BIO Ventures for Global Health

# The Vaccine Landscape for Neglected Diseases

*A Perspective from the Global Health Primer*

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## Executive Summary

Vaccines represent an integral tool in the fight against infectious diseases. Vaccine development has resulted in the eradication of smallpox, the near eradication of polio, and the prevention of over 2.5 million children's deaths each year. Despite the success of existing vaccines, new vaccines -- especially those for diseases that disproportionately affect the developing world -- are emerging more slowly.

Neglected diseases affect more than 1 billion of the world's poorest people. In 2011, BIO Ventures for Global Health (BVGH) published an expanded edition of its Global Health Primer, a tool that compiles and tracks drugs, vaccines, and diagnostics in development for neglected diseases. The Global Health Primer currently tracks vaccines on market and in development for 17 neglected diseases. Analysis of the data has uncovered several trends across the vaccine research and development (R&D) space for neglected diseases:

- **Lack of financing options, clear policy statements, or WHO prequalification of an approved vaccine severely limits access** and the potential to save lives.

- **Newer vaccines in development for neglected diseases are increasingly scientifically complex**, which has implications for clinical trial design and cost, regulatory approval, WHO prequalification, and delivery in resource-poor settings.

- **Lack of integration of scientific research questions into the design of vaccine clinical efficacy trials has resulted in limited learning** from failed trials or trials where only partial vaccine efficacy was observed.

- Clinical stage or approved vaccines, where proof of concept has been demonstrated, are primarily limited to viral and bacterial diseases. There are **relatively fewer vaccines in development for parasitic diseases** and proof of concept in this space is limited to malaria.

- Despite the availability of alternative control methods for some neglected diseases, such as vector control or mass drug administration (MDA), **investment in vaccination may address key gaps in control strategies** as elimination or eradication goals are pursued.

In light of these trends and the current status of vaccine development for neglected diseases, BVGH recommends the following actions:

- More **operational and clinical research on existing vaccines** to support the development of clear policy statements, accelerate WHO prequalification, and inform decisions on new product needs.

- Increased investment in the **integration of scientific research questions with efficacy studies for vaccines** in clinical development to guide future vaccine development and maximize the amount of information learned through public investment.

- A **focus on parasitic disease vaccine development** to understand the technical feasibility and potential health impact of vaccines for these biologically complex organisms.

As we look toward the future of the battle against neglected diseases, these issues will play a central role in driving and shaping vaccine development. Although vaccines will face a wide range of challenges on the path toward reaching populations in need, BVGH hopes this report will stimulate both discussion and action in the neglected disease vaccine space.

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## Introduction to the Vaccine Landscape for Neglected Diseases

Vaccines represent an integral tool in the fight against infectious diseases around the world. Vaccine development has resulted in the eradication of smallpox, the near eradication of polio, and the prevention of over 2.5 million children's deaths each year (see Box 1). The proven track record of vaccines in saving lives continues to drive focus in this area in the global health sector. In January 2010, the Bill & Melinda Gates Foundation announced a "Decade of Vaccines," renewing their commitment to fund vaccine introduction and development for the next 10 years.[1]

**Box 1. Impact of Vaccines**

The eradication of smallpox is one of the most significant advances in the history of public health and a testament to the power of an effective vaccine. Between 1959 and 1978, cases of smallpox were reduced from 2 million per year to zero with the help of aggressive vaccination campaigns.[2] The eradication of smallpox highlighted both that disease eradication is possible and that vaccination is a powerful tool for disease control and elimination.

To build on the successful eradication of smallpox through immunization, the Expanded Programme on Immunization (EPI) was established in 1974 through a World Health Assembly resolution (resolution WHA27.57).[3] EPI aims to ensure that all children in all countries benefit from life-saving vaccines. As of 2009, it is estimated that immunization averts 2.5 million deaths per year from diphtheria, tetanus, pertussis, and measles.[4] Progress towards complete vaccination coverage through EPI from 1990-2009 is summarized below.

**Global Vaccination Coverage[5]**

| Disease | 1990 Coverage | 2009 Coverage | Notes |
|---|---|---|---|
| Diphtheria, tetanus, pertussis (DTP) | 75% | 82% | 107 million children were vaccinated with the DTP3 vaccine in 2009. |
| Haemophilus influenzae type B (Hib) | N/A | 38% | Now available in 161 countries (25 new countries in 2009 alone). Hib continues to result in 260,000 deaths per year. |
| Hepatitis B | 1% | 70% | Now available in 178 countries. |
| Polio | 75% | 83% | Total cases reduced from 350,000 in 125 countries in 1988 to 1783 in 4 countries 2009. |
| Measles | 73% | 82% | Measles continues to result in 118,000 deaths per year. |

[1] Bill and Melinda Gates Foundation press release: http://www.gatesfoundation.org/press-releases/Pages/decade-of-vaccines-wec-announcement-100129.aspx
[2] Enserink M (2010) "What's Next for Disease Eradication?" Science 330: 1736.
[3] WHO, Expanded Programme on Immunization(EPI): http://www.who.int/immunization_delivery/en/
[4] WHO and UNICEF (2010) "Global Immunization Data."
[5] WHO and UNICEF (2010) "Global Immunization Data."

Despite the success of existing vaccines, new vaccines -- especially those for diseases that disproportionately affect the developing world -- are emerging more slowly. An area of particular interest is the field of neglected diseases. When the term "neglected" is applied to a disease, it can carry a wide range of implications. "Neglected" can describe the patient population affected by the disease, the scientific effort underway to understand the disease, or the extent to which new products to prevent, diagnose, or treat a disease are being pursued. "Neglected" can also describe a health disparity where drugs, vaccines, or diagnostics are available and in use in wealthier or developed countries but these technologies have not been extended to poorer countries due to challenges of cost, feasibility, or political will. The World Health Organization (WHO) estimates that of the 2.7 billion people living on less than $2 per day (the world's poorest people), more than 1 billion are affected by at least one neglected disease.[6]

From 2000-2009, 26 new products were approved for neglected disease indications.[7] However, only three were vaccines. Because the bulk of the neglected disease burden lies in marginalized populations of the developing world, vaccines for these diseases do not necessarily have the same economic incentives or political motivation for development and introduction as previous generations of vaccines used widely across both developed and developing world populations. The good news is that investment in R&D for neglected diseases is increasing. The annual G-FINDER survey found that the total funding for R&D in this space across drugs, vaccines, and diagnostics covering 31 total neglected diseases was approximately $3.2 billion dollars in 2009 as compared to $2.5 billion dollars in 2007.[8]

Understanding the R&D landscape for neglected diseases is an essential first step towards identifying key challenges, needs, and solutions for products that will impact health. In 2011, BVGH published an expanded edition of the Global Health Primer, a tool that compiles and tracks products in development for neglected diseases. The Global Health Primer focuses on 17 neglected diseases, providing both information on the biology of the disease as well as analysis of the drugs, vaccines, and diagnostics currently in development. Although lists and definitions of neglected diseases vary by organization, here we will focus on 17 diseases spanning the various categories of neglect. The list includes:[9]

- Chagas disease (American Trypanosomiasis)
- Cholera
- Dengue fever
- Enterotoxigenic *E. coli* (ETEC)

[6] WHO (2011) "Working to overcome the global impact of neglected tropical diseases – Summary." Weekly Epidemiological Record 86: 113-120. PMID: 21438440

[7] Cohen J et al. (2010) "Development of and access to products for neglected diseases." PLoS ONE 5: e10610. PMID: 20485552

[8] Moran M et al. (2011) "Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?" Policy Cures; Moran M et al. (2009) "Neglected Disease Research & Development: How Much are we Really Spending?" The George Institute for International Health.

[9] Disease names listed here are linked to disease profiles on the BVGH Global Health Primer website: "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx; The World Health Organization (WHO) uses an overlapping but slightly different list to define neglected diseases that is available at: http://www.who.int/neglected_diseases/diseases/en/

- Hookworm
- Human African Trypanosomiasis (HAT/ Sleeping Sickness)
- Human Immunodeficiency Virus (HIV)
- Leishmaniasis
- Lymphatic Filariasis (LF)
- Malaria
- Onchocerciasis (River Blindness)
- Pneumococcal Disease
- Rotavirus
- Schistosomiasis
- Shigellosis
- Tuberculosis (TB)
- Typhoid Fever

The number of vaccines that are approved or in each stage of development for the 17 neglected diseases are displayed in Figure 1. Details on each product are available in the Global Heath Primer.

