HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 9, 2128–2131
https://doi.org/10.1080/21645515.2018.1430542

Taylor & Francis
Taylor & Francis Group

COMMENTARY

The global fight to develop antipoverty vaccines in the anti-vaccine era

Peter J. Hotez[a,b,c,d]

[a]Texas 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, Texas, USA; [b]Departmentof Biology, Baylor University, Waco, Texas, USA; [c]James A Baker III Institute of Public Policy, Rice University, Houston, Texas, USA; [d]Scowcroft Institute of International Affairs, Bush School of Government and Public Policy, Texas A&M University, College Station, Texas, USA

ABSTRACT

Antipoverty vaccines are the vaccines targeting a group of approximately 20 neglected tropical diseases (NTDs), as currently defined by the World Health Organization (WHO). The "antipoverty" moniker refers to the fact that NTDs trap populations in poverty due to their chronic and deleterious effects on child intellect and worker productivity. Therefore, NTD vaccines can be expected to promote both global health and economic advancement. Unfortunately, antipoverty vaccine development has lagged behind vaccines for major childhood infections and pandemic threats, despite evidence for their cost-effectiveness and cost-savings. Currently, the only licensed vaccines for NTDs include those for yellow fever, dengue, and rabies, although several other NTD vaccines for hookworm disease, schistosomiasis, leishmaniasis, and Zika and Ebola virus infections are in different stages of clinical development, while others are at the preclinical development stage. With the exception of the viral NTD vaccines there so far has been minimal industry interest in the antipoverty vaccines, leaving their development to a handful of non-profit product development partnerships. The major scientific and geopolitical hurdles to antipoverty vaccine development are discussed, including a rising antivaccine ("antivax") movement now entering highly populated low- and middle-income countries.

ARTICLE HISTORY
Received 5 January 2018
Accepted 17 January 2018

KEYWORDS
hookworm; schistosomiasis; dengue; yellow fever; Zika; Ebola; trials for developing countries; tropical medicine; vaccinology

Introduction: The NTDs

It's been more than a decade since a group of poverty-related tropical infections were branded as the neglected tropical diseases (NTDs) and targeted for intervention through programs of mass drug administration (MDA) and related interventions, including vector control and morbidity management.[1–7] Since then, the original list of a dozen or so NTDs was expanded to 20 different conditions by the World Health Organization (WHO).[8] Most of these conditions are listed in Table 1, together with their most recent prevalence or incidence estimates released in 2017 by the Global Burden of Disease Study 2016.[9]

The prevalence and incidence numbers are impressive, and it's not an exaggeration to say that almost all of the world's 700–800 million people living in extreme poverty (below World Bank poverty levels) suffer from at least one NTD, with many of the world's poor simultaneously infected with multiple NTDs. For most of these NTDs, their global burden of disease can be expressed in terms of prevalence because diseases such as hookworm disease and other intestinal helminth infections, schistosomiasis, Chagas disease, leishmaniasis, cysticercosis, leprosy and others are chronic conditions lasting for years or decades. The exceptions are the viral NTDs, such as the major arbovirus infections (e.g., dengue, Zika, yellow fever) and rabies, which cause acute infections so that it is more appropriate to use incidence estimates.

NTD control as an antipoverty measure

Because they are chronic and debilitating conditions, an important feature of the NTDs is that they affect not only health, but also economic productivity. Some efforts have gone into understanding mechanisms of how NTDs promote poverty, but there is much more that needs to be done. So far, however, it appears that poverty is linked to NTDs by virtue of their long-term negative effects on child intellect and cognition, the ability of adults to go to work, and maternal-child health especially around pregnancy, although there are probably other mechanisms as well.[5,7,10] Accordingly, interventions that can treat or prevent NTDs can be considered as potential effective antipoverty measures.

One of the largest programs for NTDs has been integrated mass drug administration (MDA), first proposed in 2005 for Africa,[1-4] and now supported in dozens of countries globally through funds from the US Agency for International Development (USAID) and the British Department for International Development (DFID). These funds are channeled to government contractors or health ministries in disease-endemic countries, together with technical support from a network of non-governmental development organizations (NGDOs).[6,7] The interventions are intended to target some of the world's most prevalent NTDs, including ascariasis, hookworm disease, trichuriasis, schistosomaisis, scabies, lymphatic filariasis, onchocerciasis, and yaws. According to the WHO the number of people

CONTACT Peter J. Hotez hotez@bcm.edu 1 Baylor Plaza, Houston, TX 77030, USA.

