The development of Pharmaceutical Products to Fight Tropical Diseases

Table of Contents

Introduction ................................................................................................................................. 1
Tropical Diseases Definition ...................................................................................................... 1
Tropical Diseases: Sizing and Current Situation ...................................................................... 2
Parties Involved: Goals, Interests and Limitations ................................................................. 2
General Process for Pharmaceutical Development ................................................................. 5
  Discovery ................................................................................................................................. 6
  Clinical Development ............................................................................................................. 6
Public Private Partnership Example: Malaria Clinical Trials in Mozambique ....................... 6
  Background on Malaria ........................................................................................................... 6
  Geography ............................................................................................................................... 7
  Origins of the Mozambique Clinical Trials .......................................................................... 7
  Planning Stages ....................................................................................................................... 8
  Execution of the Trials ........................................................................................................... 9
  Results ................................................................................................................................... 9
  Management Challenges and Critical Success Factors ......................................................... 10
Future Outlook .......................................................................................................................... 10

Introduction

The purpose of this paper is to introduce the complex challenges involved in the development of pharmaceutical products to fight tropical diseases. Additionally, the paper will define the parties involved in the development process.

A specific example involving malaria vaccine efforts in Mozambique will demonstrate the effectiveness of using public private partnerships to address the drug development problem.

Tropical Diseases Definition

Tropical disease is a term used for neglected infectious diseases that disproportionately affect poor and marginalized populations. The following table shows the top ten tropical diseases worldwide, and the impact as determined by DALYs (Disability Adjusted Life Years, the
number of healthy years of life lost due to premature death and disability), and deaths caused per year (data shown is from 2002).

<table>
<thead>
<tr>
<th>Disease burden</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DALYs* (thousands)</td>
</tr>
<tr>
<td>African trypanosomiasis</td>
<td>1,598</td>
</tr>
<tr>
<td>Dengue</td>
<td>653</td>
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<tr>
<td>Leishmaniasis</td>
<td>2,357</td>
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<td>Malaria</td>
<td>42,280</td>
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<tr>
<td>Schistosomiasis</td>
<td>1,760</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Chagas disease</td>
<td>649</td>
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<tr>
<td>Leprosy</td>
<td>177</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>5,644</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>987</td>
</tr>
</tbody>
</table>

(http://www.who.int/tdr/diseases/default.htm)

**Tropical Diseases: Sizing and Current Situation**

More than 500 million people – one tenth of the world’s population – suffer from tropical diseases at any one time. For example, malaria alone causes between 1.5 to 2.7 million deaths per year, almost all of them in developing countries. Ninety percent of these deaths occur in Africa south of the Sahara. Two-thirds of the remainder are concentrated in six countries -- India, Brazil, Sri Lanka, Viet Nam, Colombia and Solomon Islands, in decreasing order of prevalence. Additional high mortality rates result from African sleeping sickness, dengue fever, river blindness, elephantiasis, leishmaniasis, Chagas disease and schistosomiasis.

**Parties Involved: Goals, Interests and Limitations**

Each of the parties listed below contributes to the development of drugs to fight tropical diseases. Though each party plays a critical role, the differing goals, strengths, and weaknesses of each type of organization make coordination between them difficult.

- Pharmaceutical Producers
- International Agencies
- Non-Government Organizations (NGOs)
- Donor Government organizations
Recipient Government organizations

Pharmaceutical Producers: Multinational pharmaceutical companies are the major developers of important new drugs, and they view rich countries as their core markets. These companies tend to disregard the “needs” of poor countries (particularly countries with small markets and poor growth prospects), because private firms are primarily demand-oriented and profit-driven.

When companies discover a new drug that can benefit poor people in poor countries, they confront a series of problems:

The first problem is pricing. Many multinational companies are seeking to set single global prices for new products—at least as much as national regulatory authorities will allow the firms to do so. This pricing strategy would effectively deny many new products to poor people in poor countries, since the governments lack the necessary foreign exchange resources to pay the full price, and poor patients cannot pay the private market prices.

A second problem is purchasers. The private market in many developing countries at the initial launch price is very limited, and even the market at the concessionary price is limited. Donor agencies are often unwilling to provide grants for procuring new drugs on a continuing basis. Some bilateral aid agencies may be willing to provide project grants that include procurement funds for several years, as a form of indirect support for their nation’s firms, but this approach does not always work. For example, Merck &Co. was unable to persuade USAID to purchase ivermectin for treatment of onchocerciasis.

