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Maria Elena Bottazzi & Peter J. Hotez

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REVIEW

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"Running the Gauntlet": Formidable challenges in advancing neglected tropical diseases vaccines from development through licensure, and a "Call to Action"

Maria Elena Bottazzi oa,b and Peter J. Hotez a,b,c,d

^aTexas Children's Hospital Center for Vaccine Development, Departments of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX, USA; Department of Biology, Baylor University, Waco, TX, USA; James A. Baker III Institute of Public Policy, Rice University, Houston, TX, USA; dScowcroft Institute for International Affairs, Bush School of Government and Public Policy, Texas A&M University, College Station, TX, USA

ABSTRACT

Translational science for new biotechnologies (e.g. drugs, vaccines, devices, or diagnostics) depend on the development of a robust 'business case'. This is driven by complex scientific, technical, logistical, financial and operational elements to determine the feasibility and probability of traversing the "valleys of death" leading to licensure. The potential results in terms of profitability and financial realization, called 'product value proposition' play a crucial role in establishing incentives for investment during and after development. With this review, our goal is to summarize the challenges in taking vaccines against neglected tropical diseases (NTDs) from development through licensure and provide a perspective that these vaccines can have measurable public health and economic profitability and market success. Understanding these processes and its challenges would open the opportunity to accelerate and advance these essential NTD vaccines through the last mile towards licensure and for the delivery to afflicted populations in low- and middle-income countries.

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Vaccines; neglected tropical diseases; poverty; business case; public health; value proposition; product development partnership

Introduction

The translation of basic biomedical research discoveries into robust pipelines of products yielding licensed, appropriate, usable, affordable, equitable and accessible tools, such as diagnostics, vaccines, drugs or devices, is essential to achieving universal and global health.

As defined by the director of the National Center for Advancing Translational Science (NCATS), the term 'translation' in biomedicine refers to 'the process of turning observations in the laboratory, clinic, community, into interventions that improve the health of individuals and the public'.

This multi-step and bi-directional process, to determine which reproducible and robust laboratory discoveries or translational research are appropriate or feasible to advance through the critical path of (product and clinical) development and towards licensure and commercialization of a public health intervention (Figure 1), has traditionally been the responsibility and a role primarily led by private pharmaceutical corporations or biotechs. Recently, due to the competihigh-risk/high-reward markets, private tive, biopharmaceutical corporations have been relying more on universities as a place to not only to capture the next generation of entrepreneurs but as incubator spaces to facilitate the inception of innovative ideas leading to the discoveries that merit further development. In addition, organizations such as WIPO Re:Search, which is administered by the World Intellectual Property Organization (WIPO) in collaboration with BIO Ventures for Global Health (BVGH), collaborates

with a consortium of partners to broker the access of intellectual property (IP) and make it accessible to academic researchers and therefore catalyze the development of new technologies.2

Even though the translational process or science is similar regardless of the intended intervention (drug, vaccine, device or diagnostic), the decision-making process changes and depends on the 'business case' of the product or intervention. Such business cases are driven by complex scientific, technical, logistical and operational elements ultimately determining the feasibility of crossing the well-known "valley of death", the introduction or post-licensure phase, and the effects on profitability and financial realization, also called 'the product value proposition'. 1,3

For the development of global health technologies needed to prevent, treat or diagnose chronic and debilitating infectious diseases (also known as the neglected tropical diseases or NTDs) mostly affecting people living in extreme poverty, the business cases and value propositions are driven by much different and sometimes unique factors when compared to technologies or interventions with clear profitability and potential for market success.

In an effort to increase the efficiency, reduce the risk of failures, accelerate translational science and highlight innovative models to build business cases and value propositions for products targeted to NTDs, more than two decades ago the product development partnerships (PDPs) were created.^{4,5} PDPs, which comprise of public, private, academic, and

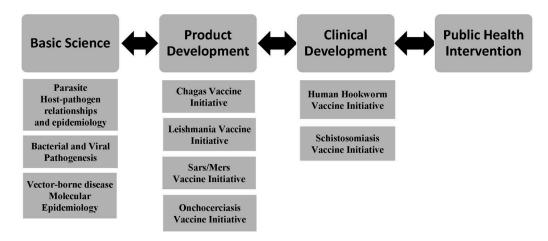


Figure 1. Texas Children's CVD portfolio uses a multi-step bi-directional process to advance through the critical path of vaccine development.

philanthropic entities, utilize a nonprofit organizational structure that enables them to collectively secure funding and advance the development of drugs, vaccines, and other health tools as public goods. These are products that will bring global health innovation and solutions but that currently the pharmaceutical companies are unable to invest in due to inabilities to promise shareholder returns.

Texas Children's Center for Hospital Vaccine Development (Texas Children's CVD) at Baylor College of Medicine's National School of Tropical Medicine and its consortium partners is leading the development and testing of low-cost and effective vaccines against emerging and NTDs such as human hookworm, schistosomiasis, Chagas disease and other NTDs. As a PDP, it seeks to apply lessons learned from the community of vaccinologists and strive to advance our translational or preclinical research with more defined and predictive systems rather than empirical decisions, such that our vaccine candidates can enter into the clinical path with intelligent and more efficient study Furthermore, our goal is to break the paradigm that vaccines against NTDs have no measurable business case or insufficient value proposition.

