

Spotlight

Malaria vaccines: Renewed promise

Filip Dubovsky only treated a single case of malaria while working as a pediatrician in California, and his diagnosis of this case was entirely unexpected. While treating a young patient with appendicitis, he also noticed the telltale signs of malaria. Several years after this brief encounter with the parasitic disease, Dubovsky is the scientific director for a US-based nonprofit organization that is devoted to the development of a vaccine to help end the scourge of malaria in developing countries. Malaria, along with tuberculosis and HIV/AIDS, is among the most deadly communicable diseases, killing nearly 3 million people each year. The Malaria Vaccine Initiative (MVI), a division of PATH (Program for Appropriate Technology in Health) in Seattle where Dubovsky works, is trying to accelerate the discovery process for an effective malaria vaccine and the field may soon reap the benefits.

"This is the golden age for malaria vaccine research and we are going to see a lot of data coming in over the next few years," says Dubovsky. "We now have real proof that a malaria vaccine is possible and that it can save the lives of children in Africa."

This new evidence was a long time in coming. Vaccinologists and parasitologists have been trying for decades to develop a vaccine for malaria. But there were many scientific obstacles to overcome first, not the least of which was decoding the sequence of more than 5,000 genes that make up the *Plasmodium falciparum*—the most lethal of the malaria parasites. After this was accomplished

three years ago, the pace of vaccine research gathered speed. "The science is here, and finally the biotechnology is at a point where we can develop promising candidates," adds Dubovsky.

There are now dozens of promising malaria vaccine candidates in various stages of clinical development. There are two main ways these experimental vaccines can help control malaria. There is a critical turning point in the parasite's development once it enters humans. Vaccines that act before this point would offer sterilizing protective immunity, because they would prevent immunized individuals from developing an established malaria infection. Other vaccines that act after this point would work by limiting the severity of disease. Scientists are currently faced with a similar situation in the pursuit of an AIDS vaccine.

The malaria vaccine candidates that are the furthest along in development work by the second route and do not offer complete sterilizing immunity. This type of vaccine could still make great strides in reducing the mortality associated with malaria and could have immense social and economic benefits in the hardest hit areas. In countries where malaria is widespread, the parasite is responsible for up to one quarter of all deaths in children under the age of five. Malaria's burden falls primarily on the younger generations that would eventually become important contributors to the welfare of both their household and community. Malaria is also increasingly linked with other diseases like AIDS. Children and women, particularly pregnant women that are HIV infected, are disproportionately affected by malaria and in many African countries the diseases overlap geographically. In people who are co-infected, both diseases can progress more rapidly and

this can have grave implications.

Meanwhile researchers are continuing the search for vaccine candidates that could provide sterilizing protective immunity. "We have several candidates going forward now, and we've already eliminated a lot that don't work. All this is great news," says Dubovsky. However the ultimate challenge for the malaria vaccine field will come once a successful candidate progresses through clinical trials. Then the test will be getting the vaccine to those who need it most.

From mosquito to human

A malaria infection occurs when a female mosquito bites a human. In the process, the mosquito transmits parasites into the blood. At this point, the parasite is in an early stage of maturity known as a sporozoite. Once inside a human, the parasite goes through a complex growth process. To reach the next stage the sporozoites must make the journey to the liver, where they use liver cells to reproduce. This is the critical turning point where an established infection occurs. A sterilizing vaccine would stop the parasite before reaching the liver. To do this successfully it must block all of the parasites because even if just one sporozoite finds its way to the liver, it can rapidly multiply and still cause a lethal infection.

After replicating in the liver, the

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parasite is then released into the blood. This stage of the parasite is called a merozoite. The merozoite then enters red blood cells where it can produce even more parasites. Once huge numbers of parasites form it causes the red blood cells to rupture resulting in shock, severe anemia, coma, and eventually death. A vaccine that acts after the parasite reaches the liver would hinder reproduction so that fewer parasites make it into the blood. This type of vaccine would reduce the severity of disease and lessen the likelihood of death. Researchers refer to a vaccine that does not offer sterilizing immunity as “leaky” because it allows some of the parasites to leak through the immune response. Designing this type of vaccine is now proving a simpler task than one that induces sterilizing immunity.