A third problem is patents. Multinational drug companies strongly supported the efforts to strengthen intellectual property protection in the Uruguay round of the GATT international trade negotiations. These companies have argued that all countries, including poor countries, should enforce product patents, and not allow the weaker protection of process patents. The companies generally consider the development of alternative manufacturing processes to be free-riding on their development costs, an infringement on their intellectual property rights, and a form of patent piracy, while many developing countries have considered this practice a fair strategy in their national efforts to catch up in the race for technology development.

However, increasingly, a case can be made for pharmaceutical firms to invest in drugs to fight tropical diseases regardless of the profit they may receive. This is because the public relations value of the efforts will benefit the companies in the long run, particularly in the current environment where the business practices and high profitability of pharmaceutical firms are facing close scrutiny.

An interesting gauge of the pharmaceutical companies that have been successful in balancing profit with global responsibility is found in the Top 100 Corporate Citizens list in Business Ethics magazine. The list shows companies’ efforts to serve seven different stakeholder groups: the shareholders, community, minorities and women, employees, environment, non-U.S. stakeholders, and customers. Top pharmaceutical companies were as follows: Merck & Co. (48th), Rohm and Hass (67th), and Baxter (73rd). Merck, for example, has helped its public image by forming a landmark public/private partnership with the government of Botswana, the Bill & Melinda Gates Foundation to fight AIDS and HIV.
International Agencies:
International agencies are concerned with the availability of new drugs for tropical diseases for multiple reasons. Some agencies, such as the World Health Organization, have a mandate to improve global health, and new drugs for tropical diseases can offer an effective means to achieve health improvements. Other international bodies, such as the World Bank, seek primarily to promote economic growth and development, and new drugs for tropical diseases can provide a mechanism for dealing with unwanted side-effects of growth (such as water-borne diseases associated with water resource development projects) and for raising the productivity of workers, as well as improving overall social welfare. And UNICEF seeks to expand access to those pharmaceutical products that can improve the health condition of specific populations (especially mothers and children). The policy measures to achieve these diverse organizational goals also differ among the international agencies.

Nongovernmental Organizations (NGOs): NGOs have, in some instances, served as viable alternatives to both the public and the private sectors in health care delivery by reaching under-served populations in developing countries.

But often NGOs are unable to affect the basic rules that shape drug development and drug distribution for tropical diseases. NGOs have had little direct impact on the decisions taken by the major producers or the international agencies. For off-patent products, non-profit supplier organizations may be able to expand distribution in markets that multinational corporations and international agencies do not reach. Problems seem likely to remain, however, for the distribution of new (and high-priced) drugs for poor people in poor countries.

Some of the largest NGOs in the world, such as Medicines Sans Frontiers, Health Action International, Peoples Health Movement, OXFAM and Health GAP have been extremely vocal recently on this issue of intellectual property rights (IPR) for pharmaceutical patents. Despite the fact that the United States maintains the view for that IPR protection is the key to promote research and development in pharmaceutical industry, these NGOs help to keep the discussion on this topic going on behalf of the people who need the drugs the most.

Recipient National Governments: Governments affected by tropical diseases stand to reduce the cost of the disease burden by cooperating with vaccine-development efforts. The disease burden costs to governments include: maintenance of health facilities; purchase of drugs and supplies; public health interventions (in the case of malaria, these includes such initiatives as insecticide spraying or distribution of insecticide-treated bed nets); lost days of work with resulting loss of income; and lost opportunities for joint economic ventures and tourism.

The costs listed above can add substantially to the economic burden of tropical diseases on endemic countries and impede their economic growth. For example, it has been estimated in a retrospective analysis that economic growth per year of countries with intensive malaria was 1.3% lower than that of countries without malaria.