This review provides our assessment of the framework and translational processes used to establish a full public health value proposition and business case for technologies addressing global health gaps for NTDs. To provide examples, we purposely will focus on two vaccines, the human hookworm and schistosomiasis vaccine, providing a perspective, a probable road map and a forward-looking opinion of how academic institutions, medical research organizations and PDPs. Such consortiums continue to be the source of biomedical innovation and discoveries and have progressed from mostly being spectators to actively engaging in accelerating and advancing essential vaccine candidates urgently needed in low- and middle-income countries.

The NTDs and their health and economic disease **burdens**

The term neglected tropical diseases (NTDs) is used to refer to approximately 20 or more infections with a common set of

features.⁶ The majority of the NTDs are parasitic infections, such as hookworm infection, schistosomiasis, onchocerciasis, Chagas disease and leishmaniasis, and most of these diseases tend to be chronic and debilitating conditions, which is why leprosy and other bacterial and fungal diseases are also included. However, there are also some viral NTDs, including rabies and the major arbovirus infections, such as dengue and yellow fever. A universal feature of the NTDs is their disproportionate impact on populations living in extreme poverty (Box 1). In addition, all of the NTDs also cause poverty through their adverse health and economic effects, and many of them exhibiting long-term effects on the development of children, productive work capacity, and the success of girls and women.6

Still another aspect of the NTDs is that they are not generally major causes of mortality. The fact that NTDs do not typically kill means we need to evaluate alternative methods to express their global public health importance.⁶ There are several approaches used currently to measure impact. First, most of the major NTDs are widely prevalent including some parasitic helminth infections such as hookworm and schistosomiasis that affects hundreds of millions of people. However, the viral NTDs are an exception - for these diseases, the incidence figures are more relevant. Overall, when combined the NTDs may comprise the most common afflictions of the poor. A second metric commonly used to report on the NTDs are disability-adjusted life years (DALYs) referring to years a combination of years lived with disability (YLDs) together with years of life lost (YLLs). Because of their disabling features, the YLDs component of the NTDs DALYs calculations predominates.

Shown in Table 1 are the nine NTDs that are currently targeted by human vaccines (in different stages of development).⁷⁻¹⁵ Also, in development, there are two

Box 1. Major features of the NTDs:

- Chronic and debilitating
- Ancient afflictions
- Disproportionately affecting populations living in poverty
- Illnesses that promote poverty

Table 1. Disease burdens of major NTDs being targeted by human vaccines.

Disease	Stage of Vaccine Development	Prevalence in 2017 ⁷	Incidence in 2017 ⁷	Estimated DALYs in 2017 ⁸	Alternative disease burden estimates in DALYs
Hookworm Infection	Phase 1-2	229.217 million	Not Determined	845,000	4.087 million ⁹
Schistosomiasis	Phase 1-2	142.788 million	Not Determined	1.430 million	13-15 million ¹⁰
Dengue	Licensed	6.267 million	104.772 million	2.920 million	0.3-5 million for the major arboviral diseases, including dengue ¹¹
Onchocerciasis	Preclinical	20.938 million	Not determined	1.340 million	128,000 additional DALYs from Onchocerca-associated epilepsy, or approximately 1.1 million total ¹²
Chagas disease	Preclinical	6.197 million	162,500	232,000	806,170 ¹³
Leishmaniasis	Phase 1-2	4.130 million	669,100	774,000	>2 million just for cutaneous leishmaniasis ¹⁴
Leprosy	Phase 1	518,500	48,500	31,500	Local or regional estimates only
Yellow Fever	Licensed	2,600	97,400	314,000	0.3-5 million for the major arboviral diseases, including dengue ¹¹
Rabies	Licensed	500	13,400	634,000	3.7 million for canine rabies ¹⁵
Total NTDs	-	~400 million	Not determined	8.5 million	> 30 million

vaccines for cysticercosis and echinococcosis, respectively, which would be used as veterinary vaccines to prevent transmission to humans. 16

In terms of the NTDs targeted by human vaccines, according to the Global Burden of Disease (GBD) Study 2017 together these diseases affect approximately 400 million people at any given time, ⁷ a population that largely represents most of the world's approximately 700 million people now believed to be living below the World Bank poverty figure of \$1.90 per day. 17

The nine NTDs currently being targeted by human vaccines exert a huge global health impact. According to the GBD 2017, together they result in 8.5 million DALYs annually, a value that exceeds the DALYs from global cervical cancers.8 However, many investigators in the community of NTDs scientists and researchers feel that even 8.5 million DALYs is a "low-ball" estimate. For example, the current disease burden estimates for hookworm infection may not adequately encompass the cases of severe and moderate anemia resulting from this helminthiasis, while current DALYs estimates for schistosomiasis fail to consider all of the chronic morbidities and end-organ pathologies, as well as increased susceptibility to HIV/AIDs among adolescent girls and women.¹⁰ Thus, a full consideration of all of these aspects of NTDs morbidities could result in at least a tripling of GBD disease burden estimates.

