

Spotlight

An industrial incentive

Several organizations are pursuing new ways to encourage the pharmaceutical industry to increase investment into the research and development of an AIDS vaccine.

Investing in biomedical research is a risky business. University research laboratories and small biotechnology companies are often where key scientific advances occur, but these institutions are unable to spend the large sums of money that are required to transform this basic research into a drug or effective vaccine that can be approved and licensed. This transition is more likely to occur at large pharmaceutical companies, which have the necessary technological, regulatory, and manufacturing expertise. Only a handful of companies have historically developed many of the vaccines that protect people from diseases.

However, the involvement of pharmaceutical companies in the research and development of AIDS vaccines has so far been limited. Even though the total investment in AIDS vaccine research has climbed from US\$160 million in 1996 to an estimated \$690 million in 2004, annual spending on AIDS vaccine research and development from all sources still represents less than one percent of the total spent on all health-related research. And while about 48% of the world's investment in new health products comes from the pharmaceutical industry, it accounts for just 10% of all AIDS vaccine funding.

One obstacle to industry's participation is the high cost associated with developing an effective vaccine. It can

cost around \$800 million to develop a new medicine and the price tag on a new vaccine will be even higher. This is especially true for an AIDS vaccine since the scientific challenges remain so great. But companies aren't likely to put forth more resources if they can't recover their extensive research, development, and production costs. "The main thing that causes companies to enter a field is the prospect of a market," says Stanley Plotkin, emeritus professor of pediatrics at the University of Pennsylvania and executive adviser to the chief executive officer of the vaccine company Sanofi Pasteur.

And the market for an AIDS vaccine is primarily in the world's poorest countries, where the total market for vaccines is only about \$500 million a year. This may sound like a big payoff, but it's small when compared to drug profits that can soar to billions of dollars. In terms of profits, vaccines are sure to lose out since a vaccine may be used only a few times in a lifetime while drugs are often taken every day.

So to encourage more pharmaceutical companies to pursue AIDS vaccine research, many public health experts are exploring a new process that could guarantee vaccine manufacturers that if they develop an effective vaccine, there will be a market or group of governments and organizations that will be willing to pay and provide the company with financial returns comparable to those they could expect from developing a successful drug for the American or European markets. This incentive is called an advance market (or purchase) commitment (AMC). Increasingly private foundations, governments, and the global health community are considering this as a way to get companies

involved in vaccine research that targets diseases including AIDS, malaria, and tuberculosis.

Gaining momentum

Although the concept has been around for some time, AMCs have received support in recent years from donors such as the Bill & Melinda Gates Foundation, the World Bank, the G8 Finance Ministers, and many biopharmaceutical industry representatives. In 2003 the Center for Global Development, an independent organization working to reduce global poverty, assembled a group of economists, public health professionals, lawyers, and pharmaceutical experts to transform a rough idea into an actual proposal. Their report issued in May of this year examines the major issues associated with this approach (www.cgdev.org/section/initiatives/_active/vaccinedevelopment).

AMCs have also received attention from some governments. In late 2004 the UK government expressed support for this concept as part of a larger package of new ideas to expand financing for international development. The UK and the other G8 nations asked the World Bank in May to determine the feasibility of establishing an AMC to support development of vac-

In This Issue

Spotlight

- An industrial incentive

Global News

- US Senators introduce bill on accelerating AIDS vaccine research
- First meeting of Clinton Global Initiative draws funding and attention for development issues
- Vice President of Uganda addresses major AIDS vaccine meeting

Primer

- Understanding test of concept trials

cines against AIDS, malaria, and other diseases. The G8 heads of state asked the Italian government in July to lead the development of a proposal by the end of this year. These global leaders hope that AMCs will succeed in drawing more private sector or industry investment into vaccines.

The proposed model for an AMC consists of a binding agreement between companies and donors, either from governments or private foundations. The donors would pledge to purchase an effective new vaccine to immunize a pre-determined number of people at a set price that would be high enough to generate revenues similar to those for other products. They would only be required to pay after an effective vaccine is developed.