Table 1. Global Burden of Disease 2016 estimates of the neglected tropical diseases (NTDs). Estimates are based on GBD 2016 Disease and Injury Incidence and Prevalence Collaborators.[9]

Disease	Estimated Prevalence or *Incidence*	Vaccine under development?	Stage of development
Ascariasis	799.683 million	Yes	Preclinical
Hookworm disease	450.683 million	Yes	Phase 1 testing in endemic areas
Trichuriasis	435.095 million	Yes	Preclinical
Schistosomiasis	189.774 million	Yes	Phase 1 testing in endemic areas
Scabies	146.785 million	Yes	Preclinical
Dengue	*101.064 million*	Yes	Licensed vaccine and additional candidates in clinical development
Food-borne Trematodiases	74.725 million	No	—
Lymphatic Filariasis	29.382 million	No	—
Onchocerciasis	14.650 million	Yes	Preclinical
Zika virus disease	*7.598 million*	Yes	Phase 1–2 testing in endemic areas
Chagas disease	7.201 million	Yes	Preclinical
Leishmaniasis	4.835 million	Yes	Phase 1–2 testing in endemic areas
Trachoma	3.338 million	No	—
Cysticercosis	2.676 million	Yes	Veterinary transmission blocking vaccine
Cystic Echinococcosis	0.974 million	Yes	Veterinary transmission blocking vaccine
Leprosy	0.523 million	Yes	Preclinical
Yellow Fever	*0.112 million*	Yes	Licensed vaccine
Rabies	*0.013 million*	Yes	Licensed vaccine
African trypanosomiasis	0.007 million	No	—
Ebola virus disease	0.001 million	Yes	Pre-licensure
Guinea worm disease	0.000	No	—

receiving NTD essential medicines for these NTDs has now surpassed one billion, although almost one-half of the world's population requiring such medicines has yet to receive them.[11] Integrated MDA is now having an impact in terms of reducing the prevalence and disease burden of several of these NTDs,[12] and could be critical for the eventual elimination of LF, onchocerciasis, ascariasis, trachoma, scabies, and yaws. However, for other diseases such as hookworm and schistosomiasis, the impact has not been as great, possibly due to post-treatment re-infections and lower than expected drug efficacies. Accordingly there is a need for additional biotechnologies for these diseases.

In addition to hookworm and schistosomiasis, there is also a need for new biotechnologies to combat many of the other NTDs, especially insect-borne diseases, including the major arbovirus infections (e.g., dengue and Zika virus infection), as well as vector-borne parasitic infections, such as leishmaniasis and Chagas disease. For these diseases, there are also efforts underway to develop antipoverty vaccines.

Antipoverty vaccines

The framework of antipoverty vaccines was shaped beginning in 2006,[10] in order to promote the concept of developing new vaccines for poverty-promoting NTDs. But progress in antipoverty vaccine development has been slow relative to scale-up for integrated MDA.[13–16] Listed in Table 1, is the current status for each of the NTDs currently being targeted for antipoverty vaccine development. With the exceptions of lymphatic filariasis, food-borne trematodiases, trachoma, African trypanosomiasis, and guinea worm disease, there is some level of vaccine development underway for all of the NTDs. However, most of these vaccines are in very early stage development or even at the preclinical stage of testing. Only three NTDs currently have licensed vaccines – vaccines for dengue, yellow fever, and rabies – while only five others, including hookworm disease, schistosomiasis, Zika virus infection, leishmaniasis, and Ebola virus infection, currently have vaccines in clinical testing.

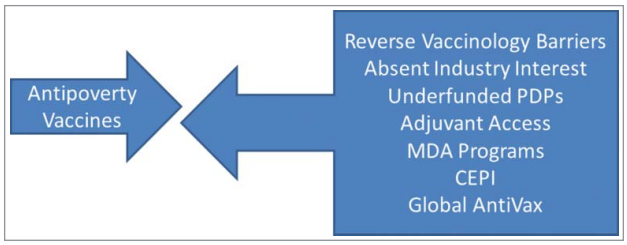

Figure 1. The global fight to produce antipoverty vaccines.

Indeed, antipoverty vaccine development has lagged behind the rest of the vaccine industry, due to a combination of both scientific and geopolitical barriers illustrated in Fig. 1.[13–16]

In terms of scientific hurdles, while reverse vaccinology approaches have greatly benefited the advancement of bacterial and viral infections, this strategy is often problematic for the NTDs. Many of the NTDs are caused by complex eukaryotic parasites with large genomes oftentimes around the size of the human genome, making target selection a daunting task. The problem is compounded by the absence of high throughput expression systems for producing recombinant eukaryotic antigens, or the availability convenient small laboratory animal models in order to get a clear efficacy signal at the preclinical stage of testing.