Finally, developing country governments seek access to new drugs for tropical diseases because those products can improve the welfare of their people. Many governments, however, have confronted extremely difficult financial situations in the 1980s and 1990s, with limited foreign exchange reserves, poorly performing economies, and external pressures to adjust their economic policies. Structural adjustment programmes sought to reduce government
expenditures, which often restricted funds available for purchasing medicines. Governments that could not afford to spend major portions of their medication budget on new products either sought external aid, purchased old drugs, or directed patients to the private market. But in many poor countries, new pharmaceutical products are often not available in the private market, or are priced far beyond the means of the majority of the people. (http://www.who.int/medicines/library/dap/who-dap-ctd-98-5/who-dap-ctd-98-5.pdf)

Donating National Governments: A broad range of motivations drive countries to allocate aid to the cure of tropical diseases. In many cases, the countries act out of economic interests. An example of this would be to build good will with an impoverished resource-rich country.

It is interesting to note how countries aim to develop good will with developing countries. The OECD said that Combating AIDS and Malaria was the sixth most important goal in their Millennium Goals development efforts. (http://www.oecd.org/dataoecd/51/35/33670335.pdf).

General Process for Pharmaceutical Development

The framework for the process of getting a new chemical entity to patients is shown below. This progresses from the understanding of a disease mechanism to the discovery of a candidate product through to the consumption of a medicine and the achievement of health gain for the patient.

![Diagram depicting the drug development process.](http://www.sma.org/smj2003/12/02ADECeview%20of%20Drug%20Development%20in%20the%20United%20States%20and%20Current%20Challenges.pdf)
Two sections of the process are described in detail below: discovery and clinical development

**Discovery**

This begins with an understanding of the disease that allows a target to be identified. In some cases genomic databases will be used to assist in this process. This target has to be validated. Is its elimination likely to lead to a modification of the progression of the disease to the benefit of a sufferer? This can be tested in the laboratory using animal models including transgenic animals. The next task is to find compounds that may have an effect on the target. To do this a library of compounds is screened. This can be done using computer modelling (in silico) to see which molecules “fit” into the structure of the target or biologically using high throughput screening in which robotics are used to test the reactions of thousands of assays of different compounds against the target.

A lead series of compounds is then identified, i.e. those with the chemical structures that appeared to have the greatest impact on the target. Lead optimisation is then carried out in which a sub set of more promising compounds are identified, again using chemistry and/ or computing, on the basis of their apparent efficacy and safety. Genomic databases may again be helpful at this stage if one factor influencing response may be pharmacogenetic (i.e. dependent on a patients' genetic make-up). Other factors will also be important, including the likely difficulty of turning the compound into a drug (e.g. is it likely to be available in a convenient dosage regimen, how stable is it likely to be and how difficult to manufacture.) Candidates for pre-clinical and clinical work are then selected. Usually a lead candidate is identified together with some back ups.

**Clinical Development**

This is the most well known element of drug development. In Phase I the compound is tested on healthy volunteers to assess safety and also the pharmacokinetics of the drug, i.e. its ADME (absorption, distribution, metabolism, and excretion) characteristics. In Phase II the drug is tested on patients with a particular emphasis on finding the dose that best balances efficacy and safety. In Phase III the drug is tested on large numbers of patients in at least two well controlled trials (usually double blinded and often with an active control to enable a regulatory submission to be made to get the drug approved for sale. In phase IV, post launch, additional clinical trials may be needed to identify longer term outcomes, or to compare the product with other treatments. Observational rather than experimental data may be collected, for example using disease registries in which the progress of patients with a particular disease is tracked to enable increased understanding of the disease, pattern of routine care, and the impact of the product and other treatments on patients’ health status. Increasingly data is collected on resource use to enable value for money or cost-effectiveness analyses to be done to inform payers of the value as well as of the efficacy of the product. Work will also be done to identify additional uses – new indications - for the drug.

(http://www.cmhealth.org/docs/wg2_paper21.pdf)

**Public Private Partnership Example: Malaria Clinical Trials in Mozambique**

**Background on Malaria**

Malaria is the most important and the most widespread of the transmissible diseases. It threatens almost one third of Humanity, affects around 600 million people and is responsible, each year, for more than 2 million deaths. Caused by microscopic parasites, Plasmodia, this disease is transmitted by the bite of certain
mosquitoes, the Anopheles. Its symptoms include bouts of a special type of fever, as well as an increase in the volume of the spleen and various other disorders. But malaria may involve complications such as cerebral attacks causing a fatal coma, especially among young children living in malaria-endemic areas or among expatriates and tourists.

