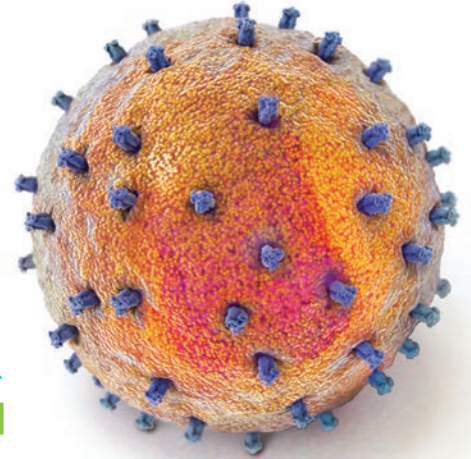


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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

A Shot at Fighting Malaria

The first results of a Phase III trial of a malaria vaccine candidate show it can cut cases of severe malaria in young children by nearly half
By Regina McEnergy

Malaria, a parasitic illness in humans and animals spread by Anopheles mosquitoes, is a global killer that is particularly devastating to young children. Of the estimated 781,000 deaths from malaria every year, most occur in young children from sub-Saharan Africa, where the disease is endemic and existing tools such as insecticide-treated bed nets or residual spraying are underutilized or not available. The immature immune systems of toddlers and infants are particularly vulnerable to severe malaria, which is characterized by severe anemia, high fever, respiratory problems, renal and nervous system failure, and often death.

So it was welcome news indeed last month when the first results of a Phase III trial of a malaria vaccine candidate tested in more than 15,460 African infants and toddlers showed a 56% reduction in clinical episodes of malaria and a 47% reduction in severe malaria primarily among children 5-17 months old up to a year after vaccination. The findings were published Oct. 18 in the *New England Journal of Medicine*. The trial is still ongoing, with results from a separate arm of the trial involving children 6-12 weeks old not expected until the fourth quarter of 2012.

The vaccine candidate, known as RTS,S, evaluated in this multi-center, double-blind,

placebo-controlled trial, targets *Plasmodium falciparum*, the parasite responsible for most of the complications and death from malaria. It was developed and manufactured by GlaxoSmithKline (GSK) Biologicals and contains a protein on the surface of the *P. falciparum* sporozoite, the form of the parasite transmitted from mosquitoes to people, combined with a protein on the surface of the hepatitis B virus. The two proteins stimulate an immune response against the malaria parasite when it first enters the human host's bloodstream, or later when it invades liver cells. To further boost the immune response, RTS,S also contains AS01, an adjuvant manufactured by GSK.

Investigators were clearly excited by this first round of results. "This is an historic moment," says Mary Hamel, a medical epidemiologist with the US Centers for Disease Control and Prevention and a principal investigator at one of the trial's clinical research centers in Kisumu, Kenya. "Scientists have been working to develop a vaccine for over 30 years and this is the first time we have seen efficacy in a large Phase III trial. This could be an incredible new tool." While these results were promising, investigators are particularly curious about the vaccine's efficacy in the younger age group because a licensed malaria vaccine would

likely be administered during early infancy.

Getting to these historic results was not a short path. The RTS,S candidate has been in development for nearly 30 years and would likely not have progressed this far were it not for the Malaria Vaccine Initiative (MVI) at PATH, a Seattle-based non-profit formed 30 years ago to improve global health through science and technology. PATH established MVI in 1999 with an initial US\$50 million grant from the William H. Gates Foundation (renamed in 2000 the Bill & Melinda Gates Foundation) to accelerate the development of a vaccine and ensure its availability and accessibility in developing countries. MVI formed a product development partnership with GSK in 2001 to develop RTS,S.

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Ashley Birkett, the director of research and development at PATH, says MVI made it possible to push forward a vaccine that otherwise might have languished given the severe economic challenges faced by countries where a malaria vaccine is needed most. “We are dealing with a disease exclusively associated with morbidity and mortality in the developing world and the impetus for any commercial driver is minimal,” says Birkett.

