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Vaccinating the World's Poorest

Plus: A conversation with IAVI's new CEO Mark Feinberg

EDITOR'S LETTER

A few days ago I took my daughter for her flu vaccine. She's three, and like most three-year-olds she has a lot of questions about everything. I don't always know the answers. Many of them require a Google search (what sound does a walrus make, is just one that stumped me). But when she asked what a flu vaccine was and why exactly I was going to let someone squirt a spray up her nose, I was only too eager to answer. For her, hearing that a vaccine keeps you from getting sick was enough. In fact she enjoyed the experience so much she asked when she gets to go back for another, providing the perfect opportunity for me to discuss why flu vaccines are needed every year!

For many children around the world vaccines are an unaffordable luxury. But thanks in large part to Gavi, The Vaccine Alliance, that is changing. Over the last 15 years, Gavi has successfully worked in multiple ways to bring life-saving vaccines to the poorest children in the world. They report immunizing 500 million children so far, and will use the hefty donor resources they raised through their replenishment conference earlier this year to vaccinate 300 million more, an effort they estimate could save six million lives. In this issue we look at how Gavi works to negotiate lower prices for vaccines in the poorest nations and how vaccine prices have changed given the introduction of newer and more complex shots (see page 9).

This issue also features an exclusive interview with Mark Feinberg, who stepped into the role of President and Chief Executive Officer of IAVI in early September. Feinberg brings a wealth of experience in vaccine research, development, and deployment to IAVI. His most recent position in his wide-ranging career was Chief Public Health and Science Officer for Merck Vaccines. Feinberg discusses his vision for the organization and how his experiences at Merck introducing new vaccines, as well as his most recent efforts to test a vaccine candidate against Ebola, have shaped his views about the HIV vaccine field (see page 4).

Finally, we round out the issue with some talk about science and policy. We have a commentary piece on the critical role non-human primate studies can and should play in HIV vaccine development (see page 15), a brief outlining several bold steps taken recently by international agencies that are all meant to slow the spread of HIV/AIDS or eliminate it entirely (see page 17), and another brief on a recently held symposium on germinal center dynamics and HIV antibody maturation (see page 18). I'm just waiting for my daughter to ask me about germinal centers— I'll be ready.

– KRISTEN JILL KRESGE

The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. IAVI supports a comprehensive approach to addressing HIV and AIDS that balances the expansion and strengthening of existing HIV-prevention and treatment programs with targeted investments in the design and development of new tools to prevent HIV. IAVI is dedicated to ensuring that a future AIDS vaccine will be available and accessible to all who need it. IAVI relies on the generous donations from governments, private individuals, corporations and foundations to carry out its mission. For more information, see www.iavi.org.

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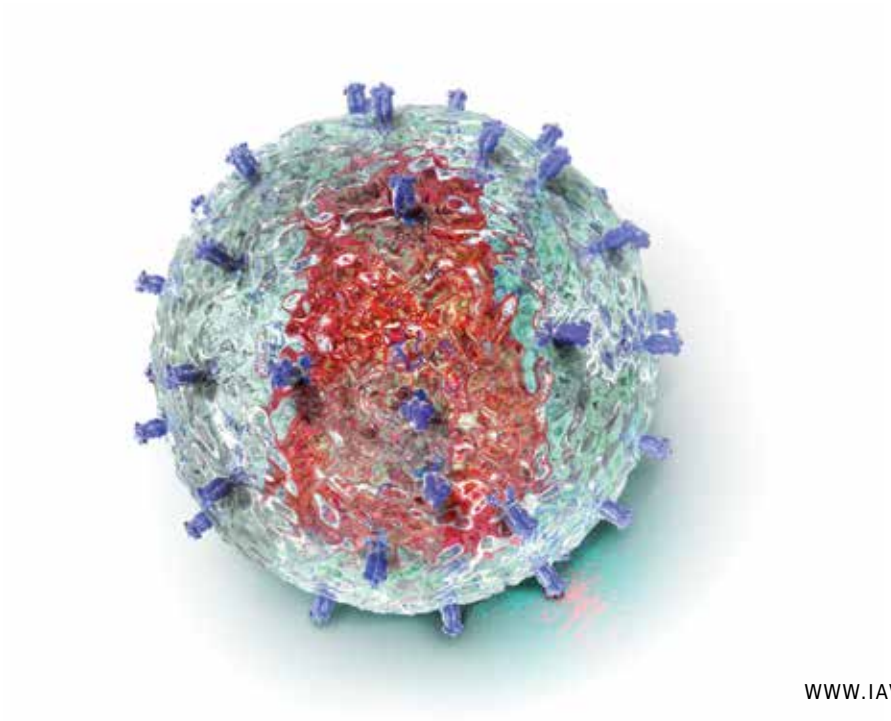