Still another consideration of the nine NTDs that would potentially be targeted by human vaccines is their economic impact. 18 There are now multiple health economic estimates of these NTDs, both globally and among local or regional populations. 9,13,19,20 These studies primarily look at the economic burden of NTDs, or the benefits of mass drug administration or other programs linked to NTDs. 21-23 In addition, the studies have focused on health-care costs, and the impact on human capacity, especially for agricultural workers and women and children, 18,24 while others look at cost-effectiveness in the context of the PDP ecosystem. 25-27 Additional efforts have modeled the cost-effectiveness of NTD vaccines, 19,20 or vaccines linked to chemotherapy.^{28,29} For example, a modeling study to evaluate a hookworm vaccine delivered with preventive chemotherapy has the potential for positive societal benefits, while at the same time be cost-effective.²⁹ Therefore, more costeconomic studies are needed to investigate the mechanisms by which NTD or "antipoverty" vaccines could prevent debilitating disease and improve long-term economic outcomes. 23-25

The framework of Texas Children's CVD

Similar to what was presented by Denee, et al. in 2012,²⁶ for the past two decades, Texas Children's CVD has adapted and refined an operational framework with guiding principles (Table 2) and objectives (Box 2) that allows to measure indicators of success as well as recognize, early on, the challenges of each vaccine development program:

Network

We have partnerships with more than 40 academic, public and private sector organizations to leverage expertise. The exchange of information is guided by formal research collaborative agreements and program or project charters leading to a robust project pipeline of more than half a dozen funded vaccine programs at different stages of development (Figure 1).

Know-how

To advance research and development (R&D), product and clinical development we focus on capacity building, infrastructure development and knowledge-sharing to meet Lowand Middle-Income Country (LIMC) needs and World Health Organization (WHO) requirements. We have more than 100 joint partnership publications and continuously exchange information during scientific conferences, partner meetings and workshops.

Human capital

Because our PDP is embedded within an academic health center, the Texas Medical Center, and it is a key research and training arm of the National School of Tropical Medicine at Baylor College of Medicine, 27 we have established a hybrid model (of biotech and academic cultures) to train the next generation of vaccine researchers. Trainees can learn both at their site or via short exchanges the ins and out of

Table 2. Texas Children's CVD guiding principles.

Vision: Be a Global Leader in the Development of Neglected Disease Vaccines

- 1. Pursuit of neglected disease vaccines not under development by Pharma or major for-profits
- · Produce clinical-grade material and reach Phase 1 Clinical Trials as quickly and cost effectively as possible
- Elevate the profile of Neglected Tropical Diseases
- Use proven product development technologies
- Selectively leverage product development capacity and expertise to pursue additional public health needs and generate revenue
- Diversify funding sources to ensure sustainable progress
- Pursue all options to advance product development of antigens

2. Leverage PDP Model to Maximize Success and Reduce Risks

- Partner with collaborators and manufacturers and build preclinical/clinical infrastructure in resource poor settings and endemic regions
- Build capabilities and share knowledge with global partners
- Pursue fully transparent partnerships that
- support the mission and strategy
- Clearly identify and communicate goals and success criteria of each partnership
- Ensure safe and ethical clinical studies for populations at risk

3. Grow as an Effective, Unified Organization

- Build culture of leadership, collaboration, and continuous improvement
- · Identify, accept, and learn from mistakes
- Invest in the development of all staff and collaborators and ensure academic freedom
- Value input from all staff and collaborators and partners
- · Remain nimble and responsive to emerging opportunities
- Communicate and stick to decisions

Box 2. Texas Children's CVD is committed to:

- Achieving improved health outcomes in the most cost-effective manner possible
- Early inclusion and understanding of LMICs needs and preference
- Incentivizing disease-endemic country ownership
- Building self-reliance and sustainability

the technical and operational systems used during vaccine development contributing to the percent of trained investigators working in positions tackling NTDs.

Financials and operations

As a strategic necessity and to ensure continuity and sustainability of the vaccine programs, Texas Children's CVD and its partners has established a diversified financial portfolio obtained from different and distinct national and international sources. Each fund covers specific areas during the vaccine development continuum, addressing challenges and complexities of when and how to apply for each funding opportunity based on the stage of maturity of a given project. In addition, once funding for a project is made available, the management and expenditures of the fund encompassing the elements of accountability and transparency is essential. Such activities are managed through a team of dedicated program and project managers that keep track of the timelines, milestones, decision points and Go No Go criteria.

Business case and full public health value proposition for NTD vaccines

Through health economic modeling, the return on investments for several NTD vaccines including vaccines for hookworm

infection, Chagas disease, and leishmaniasis clearly point to major economic returns in terms of improved productivity, a more robust workforce, reduced hospitalization, and other social goods that translate into overall national development.^{9,28} Additional modeling studies have shown how NTD vaccines can accelerate the control and elimination of these povertypromoting diseases, 28,29 especially for hookworm infection and schistosomiasis. However, while modeling and other evidence support the economic dominance of NTD and antipoverty vaccines, these aspects by themselves have not yet been sufficient to promote substantial and timely global investments. In the end, the long-time horizons, risk of failure, and absence of robust commercial markets make vaccines daunting financial investment prospects. Fueling investor hesitancy are the recent shortcomings and public reactions to newly introduced vaccines for malaria and dengue despite billion-dollar investments from Glaxo Smith Kline (GSK) and Sanofi Pasteur, respectively, 30,31 on top of an accelerating global antivaccine movement. Still another factor is the fact that recent financial "pull mechanisms" such as advanced market commitments and priority review vouchers so far benefit only larger for-profit organizations that have the ability to use internal resources in order to advance development of products. These realities have left the remaining vaccine PDPs, often on the outside-lookingin in terms of the investment ecosystem.