Although a leaky vaccine is not 100% effective it will allow children to slowly develop natural immunity to the parasite. In areas where malaria is prevalent, people are repeatedly bitten by infected mosquitoes and are continuously exposed to the parasites. This allows them to build up some immunity against malaria so that even though parasites are entering the liver, the immune system is controlling their numbers. By the time people reach adulthood, many of them have developed enough immunity to avoid severe symptoms and death. Children and infants are therefore at the highest risk for severe malaria and death, and 90% of severe disease occurs between the ages of 5 months and 3 years.

In the absence of a vaccine other simple interventions are effective at lowering rates of malaria infections. By reducing the number of mosquito bites, insecticide-treated bed nets can reduce the number of infections by 45% in areas where they are used regularly and properly. But as is often the case, the simplest interventions are often unavailable or not widely accepted.

There are also anti-malarial drugs that can be taken as prophylaxis before exposure to the parasite, but unfortunately these are of little use in developing countries because of increasing drug resistance in the parasite in many endemic areas. One popular anti-malarial to which there are now high levels of resistance is chloroquine. Newer and improved strategies for treating malaria involve taking

combinations of drugs, as is the strategy with HIV infection. Like antiretrovirals, combination therapies for malaria also have high price tags and are not available in all areas, making them only feasible as treatments where the risk of disease is very high. The World Health Organization (WHO) just recently adopted these updated regimens for use in its Roll Back Malaria program after being criticized by researchers and activists for treating people with outdated and sub-optimal malaria therapies.

Progress in trials

Several malaria vaccine trials are currently ongoing in Africa with a robust array of candidates. There are four candidates in trials that aim to provide sterilizing immunity with an additional nine in earlier development. The selection of candidates that may limit severity of disease is even more expansive. Nine candidates are now in clinical trials and another 28 are still in the laboratory.

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Filip Dubovsky

The field’s lead candidate was developed by the pharmaceutical company GlaxoSmithKline (GSK) and is now being readied for a large-scale efficacy trial (Phase III) in approximately 13,000 children at 6 to 8 sites throughout Africa. This vaccine candidate, known as RTS,S, seems to limit disease progression and prevent childhood deaths. GSK started malaria vaccine research in 1984 and just recently completed a Phase IIb trial in Mozambique that enrolled more than 2,000 children. Completion of this trial was a landmark in malaria research, according to Regina Rabinovich, the director of infectious diseases at the Bill & Melinda Gates Foundation.

The vaccine was 57% effective at pre-

venting severe malaria through six months. The RTS,S candidate is composed of a single protein from the surface of the sporozoite attached to a hepatitis B virus protein and is delivered with an adjuvant known as AS02. The vaccine cannot cause malaria or hepatitis B and caused few side effects in the Phase IIb trial. Preparations for the Phase III trial are now underway and the company is spending millions of dollars on refurbishing an existing manufacturing facility to produce the vaccine for the trial, according to Ripley Ballou, vice president of emerging disease at GSK. The company is also investigating the optimal dosing strategy for the trial. Ballou predicts that a prime vaccination followed by a booster shot will likely give the best response.

Many other research groups are currently investigating ways to include other parasite proteins in a vaccine candidate to find one that induces sterilizing immunity. Stephan Kappe of the Seattle Biomedical Research Institute in the US is researching which of the parasite’s 5,000 genes are required for it to establish infection in the liver. Many of the vaccines now in development have relied on the same handful of proteins to induce an immune response to the parasite. Kappe’s work is intriguing to many in the field who think additional proteins will need to be included in a vaccine for it to be completely effective at stopping the parasite.

Ensuring access

Although activity and funding in the search for a malaria vaccine has been increasing steadily, much of this work has been accomplished with a strikingly small budget. Dubovsky estimates that only US\$27 million this year will be spent on malaria vaccines. The partnerships between private companies like GSK and non-governmental organizations like MVI have helped keep malaria vaccine research on the agenda. Industry is reluctant to invest in research for products like malaria vaccines that would not be sold in the lucrative US or European markets. Drug prophylaxis is sufficient and available to travelers from areas where malaria is not prevalent to protect them from getting malaria. “For products like this, there needs to be some promise that someone is going to buy the vaccine in order for industry to make such a large

commitment,” says Ballou.