The World Health Organization estimates that:
- 41% of the world’s population is exposed to malaria
- Malaria causes more than 300 million episodes of acute illness every year
- At least one million deaths occur every year due to malaria

**Geography**

Malaria occurs mostly in poor, tropical and subtropical areas of the world. The area most affected is Africa south of the Sahara, where an estimated 90% of the deaths due to malaria occur. This is due to a combination of factors:

- A very efficient mosquito vector (A. gambiae) assures high transmission
- The predominant parasite species is Plasmodium falciparum, which causes the most severe form of malaria
- Local weather conditions often allow transmission to occur year round
- Scarce resources and socio-economic instability hinder efficient malaria control activities.

In other areas of the world malaria is a less prominent cause of deaths, but can cause substantial disease and incapacitation, especially in rural areas of some countries in South America and Southeast Asia.

**Origins of the Mozambique Clinical Trials**

Created in 1999 with a $50 million grant from the Bill & Melinda Gates Foundation, the Malaria Vaccine Initiative (MVI) at PATH was specifically designed to forge partnerships among the diverse players in the malaria vaccine development community. MVI identifies promising vaccines and drives them through the development phase and into clinical trials. In 2003, the Bill and Melinda Gates Foundation announced an additional $100 million in funding for MVI to further
expand the malaria vaccine development pipeline, accelerate the movement of promising vaccine candidates into clinical trials, and address financial and policy barriers to vaccine development.

As background, the Gates Foundation was formed through the merger of the Gates Learning Foundation, which worked to expand access to technology through public libraries, and the William H. Gates Foundation, which focused on improving global health. Led by Bill Gates’ father, William H. Gates Sr., and Patty Stonesifer, the Seattle-based foundation has an endowment of approximately $27 billion.

PATH is an international, nonprofit, nongovernmental organization that improves the health of people around the world by advancing technologies, strengthening systems, and encouraging healthy behavior. Headquartered in Seattle, Washington, since its inception in 1978, PATH operates 19 offices in 13 countries. They currently work in more than 100 countries in the areas of reproductive health; vaccines and immunization; HIV, AIDS, and tuberculosis; and children’s health and nutrition.

The roots of the clinical trials can be traced back to when MVI’s recently appointed director Regina Rabinovich identified Glaxo SmithKline’s vaccine RTSS as the most promising candidate for receiving the grant. This was based on GlaxoSmithKline’s strong track record in vaccine development. They had tested the antigen with several different adjuvants, and found the efficacy was significantly higher with AS02A. This same substance has gone through some trials before, but it was not clear that the drug would be as effective in infants in the affected areas as it was in adults in the US.

**Planning Stages**

The next step was to find a way to conduct clinical trials. This led them to Pedro Alonso’s organization, the Center for International Health, based in the Hospital Clinic in Barcelona. This organization was selected for two reasons. First, they had a strong track record in malaria testing and research. Second, they had contacts with and could secure access a suitable facility in a malaria-affected region: the Centro de Investigação em Saúde da Manhiça (CISM) in Mozambique.

For tropical disease-fighting vaccines, it is critical to perform clinical trials in a disease-affected region. This is the only area where a critical mass of affected people is available for testing. Additionally, this allows the test to be conducted in the actual circumstances in which the real vaccine would be distributed.

The CISM was founded 80 km north of Maputo in a small rural town called Manhiça, as a part of a joint collaborative program between Mozambique Ministry of Health, the Maputo School of Medicine (Universidade Eduardo Mondlane), and the Hospital Clinic of the University of Barcelona (www.hospitalclinic.org) with core funding from the Spanish Agency for International Cooperation. It forms part of a bilateral program established between Spain and Mozambique. The center was officially inaugurated by Spain’s Queen Sofia. The center houses several activities. Among them: research to safeguard the health of young African children, training programs for Mozambique’s scientists and physicians, and the provision of healthcare to the local community.

The core funding for the center was provided by the Spanish government. Specific project efforts came from other sources. These included several malaria-fighting efforts as well as research programs covering acute respiratory infections, measles, the human papiloma virus, and tuberculosis.
After the center was identified as a candidate, its representatives together with MVI started building a relationship with the Mozambican government, inviting them onto the site, and starting with informal meetings with the country’s Ministry of Health.

