From its launch 15 years ago the global private-public vaccine alliance Gavi, as an essential part of its goal to get life-saving vaccines to millions of children in the poorest countries of the world, strived to become a real influence in the global pharmaceutical market. It may now be.

On January 27 in Berlin at the alliance’s donor conference, Gavi banked US$7.5 billion, completing its second big round of funding, this one to support its vaccine programs in developing countries through 2020. In the 73 countries home to the world’s poorest populations, Gavi is the conduit to life-saving vaccines preventing the kind of common killers like measles and whooping cough, as well as to more recently introduced vaccines, such as those against pneumonia, cervical cancer, and diarrhea. It does so by effectively underwriting and negotiating lower prices for vaccines, aided in great part by flexing its muscle as a single bulk buyer with a fat wallet. Gavi brings its member nations into co-financing agreements for vaccines, sometimes at nominal costs, at the discounted prices it negotiates and finances. The alliance can then quantify demand to the vaccine producers, guaranteeing these large pharmaceutical companies a steady and large sales volume. This lends Gavi leverage to negotiate price. The countries themselves administer their own immunization campaigns, with Gavi, the World Health Organization (WHO), and the United Nations Children’s Fund (UNICEF) lending technical assistance and support in actually getting shots in arms.

A case study from Great Britain’s Department for International Development declares Gavi an “innovative business model that not only finances the introduction of new vaccines in developing countries, but also reshapes the vaccine market, spurring the development of vaccines and expanding production.” The UK is Gavi’s biggest single donor. Wiley’s Handbook of Global Health Policy says Gavi is “increasingly looking at its potential influence or role in upstream research and development,” with the added advantage that “they use a model that industry understands and responds to.” Gavi is now, by volume if not margin, pharma giant GlaxoSmithKline’s largest single customer.

Over the last five years Gavi efforts have led to the immunization of 245 million children; its goal for the next five is to administer another 300 million shots, saving possibly five to six million lives otherwise lost through preventable causes. “Looking at these challenges, Germany is taking the decision to increase our pledging,” Chancellor Angela Merkel said in announcing a $720 million pledge at the Berlin meeting. Under the styl-ish dome of a ’60s-era congress hall and showpiece of the former East Berlin, Britain pledged $1.57 billion. Rajiv Shah, Administrator of the US Agency for International Development, pledged $800 million.

The vaccine alliance’s chief executive, Seth Berkley, who founded the International AIDS Vaccine Initiative and helmed it until 2011, says Gavi created a market that didn’t exist before. “Many of those [developing country] marketplaces just didn’t have reliability of currency, or couldn’t give appropriate demand forecasts, and that meant that companies couldn’t scale up adequately to serve them. We’ve created a marketplace now that is stable, that’s predictable.”

What’s happening in the search for a vaccine against the Ebola virus is another example of Gavi’s strength and (perhaps) its limits. Through more than 30 outbreaks in three decades, even though Ebola gained the world’s
attention with its startling lethality and fearsome symptoms in books like Richard Preston’s *The Hot Zone*, it just didn’t affect enough people to attract the kind of resources it takes to develop a vaccine. That is, until last March. By last fall 22,000 were infected with Ebola in three west African nations. The WHO and other public health institutions like the US Centers for Disease Control and Prevention faced the prospect of the virus globe-hopping into African mega-cities like Lagos and on into western Europe and the US. The hunt for a vaccine suddenly intensified.

This would have happened without Gavi. What Gavi did do in December is guarantee to purchase, at scale, a future WHO-approved Ebola vaccine. The board signed off on plans to spend up to $300 million for up to 12 million courses (which, by napkin math, sets a price of $25 a course). First of all, there’s little chance even Nigeria’s health system, well off by regional standards, would be prepared to pay that kind of price. Gavi is creating stability for a product that doesn’t even exist yet: it is absorbing the risk of pricing and defining the market, which might otherwise cause friction among pharma manufacturers and governments, delaying development and action. When the vaccine comes, it will already have a buyer lined up and the promise of a consistent distributor.

But even while the alliance is poised to vaccinate millions more children, there is still need to shore up poorly managed health systems in poor countries. This may be beyond the scope of Gavi. Expert speakers and dignitaries gathered in Berlin repeatedly mentioned the need to bolster entire systems girding the creaky and failing public health infrastructure in much of the world. Panelists called for improved testing for faster diagnoses and analysis in order to aid more accurate testing and speed the response. “Systems are critically important,” Richard Sezibera, Secretary General of the East Africa Community, said during a panel in Berlin. Shoring up those systems is a global task. While Gavi seems like an institution that can contribute to these efforts, bringing a holistic fix to public health infrastructure might be a lot for it to handle.

Gavi seems more likely to make its mark in creating demand for vaccines where none exists (in market terms, if not human) and by pressing down on prices. But just what constitutes a fair price for vaccines in the poorest nations isn’t at all clear. Drug makers justify high prices in certain cases as necessary to recoup the costs of development. Duncan Moore, a former pharma analyst and now a biotech investor, says big pharma still measures and sets its earnings expectations using numbers inflated by the blockbuster drug era of the ’80s and ’90s. By this logic Gavi may be lowering prices that are set too high in the first place.