The results from the Phase III trial of the RTS,S vaccine candidate are also considered a major scientific milestone, given the unusual challenges researchers have had to contend with in designing a vaccine against the malaria parasite, which is spread from human to human through the bite of infected *Anopheles* mosquitoes. The parasites travel through the bloodstream to the liver, where they mature and release another parasitic form, the merozoites, which then enter the bloodstream and infect red blood cells. Because the parasites largely live inside cells, where they mute the body’s immune responses, humans have never been able to develop sterilizing immunity against the pathogen. This means that re-infection by the parasites is an ongoing problem in the developing world. “Children can get many episodes of malaria and still be at risk of death,” says Hamel. “It’s not like polio, where once you get the disease you are immune.”

Because of the parasite’s complicated life cycle, scientists have also had a hard time determining which target on the parasite would induce the strongest immune response and designing a vaccine capable of inducing those immune responses. “We don’t know exactly how this vaccine works, but we know it does work,” says Hamel.

The initial results of the trial found adverse events were reported in about 18% of the children in the older age group, compared to 13% in the younger group. The proportion of vaccinated children who died compared to those in the control arm was similar in each age group, and serious adverse events considered

to be vaccine-related occurred in 11 children in the 5-17 month age group, but only one child in the 6-12 week old age group.

Thus far developers do not view RTS,S as the final malaria vaccine, says Birkett. “But because of the burden of malaria, we do think this vaccine has the potential to save lives,” he says. “And so the Phase III trial was designed with the intention of supporting the release of a product.”

Birkett says final data from the RTS,S trial is expected to be submitted to the World Health Organization (WHO) and the European Medicines Agency in late 2014, at which time the WHO could issue a policy recommendation on whether the vaccine candidate should be used. That still doesn’t guarantee infants will actually receive the vaccine. “It will be up to individual countries to make their own decision whether RTS,S has a place in their immunization campaign,” says Birkett.

But Christopher Whitty, a professor of international health at the London School of Hygiene and Tropical Medicine, says that while the initial results are a scientific achievement, hopes raised by an earlier, smaller trial that it might be even more effective were not confirmed. “Although these are only initial data, the [Phase III] study is large enough and the sites of the trial varied enough to be fairly confident that the 50-60% efficacy in the first year after vaccination will be roughly the final figure,” Whitty wrote in an Oct. 27 editorial in the *British Medical Journal*.

However, Whitty noted in the editorial that it is unrealistic to assume that first-generation malaria vaccines like RTS,S, as well as those for tuberculosis and AIDS, where complete immunity is difficult to acquire from natural infection, will have similar efficacy as those against rubella or measles, where natural disease induces life-long immunity. “Partially effective vaccines are, where cost effective, a great deal better than no vaccine and should be celebrated as such,” he wrote. ■

The Phase III RTS,S Efficacy Trial

The vaccine candidate:

The RTS,S candidate was originally developed in 1987 by GlaxoSmithKline (GSK) Biologicals as part of an ongoing collaboration with the US Walter Reed Army Institute of Research. It was first tested in 1992 in a trial involving adults in the US. The first trial in Africa occurred in 1998 involving adults in The Gambia.

The trial:

The trial was launched in 2009 and conducted at 11 sites in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania.

There were 8,923 children ages 5-17 months old and 6,537 children ages 6-12 weeks old enrolled in the study. The first results were primarily from the older age group. Results from the younger age group are expected in the fourth quarter of 2012. Children in the younger age group of the trial received the first three doses of the vaccine candidate at the same time as the licensed vaccines for diphtheria, tetanus, pertussis, and haemophilus influenza type B.

Trial design:

There are three study arms in each age category: children who received all three doses of RTS,S vaccine formulated with the AS01 adjuvant at 0, 1, and 2 months plus a booster dose 18 months after the third dose; children who received the RTS,S vaccine and AS01 adjuvant without a booster; and a control group that received a non-malaria vaccine—rabies vaccine for the older children and meningitis C vaccine for the younger children. The vaccines were all administered intramuscularly.

Trial sponsors:

GSK, the clinical sponsor of the trial, and the PATH Malaria Vaccine Initiative (MVI), which provides funding and technical support, entered into a unique product development partnership in 2001 to develop the vaccine candidate, through an initial grant from the Bill & Melinda Gates Foundation.

Funding:

The Phase III efficacy trial is funded through grants to MVI by the Bill & Melinda Gates Foundation and GSK. —RM

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Global HIV Vaccine Enterprise Changes Course

Following an extensive review by its board of directors, the Global HIV Vaccine Enterprise and its New York City-based Secretariat is streamlining its focus.