Support of the government was viewed as critical, and every effort was made to include Mozambicans in the planning process. This was part of the overall effort to build a strong relationship based on trust with the country.

This goodwill was very important in the interactions with the participating communities, given the fact that the trials would involve the most vulnerable people in their population: children below age 5. As part of a legal requirement of the clinical trials, the center’s volunteers had to read a 5-page document to the mothers, most of whom could not read themselves, in order to make them aware of their rights. Thanks to the trust that was built in the community, which was gradually built since the opening of the center in 1996, it was much easier to persuade the mothers to allow their children to participate. The fact that the CISM had become a permanent part of the community, and had shown commitment to improving the overall health of the local population helped to reassure the mothers.

**Execution of the Trials**

During the trials, safety was given utmost attention. The protocol was approved by the national Mozambican Ethics Review Committee, the Hospital Clinic of Barcelona Ethics Review Committee and the PATH Human Subjects Protections Committee. The trial was undertaken according to the International Conference on Harmonization Good Clinical Practice Guidelines and was monitored by GSK Biologicals. A local safety monitor and a data and safety monitoring board closely reviewed the conduct and results of the trial.

Malaria trials are particularly challenging for two reasons. First, there is no way to measure the level of immunity a participant has acquired due to the administration of a vaccine. Second, the steps by which malaria immunity is acquired are not known. This means that extensive testing is needed on large numbers of participants to gather sufficient data to draw conclusions.

The study was a phase IIb, double blind, randomized controlled trial to assess the safety, immunogenicity, and efficacy of the RTSS-AS02A malaria vaccine in a malaria endemic area.

This means that phases Ia, IIa, and Ib had been successfully completed. Phase Ia proved safety and immunogenicity. Phase IIa proved efficacy against experimental challenge. Phase Ib proved safety and immunogenicity in a malaria endemic area.

The actual trial was conducted at the CISM between April 2003 and May 2004. The design of the study was unique because it was conducted with two separate cohorts or groups of participants. The first cohort (which involved 1996 participants) contributed to the assessment of the primary endpoint of protection against clinical diseases determined through passive case detection. The second cohort (which involved 588 participants) detected new infections through a combination of active and passive surveillance. The two cohorts allowed for an accelerated clinical trial process.

**Results**

The results of the trials were that the RTS,S/ ASO2A vaccine was well tolerated, safe, and immunogenic. Antibody titre was high in vaccinated children after three vaccine doses, with a decay of 75% of antibody level at 6 months but with sustained protection. An efficacy of nearly 30% in
terms of prevention of clinical episodes was seen in the first cohort and, more surprisingly, nearly 58% of severe malaria episodes were prevented.

These results were remarkable, given the fact that attempts to develop a malaria vaccine go back more than 50 years. Some candidate products have shown promising results and potential. However, inconsistency with other trials and failure of the product to prevent malaria in infants, together with limitations in product availability or reproducibility, resulted in termination of development of these candidate vaccines.

Management Challenges and Critical Success Factors

Managing a complex partnership that included a US philanthropic organization, a large pharmaceutical company, a bilateral intergovernmental agreement, members of academia, and health ministers is not an easy task. Three significant challenges were planning, contract development, and managing the expectations of the participating community.

Key success factors in the initiative included:
- Trust and goodwill with the participating communities, built over the years since the CISM was established
- Backing of a world class foundation, and the ability to involve experienced and capable leaders to shape and guide the initiative (see appendix)
- The expertise and strong track record at the International Health Center at the Hospital Clinic of Barcelona
- The effectiveness of the antigen-adjuvant combination developed by GSK
- Community involvement, involvement of local authorities in Mozambique
- Involvement of local research clinicians, in the practical design
- Access to a suitable base of operations situated in Mozambique
- The ability to recruit a team with the training and abilities to plan and execute the project
- Streamlined communication and data entry processes

Future Outlook

The current unprecedented public-private partnership for the development of malaria vaccines, with national and international agencies sharing the goals, should speed the development process as much as possible and boost innovations.

In the Mozambique example, the importance of an appropriate clinical testing center in the field with adequate capacity cannot be underestimated. This was made possible by public money from the Spanish government. Centers such as this one face constant difficulties, because private foundations generally allocate funds to target specific projects, and not to build long-term capacity for multi-purpose facilities. Improvements in contracts to include the necessities of such multi-purpose facilities will help solve these issues.