Despite the hurdles, some efforts are underway to sustain an NTD vaccine framework. As part of the global governance for neglected disease vaccines, the Initiative for Vaccine Research (IVR) of the World Health Organization (WHO), was established in 2010 through a Decade of Vaccines Collaboration (DoVC)³² to coordinate the development of a Global Vaccine Action Plan (GVAP).³³ The GVAP provides a framework that embraces an R&D and translational science component mostly facilitated by the Product Development for Vaccines Advisory Committee

(PDVAC)34 and which also takes into consideration a few vaccine initiatives for NTDs. Several reviews³⁵ have been published highlighting more than 100 articles and reviews of the landscape of vaccine candidates advancing through development.

Based on the 2017 assessment report of the GVAP, however, progress continues to be slow and likely most of its 2020 goals may be challenging to reach. 36,37 For instance, indicator data suggest that vaccine coverage levels are not increasing and diseases outbreaks such as measles and others continue to occur. These challenges are due to multiple global, regional and national issues which will require increased global efforts to promote more R&D, increase immunization campaigns, reduce vaccine hesitancy and address the systemic weaknesses that are limiting equitable vaccine access. 30,31 Furthermore, and to enhance the knowledge-sharing and the collaborations for the R&D and translational science agenda of the GVAP, WHO, in partnership with the US National Institutes of Health-National Institute of Allergy and Infectious Diseases (NIH-NIAID) and the Bill & Melinda Gates Foundation (BMGF) have launched the Global Vaccine & Immunization Research Forum (GVIRF) held every two years.³⁸ The latest forum, held in 2018, included a special focus on the GVAP goal to develop and introduce new and improved vaccines and technologies with an emphasis on the thought-processes to develop robust business cases with full public health value propositions (FPHVP), which are needed to make decisions for an end to end development, integration and delivery. This initiative, supported by the Strategic Advisory Group of Experts (SAGE) on Immunization,³⁹ provides the framework starting during the early stages of vaccine product development to ensure a clear definition of the global value of vaccines, allowing accurate prioritization and eventually avoid delays in the uptake especially in (LMICs).⁴⁰ Gavi, The Vaccine Alliance, has also made significant progress in support of making vaccines more equitable, affordable and accessible.41

As an example of these organizations working together, we point to the development, licensure and introduction of MenAfriVac, the vaccine for meningococcal A disease in Africa's meningitis belt that has reduced the incidence of suspected meningitis and epidemic risk, and its effect on confirmed group A meningococcal meningitis. 42,43

Understanding the FPHVP of NTD vaccines is a necessary step when building the business case primarily because it provides information on the need and the geographic and population burden. It also assists in setting the appropriate target product profile, product development and regulatory strategy and ultimately proposes the advocacy, policy and public health activities needed to ensure demand, adoption, and implementation practices.⁴⁴

In recent years, the scientific and vaccine community of thought-leaders have advocated that a FPHVP should not only include assessments related to individual benefit-risks or individually randomized clinical trials but that the translational science for a public health intervention should be more comprehensive and include the evaluation of the population impact and community benefits-risks. As elegantly described by Gessner et al., the FPHVP of vaccination should include a wider scope of vaccine benefits and not limit the assessment based solely on

economic vaccination-set health benefits but rather include the non-health benefits including productivity, health-risk reduction, equity/fairness and fiscal impacts.44

For the NTDs and emerging or emergent infectious diseases, these processes and decisions have been hampered by the perception that the development costs are substantial and that there is an implicit market failure leading to no or limited financial returns on investments.

For example, for epidemic infectious diseases, a recent study by Gouglas, D. et al. 45 highlighted how for pandemic diseases requiring vaccine stockpiling, the model should include parallel development of multiple candidates for multiple diseases and focus on platforms that have known success through the regulatory pathways. However, even with this approach, the cost to bring a discovery up to Phase 2 could be between \$31-68 million. In addition, if consideration is to be given to the logistics and ability of doing efficacy trials the cost estimates to bring these discoveries trough licensure could amount up to \$2.5 billion. Furthermore, the probability of success of a vaccine candidate to advance from preclinical to clinical usually ranges between 40% and 50% but to be successful through phase 2 the probability goes down to only 10-13%.46

The roadmap to assess translational success for a human hookworm and schistosomiasis vaccine requires an in-depth analysis of the technical, operational and profitability drivers. Generally, and for vaccine development programs related to NTDs, these roadmaps have been perceived as fragmented, slow, expensive, and poorly coordinated with important stakeholders such as governments, non-profit and academic entities and sometimes even lacking the engagement of the public. In recent publications, we highlight the technical steps, prospects and lessons learned, used by Texas Children's CVD, in an effort to follow the critical path for the development of human hookworm and schistosomiasis vaccines. 47-49

Among the greatest challenges of developing vaccines (and other biologics) for neglected and emerging infectious diseases, the mechanisms to secure the funding for the development stages rank high. Multiple attempts have been made to generate "blueprints", mostly led by the WHO, on what would be an ideal model to bring new biologics through preclinical and clinical development and through the last mile towards licensure or registration. However, even with many consultations or substantial financial supporting mechanisms provided by organizations such as BMGF, Wellcome Trust, multilateral governments and/or pharmaceutical companies, no ideal model has proven successful to fill all the shortcomings and have certainly not been designed to be a fit-for neglected and emerging infectious diseases nor have been able to bring any targeted vaccines to the eventual objective of successful licensure.

The funding to develop new NTD vaccines comes from government, philanthropic funding and occasionally from biotech funds. Seldom is any funding raised from private equity.