Discussions about potential strategies for making a malaria vaccine available at an affordable price are now being held between industry and organizations like the Gates Foundation and MVI. Similar planning and discussions are taking place around AIDS vaccines and many in that field are looking at malaria vaccines as a model.

“A vaccine can be licensed, but until someone steps up and says they are going to buy it for their country and start massive immunization campaigns, it doesn’t matter much,” warns Ballou. “You can give the vaccine away for free, and there’s still a cost involved.”

To this end, MVI is planning to get a licensed malaria vaccine included in the WHO’s Expanded Programme on Immunization in developing countries. “It’s the best system we have and our goal is to get an effective malaria vaccine integrated into it,” says Dubovsky.

In a recent speech at the Brookings Institution (a US-based public policy think-tank) Nelson Mandela reminded policymakers that African countries need improved access to treatment and prevention resources for the three biggest killers: AIDS, malaria, and tuberculosis. “Freedom, after all, means nothing to someone left to die at the mercy of these preventable and treatable diseases.”

Global News

US reverses restriction on Global Fund grant recipients

The US government has reversed its decision to force all international recipients of funding from the Global Fund to Fight AIDS, Tuberculosis, and Malaria to accept a policy saying they condemn commercial sex work.

Countries that receive money directly from the US government will still need to adhere to this pledge but Randall Tobias, director of the President’s Emergency Plan for AIDS Relief, rejected the plan to extend the policy to the 128 countries that receive grants from the Global Fund.

The US contributed a third of the money currently available through the Global Fund, which has committed US\$3 billion to more than 3,000 AIDS

organizations throughout the world. Organizations like the Global Fund had the right to refuse restrictions from donor countries until the US Justice Department amended the Bush Administration’s global AIDS initiative last year.

The announcement from Tobias comes just weeks after Brazil refused millions of dollars in grants from the US government because of its reluctance to denounce commercial sex work. This decision was based on the need to work closely with affected, and often stigmatized, groups like sex workers as an essential part of the country’s successful HIV prevention strategy. Brazil’s decision will not be affected by the change in US policy since the funds were not administered through the Global Fund.

HVTN vaccine trial opens in Botswana

The HIV Vaccine Trials Network is launching another arm of its HVTN 059 trial in Botswana and will begin enrolling volunteers next month to receive an experimental AIDS vaccine candidate. This trial is being run in cooperation with the Botswana Harvard AIDS Institute Partnership and will involve 24 HIV-uninfected people in Gaborone. Other sites in the US and South Africa are already testing the vaccine candidate, known as AVX101.

Participants in the trial will receive three injections of the candidate, which is based on HIV subtype C. The candidate uses a delivery system or vector, derived from the Venezuelan Equine Encephalitis virus that was developed by the US-based company AlphaVax. Volunteers cannot become infected with HIV from this vaccine candidate.

Botswana has one of the most serious HIV epidemics in the world with an adult prevalence estimated at 37% in 2003. The country has a nationally-sponsored treatment program for HIV-infected individuals but the uptake has been slow and the US Centers for Disease Control and Prevention estimates that only a fraction of people in need receive treatment.

World AIDS Vaccine Day

The annual World AIDS Vaccine Day took place on May 18th, eight years after US President Bill Clinton delivered an historic speech calling for new commitment worldwide toward the development of an AIDS vaccine. Clinton said, “Only a truly

effective, preventive HIV vaccine can limit and eventually eliminate the threat of AIDS.”

This year was commemorated by several international community events where people gathered to show their support for AIDS vaccine research. Many AIDS organizations also used the day to emphasize the urgent need for an effective vaccine. A statement issued by the International AIDS Vaccine Initiative (IAVI) details some of the challenges and promises of vaccine research. The AIDS Vaccine Advocacy Coalition (AVAC) also released their updated handbook on AIDS vaccines on the eve of World AIDS Vaccine Day. Visit www.iavi.org or www.avac.org to view the IAVI statement or for more information on the AVAC handbook.