But the geopolitical barriers may be even greater. Because the NTDs disproportionately affect people living in severe poverty, industry interest in long-term NTD investments has been modest at best, and in many cases non-existent for the highest disease burden NTDs. An important exemption is Sanofi-Pasteur's commitment to Dengvaxia®, a new generation dengue vaccine, but there are concerns that recent issues regarding that vaccine's safety and efficacy could derail its future, or even downstream industry investments in dengue vaccines altogether. The major pharmaceutical manufacturers have also expressed interest in advancing new Zika and Ebola virus vaccines, but again these disease targets are linked to uncertain or unreliable product markets.

Industry interest in vaccines for parasitic helminth infections such as hookworm disease and schistosomiasis, or parasitic protozoan infections such as leishmaniasis and Chagas disease has been close to zero, leaving these activities to a handful of non-profit product development partnerships (PDPs). For example the Texas Children's Hospital Center for Vaccine Development (Texas Children's CVD) in Houston is advancing vaccines for hookworm disease and schistosomiasis through clinical development, as well as earlier preclinical stage vaccines for Chagas disease and leishmanias. Seattle-based IDRI is also developing leishmaniasis and leprosy vaccines, while helping to provide adjuvant access for other NTD vaccine targets. Similarly Brazil's Oswaldo Cruz Foundation (FIOCRUZ) as well as other national research institutes and member organizations of the Developing Country Vaccine Manufacturers Network (www.dcvmn.org) are also actively engaged in antipoverty vaccine development. But compared to the multinational pharmaceutical commitment to new vaccine research and development (R&D), the overall investment from PDPs and allied organizations for antipoverty vaccines is extremely modest[17]. According the Policy Cures annual G-FINDER Report for 2015, only $20 million was invested in vaccine R&D for schistosomiasis, hookworm disease, leishmaniasis, and Chagas disease combined.[17]

The cost-effectiveness, and even cost-savings of hookworm, leishmaniasis, and Chagas disease vaccines have been confirmed through modeling studies by health economists,[18–23] yet there remain significant hurdles for PDPs committed to these antipoverty vaccines. Obstacles include generally inadequate level of project and program funding, especially since there are generally few major donor partners expressly committed to NTD vaccines. The lack of funds is especially apparent for expensive later stage clinical and product development leading to licensure. In some cases, human challenge models are under development in order to obtain early efficacy signals for the antipoverty vaccines as a potential means to de-risk R&D investments. In addition, so far the newly established Coalition for Epidemic Preparedness (CEPI) has focused exclusively on viral threats of perceived pandemic potential, rather than antipoverty vaccines.[16]

Still another important issue is the perceived benefits of integrated MDA, with sometimes inflated or exaggerated claims on the potential for MDA alone to achieve elimination for NTDs such as hookworm disease or schistosomiasis. Because NTD R&D funding is so modest, often only a single major new technology is often being advanced in order to tackle a given disease, in contrast to say HIV/AIDS, tuberculosis, or malaria for which multiple approaches are being simultaneously supported.[11] The fallacy of this "one shot on goal" approach has been highlighted.[11]

Finally, there are concerns that a rising and aggressive anti-vaccine ("antivax") movement in the US and elsewhere[24-27] could also have a chilling effect on future antipoverty vaccine development. A specific concern has been raised that the American antivax movement is spreading globally so that large low- and middle-income countries, including the BRICS nations such as Brazil, India, and China, as well as Nigeria and Indonesia could delay or halt the introduction of new antipoverty vaccines.[27] It's possible that the recent difficulties with Dengvaxia® could also strengthen resistance to introducing additional vaccines targeting NTDs.

Despite the formidable scientific and geopolitical obstacles highlighted here, antipoverty vaccine development continues, albeit at a much slower and less consistent pace than other more lucrative vaccine development programs. Ultimately, it would be desirable to have WHO and other international health agencies, including Gavi, the Vaccine Alliance, convene experts in order to better determine the needs of the PDPs and potential industry collaborators and how to best catalyze antipoverty vaccine investments and advancements. It's been pointed out that for the world's poorest people suffering from NTDs access to antipoverty technologies is a fundamental human right.[28]

Disclosure of potential conflicts of interest

The author is patentholder and lead investigator on several vaccines in development, including vaccines in clinical trials, for diseases discussed in this paper.