For government funding, in the United States, the funding strategies used by the National Institutes of Health (NIH) on biotechnology research support primarily early stage and preclinical R&D, rather than the transition of new vaccines through advanced development and into commercialization. Their emphasis is on laboratory discoveries that remain stuck within the "valley of death".50 Even if such a discovery arrives into a clinical application, there is no set path towards advanced development. There are substantial NIH funds through the Small Business Innovative Research (SBIR) pathway, but these funds are not generally available for non-profit PDPs. More recently, the NIH through the National Institute of Allergy and Infectious Diseases (NIAID) has made selective gap funding available to PDPs through their contracting mechanisms. Such funds have it possible to participate in the NIAID-NIH network of Vaccine Trial Evaluation Units (VTEUs), and Good Laboratory Practices (GLP) toxicology contractors, which were critical path elements of advancing our schistosomiasis vaccine. NIAID-NIH has also directly supported the early clinical trials of the hookworm and schistosomiasis vaccines. Outside of NIH, the Department of Defense (DOD) has provided some needed support for earlystage vaccine development through its Congressionally Directed Medical Research Program (CDMRP), which was instrumental in advancing our leishmaniasis vaccine. In the United Kingdom and Europe, promising research into vaccines has been supported through organizations such as the Innovative Medicines Initiative with European Commission funds such as those coming from the Horizon 2020 mechanism, but similarly, as in the US, these mechanisms do not typically bring innovative discoveries into a commercialization path. The new Coalition for Epidemic Preparedness Innovations (CEPI) Alliance has chosen to focus mostly on perceived viral pandemic threats, such as Lassa fever, MERS coronavirus infection, and Nipah virus infection rather than the poverty-promoting and debilitating NTDs.

Private investment in NTD vaccines from major philanthropies has also been tepid. The Gates Foundation has been gradually divesting from this space in order to focus on either alternative technologies or elimination strategies, although the Wellcome Trust has begun to prioritize some aspects of vaccine development for Ebola and other emerging infections. Recently the Carlos Slim Foundation has committed to supporting vaccines to combat Chagas disease.

Overall our assessment is that the global health technology community has largely pivoted away from NTD vaccines in order to either focus on diseases of emergency preparedness, especially those that threaten North America and Europe, or if there are NTD investments they are focused on innovations with lower risk and shorter timelines.

As highlighted in the recent commentary, "Vaccine candidates for poor nations are going to waste", the development of NTD vaccines will require help to advance towards licensure and successfully enter the market. 51 Vaccine candidates in the NTD pipeline do not even have the option of both public and private markets. Therefore, these vaccines will need to rely primarily on public markets in LMICs and high-risk development prospect and with the added difficulty of predicting the accurate return on the investments. A recent observation that a surprising burden of NTDs occurs among the poor living in a wealthy group of 20 nations (G20), a group sometimes referred to as the "poorest of the rich" potentially points a way to bring in G20 government investments from outside the US, United Kingdom, and Europe. 52 However, this framework known as "blue marble health" has not yet been widely accepted by the leaders of G20 and their policymakers.

As described in the commentary, the knowledge gaps about the mechanism of protection, the lack of a clear understanding of the burden of disease especially in areas of different endemicities and intensities, and a clear picture of the cost-of-illness in a region or a given country makes a difficult argument for how to establish the value proposition.

We are therefore joining the rest of the scientific community and ask for a call to action. But in our case we strongly encourage a new path for the development of vaccines that have a compelling but uncertain business case. We urge that the community reevaluate and include in the future path vaccines that have low, artificial, or no financial opportunity but for which the potential returns are quantified primarily via public health means.

Key issues

- · Recent investments in vaccines to combat viral diseases of pandemic potential and other emerging diseases have excluded investments for anti-poverty vaccines to combat the NTDs.
- Despite demonstrated cost savings and economic dominance, the major global health investors have pivoted away from NTD vaccines in order to focus on lower-risk technologies or those with shorter timelines and horizons.
- Anti-poverty vaccines for NTDs urgently need a new business model of development due to rising R&D costs, the need for more stringent clinical trials, exhaustive manufacturing rules and regulatory frameworks.
- Vaccine demand is rising for complex diseases, requiring better and faster development while at the same time implementation of new delivery models are hampered by vaccine hesitancy and poor advocacy.
- The probability of a new vaccine to reach the market is about half (approximately 6%) of the probability of drugs.
- Given the complexity in development and the high risks involved, innovative ways to measure the returns is needed. To attract investors better transparency is needed to predict R&D spending, clinical development and market entry, which generally can span between \$200 and \$900 million.
- Organizational, methodological, and cultural barriers within and among research institutions are necessary.
- We urgently need innovation in the finance sector to identify a new sustainable business model for these urgently needed technologies.
- We propose a new call to action for NTD vaccines.

Disclosure of potential conflicts of interest

The authors are lead investigators and patent holders on several vaccines against neglected tropical diseases. These vaccines are either in clinical trials or in development.