Some analysts and experts suggest Gavi could be driving a harder bargain with pharma. Max Lawson, Oxfam’s head of global policy and campaigns, said during Gavi’s last donor conference that the reason it was running low on funds is because it was paying too much for vaccines. Kate Elder, vaccines policy advisor at Médecins Sans Frontières (MSF), argues that profit expectations for pharma companies and their pricing calculations are unclear, making it hard to know if a discount is really a discount. “In order to have an educated discussion you really need more information from the companies on what their bottom line is,” she says.

Yet Oxfam and MSF both say they support Gavi. “Gavi’s set the lowest global price for the vaccines that they are buying. They’ve done a good job—and they can push further,” Elder says.

There are also many countries now poised to leave the Gavi umbrella of nations, having raised their economies above levels where they qualify for Gavi support, but for which western pharma prices are still out of reach. One of Berkley’s pitching points during this funding campaign is that the next five years should be the ‘peak’ of Gavi’s funding. After that 22 countries will graduate out of Gavi assistance. A key promise in the Gavi model is that these countries will take on increasing responsibilities. But as Elder points out, this also creates a dilemma: what happens if graduating countries still can’t afford market rates?

Prices for new vaccines may be high. For old ones they may be low. But for those who can’t pay either it doesn’t make a difference.

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Visions of Vaccines

Each step taken around British sculptor Katharine Dowson’s latest work, a translucent form frozen within eight crystal cubes, seems to change the look and composition of the sculpture’s surface. It’s like the glass is mutable: sometimes it is hard and opaque, sometimes fluid enough to reach through. A Window to the Future of an HIV Vaccine is a puzzle. The eight scored, polished blocks, each about the size of a biscuit tin, reflect, refract, and divide the ghostly shape etched inside: the clover-shaped protein that dots HIV’s surface known as the HIV trimer. “I’m hoping people will look at it and want to know what it’s about,” Dowson says. “And then they’ll read.”

Dowson modeled her sculpture on the precise structural details of the trimer protein obtained by researchers at The Scripps Research Institute. Her sculpture is part of “The Art of Saving a Life” project, commissioned by the Bill & Melinda Gates Foundation and bringing together photography, illustration, paintings, music, and written stories to illustrate how vaccines continue to change the course of history (theartofsavingalife.com). The project started when Christine McNab, a Bangkok-based communications consultant, began working with the foundation to prepare for Gavi’s donor conference, held recently in Berlin, Germany, at which some of the art was exhibited (see Spotlight, this issue).

Dowson has worked for some time now incorporating science and anatomy themes into her artwork, including turning magnetic resonance scans of her brain and heart into printed molds and crystal sculptures. She’s connected to the GV Art Gallery in London, which specializes in science-related art, and sometimes works with another public health charity, the Wellcome Trust. While making A Window Dowson consulted many times with Imperial College of London mucosal infection and immunity professor Robin Shattock and his team of researchers, visiting the lab and going through the complex current scientific literature. With the Scripps trimer as a model, Dowson employed laser etching to cast the image of the protein inside the glass, each cube containing part of the whole. “The laser is light. In a sense the image doesn’t exist. It’s where the light has chipped the glass. It’s like a breath or memory. It’s there, but you can only see it because a third force has made it visible. That is what, for me, science is like: this crystallography that makes the trimer visible,” Dowson says. A Window to the Future of an HIV Vaccine is presented with seven of the cubes stacked together and one missing from the group. “Each block has a bit of the puzzle that all these laboratories and all these scientists are working on,” Dowson says. “And the puzzle hasn’t been solved.”

Chris Elias, chief of the Gates Foundation’s global development program, saw the exhibit in Berlin. “There’s a tremendous diversity of perspective and story,” he says, “and a sense with vaccines that this is one of the most important things we can do to save children’s lives around the world. We’ve made great progress but we’re still missing one out of every five children.”

Not far from where Annie Liebowitz’s group collective portrait of vaccine pioneers hung, children’s book illustrator Sophie Blackall had four watercolor-wash and ink images of village and city scenes in the middle of a bustling day: children playing, laundry fluttering, men hauling carts. In each case health workers are arriving from one side of the image; bad news on the other. “We tell stories,” Blackall says, and recounts going to the Congo jungle, where she came to a village hit by measles. “The chief of the village had a two-year-old daughter. He’d carried her on foot for two days to the nearest clinic. She died in his arms. We arrived to a village in mourning.” Blackall’s work is carefree, fun, and deadly serious, all in one busy sweep of the page. “Art can transcend language,” Blackall says. “I’ve drawn myself out of many a hairy situation.”

German painter Thomas Ganter’s contribution focuses on how a single person can make a difference. Based on an image of a Nepalese health worker, Ganter’s painting The Unknown Health Worker presents a woman with no backdrop, in traditional dress, a cooler of vaccine strapped over her shoulder, and a wryly amused, beguiling expression. She seems to be saying “What, you expected something else?” or “Do you think this medicine would make it out there by itself?” Ganter is expressing respect and admiration. “I wanted to make a kind of monument to all of these health workers.”