**Figure 1. Number of Vaccines in Development by Phase**[10]

| | Discovery/ Pre-clinical Research | Phase I | Phase II | Phase III | Approved |
|---|---|---|---|---|---|
| Chagas disease | - | - | - | - | - |
| Cholera | 1 | 1 | 2 | - | 3 |
| Dengue fever | 4 | 3 | 1 | 1 | - |
| ETEC | 6 | 5 | 1 | - | - |
| Hookworm | 2 | - | - | - | - |
| HAT | - | - | - | - | - |
| HIV | 2 | 30 | 14 | 2 | - |
| Leishmaniasis | 5 | - | - | - | - |
| LF | 2 | - | - | - | - |
| Malaria | 8 | 6 | 12 | 1 | - |
| Pneumococcal disease | 7 | 2 | 1 | - | 3 |
| Onchocerciasis | 2 | - | - | - | - |
| Rotavirus | 1 | 1 | 1 | - | 2 |
| Schistosomiasis | 3 | 1 | - | 1 | - |
| Shigellosis | - | 1 | 2 | 2 | 1* |
| Tuberculosis | 9 | 6 | 4 | 1 | 1* |
| Typhoid | 2 | 1 | 3 | - | 2 |

Despite the diversity of organisms represented by the neglected diseases (including bacteria, viruses, and parasites) and the large variation in the numbers of products across the stages of development, analysis of the data reveals several trends:

- Lack of financing options, clear policy statements, or WHO prequalification of an approved vaccine severely limits access and the potential to save lives.

- Newer vaccines in development for neglected diseases are increasingly scientifically complex, which has implications for clinical trial design and cost, regulatory approval, WHO prequalification, and delivery in resource-poor settings.

[10] "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx; (*) The approved vaccine for shigellosis is only available in China, and details on the efficacy of this product are not available. The approved vaccine for TB (BCG) does not prevent active pulmonary disease in adults.

- Lack of integration of scientific research questions into the design of vaccine clinical efficacy trials has resulted in limited learning from failed trials or trials where only partial vaccine efficacy was observed.

- Clinical stage or approved vaccines, where proof of concept has been demonstrated, are primarily limited to viral and bacterial diseases. There are relatively fewer vaccines in development for parasitic diseases and proof of concept in this space is limited to malaria.

- Despite the availability of alternative control methods for some neglected diseases, such as vector control or mass drug administration (MDA), investment in vaccination may address key gaps in control strategies as elimination or eradication goals are pursued.

To understand how these trends emerged from the Global Health Primer, the following section of this report provides analysis of the vaccine R&D landscape broken down by stages of development.

## Analysis of Vaccine Pipelines by Stage of Development

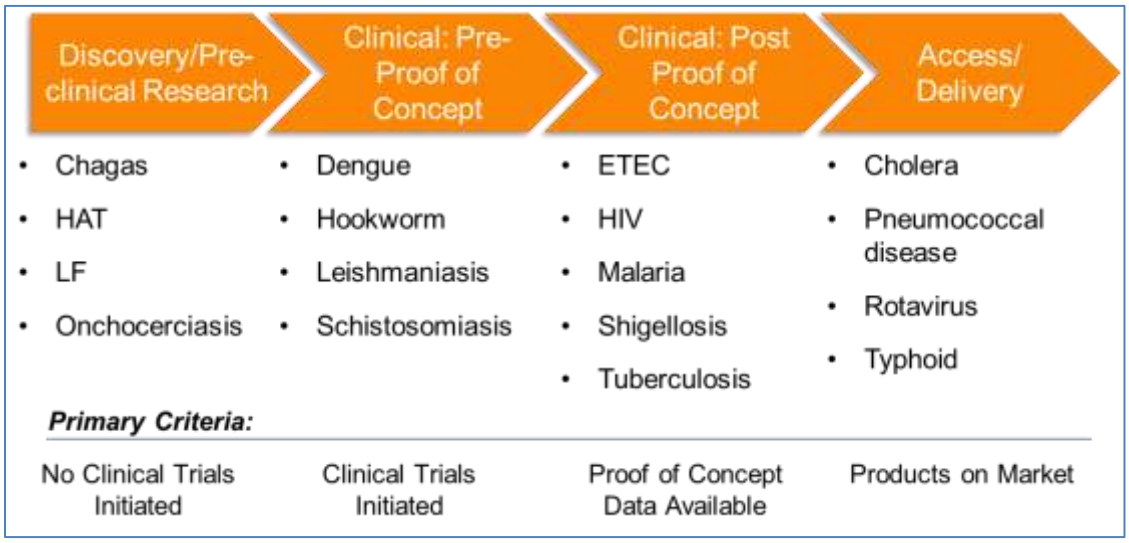
Although the majority of neglected disease vaccine pipelines have products covering multiple phases of development, it is easier to discuss common challenges or goals across neglected diseases whose most advanced vaccine products are at similar points in the development process. Rather than simply grouping these diseases by the most advanced stage of development, for analysis purposes we've grouped the diseases more broadly in order to look beyond the current active pipeline.

For instance, clinical efficacy data can originate from approved vaccines for other diseases that provide cross-protection, phase II or III trial data for products in development, or discontinued products that did not reach market but demonstrated that protection through vaccination is possible. Having clinical efficacy data, whether from an active/advanced product or otherwise, represents a significant step forward for vaccine development for a disease. Similarly, a disease having no products in clinical development because a previously tested product is currently being improved is a very different scenario than a disease for which no vaccine has ever reached the clinic. Using this type of data-centered perspective, we grouped the 17 diseases into the following four categories:

- ***Discovery/Pre-clinical:*** Diseases in this category have very early stage or empty pipelines where products have not reached the clinic.
- ***Clinical: Pre-Proof of Concept:*** Diseases in this category fall into two subgroups, (a) diseases with products currently in clinical development, but efficacy data are not yet available, or (b) diseases where products have entered the clinic but are currently being optimized based on initial trial results. These diseases have crossed the critical hurdle of having products reach the clinic but are challenging to evaluate due to a lack of efficacy data.
- ***Clinical: Post-Proof of Concept:*** Diseases in this category have proof of concept data available from active vaccine products (generally phase II or III data) or have demonstrated at least partial protection through cross-protection with other vaccines. These diseases have crossed the critical hurdle of demonstrating that vaccination can significantly prevent or impact infection.
- ***Access/Delivery:*** Diseases in this category have products approved in at least one country and now are navigating the challenges of access and delivery to reach people living in resource poor settings.

These new categories and the disease vaccine pipelines that they encompass are summarized in Figure 2. Additional rationale for inclusion of diseases in each category is presented in subsequent sections.

**Figure 2. Disease Vaccine Pipelines by Most Advanced Stage**




The following sections examine each of the four categories of vaccine pipeline in order to highlight common challenges and goals of R&D programs across diseases. By first examining products that are available for rollout and working back to discovery/pre-clinical stage programs, we can gain a perspective for the long road ahead for early stage products and identify key hurdles that will help inform the decision making process regarding whether or not vaccine investment is a priority for an individual disease. We hope that our cross-sectional view of vaccine development will allow the neglected diseases community to learn from the work of past and parallel vaccine development programs and identify opportunities for creative solutions to the challenges facing vaccines for neglected diseases.

***Access/Delivery Stage***

Of the 17 diseases currently analyzed in the Global Health Primer, four[11] are diseases that have on market vaccines. The on market products are summarized in Table 1.

**Table 1. On Market Vaccines for Neglected Diseases**

| Disease | Product (Company) | Country of Initial Approval | Year of Initial Approval | Year of WHO Prequalification[12] |
|---|---|---|---|---|
| Cholera | Dukoral (SBL Vaccin, Sweden) | Sweden | 1991 | 2001 |
| | Shanchol (Shantha Biotechnics, India) | India | 2009 | N/A |
| | mORCVAC (VaBiotech, Vietnam) | Vietnam | 2009 | N/A |
| Pneumococcal Disease | Synfloris (GSK) | Europe | 2009 | 2009 |
| | Prevnar 13 (PCV13 – replacement for PCV 7 which was approved in the U.S. in 2000; Pfizer) | U.S. | 2010 | 2010 |
| Rotavirus | RotaTeq (Merck) | U.S. | 2006 | 2008 |
| | Rotarix (GSK) | U.S. | 2008 | 2009 |
| Typhoid | Vivotif (Crucell) | Switzerland | 1981 | N/A |
| | Typhim Vi (Sanofi-Pasteur) | U.S. | 1994 | N/A |

Although some of these vaccines have been available since the 1980s, none of these vaccines are used extensively in the developing world. The challenges facing these vaccines with regard to adoption fall into three key areas:

- Financial hurdles
- Policy hurdles
- Technical hurdles

Each of these hurdles has impacted the current use of these vaccines in different ways. A summary of the financial, policy, and technical status of existing vaccines, as well as the current status of their use, is presented in Table 2.

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[11] There are two additional diseases with approved vaccines, TB and shigellosis. There is one vaccine on market for Tuberculosis, BCG, which has been in use outside of the United States since the 1920s. However, because this vaccine (1) does not prevent infection or pulmonary disease (key strategies for new TB vaccine development) and (2) the challenges faced in the TB vaccine development field are more similar to other Clinical: Post Proof of Concept vaccine pipelines as opposed to Access/Delivery stage programs, we have decided to characterize TB vaccine development as Clinical: Post Proof of Concept. There is a vaccine available for shigellosis in China but data on this vaccine are limited and there does not seem to be any plan to expand access of this vaccine outside of China.