List of abbreviations

BMGF Bill & Melinda Gates Foundation **BVGH** BIO Ventures for Global Health

CDMRP Congressionally-Directed Medical Research Program **CFPI** Coalition for Epidemic Preparedness Innovations

disability-adjusted life years DALYs Department of Defense DOD

DoVC Decade of Vaccines Collaboration **FPHVP** full public health value propositions

GBD Global Burden of Disease GLP **Good Labortory Practices GSK** Glaxo Smith Kline **GVAP** Global Vaccine Action Plan

GVIRF Global Vaccine & Immunization Research Forum

intellectual property

IVR Initiative for Vaccine Research LIMCs Low- and Middle-Income Countries

NCATS National Center for Advancing Translational Science NIAID National Institute of Allergy and Infectious Diseases

NIH National Institutes of Health

National Institutes of Health-National Institute of Allergy and NIH-NIAID

Infectious Diseases

NTDs Neglected tropical diseases **PDPs** Product development partnerships

PDVAC Product Development for Vaccines Advisory Committee

R&D Research and development SAGE Strategic Advisory Group of Experts SBIR Small Business Innovative Research (SBIR)

Texas Children's Hospital Center for Vaccine Development Texas

Children's CVD

VFTUs Vaccine Trial Evaluation Units WHO World Health Organization

WIPO World Intellectual Property Organization

YI Ds Years lived with disability YIIs Years of life lost

ORCID

Maria Elena Bottazzi D http://orcid.org/0000-0002-8429-0476 Peter J. Hotez http://orcid.org/0000-0001-8770-1042

References

- 1. Austin CP Translating translation. Nat Rev Drug Discov. 2018 Jul;17(7):455-56. PubMed PMID: 29674698; PubMed Central PMCID: PMC6023744. doi:10.1038/nrd.2018.27.
- 2. World Intellectual Property Organization. WIPO re: search 2019. [accessed 2017 Mar 30]. https://www.wipo.int/research/en/
- 3. Mohs RC, Greig NH Drug discovery and development: role of basic biological research. Alzheimers Dement (N Y). 2017 Nov;3 (4):651-57. PubMed PMID: 29255791; PubMed Central PMCID: PMC5725284. doi:10.1016/j.trci.2017.10.005.
- 4. Wheeler C, Berkley S. Initial lessons from public-private partnerships in drug and vaccine development. Bull World Health Organ. 2001;79(8):728-34. PubMed PMID: 11545329; PubMed Central PMCID: PMC2566495
- 5. Bottazzi ME, Miles AP, Diemert D, Hotez PJ An ounce of prevention on a budget: a nonprofit approach to developing vaccines against neglected diseases. Expert Rev Vaccines. 2006 Apr;5(2):189-98. PubMed PMID: 16608419. doi:10.1586/14760584.5.2.189.

- 6. Hotez PJ. Forgotten people, forgotten diseases. Washington (DC): ASM Press; 2013.
- 7. GBD Injury Incidence & Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018 Nov 10;392(10159):1789-858. PubMed PMID: 30496104; PubMed Central PMCID: PMC6227754. doi:10.1016/S0140-6736(18)32279-7.
- 8. GBD DALYs Hale Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018 Nov 10;392(10159):1859-922. PubMed PMID: 30415748; PubMed Central PMCID: PMC6252083. doi:10.1016/S0140-6736(18)32335-3.
- 9. Bartsch SM, Hotez PJ, Asti L, Zapf KM, Bottazzi ME, Diemert DJ, Lee BY, de Silva N The global economic and health burden of human hookworm infection. PLoS Negl Trop Dis. 2016 Sep;10(9): e0004922. PubMed PMID: 27607360; PubMed Central PMCID: PMC5015833. doi:10.1371/journal.pntd.0004922.
- 10. King CH Parasites and poverty: the case of schistosomiasis. Acta Trop. 2010 Feb;113(2):95-104. PubMed PMID: 19962954; PubMed Central PMCID: PMC2812649. doi:10.1016/j.actatropica.2009.11.012.
- 11. Labeaud AD, Bashir F, King CH. Measuring the burden of arboviral diseases: the spectrum of morbidity and mortality from four prevalent infections. Popul Health Metr. 2011 Jan 10;9(1):1. PubMed PMID: 21219615; PubMed Central PMCID: PMC3024945. doi:10.1186/1478-7954-9-1.
- 12. Vinkeles Melchers NVS, Mollenkopf S, Colebunders R, Edlinger M, Coffeng LE, Irani J, Zola T, Siewe JN, de Vlas SJ, Winkler AS, et al. Burden of onchocerciasis-associated epilepsy: first estimates and research priorities. Infect Dis Poverty. 2018;7(1):101. 10.1186/ s40249-018-0481-9. PubMed PMID: 30253788; PubMed Central PMCID: PMC6156959. doi:10.1186/s40249-018-0481-9.
- 13. Lee BY, Bacon KM, Bottazzi ME, Hotez PJ Global economic burden of Chagas disease: a computational simulation model. Lancet Infect Dis. 2013 Apr;13(4):342-48. PubMed PMID: 23395248; PubMed Central PMCID: PMC3763184. doi:10.1016/ S1473-3099(13)70002-1.
- 14. Bailey F, Mondragon-Shem K, Hotez P, Ruiz-Postigo JA, Al-Salem W, Acosta-Serrano Á, Molyneux DH, Jaffe CL A new perspective on cutaneous leishmaniasis-implications for global prevalence and burden of disease estimates. PLoS Negl Trop Dis. 2017 Aug;11(8): e0005739. PubMed PMID: 28796782; PubMed Central PMCID: PMC5552022. doi:10.1371/journal.pntd.0005739.
- 15. Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, Barrat J, Blanton JD, Briggs DJ, Cleaveland S, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis. 2015 Apr;9(4):e0003709. PubMed PMID: 25881058; PubMed Central PMCID: PMC4400070. doi:10.1371/journal.pntd.0003709.
- 16. Lightowlers MW. Cysticercosis and echinococcosis. Curr Top Microbiol Immunol. 2013;365:315-35. PubMed PMID: 22641401. doi:10.1007/82 2012 234.
- 17. World Bank. Poverty. 2018. [updated 2018 Sep 24; 2019 Mar 21]. https://www.worldbank.org/en/topic/poverty/overview
- 18. Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. Lancet. 2009 May 2;373(9674):1570-75. PubMed PMID: 19410718. doi:10.1016/S0140-6736(09)60233-6.
- 19. Bacon KM, Hotez PJ, Kruchten SD, Kamhawi S, Bottazzi ME, Valenzuela JG, Lee BY. The potential economic value of a cutaneous leishmaniasis vaccine in seven endemic countries in the Americas. Vaccine. 2013 Jan 7;31(3):480-86. PubMed PMID: 23176979; PubMed Central PMCID: PMC3763201. doi:10.1016/j. vaccine.2012.11.032.
- 20. Lee BY, Bacon KM, Shah M, Kitchen SB, Connor DL, Slayton RB The economic value of a visceral leishmaniasis vaccine in Bihar state, India.