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VAX is a monthly bulletin from *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, German, Spanish and Portuguese as a downloadable pdf file (www.iavireport.org) or an e-mail bulletin. If you would like to receive VAX by e-mail, please send a request including language preference to: vax@iavi.org

IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it.

What role do Community Advisory Boards have in vaccine trials?

An important part of preparing for clinical trials of preventive AIDS vaccine candidates is engaging policymakers, government leaders, non-governmental organizations (NGOs), and members of the community where the trial is taking place. Each of these groups has a role in ensuring that trials are run ethically and that the entire community benefits from having access to information about AIDS vaccines and other prevention strategies.

The involvement of members of the local community is vital to a successful trial because they are the people who will be volunteering. Community Advisory Boards (CABs) are one way for members of the community to be closely involved in the process of planning and running vaccine trials.

CABs became part of the clinical trials process in the US and Europe in the early 1980s when AIDS activists urged researchers and regulatory groups, including the US Food and Drug Administration (FDA), to quickly find and approve treatments for HIV infection. Many community activists educated themselves about HIV and demanded that they be involved in the design of treatment trials. The community activists were successful in changing the drug approval process in the US so that essential drugs could be approved faster. Activists were also part of CABs that met with pharmaceutical companies and the FDA to review how trials were being run. The CAB members then shared this information with others, making them the liaison between the researchers and the community.

CABs were also part of the first AIDS vaccine trials that took place in the US and Europe and are now an important part of trials that are run throughout developing countries. Uganda formed one of the first CABs in Africa in the

late 1990s, a year before the first AIDS vaccine trial began on the continent. The goal of CABs is to build a strong relationship between the researchers running vaccine trials and the local community where the vaccine candidates are being tested to ensure that the community has input into the process.

Who attends CAB meetings?

Participation in CABs is voluntary but in some communities members are asked to remain committed to the group for a set amount of time. The CABs for vaccine trials usually include community leaders like nurses, teachers, members of the media, or NGO staff. Many may also involve local religious leaders. CABs try to be as diverse as the local populations they represent so that all members of the community can benefit. The members of a CAB will have different educational backgrounds and concerns. Some members may understand medical or scientific issues while others may just be interested in HIV prevention. The early CABs in the US included mostly people who were HIV infected because the trials were testing HIV treatments. For vaccine trials, CABs may include people who are current or past volunteers in a trial and want to help improve the process in the future.

There are typically around 20 members in each CAB who meet regularly to discuss the trial process. A researcher or investigator from the trial site will often attend the meetings to provide updates on trials that are in progress or to explain those that are starting soon.

What does the CAB discuss?

CAB members are often asked to provide comments on the way trials are designed, including how volunteers are recruited for the trial. Members of the CAB can help recruiters by giving them culturally-specific advice on how to reach local populations that are important to include as trial volunteers. This

may include where the best locations are to recruit volunteers or how the trial staff can use gender-specific approaches to encourage women to enroll in vaccine trials. The CAB also encourages other members of the community to volunteer by giving them information about the trial. For example, CAB members can explain that you cannot become infected with HIV from the vaccine candidate, which may ease some of the worries people have about participating in a trial.

CABs are also asked to share their questions and concerns about the informed consent process that all volunteers must participate in before joining a trial. This process includes a description of the trial, details of what participation in the trial entails, and explains the possible side effects of the vaccine candidate. Informed consent is one area where CABs can have a direct influence on trial protocols. CABs can advise the trial coordinators about what information to include in the process to ensure that volunteers understand the aim of the trial. They can also help researchers understand how to explain the process of informed consent to volunteers in a way that is culturally acceptable. Other issues a CAB may address include the compensation for volunteers in vaccine trials, the community's fears about participating in research, the stigma involved with HIV research, and understanding the results of vaccine trials.

The CAB meeting is a place where the members can ask questions and comment on any part of the trial process and where there is an exchange of information between the community and the research staff. This creates a supportive environment for vaccine trials because CAB members can be certain that researchers are considering the perspective of the participants.