[12] A database of prequalified vaccines can be found on the WHO website: http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

### Table 2. Status of Access/Delivery Stage Vaccines

| | Cholera | Pneumococcal Disease | Rotavirus | Typhoid |
|---|---|---|---|---|
| **Financial Status** | Reviewed by GAVI, but NOT selected for GAVI support | Eligible for GAVI support; AMC encouraging production of low-cost products | Eligible for GAVI support | Short-listed for future GAVI support |
| **Policy Status** | WHO cholera vaccination policy[13] states that vaccines should be used in conjunction with other cholera control strategies in endemic areas but should not be prioritized over other strategies. WHO suggests that more research is needed to understand how vaccination should be used in the context of outbreaks. Only one vaccine is prequalified by WHO. | In 2007, WHO recommended the use of pneumococcal vaccines in all countries, urging that the highest priority for introduction be given to countries with high pneumonia and under five mortality rates.[14] | In 2009, WHO recommended that rotavirus vaccine for infants should be included in all national immunization programs with priority in countries where diarrheal deaths account for ≥10% of mortality among children aged <5 years.[15] | Current WHO policy recommends vaccination for travelers and for high risk groups in endemic areas.[16] Two new initiatives aim to generate data to inform policy decisions:[17] 1) Typhoid Surveillance in Sub-Saharan Africa Project, IVI 2) Coalition Against Typhoid, Sabin There are no WHO prequalified typhoid vaccines. |
| **Technical Status** | Dosing schedule and roll out strategy in outbreak and endemic settings need to be optimized. | There are more than 90 serotypes of *Streptococcus pneumoniae* bacteria, vaccines protect against a subset. Vaccines in development looking for recombinant proteins that protect against more strains. | Cold chain and multiple doses required. Vaccines in development looking to improve stability, reduce dosing frequency, and allow for at birth dosing. | Although the oral vaccine is more effective, it requires cold chain and complicated dosing. Improved versions of both existing vaccines are in development. |
| **Current Use** | Limited supply and limited rollout in part due to ongoing debate about the role of vaccination for cholera outbreaks.[18] | Introduced into 44 countries as of 2009.[19] Five additional countries, out of 19 total approved for support, are rolling out the vaccine through GAVI in 2010 and 2011.[20] | Introduced into 23 countries as of 2009.[21] As of 2009, four countries received approval for GAVI support of vaccine rollout. | In use for travelers visiting high-risk areas and several disease endemic areas have individual initiatives including Delhi State in India, Fiji, and Sri Lanka.[22] |

[13] WHO (2010) "Cholera vaccines: WHO position paper." Weekly Epidemiological Record 85: 117-128.
[14] WHO (2007) "Pneumococcal conjugate vaccine for childhood immunization – WHO position paper." Weekly Epidemiological Record 82: 93-104.
[15] WHO (2009) "Rotavirus vaccines: an update." Weekly Epidemiological Record 84: 533-540.
[16] WHO (2008) "Typhoid vaccines: WHO position paper." Weekly Epidemiological Record 83: 49-60.
[17] WHO (2011) "Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010 – summary, conclusions, and recommendations." Weekly Epidemiological Record 86: 1-16.
[18] See commentary in: Cyranoski D (2011) "Cholera vaccine plan splits experts." Nature 469: 273-274.
[19] WHO and UNICEF (2010) "Global Immunization Data."
[20] GAVI website: http://www.gavialliance.org/vision/programme_support/new_vaccines/pneumococcal/impact.php
[21] WHO and UNICEF (2010) "Global Immunization Data."

*Financial Hurdles*

The burden for financing vaccination falls largely on countries. Unfortunately, for countries with few financial resources, the amounts of money available for vaccination are not always sufficient. The GAVI Alliance is a public-private global health partnership that was created in 2000 to increase access to immunization in the world's poorest countries. GAVI has played an essential role in improving vaccine coverage and is attributed with saving over 5 million lives in its first 10 years of operation.[23] The breakdown of the impact of GAVI-funded vaccination is presented in Table 3.

**Table 3. Deaths Averted Through GAVI-Funded Vaccination, 2000-2009[24]**

| Vaccine-Preventable Disease | Deaths Averted Through Vaccination |
|---|---|
| Hepatitis B | 3,407,000 |
| *Haemophilus influenza* b (Hib) | 560,000 |
| Pertussis | 474,000 |
| Measles | 1,200,000 |
| Yellow Fever | 140,000 |
| Polio | 30,000 |
| Pneumococcal Disease | 8,000 |
| Rotavirus | 1,000 |

Beyond direct support for vaccination, GAVI has also been involved in promoting creative financing solutions to improve vaccine access. The most prominent example is the Advanced Market Commitment (AMC) for pneumococcal vaccines. Although a significant market for pneumococcal vaccines exists in the developed world, the current vaccines have been cost prohibitive for use in the developing world. In order to incentivize access, a US$1.5 billion AMC was established in 2009 to create a market for pneumococcal vaccines in the developing world. In March 2010 the first deal under the AMC was reached; GSK and Pfizer signed a ten-year deal with GAVI to supply 60 million doses per year of their approved vaccines for US$3.50-7.00 per dose.[25] Creative financing solutions, like the AMC, could help accelerate the rollout of other lifesaving vaccines.

The impact of GAVI on vaccine rollout and global health has been enormous. However, for vaccines that are not qualified for GAVI funding, it is unclear how rollout will be paid for. For instance, typhoid and cholera vaccines have existed much longer than pneumococcal and rotavirus vaccines, but their delivery in the developing work is significantly more limited. Typhoid

[22] WHO (2011) "Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010 – summary, conclusions, and recommendations." Weekly Epidemiological Record 86: 1-16.
[23] GAVI Website: http://www.gavialliance.org/performance/global_results/GAVI_Alliance___Results_2008___Vaccines.php
[24] GAVI Website: http://www.gavialliance.org/performance/global_results/GAVI_Alliance___Results_2008___Vaccines.php
[25] GAVI press release, available here: http://www.gavialliance.org/media_centre/press_releases/2010_03_23_amc_commitment.php

is now one of four vaccines under consideration by GAVI for future funding eligibility.[26] It will be interesting to see what impact GAVI funding will have on typhoid vaccine use if this vaccine is selected for support. Unfortunately, cholera vaccines did not make the GAVI shortlist. Also, malaria and dengue vaccines were eliminated early in the prioritization process because they have not come to market yet. This raises the question: If a new vaccine comes to market, how long will it take before it has the opportunity to be added to the GAVI list? If a vaccine is not accepted for funding, what will happen to it? In other words, is this funding risk a disincentive to some would-be vaccine developers to continue development, especially of vaccines where no developed world market exists? These questions have implications not just for those vaccines that exist today but also future vaccines that may or may not come to market. Additional creative funding streams that complement the ongoing work by GAVI would provide an opportunity to broaden the vaccines available to the developing world.

*Policy Hurdles*

The decision to recommend use of a vaccine is often complex. Factors including efficacy, safety, cost, and potential health impact are all important; not all vaccines are appropriate or feasible for use in all scenarios. To help countries and funding organizations make decisions regarding vaccination, the WHO prepares position papers evaluating the scientific evidence for use of a vaccine as well as other factors that may impact vaccine utility.[27] The papers are reviewed by a number of experts within and outside WHO and since April 2006, have been reviewed and endorsed by WHO's Strategic Advisory Group of Experts (SAGE) on vaccines and immunization.

Establishing vaccine priorities through policy can have a significant effect on funding and access. We can use the outbreak of cholera in Haiti in 2010 as an interesting example. The WHO policy on the use of vaccination for cholera states that vaccination during an outbreak should be considered, but it is unclear at best on how to determine when this approach should be taken.[28] Furthermore, although there are now three cholera vaccines, only Dukoral is currently "prequalified" by WHO for prevention of cholera, meaning only Dukoral can be purchased by multilateral organizations that want to use the cholera vaccines. As the cholera outbreak in Haiti swelled, and calls for vaccination increased, several arguments against vaccination were presented, including (1) the limited supply of Dukoral and (2) the lack of clarity on the benefits of vaccination in an outbreak scenario. This resulted in limited effort to initiate a cholera vaccination campaign. Because Shanchol (and mORCVAC, which is the same vaccine produced by a different manufacturer) were not prequalified by WHO, stockpiles of those products were not considered in the initial evaluation of whether or not to launch a vaccination campaign in Haiti.

In a new model of cholera in Haiti published in the Lancet in March 2011, the potential impact of a vaccination campaign in Haiti is quantified. Andrews and Basu estimate that vaccination of

[26] GAVI Website: http://www.gavialliance.org/vision/strategy/vaccine_investment/index.php
[27] WHO "Vaccine Position Papers," available at: http://www.who.int/immunization/documents/positionpapers/en/index.html
[28] WHO (2010) "Cholera vaccines: WHO position paper." Weekly Epidemiological Record 85: 117-128.

just 10% of the population, a feasible number based on the combined availability of the Dukoral and Shanchol vaccines, would avert 63,000 of the projected 779,000 infections and 900 of the 11,100 deaths projected for March through November 2011 in Haiti. [29] Beyond the argument of potential lives saved, there is an equity argument that the poorest, most marginalized populations could receive vaccination even before a new wave of the epidemic starts, as they would be the least likely to reach and receive medical care once the epidemic begins.[30] The question now becomes how these data will be interpreted by policy makers and whether or not the Shanchol vaccine will be used without WHO prequalification.