The vaccine company would be obligated under this agreement to sell the vaccine to eligible developing countries at an affordable price. Such a fixed-price commitment would only apply to low-income countries, leaving companies free to sell the vaccine at much higher prices in rich countries.

IAVI has held consultations with industry to gauge the interest in the proposed AMC structure. Recent consolidation has left just five major vaccine manufacturers; GlaxoSmithKline, Sanofi-Aventis, Merck, Wyeth, and Chiron. In general the response from executives has been positive, although most agree that the specific details remain to be worked out. "If you don't put significant resources into a vaccine commitment then you will fail," says Rudi Daems, executive director of policy and corporate affairs at Chiron Vaccines.

Promising Profits

One reason that vaccines create lower profits for companies is the power of international agencies such as The United Nations Children's Fund (UNICEF) to negotiate lower prices. These reduced prices have helped ensure the expansion of child immunization programs around the world, writes World Bank senior health specialist Amie Batson in a recent issue of the *Journal Health Affairs*. But they have also discouraged several companies from investing in new research. Experts

suggest that the urgent need for an AIDS vaccine could put additional pressure on the vaccine maker to sell the product at a heavily discounted price or even to give it away free.

An AMC could prevent this from happening since vaccine developers would be assured the money promised to them through a legally binding agreement. An independent group composed of experts from industry and the global public health community would decide if the product has met the qualifying efficacy criteria.

Several organizations are exploring the AMC concept for different diseases. The National Bureau of Economic Research released a preliminary proposal on how malaria vaccine development could benefit from the AMC

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Kate Taylor

model. For an AIDS vaccine, IAVI has proposed a draft market commitment that would require the vaccine to be at least 50% effective at preventing the transmission of HIV subtypes A and C, the most common subtypes in the poorest nations. Eligible countries would be required to contribute a small payment and the donor organizations would make up the rest.

While the AMC proposal is designed to entice vaccine developers, it also has numerous benefits for donors. An AMC is meant to ensure donor organizations that an effective vaccine developed by the pharmaceutical industry will be made available to those who need it the most, including the low-income countries in Africa and Asia that bear the biggest disease burden. Millions of needless deaths can occur when a vac-

cine is too expensive for purchase by developing countries, causing children to remain unvaccinated. An estimated 4.5 million children have died from *Haemophilus influenzae* serotype b (Hib)-related disease over the last decade, even though an effective vaccine exists.

AMCs would also stimulate competition among manufacturers to produce the vaccine as quickly as possible in order to claim the guaranteed price described in the agreement. Importantly, since donors would only pay when a vaccine is developed they would be free to spend their current funds on vaccine-promoting efforts.

But efforts to ensure the vaccine is accessible to people in developing countries must extend beyond setting an affordable price. Also of concern are infrastructure problems in many countries that can affect the delivery of vaccines. Every year about 3 million people die of diseases such as measles, hepatitis B, and tetanus that can be prevented with existing and affordable vaccines. These issues are another essential component and are now being addressed by the Global Alliance for Vaccines Initiative and its partner, the Vaccine Fund, both of which are supportive of AMCs. "We very much welcome the conversation surrounding advanced market commitments," says Alice P. Albright, the Vaccine Fund's chief financial officer.

Many global health experts would agree that AMCs are not the entire answer to the problems that surround vaccine development and delivery. "Advanced market commitments are part of a menu of things that are necessary, none of which alone is sufficient," says Seth Berkley, president and CEO of IAVI. As the research efforts progress so must capacity building for testing, distributing, and delivering vaccines to the people who need them most.

Vaccines are the best way to protect the most vulnerable victims of the AIDS pandemic, such as women and children, says Kate Taylor, IAVI's senior director of policy and advocacy. "It is critical to continue care today but also to develop the next generation of preventive technologies because the tools we have today are not sufficient," she says. "Developing a vaccine against

HIV is one of the greatest scientific challenges of all time. The science is

really hard. Advance market mechanisms provide incentive for the

required long-term commitment and significant investment."