- Am J Trop Med Hyg. 2012 Mar;86(3):417-25. PubMed PMID: 22403311; PubMed Central PMCID: PMC3284356. doi:10.4269/ ajtmh.2012.10-0415.
- 21. Evans D, McFarland D, Adamani W, Eigege A, Miri E, Schulz J, Pede E, Umbugadu C, Ogbu-Pearse P, Richards FO Costeffectiveness of triple drug administration (TDA) with praziquantel, ivermectin and albendazole for the prevention of neglected tropical diseases in Nigeria. Ann Trop Med Parasitol. 2011 Dec;105(8):537-47. PubMed PMID: 22325813; PubMed Central PMCID: PMC4089800. doi:10.1179/2047773211Y.0000000010.
- 22. Chu BK, Hooper PJ, Bradley MH, McFarland DA, Ottesen EA, Carabin H. The economic benefits resulting from the first 8 years of the global programme to eliminate lymphatic filariasis (2000-2007). PLoS Negl Trop Dis. 2010 Jun 1;4(6):e708. PubMed PMID: 20532228; PubMed Central PMCID: PMC2879371. doi:10.1371/journal.pntd.0000708.
- 23. Hotez P A handful of 'antipoverty' vaccines exist for neglected diseases, but the world's poorest billion people need more. Health Aff (Millwood). 2011 Jun;30(6):1080-87. PubMed PMID: 21653960. doi:10.1377/hlthaff.2011.0317.
- 24. Hotez PJ, Ferris MT. The antipoverty vaccines. Vaccine. 2006 Jul 26;24 (31-32):5787-99. PubMed PMID: 16759763. doi:10.1016/j. vaccine.2006.05.008.
- 25. Hotez PJ. The global fight to develop antipoverty vaccines in the anti-vaccine era. Hum Vaccin Immunother. 2018;14(9):2128-31. PubMed PMID: 29393710; PubMed Central PMCID: PMC6183138. doi:10.1080/21645515.2018.1430542.
- 26. Denee TR, Sneekes A, Stolk P, Juliens A, Raaijmakers JAM, Goldman M, Crommelin DJA, Janssen JW. Measuring the value of public-private partnerships in the pharmaceutical sciences. Nat Rev Drug Discov. 2012 Mar 30;11(5):419. PubMed PMID: 22460037. doi:10.1038/nrd3078-c1.
- 27. Baylor College of Medicine. National School of Tropical Medicine. 2019 [accessed 2019 Mar 31]. https://www.bcm.edu/ education/schools/national-school-of-tropical-medicine
- 28. Stylianou A, Hadjichrysanthou C, Truscott JE, Xie Z, Ren P, Zhao L, Dong H, Shi M, Lv Z, Wu Z, et al. Developing a mathematical model for the evaluation of the potential impact of a partially efficacious vaccine on the transmission dynamics of Schistosoma mansoni in human communities. Parasit Vectors. 2017;10(1):294. 10.1186/ s13071-017-2227-0. PubMed PMID: 28623957; PubMed Central PMCID: PMC5474049. doi:10.1186/s13071-017-2494-9.
- Bartsch SM, Hotez PJ, Hertenstein DL, Diemert DJ, Zapf KM, Bottazzi ME, Bethony JM, Brown ST, Lee BY. Modeling the economic and epidemiologic impact of hookworm vaccine and mass drug administration (MDA) in Brazil, a high transmission setting. Vaccine. 2016 Apr 27;34(19):2197-206. PubMed PMID: 27002501; PubMed Central PMCID: PMC5547742. doi:10.1016/i. vaccine.2016.03.018.
- 30. Hotez PJ Immunizations and vaccines: a decade of successes and reversals, and a call for "vaccine diplomacy". International Health. Oxford University Press; 2019. doi:10.1093/inthealth/ihz024.
- 31. Hotez P. America and Europe's new normal: the return of vaccinepreventable diseases. Pediatr Res. 2019;85:912-14. 10.1038/s41390-019-0354-3. PubMed PMID: 30812027. doi:10.1038/s41390-019-
- 32. Alonso PL, de Quadros CA, Robert M, Lal AA. Decade of Vaccines. Editorial. Vaccine. 2013 Apr 18;31(Suppl 2):B3-4. PubMed PMID: 23598490. doi:10.1016/j.vaccine.2013.02.035.
- 33. World Health Organization. Global vaccine action plan 2011–2020. Geneva, Switzerland: World Health Organization; 2013.
- 34. World Health Organization. Immunization, vaccines and biologicals. Product Development for Vaccines Advisory Committee. [established 2014 Apr; 2019 Mar 30]. https://www. who.int/immunization/research/committees/pdvac/en/
- 35. Giersing BK, Modjarrad K, Kaslow DC, Okwo-Bele J-M, Moorthy VS. The 2016 vaccine development pipeline: a special issue from the World Health Organization Product Development for Vaccine Advisory Committee (PDVAC). Vaccine. 2016 Jun 3;34(26):2863-64. PubMed PMID: 27108194. doi:10.1016/j.vaccine.2016.04.041.