In contrast to the scenario with cholera, clear policy decisions by WHO have accelerated the roll out of newer vaccines for pneumococcal disease and rotavirus. WHO recommended universal roll out of pneumococcal vaccine in children in 2007.[31] By 2009, 44 countries were using pneumococcal vaccines and 19 countries received GAVI approval for support. In the case of rotavirus, a change in WHO policy between 2007 and 2009 resulted in an immediate impact on vaccine use. In 2007 the WHO rotavirus policy stated:[32]

"*WHO strongly recommends the inclusion of rotavirus vaccination into the national immunization programmes of regions where vaccine efficacy data suggest a significant public health impact and where appropriate infrastructure and financing mechanisms are available. However, until the full potential of the current rotavirus vaccines has been confirmed in all regions of the world, in particular in Asia and Africa, WHO is not prepared to recommend global inclusion of rotavirus vaccines into national immunization programmes*."

Despite adding rotavirus to its portfolio in 2006, the WHO's recommendation restricted financial support for rollout of rotavirus vaccines by GAVI to just Latin American and European countries. In 2009, following new clinical trial information on the use of existing vaccines in endemic countries in Africa and Asia, the WHO changed the recommendation to state that rotavirus vaccine for infants should be included in all national immunization programs with priority in countries where diarrheal deaths account for ≥10% of mortality among children aged <5 years.[33] GAVI immediately expanded its list of countries eligible to receive rotavirus support. Rotavirus vaccines are now available in 23 countries (as of 2009) and four countries have now been approved to receive GAVI support.

The contrasting scenarios of cholera, pneumococcal disease, and rotavirus illustrate the impact policy decisions have on finance and ultimately access and delivery of a vaccine.

*Technical Hurdles*

Government regulatory approval for a vaccine is based on evidence that it is safe and effective, but not necessarily on the practical aspects of its use, especially in resource-poor settings.

[29] Andrews JR and Basu S (2011) "Transmission dynamics and control of cholera in Haiti: an epidemic model." The Lancet, in press.
[30] Sacks DA (2011) "How many cholera deaths can be averted in Haiti?" The Lancet, in press.
[31] WHO (2007) "Pneumococcal conjugate vaccine for childhood immunization – WHO position paper." Weekly Epidemiological Record 82: 93-104.
[32] WHO (2007) "Rotavirus vaccines: WHO Position Paper." Weekly epidemiological Record 82: 285-296.
[33] WHO (2009) "Rotavirus vaccines: an update." Weekly Epidemiological Record 84: 533-540.

Additional technical hurdles beyond the approval process, such as in vaccine storage, delivery, dosing schedule, or duration of protection, can translate into larger hurdles in obtaining policy and financial support needed for adoption of a vaccine. Overcoming technical hurdles to make existing vaccines more useful or to replace existing vaccines with more practical or more effective options is a key focus of the vaccine pipelines for access/delivery stage diseases. The vaccine development pipelines for cholera, pneumococcal disease, rotavirus, and typhoid are available in the Global Heath Primer. The key advantages of products in development for each disease are summarized in Table 4.

**Table 4. Analysis of Vaccine Pipeline for Access/Delivery Stage Diseases**[34]

| Disease | Key Advantages of Pipeline Products |
|---|---|
| Cholera | • Exploring live attenuated vaccine approach to potentially elicit more robust immune response |
| Pneumococcal Disease | • Exploring recombinant protein vaccine approach that could provide protection to wider range of serotypes |
| Rotavirus | • Reformulation of Rotateq to eliminate need for refrigeration<br>• More potent live attenuated strains that allow for single dose vaccination |
| Typhoid | • Reduce number of doses of live attenuated vaccine<br>• Improve immune response in children to polysaccharide-protein conjugate vaccine |

Improving existing vaccines and exploring alternative vaccine approaches that make these products more practical for delivery in the developing world will enhance the likelihood they receive positive policy support, e.g., WHO prequalification, and subsequently positive financial support to promote access and uptake.

[34] "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx

***Clinical: Post-Proof of Concept Stage***

Of the diseases included in the Global Health Primer, 5 could be considered to be "Post-Proof of Concept" meaning that the vaccines currently in development or previous vaccines have completed at least one human efficacy trial (generally phase II or phase III clinical trial) and demonstrated statistically significant efficacy in a clinical setting for these diseases, as summarized in Table 5.

**Table 5. Vaccine Proof of Concept Studies**

| Disease | Proof of Concept Studies |
|---|---|
| ETEC[35] | Dukoral, a vaccination developed for cholera, shows some cross protection against *E. coli* in endemic populations and travelers. |
| HIV[36] | A Phase III trial demonstrated approximately 30% efficacy relative to placebo in over 16,000 subjects in Thailand using ALVAC/AIDSVAX in prime-boost combination. |
| Malaria[37] | In a series of Phase II field trials, the RTS,S vaccine showed efficacy ranging from 30-50%. |
| Shigella[38] | In China, a recombinant, live, oral, bivalent vaccine, produced by the Lanzhou Institute of Vaccines and Biological Products, is available for adults. The vaccine has approximately 60% efficacy for both *S. flexinari* and *S. sonnei* but has never been evaluated or approved outside of China. |
| Tuberculosis[39] | BCG vaccine has been in use for over 80 years and is known to protect newborn infants from TB-related meningitis and other systemic TB infections. Meta-analysis of studies using BCG suggests some protection against pulmonary disease, but this is highly variable. |

Although most proof of concept data is available for only one or a limited number of products (primarily from phase II or III clinical trials), most of these diseases have multiple early stage products moving through clinical trials as summarized graphically in Figure 3.

[35] PATH and BVGH (2011) "The Case for Investment in Enterotoxigenic *Escheriscia coli* Vaccines."; Clemens JD et al. (1988) "Cross-protection by B subunit-whole cell cholera vaccine against diarrhea associated with heat-labile toxin-producing enterotoxigenic Escherichia coli: results of a large-scale field trial."J Infect Dis 158: 372-377. PMID: 3042876; Peltola H et al. (1991) "Prevention of travellers' diarrhoea by oral B-subunit/whole-cell cholera vaccine." Lancet 338: 1285-1289. PMID: 1682684

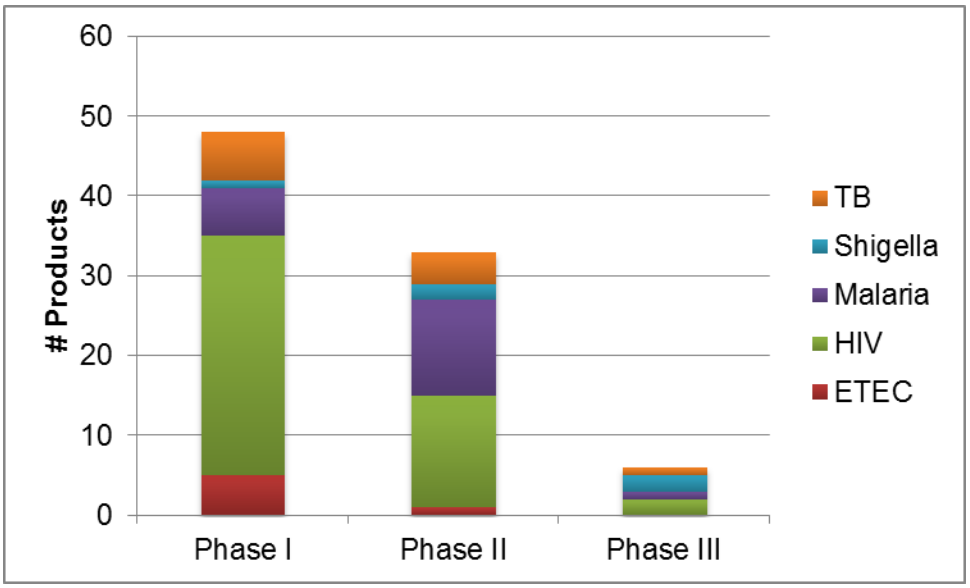
[36] Rerks-Ngarm S et al. (2009) "Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand." New England Journal of Medicine 361: 2209-20. PMID: 19843557

[37] Clinical data reviewed in: Casares S et al. (2010) "The RTS,S malaria vaccine." Vaccine 28: 4880-94. PMID: 20553771

[38] PAHO et al. (2004) "Progress in Shigella vaccine development." in *Vaccines: preventing disease & protecting health*. Available at: http://www.paho.org/english/dd/pub/SP_596.htm

[39] Colditz GA et al. (1994) "Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature." JAMA 271: 698-702; WHO (2004) "BCG Vaccine: WHO Position Paper." Weekly Epidemiological Record 79: 27-38.; Although BCG is approved for the prevention of meningitis or disseminated infection in children, it is not approved to prevent active pulmonary TB in adults (see footnote 11 for more detail).

### Figure 3. Products in Clinical Development[40]




R&D investment in diseases whose pipelines are in the post-proof of concept stage of clinical development is high. These products require large amounts of money to conduct expensive clinical trials (Table 6).