References

1. Molyneux DH, Hotez PJ, Fenwick A. "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med. 2005;2(11):e336. doi:10.1371/journal.pmed.0020336
2. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med. 2006;3(5):e102. doi:10.1371/journal.pmed.0030102
3. Hotez P, Ottesen E, Fenwick A, Molyneux D. The neglected tropical diseases: the ancient afflictions of stigma and poverty and the prospects for their control and elimination. Adv Exp Med Biol. 2006;582:23–33. doi:10.1007/0-387-33026-7_3. PMID:16802616
4. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, Savioli L. Control of neglected tropical diseases. N Engl J Med. 2007;357(10):1018–27. doi:10.1056/NEJMra064142
5. Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. Lancet. 2009;373(9674):1570–5. doi:10.1016/S0140-6736(09)60233-6
6. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130434. doi:10.1098/rstb.2013.0434
7. Hotez PJ. Forgotten People Forgotten Diseases: The Neglected Tropical Diseases and their impact on Global Health and Development. ASM Press.
8. World Health Organization. Neglected Diseases. http://www.who.int/neglected_diseases/diseases/en/, accessed December 26, 2017.
9. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1211–59. doi:10.1016/S0140-6736(17)32154-2. PMID:28919117
10. Hotez PJ, Ferris MT. The antipoverty vaccines. Vaccine. 2006;24(31–32):5787–99. doi:10.1016/j.vaccine.2006.05.008
11. Hotez PJ Ten failings in global neglected tropical diseases control. PLoS Negl Trop Dis. 2017;11(12):e0005896.
12. Hotez PJ, Fenwick A, Ray SE, Hay SI, Molyneux DH. "Rapid impact" ten years after: the first "decade" (2006–2016) of integrated neglected tropical disease control. PLoS Negl Trop Dis. 2018;12: In press. doi:10.1371/journal.pntd.0005896. PMID:29267282
13. Hotez P. A handful of 'antipoverty' vaccines exist for neglected diseases, but the world's poorest billion people need more. Health Aff (Millwood). 2011;30(6):1080–7.

14. Hotez PJ, Bottazzi ME, Strych U. New vaccines for the world's poorest people. Annu Rev Med. 2016;67:405–17. doi:10.1377/hlthaff.2011.0317. doi:10.1146/annurev-med-051214-024241. PMID:26356803
15. Hotez PJ, Strych U, Lustigman S, Bottazzi ME. Human anthelminthic vaccines: Rationale and challenges. Vaccine. 2016;34(30):3549–55. doi:10.1016/j.vaccine.2016.03.112
16. Hotez PJ. Developing and financing neglected disease vaccines in our new era of "blue marble health" and the anthropocene epoch. Vaccine. 2017;35(40):5403–5405. doi:10.1016/j.vaccine.2017.02.002
17. Policy Cures. G-FINDER Report 2015. Neglected Disease Research and Development: The Ebola Effect http://www.policycures.org/downloads/Y8%20GFINDER%20full%20report%20web.pdf, accessed December 28, 2017.
18. Lee BY, Bacon KM, Wateska AR, Bottazzi ME, Dumonteil E, Hotez PJ. Modeling the economic value of a Chagas' disease therapeutic vaccine. Hum Vaccin Immunother. 2012;8(9):1293–301. doi:10.4161/hv.20966
19. Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. Lancet Infect Dis. 2013;13(4):342–8. doi:10.1016/S1473-3099(13)70002-1
20. 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;31(3):480–6. doi:10.1016/j.vaccine.2012.11.032
21. Bartsch SM, Hotez PJ, Asti L, Zapf KM, Bottazzi ME, Diemert DJ, Lee BY. The Global Economic and Health Burden of Human Hookworm Infection. PLoS Negl Trop Dis. 2016;10(9):e0004922. doi:10.1371/journal.pntd.0004922
22. 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;34(19):2197–206.
23. Lee BY, Alfaro-Murillo JA, Parpia AS, Asti L, Wedlock PT, Hotez PJ, Galvani AP. The potential economic burden of Zika in the continental United States. PLoS Negl Trop Dis. 2017;11(4):e0005531.
24. Hotez PJ. Texas and Its Measles Epidemics. PLoS Med. 2016;13(10):e1002153.
25. Lo NC, Hotez PJ. Public Health and Economic Consequences of Vaccine Hesitancy for Measles in the United States. JAMA Pediatr. 2017;171(9):887–892.
26. Hotez PJ. "Melanie's measles" is deadly and causes permanent neurologic impairment. Microbes Infect. 2017. pii: S1286–4579(17)30179-X. doi:10.1016/j.micinf.2017.10.004. [Epub ahead of print].
27. Hotez PJ. Will an American-Led Anti-Vaccine Movement Subvert Global Health? Sci Am https://blogs.scientificamerican.com/guest-blog/will-an-american-led-anti-vaccine-movement-subvert-global-health/
28. Hotez PJ. The poverty-related neglected diseases: Why basic research matters. PLoS Biol. 2017;15(11):e2004186.