In a letter distributed Oct. 26, Jose Esparza, the interim president of the Enterprise's Board of Directors, said the updated Enterprise would continue as an alliance of independent organizations dedicated to accelerating the development of AIDS vaccine candidates and would continue to focus on facilitating "mutual coordination, collaboration, knowledge sharing, and the optimization of resources and efforts in the field."

But reflecting what Esparza described as a "leaner, more efficient" operation, the Enterprise will largely restrict its attention to three core functions that reflect these priorities. As it has done since 2007, the Enterprise's Secretariat will continue to organize the annual AIDS Vaccine Conference. The Enterprise will also organize an annual Funders' Forum to optimize use of current financial resources and hopefully attract new funding to the field. Finally, it will convene meetings on strategic issues where a collective effort is deemed most effective.

"The board is working very hard to rejuvenate the Enterprise with a model that is more agile, focused, streamlined, and relevant to the field," says Esparza, senior advisor on vaccines for the Bill & Melinda Gates Foundation, who has served as interim president of the Enterprise board since late 2010, when Peter Piot, director of the London School of Hygiene & Tropical Medicine, resigned the post.

The genesis of the Global HIV Vaccine Enterprise occurred about a decade ago when a handful of leaders in the field of AIDS vaccine research began considering creating an organization that would bring greater coordination, collaboration, and transparency to the field. But there has always been a lack of consensus on

how the Enterprise should be structured, what its role should be, and what kind of leader would best suit the organization's needs, as well as those of the field (see *The Enterprise Changes Course, IAVI Report*, Sep.-Oct. 2011). These questions became even more apparent since Alan Bernstein, the first executive director of the Enterprise, resigned in June after three years at the helm.

Though Bernstein's credentials included a background in research—he specialized in oncology and was founding president of the Canadian Institutes of Health Research—the Enterprise board may not necessarily select another scientist for the top slot, several Enterprise board members contend.

Along with a new executive director, the Enterprise Secretariat will also expand its board, which now has seven members, to comprise representatives of funders of research, advocacy groups, consortiums and institutions, global health organizations, governments and multilateral agencies, and industry partners. The new board will include approximately 15 members, says Mitchell Warren, executive director of the global advocacy organization AVAC and a member of the Enterprise board.

What isn't likely to change is the Secretariat base of operations. Warren says the Enterprise will remain in New York City, where Bernstein established the Secretariat.

One program not explicitly defined in the Enterprise's revised list of priorities and activities is its young and early career investigators (YECI) committee. The Enterprise created YECI in 2008 to address issues that posed challenges to the recruitment of young researchers into the HIV vaccine field. Warren says the concerns of young and early career investigators are still important and the board considers the work of YECI to be one of the great strengths of the Enterprise. "No one thinks we are going to step away from that," he adds.

With HIV Incidence Plateauing, a Push for an AIDS-free Society

US Secretary of State Hillary Clinton, whose department oversees the President's Emergency Plan for AIDS Relief (PEPFAR), laid out an ambitious goal of achieving an AIDS-free generation in a Nov. 8 address to the US National Institutes of Health. Clinton said prevention of mother-to-child transmission, expanding adult male circumcision programs, and more widespread treatment of HIV-infected individuals to curb transmission will all help pave the way to an AIDS-free generation.

According to an annual report released Nov. 21 by the Joint United Nations Programme on HIV/AIDS (UNAIDS), there is continued progress in battling AIDS, but achieving an AIDS-free generation remains a daunting task. UNAIDS estimates that 2.7 million people have become newly HIV infected each year for the last five years. The report noted that the number of new HIV infections occurring globally in 2010 dropped by more than 21%

since 1997, when incidence peaked worldwide, which UNAIDS attributes primarily to behavioral changes including reductions in the numbers of sexual partners, increased condom use, and delayed age of first sex. In some countries, like Botswana, declines in incidence were also attributed to wider availability of antiretroviral (ARV) treatment. The number of people receiving treatment globally has steadily increased. Now, 6.6 million or 46% of the HIV-infected people in low- and middle-income countries eligible for treatment are receiving ARVs.

In sub-Saharan Africa, new cases declined by 26% since 1997, led by a 33% drop in South Africa, which continues to have the highest number of HIV-infected individuals. But from 2008 to 2010, there was an alarming 23% surge in the number of new HIV infections among adults and children in Eastern Europe and Central Asia, helping keep the global number of new infections steady.