### Table 6. Vaccine R&D Investment by Disease

| Disease | Total Products in Clinical Development[41] | Vaccine R&D Investment Level (G-FINDER)[42] |
|---|---|---|
| ETEC | 6 | $15.6 million |
| HIV | 46 | $1,374 million |
| Malaria | 19 | $116.4 million |
| Shigella | 5 | $14.0 million |
| Tuberculosis | 11 | $187.0 million |

The full product development pipeline and product details for each disease are available in the Global Health Primer.

[40] "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx
[41] "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx
[42] Moran M et al. (2011) "Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?" Policy Cures.

While none of the existing proof of concept trials have shown excellent efficacy, they raise a key question: Where do we go from here? Should vaccines with partial efficacy be moved forward? Should newer vaccine technologies be pushed forward to catch up and allow direct comparison in the clinic? How can we get the maximum amount of information out of past trials to best inform new trials? These and other questions have led to three key focus areas for diseases with vaccines in the post proof of concept stage of development:

- Correlates of protection
- Proof of concept of new vaccine technologies
- Clinical trial strategies

The status of vaccines for ETEC, HIV, malaria, shigella, and TB with respect to these focus areas is summarized in Table 7.

### Table 7. Status of Post Proof of Concept Vaccine Focus Areas

| | Correlates of Protection | Vaccine Technologies in Clinical Development | Clinical Trial Strategies |
|---|---|---|---|
| **ETEC** | Recent Phase III vaccine failed to show protection against diarrhea despite what were thought to be protective levels of antibodies against ETEC heat labile toxin. | ***Live attenuated:*** Phase II<br><br>***Recombinant/purified protein:*** Phase I (recent failure of product in Phase III; recombinant protein is the component of Dukoral with cross protection)<br><br>***Inactivated:*** Phase I | Prototype strain for challenge studies under investigation which would potentially accelerate trials.[43] |
| **HIV** | No clear correlates of protection were identified in patients from the Phase III Thailand trial. Funding not sufficient to follow 16,000 patients. | ***Viral vector:*** Phase III<br><br>***Recombinant/purified protein:*** Phase III<br><br>***DNA:*** Phase II | Choice of patient population is unclear as Phase III trial was in only moderate risk population resulting in very few total infections (hard to judge true efficacy or identify correlates of protection).<br><br>Exploring therapeutic vaccine trials as adjunct to therapy and monitoring infected patients from Thailand trial for differences in disease progression with prior vaccination. |
| **Malaria** | No clear correlates of protection were identified in field studies. | ***Recombinant/purified protein:*** Phase III<br><br>***Live attenuated:*** Phase II<br><br>***Viral vector:*** Phase II<br><br>***DNA:*** Phase II | Interest in exploring more diverse prime-boost combinations with different vaccine technologies.<br><br>Working to define decreased morbidity or severity of disease endpoints that may show more impact than absolute protection from infection. |
| **Shigella** | Some information from Israeli Defense Force Study showed that serum IgG anti-LPS confers some immunity but correlation not as strong in children.[44] | ***Polysaccharide protein conjugate:*** Phase III<br><br>***Live attenuated:*** Phase II<br><br>***Inactivated (in combination with polysaccharide protein conjugate):*** Phase II | Challenge studies possible which can accelerate trials. |
| **Tuberculosis** | No clear correlates of protection although vaccines that promote different components of immune response are entering clinical trials which may inform our understanding when efficacy data become available. | ***Live attenuated:*** On market BCG vaccine; Phase I<br><br>***Inactivated:*** Phase III<br><br>***Recombinant/purified protein:*** Phase II<br><br>***Viral vector:*** Phase II | New vaccines as boost in patients with prior BCG vaccination.<br><br>New prime-boost combinations of BCG replacement vaccines with new boost vaccines.<br><br>Alternative vaccination strategies (e.g. pre-exposure vaccination, post-exposure vaccination to prevent active disease, post-exposure vaccination to control disease in HIV positive population) |

[43] Clinical Trial Notes, available at: http://clinicaltrials.gov/show/NCT01060748
[44] Clinical Trial Notes, available at: http://clinicaltrials.gov/show/NCT00368316

*Correlates of Protection*

Correlates of protection are key immune response markers that can predict if a person is protected against infection. Correlates of protection can be informed by studies of immunity in naturally exposed populations or from studies done in conjunction with vaccine development. For most on market vaccines, correlates of protection include host antibody levels to specific pathogen antigens.[45] By studying large cohorts of vaccinated patients, specific antibody levels have been established that indicate whether or not a person is protected. For other vaccines, including the BCG vaccine for tuberculosis and the zoster vaccine to prevent shingles after chickenpox infections, the mechanism of protection is less well understood. Cellular, rather than antibody, mediated immune responses play a critical role, but predictive markers of who will be protected versus susceptible after vaccination are not known.

Understanding correlates of protection has several benefits for vaccine development, such as:

1) Potential to rationally design or improve vaccines to promote desired immune responses
2) Ability to estimate potential vaccine efficacy and duration of protection, even without exposure to a pathogen, using surrogate markers or correlates of protection

However, understanding correlates of protection for a vaccine is dependent on several factors:

1) The nature of the protective immune response induced by the vaccine (i.e. antibody mediated immune responses are generally easier to monitor and quantify than cell-mediated mechanisms of immunity)
2) The availability of basic scientific research to understand protective immunity and immune responses involved in responding to infection
3) The availability of patient samples and/or the existence of natural immunity to a pathogen in patients living in endemic areas to understand non-vaccine induced immunity
4) The availability of animal models whose immune response mimics that of humans for a particular disease

Having a surrogate marker of immunity or panel of correlates of protection would be especially helpful for diseases such as HIV and tuberculosis where challenge studies with pathogens[46] are not ethical and infection rates in endemic populations are low and variable. For TB and HIV, clinical trials require large numbers of patients and long time periods for follow up to look for vaccine efficacy.

Correlates of protection are also helpful for diseases where partial vaccine efficacy would be acceptable as long as this partial efficacy results in reduced severity of disease. An immune

[45] Plotkin SA (2010) "Correlates of Protection Induced by Vaccination." Clinical and Vaccine Immunology 17: 1055-1065. PMID: 20463105

[46] Challenge studies are clinical trials where people are purposely infected with a pathogenic organism to test whether or not vaccination was protective. These studies are only possible for diseases with effective treatment and that have no risk for chronic infection. When challenge studies are not possible, longer clinical trials that wait for clinical trial participants to be naturally exposed to pathogens in their environment are required.

response that prevents infection with an organism may be quite different than an immune response that limits severity of disease. Understanding correlates of protective versus palliative immunity could guide development of vaccines with different strategies.

Unfortunately, for all of the neglected diseases categorized in the post proof of concept phase of clinical vaccine development, understanding of correlates of protection is minimal. Patient samples from clinical trials where at least partial efficacy is observed, as well as longitudinal studies following vaccinated patients over time, will be essential moving forward, especially for those diseases were animal models or natural immunity are not understood. The value of integrating correlates of protection into ongoing vaccine development is discussed further in the section on clinical trials below.

*Vaccine Technologies*

Approaches to vaccination vary from disease to disease. Not every vaccine technology is applicable to every neglected disease, but examining the application of vaccine technologies across multiple diseases makes it easier to observe trends, advances, opportunities, and risks for new vaccine development.

There are four primary vaccine technologies on market today:[47]

- *Live attenuated:* Live attenuated vaccines are created by reducing the ability of an infectious organism to cause disease without killing the organism. Vaccination with the live but weakened organism generates an immune response that protects the vaccinated person against severe disease.
- *Inactivated:* Inactivated vaccines use killed organisms to protect against subsequent infection with live organisms that cause disease.
- *Recombinant/purified protein:* Recombinant or purified protein vaccines consist of protein antigens that have either been produced in a heterologous expression system (e.g., bacteria or yeast) or purified from large amounts of the pathogenic organism. The vaccinated person produces antibodies to the protein antigen, thus protecting him/her from disease.
- *Polysaccharide-protein conjugate:* Polysaccharide protein conjugate vaccines consist of polysaccharides, generally from the surface coat of bacteria, linked to protein carriers. The combination of the polysaccharide and protein carrier induces an immune response against bacteria displaying the vaccine polysaccharide on their surface, thus preventing disease.

Vaccines in development for neglected diseases include the previous approaches above but also include newer technologies, such as:

- *DNA vaccines:* DNA vaccines are circular pieces of DNA, known as plasmids, that contain the sequence(s) for one or more protein antigens, are independent of the cell

[47] Technology names listed here are linked to technology profiles on the BVGH Global Health Primer website: "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx

chromosome, and can autonomously replicate. When the DNA plasmid is introduced into human cells, the human cells express the protein encoded on the plasmid, thus stimulating an immune response against the encoded antigen.

- *Viral vector vaccines:* Viral vector vaccines use live viruses to carry DNA into human cells. The DNA contained in the virus encodes antigens that, once expressed in the infected human cells, elicit an immune response.

