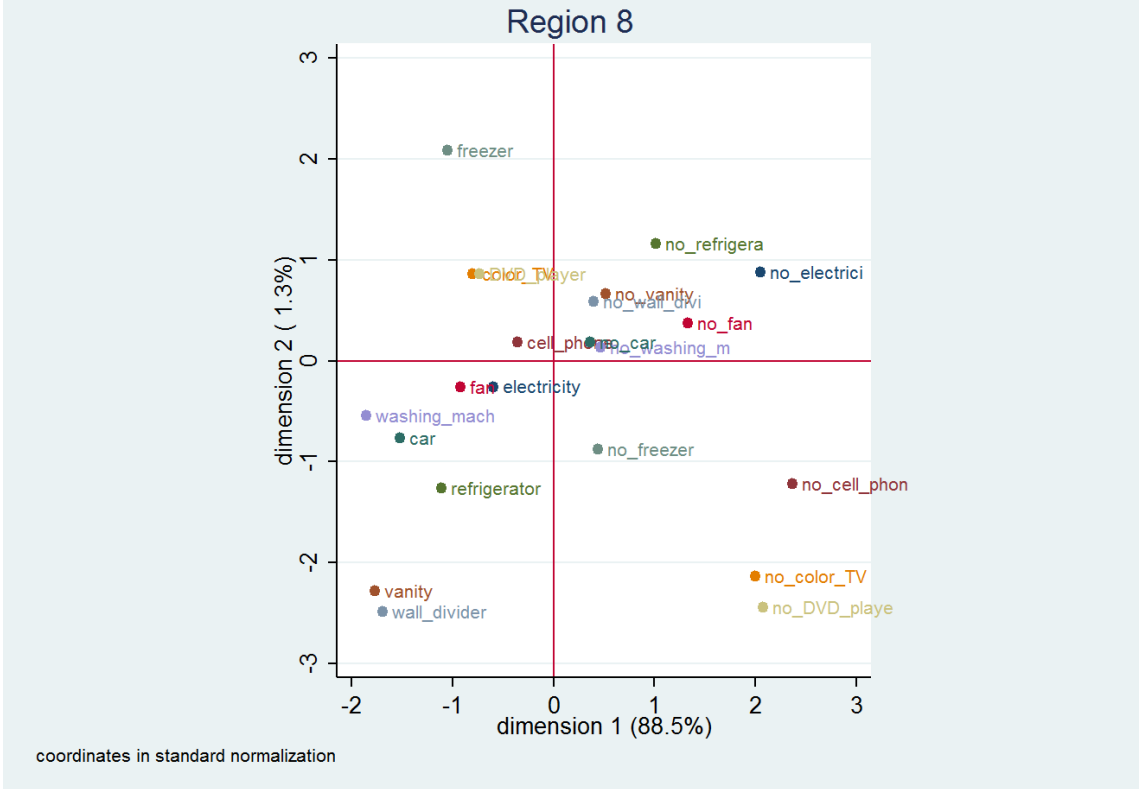
S1 Figure: Multiple correspondence analysis per region







coordinates in standard normalization



coordinates in standard normalization

S1 Table: Keywords cited per disease

Malaria	
Do you know malaria? If yes, could you please describe what you know about malaria?	
Variables	**% (N=497)**
Do not know	11.87%
keywords	
Mosquito(es)	25.68%
Fever	24.09%
Headache	18.73%
Cold sweat	13.44%
Vivax	8.99%
Falciparum	9.06%
Dengue fever	
Do you know dengue fever? If yes, could you please describe what you know about dengue fever?	
Variables	**% (N=497)**
Do not know	32.6%
keywords	
Mosquito(es)	49.32%
Fever	47.16%
Skin rash	3.52% (18)
Zika virus	
Do you know zika virus? If yes, could you please describe what you know about zika virus?	
Variables	**% (N=497)**
Do not know	53.52%
keywords	
Mosquito(es)	50.83%
Fever	18.05%
Pregnancy	13.30%
Microcephaly	13.06%
Skin rash	3.80%
Paralysis	0.95%
Cutaneous leishmaniasis (CL)	
Do you know cutaneous leishmaniasis? If yes, could you please describe what you know about cutaneous leishmaniasis?	
Variables	**% (N=497)**
Do not know	77.46%
keywords	
Skin lesion	82.69%
Sandfly	16.67%
Dog	0.64%

Legend: freq.=frequency

S2 Table: Vector control measures used per disease

What do you do to avoid disease x?