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[ON THE COVER]

Confocal montage image of a B cell follicle during chronic infection (8 wpi) stained for simian immunodeficiency virus vRNA by RNAscope *in situ* hybridization demonstrating the immense accumulation of virions bound to the follicular dendritic cell network.

Image courtesy of Dr. Jake Estes, AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc.

An Interview with MARK FEINBERG

The newly appointed president and chief executive officer of IAVI is no stranger to HIV research, having spent more than 30 years of his varied career battling the virus.

By Kristen Jill Kresge

Mark Feinberg has a broad perspective on vaccine development. He worked in government, serving as a Medical Officer in the Office of AIDS Research at the National Institutes of Health; in academia, as a basic and translational researcher, teacher, clinician, and clinical investigator, including a post as the founder and first Medical Director of the Hope Clinic at the Emory Vaccine Research Center; and for the last 11 years in the pharmaceutical industry, holding various positions at Merck & Co. working on vaccines and infectious disease therapeutics. His most recent position at the company was Chief Public Health and Science Officer for Merck Vaccines.

Beginning September 8, Feinberg added yet another role to his varied career—President and CEO of IAVI. He succeeds Margie McGlynn, another Merck alum who stepped down after four years as IAVI's head, becoming the organization's third leader in its nearly 20-year history. Feinberg says the common goal underlying his career is finding a way to "translate science into public health benefit."

In some ways joining IAVI is like returning home. Feinberg was an MD-PhD student at Stanford University when the first cases of a new and deadly disease that would later become known as AIDS were first reported in New York, Los Angeles, and San Francisco. His thesis research at Stanford with Irv Weissman and Henry Kaplan involved studying the molecular mechanisms of leukemogenesis of human T-lymphotrophic virus (HTLV)—the first human retrovirus to be reported and the only one until HIV was discovered. He then had the opportunity to apply emerging tools of molecular biology to study the role that HIV genes of then unknown function played in the virus life cycle in the laboratory of Robert Gallo, one of the co-discoverers of HIV, at the National Cancer Institute. "I thought that would be an important opportunity," recalls Feinberg. "I finished my thesis research working on HIV and have been involved in one way or another with the disease since then. That's more than 30 years, which is remarkable to reflect on."

Feinberg joined Merck when the company was actively involved in the initiation of the large Phase IIb STEP and Phambili trials, the first HIV efficacy vaccine trials to test a viral-vector based vaccine candidate designed to induce primarily

cellular immune responses against the virus. However, his involvement in vaccine research while there extended far beyond HIV. At Merck he was also involved with the development and licensure of several novel vaccines, including those against human papilloma virus (HPV) and rotavirus. Most recently he led the company's involvement in the public-private partnership to expedite development and testing of a vaccine against Ebola. This candidate, rVSV-ZEBOV, showed great promise in a recent clinical trial in Guinea. Despite these varied experiences, Feinberg says his "scientific heart and mind remained committed to doing something about HIV or at least doing my best to help the overall effort be as successful as it possibly can."

Nelson Michael, director of the US Military HIV Research Program, has known Feinberg since they were classmates at Stanford in 1979. "I was thrilled to learn that Mark was chosen to lead IAVI," says Michael, who reflected on how both of their lives and careers have been shaped by the HIV pandemic. "Mark and I have become dedicated HIV vaccine developers. We are now in the enviable position, as longtime friends and colleagues, to slay this dragon side by side."

As Managing Editor, I caught up with Feinberg three weeks after he joined IAVI to discuss his unique perspectives on HIV vaccine research, his broad experiences, and his vision for the organization.

During your time at Merck you were involved in the development and eventual introduction of several novel vaccines, including those against HPV and rotavirus. What was that experience like?