Because there are no DNA or viral vector vaccines on market for humans, these vaccines may face greater regulatory scrutiny and/or require more effort to bring to market. A vaccine for Japanese encephalitis (JE) using an attenuated yellow fever virus (YFV-17D) encoding the JE preM-Env protein has completed phase III trials and is currently in pre-registration. The JE vaccine IMOJEV®, previously known as ChimeriVax-JETM, is being developed by Sanofi Pasteur and is poised to be the first human viral vectored vaccine on market.[48] There are also twelve viral vector vaccines currently in use for veterinary diseases.[49] The veterinary approved vaccines include adenovirus, fowlpox virus, attenuated yellow fever (YFV-17D), and vaccinia virus vectors, all of which are relevant as potential human viral vectored vaccines. There are no DNA vaccines currently on market for use in humans, but, in 2005, a DNA vaccine that protects against West Nile virus was approved for use in horses.[50]

Exploring new vaccine technologies provides the opportunity to exploit a wider range of mechanisms of stimulating the immune system to elicit protection. However, the diversity of vaccine technologies being explored even for a single neglected disease raises questions as to how these vaccines may be combined and whether or not they can be compared in head-to-head trials to evaluate relative efficacy. Also this raises regulatory questions regarding how new vaccines will be evaluated both by government regulatory agencies and by WHO in the prequalification process. As proof of concept trials and regulatory approval are pursued for a neglected disease vaccine based on a new technology, these activities will most likely support the expansion of this technology into other neglected disease applications.

*Clinical Trial Strategies*

Clinical trial strategies vary by disease. In general, early stage trials focus on safety and induction of general or specific immune markers. If correlates of protection are known, these responses are also examined. Efficacy trials come in two forms. For those diseases where challenge studies are possible, evaluation of immune markers and disease outcomes following purposeful exposure to a pathogen are performed. When challenge studies are not possible, evaluation of immune makers and then long term follow up of patients who may be naturally exposed to the pathogen are performed. All studies must be tested in the field in endemic populations, but challenge studies can help detect vaccine failures before conducting long-term field-based trials.

[48] Appaiahgari MB and Vrati S (2010) "IMOJEV®: a Yellow fever virus-based novel Japanese encephalitis vaccine." Expert Reviews Vaccines 9: 1371-1384.
[49] Draper SJ and Heeney JL (2010) "Viruses as vaccine vectors for infectious diseases and cancer." Nature Reviews Microbiology 8: 62-73.
[50] CDC press release, CDC and Fort Dodge Animal Health Achieve First Licensed DNA Vaccine, available at: http://www.cdc.gov/media/pressrel/r050718.htm

Two key focus areas in clinical trials are (1) improving immunity through combination vaccine strategies and (2) exploring alternative vaccination approaches where the goal is reduction of disease severity or progression rather than absolute protection from infection.

Unlike diseases such as smallpox, polio, or measles, many of the diseases presented here that have vaccines in post proof of concept trials do not result in natural protective immunity after infection (see Table 8). This fact alone suggests using vaccination to prevent these diseases will be difficult. As a result, many vaccines in the neglected diseases space are exploring "heterologous prime-boost" strategies whereby a patient receives one vaccination followed by a second vaccination that is based on a distinct vaccine technology[51] and/or contains unique antigens relative to the original vaccine.[52] The rationale behind this strategy is that a more robust and potentially diverse immune response will be produced that has a better chance of fighting the disease.

As more products enter clinical development, more questions are raised as to how vaccines should be combined into prime-boost regimens for efficacy testing. Performing large numbers of permutations of combinations would take enormous amounts of time, effort, and careful negotiation of issues, such as access to intellectual property, that arise when products developed by distinct organizations are evaluated together in clinical trials. Furthermore, the lack of infrastructure in resource-poor countries where many of these diseases are endemic makes it challenging to recruit, track, and monitor large numbers of patients over time. A simple solution to this challenge would be to conduct these permutation studies in animals; however, most of the diseases in question do not have animal models that closely mimic the human immune response and are therefore unlikely to be helpful in optimizing these combinations (see Table 8).

[51] See next section of "Vaccine Technologies" for details.

[52] Hill AVS et al. (2010) "Prime-boost vectored malaria vaccines: progress and prospects." Human Vaccines 6: 78-83. PMID: 20061802; Kaufmann SHE (2010) "Future Vaccination Strategies against Tuberculosis: Thinking outside the Box." Immunity 33: 567-577. PMID: 21029966; Newman MJ (2002) "Heterologous prime-boost vaccination strategies for HIV-1: augmenting cellular immune responses." Curr Opin Investig Drugs 3: 374-378. PMID: 12054082

**Table 8. Tools Available to Guide Clinical Trial Design**

| | Natural Immunity Well Characterized | Predictive Animal Models |
|---|---|---|
| **ETEC** | Yes, natural immunity develops after several exposures | Most commonly mouse and pig |
| **HIV** | No, patients are unable to clear the infection, although some spontaneously control viral replication to very low levels. Potent T-cell responses in long-term non-progressors to AIDS suggest cellular immunity is important | Non-human primates, but predictive capacity is unclear |
| **Malaria** | No, natural immunity minimal, transient, and not well understood | Although multiple mouse models available, little correlation with human response |
| **Shigella** | Yes, serotype specific immunity develops following exposure most likely due to anti-LPS antibodies | Guinea pig inoculated intra-rectally |
| **TB** | Currently being evaluated, polyfunctional CD4+ memory T-cells and CD8+ effector T-cells both appear to be important | Animal models primarily used to evaluate safety not potential efficacy, predictive capacity is unclear |

Alternatively, for some diseases therapeutic trials or alternative endpoints, such as reduction in the severity or duration of disease, rather than sterilizing immunity are being examined. As a follow up to the phase III HIV vaccine trial in Thailand, 130 study subjects who were infected with HIV during the trial will be followed for an additional 8 years to compare the course of infection in those who were vaccinated in the original HIV vaccine trial to those who received placebo vaccination.[53] The goal of this trial is to determine if previous vaccination will result in altered disease outcomes with respect to viral load and immune function. Furthermore, there are 5 additional HIV vaccines currently in clinical trials as therapeutic vaccines or adjuncts to treatment for HIV as summarized in Table 9.

[53] Clinical Trial notes: http://clinicaltrials.gov/show/NCT00337181

### Table 9. Therapeutic Vaccine Trials for HIV[54]

| HIV Vaccine Name | Developers | Therapeutic Trial Phase | Therapeutic Trial Information |
|---|---|---|---|
| GTU-MultiHIV | Imperial College of London School of Medicine<br>Medical Research Council | Phase I | NCT01130376 |
| MVA-B | EuroVacc<br>NIAID<br>HIV Vaccine Trials Network | Phase I | EuroVacc |
| HIV p17/p24:Ty-VLP | GlaxoSmithKline | Phase II | NCT01092611<br>NCT01218113 |
| MVA-BN | National Institutes of Health<br>Bavarian Nordic | Phase II | NCT00390078<br>(completed) |
| Vacc-4x | Bionor Pharma ASA | Phase II | NCT00659789<br>(completed) |

To date there are no data available from these trials, but the efficacy of HIV vaccines as an add-on or alternative to treatment may provide more rapid feedback on vaccine efficacy than a large scale prevention trial that relies on natural transmission of the pathogen. Clinical trials that provide faster results and robust endpoints promote a strategy of "failing early" for vaccines that are going to fail, avoiding excess investment of time and money into a product that will never make it to market.

In the malaria field, the focus now is on measures of reduced disease severity with prior vaccination. Following multiple phase II field trials that demonstrated partial vaccine efficacy for the GSK and MVI RTS,S malaria vaccine, a phase III trial was initiated in March 2009. This trial will involve vaccination of 16,000 children and infants. Although prevention of clinical malaria will be measured as the primary endpoint, secondary endpoints for the trial include the rate of severe malaria disease, incidence of severe anemia and malaria hospitalization, prevalence of parasitemia, prevalence of moderate and severe anemia, incidence of fatal malaria and all-cause mortality, and impact on childhood weight/growth.[55] By expanding these secondary endpoints, impact of the vaccine on disease severity beyond absolute prevention from infection can be analyzed quantitatively.

The high cost of late stage clinical trials remains a barrier. Difficult decisions regarding prioritization of research on correlates of protection or trials to explore novel vaccine technologies or combinations have to be balanced with the cost of trials to keep late stage products moving forward. For diseases where natural immunity and correlates of protection are poorly understood and only partial efficacy has been demonstrated through vaccination thus far, it is essential that scientific questions be integrated into clinical trial design. Although this may

[54] "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx
[55] Clinical Trial notes: http://clinicaltrials.gov/show/NCT00866619

increase the cost of trials in the short term, answering these scientific questions will guide future vaccine development potentially reducing the overall cost of bringing an effective vaccine to market. Scientific understanding gained from clinical trials will provide value for financial investment even if the product being evaluated fails. The ability to learn from failures as well as successes is particularly important to ensure a return on investment for the large amount of public sector funding used for neglected disease vaccine development.