		Malaria	Dengue fever	Zika virus	Cutaneous leishmaniasis
Provided by the government	Bed nets	87.67%	68.36%	63.20%	23.88%
	Indoor residual spray	27.40%	35.22%	37.23%	20.90%
	Fogging	13.47%	17.31%	9.52%	14.18%
Not provided by the government	Skin repellent	26.48%	21.49%	39.83%	11.94%
	Mosquito coils	34.93%	15.82%	19.48%	3.73%
	Screened windows	4.34%	2.39%	4.33%	1.49%
	Mosquito zapper racket	2.28%	2.09%	3.46%	1.49%
	Sitting next to a fire	0.68%	0.30%	0.43%	0
	Bracelets	0.68%	0	0	0
	Beeper mosquito	0.23%	0	0.43%	0

Legend: freq.= frequency

V. Summary of the results and discussion

The studies presented in this thesis shed light on some of the barriers in achieving the control and elimination of NTDs. More specifically, of the obstacles encountered throughout product innovation, implementation and adoption. Investment in innovation for NTDs is difficult to incentivize among pharmaceutical companies, but yet, even when successfully doing so through for instance PDPs, the final product may not be cost-effective for the targeted (endemic) country (e.g. LAMP in Afghanistan). Last but not least, final products implemented in the endemic country may not be adopted by the community due to characteristics that are inherent to them, such as low educational level and low risk perception of the disease. Therefore, a better grasp of these challenges is crucial for maximizing the time and resources invested in policy-making that will free people from the vicious cycle of poverty, a cycle that is fueled by NTDs.

Development

Until recently, PDPs, have mainly relied on push mechanisms through R&D grants. However, these are criticized for issues related to moral hazard and adverse selection, which arise due to asymmetric information between the donor and the grant's recipient. Moreover, it is argued that the cost of R&D per se is not the real barrier to the development of products for NTDs but that the real one is the foreseen lack of market. Rewarding final products is the motive behind pull mechanisms such as AMC and PRV but these are neither perfect and suffer from challenges (i.e. AMC: setting the right final price and quantity; PRV: rewarding true innovations). Despite those challenges for both push and pull schemes, there is a general consensus in the literature that PDPs should adopt mixed schemes. That is, R&D grants to stimulate investment in the initial phases combined with a pull scheme for the last development phase. From the literature, it is clear that the primary objectives of PPPs are to respond to the lack of adequate products and to ensure their delivery to the population in need. Delivery of products has so far relied on MDA programs, which although generally claimed as successful, are criticized for a reliance on a for-profit organization (a pharma company) and for a lack of surveillance on disease re-emergence following the end of the program. Another finding arising from this review is that PPPs are not targeting all NTDs equally. For some NTDs, no partnerships could be attributed. While this makes sense for diseases that are close to elimination (e.g.

dracunculiasis), it is not justifiable for others that do not have adequate products yet. These diseases are often referred to as “the neglected of the neglected” and include among others, buruli ulcer, taeniasis and mycetoma. Moreover, although PPPs have proliferated in the last two decades and are considered as ‘the’ model for NTDs, very little is known about their performance. The literature on PPPs is primarily descriptive and severely lacks robust empirical research. This finding is likely to be a consequence of the lack of transparency on PPP models. There is no single database which routinely reports updates and advances from PPPs such as funding received, private investments made, R&D time frame and success rates. However, in order to make the best of these partnerships, one must evaluate their impact; for instance, analyze how differences in their characteristics affect their performance. As a result, a key policy recommendation arising from this study is to promote greater transparency among PPPs, potentially through registration on a unique platform that would monitor their development and report their funding invested. This refers to the idea of “transparency in exchange for public funds” (Granville and Trushin, 2015).

Digging further into a specific pull mechanism, the PRV, we showed that it has been ineffective at stimulating R&D for the intended neglected diseases. That is, so far, the PRV has not stimulated the registration of clinical trials for neglected diseases, even when looking at potential delayed effects of the policy. These findings were confirmed across robustness tests and support our initial assumption that the reward of the voucher – 4 months earlier market launch – whether used or sold, is not sufficient to trigger pharmaceutical interest to invest in developing innovative products for neglected diseases. To our belief, pharmaceutical companies are unlikely to embark in risky projects based on a voucher that can be sold for as ‘little’ as $67 million. As Ridley put is, if the value of the voucher goes below $100.000 million, it is not even sufficient to cover the costs of phase 3 registration (Ridley and Régnier, 2016). While it is potentially true that large pharmaceutical companies may have a greater interest than smaller ones in using the voucher rather than selling it (as they are more likely to have a blockbuster candidate), the benefit of a 4 months earlier entry on the market is not a sufficient compensation for having invested time and resources in a completely different type of disease. Accordingly, if pharmaceutical companies