Understanding the Effects of Hormonal Contraception on HIV Transmission

What are the risks and benefits of using hormonal contraception in HIV prevention trials? *By Regina McEnergy*

Because little or no human data exist regarding safety of HIV vaccine candidates during pregnancy, either for the woman or the fetus, investigators usually require women of reproductive age to use contraception when they decide to participate in AIDS vaccine trials. Pregnant or breastfeeding women are excluded from participating in HIV vaccine trials.

If women choose to volunteer for an HIV vaccine trial, the nurses and staff at clinical trial centers go to great lengths to deliver pregnancy prevention counseling before the study begins, and to provide women with different contraception options, such as male or female condoms, oral hormonal contraceptives that must be taken daily, or injectable hormonal contraceptives such as Depo-Provera, which lasts for three months.

Injectable hormonal contraception is the most popular among women in developing countries, where the burden of HIV/AIDS is highest and the need for an AIDS vaccine is greatest. In sub-Saharan Africa,

for instance, about 12 million women use injectable contraceptives, 8 million use oral contraceptives, and another 11 million use condoms, according to the Alan Guttmacher Institute, a New York City-based non-profit that advances sexual and reproductive health research. About 140 million women worldwide use hormonal contraceptives. Injectable contraceptives have the clear advantage of lasting for three months. All of the other methods are behavior dependent. This makes injectable contraception a preferable method.

However, a number of studies have suggested that the use of hormonal contracep-

tion may increase a woman's risk of HIV acquisition. The most recent and strongest findings appeared in the October 18 issue of the scientific journal *Lancet Infectious Diseases*, in which researchers from the University of Washington reported a doubling of the risk of HIV infection among women and, for the first time, a doubling of the risk of HIV transmission from women to men.

While the study did not differentiate between oral or injectable hormonal contraceptives, the long-acting injectable hormonal contraceptives were the most commonly used by women in the study, involving 3,790 heterosexual serodiscordant couples—in which one partner is HIV infected and the other is not. The cohort of serodiscordant couples was enrolled in Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia, and is the largest group in which the effect of hormonal contraception on HIV transmission has been studied.

The mechanism

Despite the recent data, the mechanism of how hormonal contraception increases the risk of HIV infection is not entirely clear. Hormonal contraceptives primarily work by suppressing the release of protein hormones that regulate reproductive development, which in turn prevents the ovary from releasing eggs and deprives sperm of their targets.

Some hormonal contraceptives, such as birth control pills, contain small amounts of synthetic reproductive hormones from both the estrogen and progestin families. Others, such as Depo-Provera, contain only progestin.

Hormonal contraceptives that contain just progestin also appear to be able to cause the cervical mucus to thicken, which blocks and prevents sperm from fertilizing an egg. And progestin-only hormonal contraception also thins the lining of the

uterus, which in theory could prevent pregnancy by keeping a fertilized egg from attaching to the uterus.

An animal model

Scientists have been studying the effects of hormonal contraception in non-human primates. The vaginal mucosa is a common portal of entry for both HIV and simian immunodeficiency virus (SIV), the monkey equivalent of HIV, and identifying the mechanisms that accelerate or block viral entry in this region is important both in the study of HIV pathogenesis and prevention.

By labeling HIV with a fluorescent protein that causes the pathogen to light up like a neon sign, scientists were able to track viral particles within the vaginal mucosa of monkeys, some of which had been given the hormonal contraceptive Depo-Provera. Scientists observed more T cells—the primary targets of HIV—close to the mucosal surfaces of monkeys treated with Depo-Provera. This might explain why the use of the hormonal contraceptive increases HIV transmission.

While researchers continue to study how reproductive hormones may or may not influence HIV transmission and infection, it is likely that women will still be offered multiple contraception options, including hormonal contraceptives, if they are enrolled in HIV vaccine and other prevention trials.

However, some caution may be warranted in the future. The World Health Organization is convening a meeting in January to consider whether the evidence suggesting hormonal contraception increases HIV infection and/or transmission risk is now strong enough for them to issue a warning. Still, researchers who conducted the most recent study expect hormonal contraception will continue to be offered in HIV prevention trials. ■