The effectiveness of public private partnerships is easy to see in comparison with previous efforts by private-only or public-only efforts. Often private-only efforts lack the commitment necessary to make a difference when a problem is as complex and widespread as the world malaria burden. Public-only efforts, though sufficiently committed, are often limited by their financial resources. Together, public and private organizations can leverage their respective strengths to tackle the most serious health problems facing the world.
Appendix A – Organizations Involved in Clinical Trials in Mozambique

**Mozambique’s Ministry of Health** has as its mission to promote and preserve the health of the Mozambican population and to promote and provide quality and sustainable health care services, gradually increasing its accessibility to all Mozambicans with equity and efficiency.

**The Centro de Investigação em Saude da Manhiça (CISM)** is the first peripheral health research centre in Mozambique to undertake medical research into the key health problems in that country. Founded in 1996, CISM was developed under a collaborative programme between the Mozambique Ministry of Health, the Maputo School of Medicine (Universidade Eduardo Mondlane), and the Hospital Clinic of the University of Barcelona (www.hospitalclinic.org) with core funding from the Spanish Agency for International Cooperation. www.manhica.org.

**GlaxoSmithKline Biologicals (GSK Biologicals)**, one of the world’s leading vaccine manufacturers, is located in Rixensart, Belgium. In 2003, GSK Biologicals distributed more than 850 million doses of vaccines to 152 countries in both the developed and the developing world – an average of 27 doses per second. For information, visit GSK Biologicals’ vaccines website at [www.gsk-bio.com](http://www.gsk-bio.com). GlaxoSmithKline – one of the world’s leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer.

**PATH’s Malaria Vaccine Initiative (MVI)** is a global program established through an initial grant of $50 million from the Bill & Melinda Gates Foundation, which awarded it an additional $100 million in 2003. MVI’s mission is to accelerate the development of promising malaria vaccines and ensure their availability and accessibility for the developing world. MVI’s vision is a world where vaccines protect children from death and severe disease caused by malaria. For information, visit [www.malariavaccine.org](http://www.malariavaccine.org). PATH is an international, non-profit organization that creates sustainable, culturally relevant solutions enabling communities worldwide to break longstanding cycles of poor health. For more information, please visit [www.path.org](http://www.path.org).

**European and Developing Countries Clinical Trials Partnership (EDCTP)** has as its mission to accelerate the development of new clinical interventions to fight HIV/AIDS, malaria and tuberculosis in developing countries, particularly sub-Saharan Africa, and to improve generally the quality of research in relation to these diseases. It was founded with participants from academic and governmental organizations in Africa and the European Community.
Appendix B – Leadership in Clinical Trials in Mozambique

Centro de Investigação em Saúde Manhiça (CISM)

Pedro Alonso, M.D., M.S., Ph.D.
Director

Pedro Alonso is a medical epidemiologist who has devoted most of his professional life to Public Health in Africa, having lived and worked in The Gambia, Tanzania and Mozambique. He currently heads the Center for International Health at the Hospital Clinic and holds the UNESCO chair at the School of Medicine of the University of Barcelona. He is also the Scientific Director of the Manhiça Health Research Center (CISM) in Mozambique.

Most of the research he has carried out has been in the area of clinical epidemiology of priority health issues in Africa, including malaria, HIV, hepatitis, tuberculosis, human papilloma virus and respiratory syncytial virus. The cornerstone of his research activity has been and continues to be the development and testing of new control tools against malaria. He was involved in the first trials of insecticide treated bednets documenting an impact on mortality, the first phase IIb clinical trials in Africa of a malaria vaccine candidate, as well as the evaluation of new drugs and combinations of drugs to inform policy on first line treatment for clinical malaria.

Strengthening local human capacity, as well as research and development institutions in Africa is also at the centre of his professional activities. Both in Tanzania and Mozambique his group has run a strong training programme for local scientists based on a fellowship model leading to a PhD, as well as contributing to the development and support of two of the leading research and training institutions in sub Saharan Africa: the Ifakara Health Research and Development Center (Tanzania) and the CISM (Mozambique).

In the context of a partnership with the Ministry of Health of Mozambique and the Spanish Agency for International Cooperation, his team has led the establishment and development of the CISM, the first peripheral research center in rural Mozambique which aims to improve health and promote development through provision of healthcare, scientific and technical capacity strengthening and research into priority health problems.