are involved in neglected diseases projects, it is more likely to be within product-development partnerships (PDPs) – as seen from the awarded vouchers so far. In that case, the PRV may not actually act as a real “pull” mechanism but as a recompense for doing things right. Therefore, the PRV may be better suited at incentivizing the continuation or take up of projects that were already somewhere in the development process. Similarly, the PRV may appear particularly attractive for products that are known to be safe but that have not yet been registered in the US or for which new combinations or repurposed usages can be explored. Those products may not need to go through the entire trial cycle but may be approved on a pivotal phase 2/3 combined. Overall, our results are consistent with the outcomes of 12 years of PRV implementation: 33 vouchers awarded, 11 of which were awarded to tropical diseases. These vouchers mainly rewarded products that were already licensed outside the US or that were born of new formulations of previously existing drugs, and in many cases, developed through a PDP. While rewarding the latter may not seem problematic, the same cannot be said for rewarding products that were already in use outside the US. Accordingly, policy recommendations drawn from this study would need to address and correct the main program’s flaw: a product cannot be awarded a voucher if it was already licensed outside the US. Doing so would decrease the supply of vouchers, restraining the current depreciation of its market value. Nonetheless, this is unlikely to be sufficient to convince pharmaceutical companies to invest alone in such risky project. Accordingly, if one wants to encourage industry-funded research, the PRV may need to be supplemented with an additional pull mechanism such as the advance market commitment (AMC) to guarantee a minimum level of market profitability from the product awarded the voucher. Furthermore, as opposed to the PRV, accessibility to the product is also enhanced by the AMC.

Implementation

To take into account the respective strength of the microscopy, LAMP and RDT, several scenarios were hypothesized in the Afghan context. More precisely, if tests are to be done in the reference clinic only and in a period of low incidence rate, microscopy remains preferred and should not be replaced by any of the novel tools. However, if tests are to be done in the reference clinic but in a period

of high incidence rate such as during outbreaks, conflict times or during the CL main transmission season (i.e. winter), then LAMP becomes potentially cost-effective. More precisely, LAMP is preferred over microscopy if at least 35 tests can be performed at once. RDT becomes cost-effective when implemented in remote health facilities. Nevertheless, despite being cost-effective, this scenario implies that more than a third of the patients tested with RDT will appear as negatives while they are positives. As it may not seem completely correct to leave sick patients without a correct diagnostic, a final scenario was hypothesized. In the latter, patients who tested negative in remote facilities – but with symptoms of CL – are sent to the reference clinic in Kabul to be tested again with microscopy or LAMP. Again, if more than 35 tests can be done at once (although less probable if a primary screening is done in remote health facility), it is better to employ LAMP for the second diagnostic. If this is not the case, microscopy remains the preferred option for a second screening strategy. One limitation of this study is the small difference in effectiveness (i.e. DALYs) across the different tools, which made the analysis very sensitive to changes in cost parameters. In other words, costs were the main driver of the results. This similar effectiveness across the tools is a consequence of the low value assigned – according to the GBD report – to the CL disability weight, which only accounts for the resulting physical deformities but not for the emotional burden nor the social stigma that the disease generate. A take-away from this study is that novel tools may not necessarily end up being cost-effective for countries that need them the most. This being said, as seen from the various scenarios, the outcome may change when tapping on their respective strengths, keeping the context into account. Using the capacity of the LAMP to perform several tests at once may be particularly relevant in a country like Afghanistan where laboratory experts are lacking due to decades of war. Similarly, RDT is convenient in areas of the country where there is no or little diagnostic capacity.

Adoption

Higher risk perception translates into the take up of preventive measures – the more people fear, the more they protect themselves – which in turn decreases risk perception. Moreover, measures subsidized by the government are more likely to be used, regardless of the perceived risk. This article also showed that