Global News

US Senators introduce bill on accelerating AIDS vaccine research

Two prominent US senators introduced legislation in Congress recently calling for increased funding to accelerate the research and development of vaccines for AIDS, tuberculosis, and malaria, as well as other infectious diseases. The proposal, called the "Vaccines for the New Millennium Act of 2005", highlights several ways that both the US government and private industry can work to bring new and important vaccines to the people in greatest need.

The bill calls for an increase in the number of public-private partnerships as one strategy for achieving this objective, and mentions in particular IAVI, the Malaria Vaccine Initiative, and the Global TB Drug Facility as examples of these partnerships. Other strategies include exploring economic incentives for private companies to encourage them to get more involved in developing vaccines that target diseases primarily affecting developing countries. Among the incentives suggested are advance market commitments (see *Spotlight*, this issue), tax credits, and improved regulatory procedures.

Within the legislation, the senators that co-authored the bill cite several examples of how vaccines have had a profound impact on global health including the eradication of smallpox and drastically reducing rates of childhood mortality worldwide. The legislation is yet to receive approval by the US government.

First meeting of Clinton Global Initiative draws funding and attention for development issues

The foundation established by former US President Bill Clinton launched its Global Initiative by holding its first meeting in New York City to discuss

strategies for addressing poverty and its affects on the AIDS pandemic, as well as other prominent development issues. The meeting coincided with the 2005 World Summit being held at the United Nations (UN) headquarters in New York City where strategies for achieving the Millennium Goals were discussed.

Several heads of state and other leaders from the business sector attended the meeting, including UN Secretary General Kofi Annan, British Prime Minister Tony Blair, South African President Thabo Mbeki, Nigerian President Olusegun Obasanjo, and Mozambican President Armando Guebuza. At the conclusion of the three-day summit more than US\$1 billion were committed to various development goals around the world, including direct investments into projects targeting women and children affected by the AIDS pandemic.

Clinton's foundation has also been active in negotiating lower prices for antiretroviral treatment and securing funding for treatment programs in Africa and Asia.

Vice President of Uganda addresses major AIDS vaccine meeting

Vice President Gilbert Bukenya of Uganda addressed AIDS vaccine researchers and scientists at *AIDS Vaccines 2005*, a large international meeting held in Montreal recently, and provided a perspective on how African countries can play an important role in the discovery of an effective vaccine.

Bukenya urged African countries to provide an environment conducive to vaccine research and clinical trials, including putting in place the policy and legislation that allows this work to move forward. He also highlighted the need for developing countries to work with international partners in building the human capacity and infrastructure required for clinical trials, which Bukenya says can not happen without support from the highest political level. But he also pointed out that only half of

the financial resources necessary for vaccine development are currently available.

Uganda has been a leader in starting programs that provide its citizens with antiretroviral therapy as well as in AIDS vaccine research and is now hosting three ongoing Phase I AIDS vaccine trials. As a result, the number of Ugandan citizens accessing voluntary counseling and testing (VCT) services has increased by 70%, according to Bukenya.



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Spotlight article was adapted from an article by Catherine Zandonella (*IAVI Report*, 9/3, 2005).

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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.

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Why are Phase IIb trials an important step in evaluating AIDS vaccine candidates?

AIDS vaccine candidates are evaluated in a stepwise manner in a series of clinical trials known as Phase I, II, and III. Phase I and II trials generally involve a small number of volunteers and provide researchers with critical information about the safety and immunogenicity of the vaccine. It isn't until Phase III trials that the efficacy of the vaccine is assessed. These trials test the ability of the candidate to prevent infection and/or slow progression of disease. These trials require large numbers of volunteers, are extremely expensive (can cost more than a hundred million dollars), and take a long time to set up and complete. Phase III efficacy trials are the final step before a vaccine can get approval for licensure from a regulatory body like the Food and Drug Administration in the US or the Agency for the Evaluation of Medicinal Products in Europe. To learn more about these trials see *Primer on Understanding Vaccine Trials* from August 2003.