***Clinical: Pre-Proof of Concept***

Of the diseases presently included in the Global Health Primer, four could be considered to be "Pre-Proof of Concept" with regard to vaccine development meaning that these diseases have vaccines that have entered human safety or efficacy trials and either have pending efficacy data or are in an iterative process to refine the vaccine to re-enter clinical trials. Of the four diseases in this category, we can split the diseases roughly into two categories. Vaccines for hookworm and leishmaniasis have entered clinical trials but are currently in an iterative process of preclinical improvements and phase I safety trials. In contrast, the first vaccines for dengue fever and schistosomiasis are in proof of concept efficacy trials now. However, the results of these trials are not yet available, leaving open the question as to whether or not they are working. The full product development pipelines and product details for these diseases are available in the Global Health Primer. The status of clinical trials on these four diseases is summarized in Table 10.

### Table 10. Status of Clinical Trials for Pre-Proof of Concept Diseases

| Disease | Status of Clinical Trials |
|---|---|
| **Pre-Proof of Concept** | |
| Hookworm | A previous effort for hookworm vaccine development using a larval protein antigen, Na-ASP-2, included an initial phase I clinical trial in 2005 in the U.S. and a subsequent phase I in Brazil. Although the U.S. trial was successful, vaccine development was halted in 2007/2008 after patients in Brazil, who had previous hookworm exposure, experienced allergic reactions immediately after vaccination.[56] In order to avoid the risk of negative allergic reactions in the future, the hookworm vaccine community decided to shift its strategy from focusing on protein antigens from larval stage worms to focusing on antigens associated with worm blood feeding.<br><br>There are currently two vaccines in pre-clinical development for hookworm. Neither vaccine has entered clinical development at this point. |
| Leishmaniasis | Two vaccines for leishmaniasis were evaluated in phase II trials recently. These trials were iterative evaluations of a vaccine being produced by IDRI. Now a third vaccine, again a follow-on to the original, is being evaluated in pre-clinical trials. The ultimate goal for vaccination is to prevent visceral leishmaniasis, the most deadly form of the disease, but clinical trials thus far have focused on variations of the disease with shorter endpoints to speed evaluation of candidate vaccines.<br><br>There are multiple additional products in pre-clinical development that will undoubtedly benefit from the clinical trial groundwork laid by IDRI. |
| **Proof of Concept Trials Initiated: Data not yet available** | |
| Dengue | No efficacy data have been released for dengue vaccines. The results of phase II clinical trials in the U.S., Mexico, and the Philippines with a chimeric yellow fever and tetravalent dengue vaccines were released in 2009 by Sanofi Pasteur. These trials showed only mild to moderate transient adverse reactions and demonstrated 100% seroconversion against all four dengue serotypes in flavivirus naïve adults in the U.S. and 77-92% seroconversion to all four serotypes in Mexico (7.9% previous exposure to flavivirus). In the Philippines, where baseline flavivirus immunity was 80.1%, overall seroconversion was not presented.[57] The first phase II efficacy trial was launch in Thailand in 2009 with 4,002 children.[58] A phase III trial was launched in 2010 to compare the immune induction of multiple manufacturing lots of vaccines in preparation for larger trials.[59]<br><br>There are also four additional vaccines in clinical development, but information on the immune induction and potential efficacy of these vaccines is not yet available. |
| Schistosomiasis | There is currently one vaccine for schistosomiasis currently being evaluated in an efficacy trial. Bilhvax is in a phase III trial in Senegal to determine the efficacy of the vaccine in conjunction with praziquantel drug treatment to prevent reinfection of children with *S. haematobium*.[60] Data from this trial are not yet available.<br><br>There is one additional schistosomiasis vaccine in a phase I clinical trial in Brazil. |

[56] Clinical Trial notes: http://clinicaltrials.gov/show/NCT00473967
[57] Lang J (2009) "Recent progress on sanofi pasteur's dengue vaccine candidate." Journal of Clinical Virology 46 S2: 20-24. PMID: 19800562
[58] Clinical Trial notes: http://clinicaltrials.gov/show/NCT00842530
[59] Clinical Trial notes: http://clinicaltrials.gov/show/NCT01134263
[60] Clinical Trial notes: http://clinicaltrials.gov/show/NCT00870649

It is difficult to make sweeping assessments of vaccine pipelines in this stage of development due to the lack of efficacy data. However, one of the starkest contrasts between the diseases with pre-proof of concept stage pipelines as compared to those with post proof of concept stage pipelines is the total number of products in development as summarized in Figure 4.[61]

**Figure 4. Comparison of Products in Development for Pre- and Post- Proof of Concept Diseases**


| | | | | |
|---|---|---|---|---|
| **Pre-Proof of Concept** | | | | |
| Dengue fever | 4 | 3 | 1 | 1 |
| Hookworm | 2 | - | - | - |
| Leishmaniasis | 5 | - | - | - |
| Schistosomiasis | 3 | 1 | - | 1 |
| **Post-Proof of Concept** | | | | |
| ETEC | 6 | 5 | 1 | - |
| HIV | 2 | 30 | 14 | 2 |
| Malaria | 8 | 6 | 12 | 1 |
| Shigellosis | - | 1 | 2 | 2 |
| Tuberculosis | 9 | 6 | 4 | 1 |

With the exception of dengue (which has five products in clinical development), hookworm, leishmaniasis, and schistosomiasis each have only two active vaccine development programs in clinical development as compared to the five to 46 products in clinical development for the post-proof of concept diseases.

In addition to having fewer products overall, the types of organisms represented in the pre-proof of concept stage are quite different than the post proof of concept stage. Namely, pre-proof of concept stage diseases are predominantly parasitic diseases. Overall parasitic diseases represent a large portion of the organisms that cause neglected diseases (eight out of the 17 disease presented in this report) but are severely underrepresented in terms of the number of products in development as summarized in Figure 5.

[61] "Global Health Primer," (last updated: April 4, 2011), BIO Ventures for Global Health, accessed 5 April 2011, http://www.bvgh.org/GlobalHealthPrimer.aspx

**Figure 5. Vaccines in Development by Organism Type**[62]


| Organism Class (Number of Neglected Diseases) | | | | | |
|---|---|---|---|---|---|
| Bacteria (6) | 25 | 16 | 13 | 3 | 10 |
| Virus (3) | 7 | 34 | 16 | 3 | 2 |
| Unicellular Parasites (4) | 13 | 6 | 12 | - | - |
| Multicellular Parasites (4) | 9 | 1 | - | 1 | - |

The scientific challenges for vaccine development for parasitic diseases are significantly greater than for bacteria and viruses primarily because parasitic organisms are significantly more complex than bacteria or viruses. Unicellular parasites, such as the parasites that cause leishmaniasis, have complex life cycles with many forms, each of which interacts differently with the immune system. Multicellular parasites, such as hookworm, are large organisms that cannot be cleared by a single immune cell like smaller organisms. Because of these hurdles, to date there are no vaccines for parasitic disease on market for use in humans.

[62] Bacteria include cholera, ETEC, pneumococcal disease, shigellosis, tuberculosis, and typhoid; Viruses include dengue, HIV, and rotavirus; Unicellular parasites include Chagas disease, HAT, leishmaniasis, and malaria; Multicellular parasites include hookworm, lymphatic filariasis, onchocerciasis, and schistosomiasis

***Discovery/Preclinical Stage***

Of the diseases included in the Global Health Primer, four could be considered discovery or preclinical stage with regard to vaccine development: Chagas Disease, Human African Trypanosomiasis (HAT), Lymphatic filariasis (LF), and Onchocerciasis (River Blindness). For these diseases, vaccine development pipelines are minimal or primarily represent academic efforts that do not yet have company or non-profit support to move towards clinical development. Following on the trend observed for pre-proof of concept vaccine diseases in the previous section, the discovery/preclinical stage diseases are all parasitic diseases. The full product development pipelines and product details for these diseases are available in the Global Health Primer.

For the most part, diseases in this category benefit from the existence of other tools for disease control or would require significant advances in scientific understanding of the disease before vaccine development could progress. Other methods for disease control include vector control programs, active case detection and treatment, or mass drug administration (MDA). From the scientific perspective, a lack of understanding of the biology or the organism, a lack of understanding of host immune response to the organism, or a lack of scientific tools needed for vaccine development can each restrict the progress of vaccine development. In each of these scenarios, questions are raised about the relative funding priority of supporting existing control efforts and new basic research versus investing in a vaccine program that will take many years to produce a product, if a product is produced at all.

The challenges and potential value for new vaccines for these diseases are summarized in Table 11.