in the context of Guyana, better knowledge increases the demand for prevention for malaria and dengue but without affecting risk perception. This can be explained by the following: the more people know about the diseases, the more measures they will demand, the more in control they will feel, and the less affected is their risk perception. In line with this, better knowledge of Zika and CL does not increase the up-take of preventive measures potentially because of a general lower risk perception. In short, if risk perception is low, a better knowledge of the disease will not translate into an increase in the demand for prevention. Yet, knowledge and risk perception may not be the only determinants of behavior: the type of region in which the respondent lives plays a crucial role. Throughout the analysis, the variable *region* played a key role in explaining behavior, knowledge and the perceived risk. More precisely, people living in the hinterland tend to use fewer vector control measures but have a higher knowledge of the diseases (except for CL) and an accurate perception of the risk (i.e. higher for malaria and CL). This suggests that not only the variable region is a good proxy for the actual prevalence – and that the perceived risk is consistent with the actual risk of infection – but that it captures other features that are specific to the region such as accessibility. Accordingly, geographic isolation may act as a substantive barrier to the usage of additional vector control measures. As for the sociodemographic variables education and sex, the former only influenced (positively) knowledge while the latter had no influence on any of the variables but which can be explained by the overrepresentation of women (i.e. 76%) in our sample. Those findings have considerable implications for public health interventions as they can help modelling the impact of outbreaks on behavioral practices. Indeed, when facing an epidemic, by providing the population with an accurate perception of the risk, people will respond through safer behavior. In addition, increasing disease knowledge through the provision of information on the causes and symptoms of the diseases will also lead to the adoption of additional vector control measures. Similarly, in a context of disease elimination, effective communication with the population at risk is crucial, particularly during the so-called “last mile” (i.e. eliminating the few remaining cases) so that behavior does not decrease from a lower risk perception. This is even more important for diseases that are asymptomatic or for diseases that are characterized by common symptoms such as fever and nausea, which lack a routine surveillance

system (e.g. dengue and Zika), and which elimination is likely to be further challenged by an underestimation of the actual risk of infection.

VII. Conclusions

1. There is a lack of empirical research on the effectiveness and cost-effectiveness of public-private partnerships (PPPs), and more precisely of product-development partnerships (PDPs), which is likely to be a consequence of their limited transparency. Policy recommendations should thus mandate greater transparency on funding invested as well as on research and development (R&D) timeframes and success. Only then will it be possible to properly evaluate the impact of PPPs and understand how these models can be improved and optimized given the resources available.

2. Overall, there is a consensus that PDPs should rely on mixed schemes with push schemes stimulating the initial phases of R&D and pull schemes the final ones. In addition to this, improved synergies between PDPs and Access PPPs are essential if we are to reach the elimination of neglected tropical diseases (NTDs).

3. The priority review voucher (PRV), which was implemented by the US congress in 2007, has so far been unsuccessful at stimulating R&D for the intended tropical diseases. The benefit of the voucher, whether used or sold, is unlikely to be sufficient to trigger pharmaceutical interest. Accordingly, the policy may need to be reconsidered to attract industry-funded research, for instance by supplementing it with other types of mechanisms that can generate a certain level of market profitability.

4. Regarding diagnostics for cutaneous leishmaniasis, recent efforts have resulted in the development of two novel tools: the Loopamp™ Leishmania Detection Kit (LAMP) and the CL Detect™ Rapid Test (RDT). However, their cost-effectiveness in comparison with current practices appears context-specific. In Afghanistan, LAMP should be used only when a minimum number of tests can be processed at a time (at the reference hospital), whereas RDT should be used only when implemented in peripheral health facilities, ideally serving as a primary screening. Otherwise, microscopy remains preferred.

5. Unpacking the direct and mediating effects of the use of preventive measures against vector-borne diseases (VBDs), we saw that the perceived risk and the level of knowledge (if the perceived risk is high enough) are key in Guyana. Moreover, easier access to preventive measures is also essential to the adoption of vector control measures in order to improve the behavioral responsiveness to risk.

6. In a context of elimination, effective communication to improve knowledge and provide an accurate risk perception with at-risk populations is essential, particularly during the so-called “last mile”. In such a context, for the government and population to act together, it is essential for the former to promote awareness of the risk to the latter to avoid a decrease in preventive behavior arising from a lower risk perception. This is all the more important for diseases that are asymptomatic, as reaching their elimination is likely to be further challenged by an underestimation of their actual risk of infection.

7. Lastly, this thesis highlights the interconnectivity and the difficulty in guaranteeing a smooth process across product development, implementation and adoption for neglected diseases. Not only is it hard to incentivize the development of new products for neglected diseases, but even when successfully doing so through PDPs or PRVs, products may not be cost-effective for countries that need them, and/or not adopted by at-risk populations due to inherent characteristics such as low risk perception.

8. Therefore, an overall recommendation would be to involve partners from all ends: from basic research to implementation research to ensure that what is developed or intended to be, matches what is truly needed and feasible in countries endemic of neglected diseases. Along the same lines, it is essential to guarantee the involvement of local actors in the process.

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