What is a test of concept trial?

As the name implies, a test of concept trial is about finding out if the vaccine concept or the type of vaccine being tested will be effective. A test of concept trial is not designed to establish the efficacy of a particular candidate but rather to help researchers decide if this candidate is worth testing in larger Phase III trials. These intermediate studies are also referred to as "proof of concept" or Phase IIb trials.

The number of volunteers required for such trials is smaller, only around 2-5,000 volunteers as compared to over 10,000 for Phase III trials. Phase IIb trials are therefore much easier to design and manage, and are less costly. Since fewer doses of vaccine are required, these trials are also much faster to implement because the manufacturing process is limited. Very importantly, they may also provide researchers with the immune correlates of protection, or

the immune response generated by the vaccine that cause it to be effective. This can often be difficult to do in large Phase III trials.

However because Phase IIb trials are run in smaller populations, the precision of the trial is less. Therefore a vaccine can not be licensed based on the results of Phase IIb testing. If the results of a Phase IIb trial indicate that this approach is promising, a Phase III efficacy trial will be required before licensing and use of the vaccine. This means that the decision to run a Phase IIb trial will extend the total amount of time it takes to complete the clinical trials process. Phase IIb trials are an important screening step for different vaccine candidates and help organizations determine which ones to move forward into Phase III trials, without expending more time and money.

The idea of using Phase IIb studies is more than a decade old but the first one involving an AIDS vaccine candidate began just last year. Test of concept trials have already been done for other vaccines as well as for other preventive technologies. US-based Merck and GlaxoSmithKline Biologicals in Europe tested their respective vaccine candidates for human papilloma virus in Phase IIb trials. These candidates are now both being tested in Phase III efficacy trials. The HIV Prevention Trials Network is also testing a microbicide candidate known as Buffergel PRO2000 in an ongoing Phase IIb trial to see if this agent can block transmission of HIV.

Why are test of concept trials especially useful for AIDS vaccines?

Because the challenge of developing an effective AIDS vaccine has proven so difficult and the need remains so great, researchers must evaluate several candidates as quickly as possible. This requires testing several candidates at the same time.

Researchers are also using new approaches to try to find an effective AIDS vaccine. Test of concept studies are one way to find out quickly if these new candidates can be successful. An example of this is the first Phase IIb

trial of an AIDS vaccine candidate, which is being conducted by Merck and the HIV Vaccine Trials Network. This ongoing study is testing the company's lead vaccine candidate known as MRKAd5 in approximately 3,000 volunteers. The MRKAd5 candidate primarily generates a cellular immune response, but scientists are unsure if this type of vaccine will be sufficient to protect people from HIV infection. Merck decided to test this type of vaccine in a Phase IIb trial to find out if this strategy will be able to prevent HIV infection or to slow the progression of disease in people who do become infected through exposure in their community. The results of this trial will influence the company's decision to go ahead with a Phase III trial and will provide the entire AIDS vaccine field with critical information about the importance of cell-mediated immune responses in vaccine efficacy.

Another advantage of a Phase IIb trial is that it allows researchers to evaluate a candidate in a more confined study population. The MRKAd5 candidate is based on a particular strain of a human virus that naturally causes the common cold (adenovirus serotype 5). This candidate may not work as well in people who have already developed immunity to this strain of natural adenovirus, due to what is called pre-existing immunity (see February *Primer on Understanding Pre-existing Immunity*). Initially Merck's Phase IIb trial was designed to include only people who had low levels of pre-existing immunity, so that they could find out if the vaccine concept was even feasible under optimal conditions. The trial has since been amended to include a more diverse population of volunteers.

The use of test of concept studies to evaluate AIDS vaccine candidates is also being considered by other organizations and more may be conducted in the future. For trial volunteers, communities, and health policy makers it is important to understand that a vaccine will not be approved based on the results of these studies even if the investigators are able to draw preliminary conclusions about its efficacy.