- 36. Ford AQ, Touchette N, Hall BF, Hwang A, Hombach J. Global vaccine and immunization research forum: opportunities and challenges in vaccine discovery, development, and delivery. Vaccine. 2016 Mar 18;34(13):1489-95. PubMed PMID: 26626210. doi:10.1016/j.vaccine.2015.11.038.
- 37. Ford AQ, Touchette N, Fenton Hall B, Hwang A, Hombach J. Meeting report: global vaccine and immunization research forum. Vaccine. 2018 Feb 8;36(7):915-20. PubMed PMID: 29338876. doi:10.1016/j.vaccine.2017.12.013.
- 38. World health Organization Immunization, vaccines and biologicals. The Global Vaccine and Immunization Research (GVIRF). Geneva Switzerland: World Health Organization; 2018. [accessed 2019 May 12]. https://www.who. int/immunization/research/forums_and_initiatives/gvirf/en/
- 39. World Health Organization. Immunization, vaccines biologicals. Interim recommendation Ebola vaccines. 2019 [accessed 2019 Mar 30]. https://www.who.int/immunization/policy/sage/en/
- 40. World Health Organization. Meeting of the strategic advisory group of experts on immunization, October 2018 - conclusions and recommendations weekly epidemiological record. Geneva, Switzerland: World Health Organization; 2019. p. 661–80.
- 41. GAVI TVA. 2019 [accessed 2019 Mar 30]. https://www.gavi.org/
- 42. Trotter CL, Lingani C, Fernandez K, Cooper LV, Bita A, Tevi-Benissan C, Ronveaux O, Préziosi M-P, Stuart JM Impact of MenAfriVac in nine countries of the African meningitis belt, 2010-15: an analysis of surveillance data. Lancet Infect Dis. 2017 Aug;17(8):867-72. PubMed PMID: 28545721. doi:10.1016/S1473-3099(17)30301-8.
- 43. World Health Organization. The MenAfriVac story. [2019 accessed March 31]. https://www.who.int/immunization/news room/events/menafrivac_video/en/
- 44. Gessner BD, Kaslow D, Louis J, Neuzil K, O'Brien KL, Picot V, Pang T, Parashar UD, Saadatian-Elahi M, Nelson CB. Estimating the full public health value of vaccination. Vaccine. 2017 Nov 1;35 (46):6255-63. PubMed PMID: 28986035. doi:10.1016/j. vaccine.2017.09.048.
- 45. Gouglas D, Thanh Le T, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen J-A Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. Lancet Global Health. 2018 Dec;6(12):e1386-e1396. PubMed PMID: 30342925. doi:10.1016/S2214-109X(18)30346-2.
- 46. DiMasi JA. Assessing pharmaceutical research and development costs. JAMA Intern Med. 2018 Apr 1;178(4):587. PubMed PMID: 29610869. doi:10.1001/jamainternmed.2017.8703.
- 47. Diemert DJ, Bottazzi ME, Plieskatt J, Hotez PJ, Bethony JM Lessons along the critical path: developing vaccines against human helminths. Trends Parasitol. 2018 Sep;34(9):747-58. PubMed PMID: 30064902. doi:10.1016/j.pt.2018.07.005.
- 48. Hotez PJ, Bottazzi ME, Bethony J, Diemert DD Advancing the development of a human schistosomiasis vaccine. Trends Parasitol. 2019 Feb;35(2):104-08. PubMed PMID: 30455112. doi:10.1016/j.pt.2018.10.005.
- 49. Diemert D, Campbell D, Brelsford J, Leasure C, Li G, Peng J, Zumer M, Younes N, Bottazzi ME, Mejia R, et al. Controlled human hookworm infection: accelerating human hookworm vaccine development. Open Forum Infect Dis. 2018 May;5(5):ofy083. PubMed PMID: 29780848; PubMed Central PMCID: PMC5952933. doi:10.1093/ofid/ofy083.
- 50. Coller BS, Califf RM. Traversing the valley of death: a guide to assessing prospects for translational success. Sci Transl Med. 2009 Dec 9;1(10):10cm9. PubMed PMID: 20368156; PubMed Central PMCID: PMC2879158. doi:10.1126/scitranslmed.3000265.
- 51. Kaslow DC, Black S, Bloom DE, Datla M, Salisbury D, Rappuoli R. Vaccine candidates for poor nations are going to waste. Nature. 2018 Dec;564(7736):337-39. 10.1038/d41586-018-07758-3. PubMed PMID: 30560957. doi:10.1038/d41586-018-07758-3.
- 52. Hotez PJ. Blue marble health: an innovative plan to fight diseases of the poor amid wealth. Baltimore (MD): Johns Hopkins University Press; 2016.