**Table 11. Challenges and Potential Benefits of Vaccine Development**

| | Challenges for Vaccine Development | Potential Value of a Vaccine |
|---|---|---|
| **Chagas** | • Disease progression in chronic phase is associated with immune response to parasite infection suggesting vaccine must be 100% effective or it may risk worsening disease progression<br>• Current vaccine development focus is on animal reservoir (i.e. dogs)<br>• Vector control has contributed significantly to progress towards disease control | • Vector resistance to pesticides is increasing, threatening the future of vector control<br>• There is no safe and effective treatment for chronic infection |
| **HAT** | • Approaching elimination<br>• Complex antigenic variation suggesting a vaccine would be difficult to develop scientifically<br>• Patient population small and extremely difficult to access for clinical trials | • Treatment remains expensive with harsh side effects<br>• Because at risk population is extremely difficult to access, vaccination once may be advantageous in areas that are not regularly accessible for screening and treatment programs |
| **LF** | • Approaching elimination<br>• Disease control has progressed significantly through MDA and vector control programs, so may be hard to justify investment in vaccines | • Current drugs only kill microfilariae so MDA treatment may be necessary for up to 15 year (lifespan of the adult worm)<br>• Could be used in areas where MDA with ivermectin cannot be used due to *Loa loa* co-endemicity or DEC cannot be used due to onchocerciasis co-endemicity because of risk for adverse reactions<br>• Potential overlapping antigens with other helminths, so it may be possible to add on to another vaccine program rather than develop a vaccine for this disease alone |
| **Onchocerciasis** | • Approaching elimination in Latin America and control in Africa<br>• Disease control has progressed significantly through MDA, so may be hard to justify investment in vaccines | • Vector control difficult and vectors travel long distances causing re-emergence of disease<br>• Could be used in areas where MDA with ivermectin cannot be used due to *Loa loa* co-endemicity because of risk for adverse reactions<br>• Potential overlapping antigens with other helminths, so it may be possible to add on to another vaccine program rather than develop a vaccine for this disease alone |

Although the need for vaccines for these diseases may not be as high a priority considering other factors, there are some alternative or parallel paths that might drive these pipelines forward. In the case of Chagas disease, vaccines for dogs, a key reservoir for the disease in Latin America, are being developed. These vaccines potentially have lower regulatory hurdles than a human product. Evidence of efficacy in a veterinary vaccination may also inform future decisions regarding support for developing a human vaccine for Chagas disease.

Vaccines for onchocerciasis and LF may benefit from lessons learned from hookworm and schistosomiasis vaccine development. There are some protein antigens that are shared in

common between helminths. For instance, the protein glutathione S-transferase (GST) is in discovery stage development as a vaccine antigen for human hookworm. An orthologue of this protein is in development as a vaccine antigen for lymphatic filariasis. More work is needed to understand the degree of overlap between protein antigens of helminths and their potential for producing cross protection if used as antigens in vaccines.

The most compelling argument for the investment in vaccine development for these diseases with very early stage pipelines despite technical challenges is the limitation of existing control strategies. As summarized above in Table 11 above, MDA for onchocerciasis and LF are restricted in areas where these two diseases are co-endemic or where either disease is co-endemic with the related parasite *Loa loa*. In the case of onchocerciasis and LF co-endemicity, DEC used as part of MDA for LF can cause a dangerous hyperreactivity response in patients with onchocerciasis. In the case of co-endemicity with *Loa loa*, ivermectin used as part of MDA for LF and onchocerciasis causes a dangerous hyperreactivity response in patients with *Loa Loa*. The induction of hyperreactivity responses poses a major challenge for control of these diseases using MDA in Africa, where all three parasites commonly overlap geographically. Furthermore, MDA for LF and onchocerciasis only kills the circulating form of the parasite that is transmitted to mosquitoes not the adult worm. In the case of onchocerciasis the adult worm can live up to 15 years, suggesting that MDA may need to be continued for up to 15 years to be effective.

In 2000, the WHO set a goal of eliminating lymphatic filariasis by 2020. So far 2.45 billion doses of medication have been distributed in 53 of the 81 endemic countries.[63] Coverage by MDA is estimated to be 32-42% of the at risk population as of 2008. With only nine years left to reach the 2020 goal of elimination, it does not appear that MDA will be sufficient to reach this goal. There are 10 countries in Africa with co-endemic *Loa loa* for which an alternative control strategy has not yet been developed. Furthermore, the criteria for stopping MDA in countries with apparent control and plans for monitoring populations for reinfection following the halt of MDA have not been laid out. As efforts for lymphatic filariasis control and elimination are likely to extend far beyond the 2020 goal, the value of investing in vaccination should be considered.

Because vaccine development for lymphatic filariasis is still in its infancy, increased investment in scientific studies is needed in order to determine the feasibility of vaccination for this and other parasitic diseases with minimal vaccine pipelines. Furthermore, market and health impact analyses are needed in parallel with scientific studies to understand how vaccine investment should be prioritized in comparison with investment in MDA and other control programs.

[63] WHO (2010) Working to overcome the global impact of neglected tropical diseases: First WHO report on neglected tropical diseases.

## Looking Ahead: Where do we go from here?

Looking ahead at the vaccine R&D pipeline for neglected diseases, the next 10 years are poised to be both exciting and challenging times. Given the landscape of vaccines in development, key needs as we look towards the “Decade of Vaccines” include:

- More **operational and clinical research on existing vaccines** to support the development of clear policy statements, accelerate WHO prequalification, and inform decisions on new product needs.

- Increased investment in the **integration of scientific research questions with efficacy studies for vaccines** in clinical development to guide future vaccine development and maximize the amount of information learned through public investment.

- A **focus parasitic disease vaccine development** to understand the technical feasibility and potential health impact of vaccines for these biologically complex organisms.

Action taken to address these key needs has the potential to significantly accelerate vaccine development and increase the health impact of vaccines for neglected diseases.

*Operational and Clinical Research on Existing Vaccines*

In order for approved vaccines to be introduced into resource poor settings, they need to be prequalified by WHO, have clear policy statements for their use in resource poor settings, and be affordable. A key driver for prequalification, policy, and financial support of a vaccine is the availability of data on the efficacy and health impact of the vaccine in the target population. The importance of operational and clinical research is best highlighted by the relatively rapid success of introduction of pneumococcal and rotavirus vaccines in contrast with the continuing struggle for support of the cholera vaccine.

Research to clarify the utility and impact of existing vaccines is also needed in order to prioritize their rollout or to shift focus and investment in these areas to the development of new, improved vaccines. For instance, despite the momentum behind introduction of pneumococcal and rotavirus vaccines, new products are in development that may improve their utility. A recombinant protein-based pneumococcal vaccine that has the potential to protect against a broader panel of bacteria and an improved formulation of the rotavirus vaccine that will have improved stability for use in resource poor settings are both in development. New vaccines for cholera and typhoid are also in development, however additional data on the benefits and limitations of the existing vaccines in the developing world would be helpful to guide new product priorities.

Beyond those vaccines that are currently on market, prioritizing research in this area will help pave the way for future vaccines that are approved. This will be especially important as current financers of vaccination begin planning for future program prioritization and as developers of new vaccines seek both policy and financial support for introduction.

*Increased Investment in Integration of Research with Efficacy Studies for Vaccines in Clinical Development*

To minimize the access and delivery hurdles of the next generation of vaccines and to maximize the information gained from public investment in clinical development of new vaccines, a focus on integrating key scientific questions into vaccine clinical trials is essential. As highlighted in this report, recent efficacy trials for malaria and HIV exemplify this need. These efficacy trials were primarily designed to measure vaccine efficacy for preventing infection. In each case, partial efficacy was observed but the trials were not designed to extensively explore alternative endpoints, correlates of protection, or long-term impact of vaccination of disease progression. In many ways these trials generated more questions than answers, but the trials were not sufficiently designed or funded to support answering scientific trials beyond their evaluation of efficacy.

As vaccines for increasingly complex diseases with increasingly poorly understood biology enter efficacy trials, integration of scientific research into efficacy trial design will become even more important. Key focus areas for research should include:

- Optimizing heterologous prime-boost strategies to understand and target immune responses that best protect against specific pathogens
- Expanding studies of correlates of protection both during and after a trial
- Creative clinical trial design that will optimize the selection of patients, biomarkers, and primary and secondary endpoints to help products that are going to fail to fail faster and provide that data needed to analyze partial efficacy more extensively
- Ensuring knowledge is gained from clinical trials that can guide future vaccine development and evaluation regardless of the success or failure of the product being evaluated

As competition for limited funding in the global health space increases, maximizing return on investment is essential for sustaining interest and support for vaccines for neglected diseases. Although new vaccines are increasing in their complexity and challenges, advancing scientific understanding of vaccination will improve the probability of success for new products as well as provide data that can inform policy and financing decisions as products reach the market.

*A Focus of Parasitic Disease Vaccine Development*

Part of the increasing challenge of vaccine development is that the organisms being targeted for vaccination are becoming increasingly complex. Parasitic organisms, which are significantly more biologically complex than bacteria and viruses, are the focus of the early stages of vaccine development. Although partial efficacy data for a vaccine for malaria are now available, the limited understanding of the mechanism of protection makes it unclear how these data will inform future malaria or other parasitic disease vaccine development. More extensive exploration of natural immunity, novel vaccine technologies, potential/need for combination vaccine strategies, and predictive animal models are all needed to inform vaccine development for these diseases.

Vaccine development for some parasitic diseases is in competition for policy and financial support with other control strategies, such as mass drug administration or vector control programs. However, as these control strategies begin to reach their limits for impact and sustainability, interest in vaccine development may be renewed. As highlighted in this study for lymphatic filariasis and onchocerciasis, a better understanding of both the scientific feasibility and potential health impact of vaccination are needed to make these difficult decisions.

The importance of advancing scientific understanding of vaccines for parasitic diseases should not be underestimated. As the scientific and technical challenges of producing an effective vaccine increase, these data will drive successful vaccine development as well as subsequent policy support.