He has published over 100 papers and is a member of a number of national and international committees, including the EU and WHO.

GlaxoSmithKline Biologicals (GSK Bio)

Jean Stéphenne
President and General Manager

Jean Stéphenne joined GSK Bio 30 years ago when the company had one product and US$3 million in annual sales. Today, he is President and General Manager of the world’s largest vaccine company, with more than US$2 billion in yearly revenues, 20 vaccines in clinical trials, and more than a quarter of worldwide vaccine sales.

By emphasizing combination vaccines and investing large amounts of money in neglected diseases such as rotavirus, malaria, TB and HIV, Jean Stéphenne has revolutionised the vaccine industry and created a new paradigm of public-private partnerships. His focus on the global marketplace has consistently increased GSK Bio’s revenues and transformed GSK Bio into the world’s pre-eminent vaccine maker with a reputation for bold action and long-term strategic vision.
By positioning GSK Bio as “vaccine maker to the world,” Stéphenne had expanded the company’s efforts beyond the 10 million children born each year in Europe and the United States to the 120 million children born each year in the rest of the world. The results are tangible. In 2003, more than 850 million doses of GSK vaccines were delivered in 152 countries, of which 722 million doses went to 117 countries in the developing world.

Stéphenne, 55, joined GSK Bio as head of bacterial and viral vaccines in 1974. He has served as vaccine production director and vice president and general manager, and in 1998 was named president of GSK Bio. Stéphenne studied engineering, chemistry and bioindustries at the University of Gembloux in Belgium, and in 1972 earned a degree in management from the University of Louvain. He has received various honours from the European Union and the Belgian government, and in 2004 was named one of Business Week’s 25 Stars of European Business.

**W. Ripley Ballou, MD**  
Vice President, Emerging Diseases, New Product Development

A co-creator of the RTS,S malaria vaccine, Dr. W. Ripley Ballou spent 20 years researching malaria at the US Army’s Walter Reed Army Institute of Research and three years at a small biotechnology company before joining GSK Bio in 2003 as Vice President of Emerging Diseases.

As both Principal Investigator and a volunteer for the infected-mosquito “challenge” of the world’s first recombinant malaria vaccine at Walter Reed in 1987, Ballou, 53, is now in charge of GSK Bio’s Emerging Diseases program that includes malaria, TB, HIV and cancer vaccine development efforts. Since 1983, Ballou has been involved creating and testing more than a dozen different versions of a malaria vaccine as part of Walter Reed’s collaboration with GSK Bio. He says he has maintained hope during two decades of failure because those trials that had protected at least one person provided a “tantalizing hint” of success.

The oldest of nine boys in a military family, Ballou moved 23 times before he went to college, attending high school in Mclean, Va. He studied applied biology at the Georgia Institute of Technology, and later attended Emory University’s School of Medicine in Atlanta, Ga, where he earned his MD in 1977. He subsequently entered the Army where he studied Internal Medicine and Infectious Diseases.

As Chief of Immunology at Walter Reed, Ballou’s initial mandate from the US Army was to develop a short-term vaccine for travellers and soldiers. Following a series of promising trials with RTS,S in the mid 90’s, he cites the partnership with the Malaria Vaccine Initiative in 2000 as the spark that inspired the team to develop RTS,S as a paediatric malaria vaccine.

**Joe Cohen, Ph.D.**  
Director of R & D, Vaccines for Emerging Diseases, HIV and Therapeutic Vaccines

Dr. Joe Cohen, one of the inventors and original patent holder of the RTS,S/AS02A malaria vaccine, joined GSK Bio in 1984 and took over the leadership of the company’s malaria vaccine program three years later. Cohen quickly became enthralled with his research and has spent 17 years working to expand upon the “fundamental insight” he and his GSK colleagues had in 1987 - that combining the recombinant technology in GSK’s Hepatitis B vaccine with pieces of the malaria pathogen and adequately formulating the resulting hybrid protein could produce a successful malaria vaccine.