For Elias the exhibit reflects many stories, all with a singular purpose. “It will help to get audiences that don’t normally think about vaccines to think about vaccines.” –Michael Dumiak

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Understanding the Importance of Striking a Balance with Vaccination

Why is it important for an AIDS vaccine to induce a balanced immune response?

The development of an AIDS vaccine presents a number of challenges stemming from HIV's structure and behavior. One of those challenges is the clever way the virus attacks its prey. HIV preferentially targets and infects CD4+ T cells, so-called “helper” cells because they help facilitate and orchestrate other immune responses to viral infections—including helping to stimulate the production of antibodies (proteins that act against the virus in multiple ways), and activating another type of T cell known as CD8+ T cells that can kill cells in the body that are already infected by viruses such as HIV. By preferentially invading CD4+ T-helper cells, the virus severely hampers the immune system’s ability to fight back (see VAX April 2008 Primer on Understanding Cellular Immune Responses).

This presents a conundrum for vaccine researchers who are trying to design AIDS vaccine candidates that can induce potent, long-lasting immune responses against HIV. Ideally a vaccine would induce both antibody and T-cell responses without inducing too many CD4+ T cells that could serve as additional targets for the virus and therefore potentially increase the risk of HIV infection. This requires careful selection of vaccine immunogens (non-infectious HIV fragments that are the active ingredients in the vaccine candidate) and the vectors that are used to shuttle these immunogens into human cells, where they are presented to the immune system and hopefully induce an immune response against HIV.

This makes designing a vaccine candidate the immunological equivalent of Goldilocks—finding one that induces immune responses that aren’t too little or too much, but just right.

Lessons learned

The value of inducing a balanced immune response is perhaps best illustrated by the 3,000-person Phase IIb trial known as STEP, which was stopped in 2007 (see VAX Oct.-Nov. 2007 Spotlight article, A STEP Back?). The candidate, MRKAd5, used a non-infectious common cold virus (adenovirus serotype 5, or Ad5) as a vector to deliver three HIV immunogens. Most licensed vaccines work by inducing antibodies but MRKAd5 was designed to induce cellular immune responses. Most vaccinated participants who received the three-shot regimen developed CD4+ and CD8+ T-cell responses against HIV, but they were insufficient to protect against infection.

Subsequent data showed an unexpected trend toward more HIV infections occurring in subsets of vaccinated volunteers—mainly uncircumcised men and/or those who were previously exposed to and therefore had pre-existing immunity to the strain of Ad5 virus that was used as the vector. Two other efficacy trials involving an Ad5 vector were also halted prematurely, although for different reasons, and also showed a trend toward higher rates of HIV infection in vaccinated volunteers compared to those who received an inactive placebo (see VAX May 2013 Global News article).

Researchers still cannot say for certain why these vaccine candidates failed to work. Nor do they have any definitive explanations for the apparent increased infection risk among some vaccinated volunteers in these trials. One hypothesis is that the vaccine candidate may have induced an influx of CD4+ T cells at vulnerable mucosal sites, such as the rectum or vagina, where HIV transmission occurs, thereby providing the virus with more targets and increasing the risk of infection. While this hypothesis remains just that, an unproven theory, it has raised questions about which vectors induce the ideal immune responses and how important a balanced immune response may be.

In contrast, the prime-boost regimen (a canarypox vector-based vaccine candidate and a genetically engineered version of HIV’s gp120 surface protein) tested in the 16,000-volunteer RV144 trial in Thailand induced only modest CD4+ T-cell responses and weak or absent CD8+ T-cell responses, yet reduced HIV infection risk by 31.2% compared to placebo. The cellular immune responses this vaccine combination induced were sufficient enough to provide T cell help, but not sufficient enough to enhance infection rates. The modest protection afforded by this regimen is credited to antibody responses, which were unfortunately fleeting, confirming that immune responses not only have to be balanced, but also persistent.

The risk of imbalance

Two recent animal studies also illustrate why balanced immune responses could be key. A study in rhesus macaques by Emory University researchers showed that five different vector-based HIV vaccine candidates induced a proliferation of CD4+ T cells in rectal tissues—specifically those bearing a protein receptor that acts as a doorway through which HIV and its monkey equivalent, simian immunodeficiency virus (SIV), can enter and infect the cells—appeared to increase the risk of SIV infection in vaccinated animals subsequently exposed to SIV. Researchers hypothesize that the viral vector may trigger inflammation at mucosal sites and therefore result in recruitment of CD4+ T cells in response, which could make the animals more susceptible to infection.

Another study in mice by researchers at the Ragon Institute shows again that inducing only cellular immune responses can be detrimental. In this study a vaccine candidate designed solely to induce T-helper cells against a rodent-borne infection ended up causing uncontrolled inflammation, multiple organ failure, and death. Providing the mice with antibodies or CD8+ T cells to balance out the CD4+ T-cell response prevented the immune-related complications and mortality. As a practical matter, researchers would never design a vaccine that just induces CD4+ T cells, but eliminating these responses is also unrealistic. What’s likely needed is just the right magnitude and quality of immune responses. A Goldilocks-like challenge indeed.