Cohen spent 11 years working on various vaccine formulations in GSK Bio’s molecular biology department, and in 1995 he became the department’s director. In 1999, Cohen helped to create GSK Bio’s new program for vaccines for emerging diseases. He has published 32 articles in peer-
reviewed scientific journals, and is currently the director of R&D for GSK Bio’s vaccines for emerging diseases, HIV, and therapeutics programme.

After nearly two decades working with partners, first at the Walter Reed Army Institute of Research, and more recently with the Malaria Vaccine Initiative, Cohen says he was “extraordinarily happy” and “beyond words” at the recent unblinding of the clinical trial in Mozambique that demonstrated the proof of concept of the RTS,S/AS02A vaccine in children. Cohen calls GSK Bio’s joint effort with WRAIR and the Malaria Vaccine Initiative “a public-private partnership before its time” and says he hopes others will have the courage to pursue unconventional partnerships to tackle neglected diseases.

Cohen earned his Ph.D. from the City University of New York’s Brooklyn College in 1979. He completed his post-doctoral studies at New York’s Albert Einstein College of Medicine and later taught there before joining GSK Bio.

Malaria Vaccine Initiative (MVI)

Melinda Moree, Ph.D.
Director

Dr. Moree develops and directs the overall strategy and implementation of MVI. Leading the team in advancing malaria vaccine development, she ensures adequate funding to fulfill MVI’s mission, the highest quality for all program activities, continued commitment to existing relationships, and the forging of new, focused partnerships.

Dr. Moree previously led business development for MVI and helped define the financial and nonfinancial basis for public-private development efforts. An earlier association with PATH included two years as an international health consultant and liaison between PATH and USAID. Dr. Moree has both public and private sector experience in product development and technology transfer. Prior to joining PATH, she was Manager of Advanced Research at EKOS Corporation. She received her Ph.D. in medical microbiology from the University of Maryland at Baltimore.

Filip Dubovsky, M.D., M.P.H., F.A.A.P
Scientific Director

A pediatrician, infectious disease specialist, and vaccinologist by training, Dr. Dubovsky directs portfolio management, technology assessment, and project development for MVI. He also provides scientific oversight to all MVI product development teams.

Dr. Dubovsky received his Doctor of Medicine from the University of Alabama-Birmingham, and completed his pediatric residency and chief residency at Stanford University. At the Center for Vaccine Development, he specialized in molecular biology, studying molecular pathogenesis of diseases that primarily affect developing countries, while being certified in Pediatric Infectious Diseases at the University of Maryland at Baltimore. He received his Master of Public Health degree and certification in Vaccine Science and Policy from the Johns Hopkins University School of Public Health. Dr. Dubovsky has served on NIH study section, participated as a WHO expert on ethics of Pediatric Clinical trials, and served as technical consultant to US and European biotechnology companies. He is currently a member of the WHO Advisory Committee on Malaria Vaccines.

Bill & Melinda Gates Foundation

Regina Rabinovich, MD, MPH
Director, Infectious Diseases, Global Health Program
Dr. Regina Rabinovich directs the foundation’s Infectious Diseases program. Previously, Rabinovich served as director of the Malaria Vaccine Initiative where she advanced efforts to develop promising malaria vaccine candidates and ensure their availability and accessibility in developing world settings.

Rabinovich spent 11 years at the National Institute of Allergy and Infectious Diseases (NIAID) where she most recently served as chief of the Clinical and Regulatory Affairs Branch of the Division of Microbiology and Infectious Diseases, which oversees the regulatory affairs for the division. At NIAID, Rabinovich managed a network of U.S. vaccine and treatment evaluation units and pilot production projects. During her tenure as branch chief, the units completed large multi-center trials of pertussis and influenza vaccines, as well as a number of phase I trials of platform technologies such as edible vaccines.

Rabinovich has served on a variety of national and international committees for the Institute of Medicine, Centers for Disease Control and Prevention, the National Vaccine Program Office, the American Academy of Pediatrics, and the World Health Organization. Rabinovich received the National Institutes for Health (NIH) Merit Award in 1993 for her contribution to NIH’s vaccine research program. In 1995, she was given the NIH Director's Award for successful advocacy for vaccine research. Rabinovich has received training in pediatrics, epidemiology, maternal and child health and preventive medicine.

Rabinovich received her B.A. from the University of Iowa, her M.D. from Southern Illinois University, and M.P.H. from the University of North Carolina, Chapel Hill.