Being at Merck was really a wonderful opportunity. When I joined there were vaccines in development that addressed diseases of major global health relevance, including rotavirus, which in the absence of a vaccine will kill around 600,000 children each year, the vast majority of them in low-income countries. There was also the vaccine against human papilloma virus, which is in many countries the leading cause of cancer mortality for women. With HPV too, the health impact occurs disproportionately in low-income countries where screening methodologies for cervical cancer and health-care infrastructure aren't as strong. These vaccines were really very promising technical innovations. It was also really imperative to work to try to make them available in places where the disease impact was greatest and where the benefit of the vaccines would be most pronounced.

At the time there was growing interest in accelerating the availability of vaccines in low-income countries, but there wasn't a lot of experience with models or success factors that govern introduction of vaccines. I had the opportunity to lead efforts to help accelerate access to these vaccines in low-income countries in partnership with the governments of those countries. We established a number of partnerships, including one with Nicaragua that led to a national introduction of Merck's rotavirus vaccine RotaTeq in the same year it was licensed in the US and a number of other developed countries. Very quickly after that program was initiated, Nicaragua had the highest rate of rotavirus vaccination of any country in the world, which clearly answered the question about whether you could achieve success in resource-limited settings. Similarly, we established partnerships with the governments of Rwanda and Bhutan early on when Merck's HPV vaccine Gardasil was first licensed, and those proved to be very successful in getting very high vaccination coverage rates in adolescent females.

In addition to having the opportunity to lead the development and implementation of initiatives to accelerate access to new vaccines in Gavi-eligible countries, I was also fortunate to be provided with the support to lead the development of new partnership models to advance research and development efforts focusing on disease targets that represent major public health concerns, but for which no commercial opportunity exists to recoup a return on the investment in product development. While one example of this is Merck's Ebola vaccine development program, another was our tremendous partnership with the Wellcome Trust to establish the MSD-Wellcome Trust Hilleman Laboratories—a research and development effort, based in New Delhi, that is specifically focused on developing new and improved vaccines to address diseases that disproportionately affect people living in poverty. All of these examples have reinforced my belief that strategic partnerships between organizations that share a common commitment to public health impact can accomplish remarkable things.

For us, the best way of addressing these questions wasn't just to speculate about possible programs, but to put concepts to the test and study what the success factors were. Those experiences were really very positive and influential in my thinking.

Were there any shared lessons for HIV that emerged from the experiences with those vaccines?

One important lesson is that understanding the circumstances under which a vaccine would be utilized is critically important, as is doing your best to tailor the product profile of the vaccine to enable it to be successfully implemented in resource-limited settings. Those are issues that need to be considered very early on in the development of a vaccine candidate. They are not something that can be easily retrofitted in the end. You have to think about how you would actually get the vaccine delivered and administered to the person who is going to hopefully benefit from it—that is fundamentally important. This includes all kinds of issues around the product profile, the scale of manufacturing, and the cost of goods. All of those are elements that need to be considered in the course of the development process.

In addition it's very clear that success in public health only comes through creative partnerships of stakeholders who share a common commitment. When that exists, great things can happen, and if it doesn't, then success is much harder to realize.

During your tenure at Merck the company was involved in the STEP and Phambili trials, the first to test the concept of a T-cell based vaccine candidate. How would you characterize the results of those trials and how they affected the course of vaccine research?

Merck's HIV vaccine program was very influential in my decision to go to work there because I had been involved in the early Phase I clinical trials of a number of the vaccine candidates that Merck was exploring and got to see just how committed the scientists and the company were to advancing that program.

At the time an important research goal was to test the hypothesis about the potential benefits of cell-mediated immunity against HIV as a way of, if not preventing HIV infection, at least enabling an infected person to better control the infection and be less likely to transmit the virus to others, which could help control the spread of the virus in the population.

The STEP and Phambili trials were, at the time, the leading edge of efforts to test this major hypothesis about how you might make an effective HIV vaccine, so when the results came in not only demonstrating a lack of efficacy but also suggesting potential for increased risk of infection, that was deeply disappointing for many people. It was profoundly disappointing for all of us at Merck who worked on the vaccine, as well as the multitude of wonderful partners and volunteers that we worked with to make that trial happen. This also had an impact on the field more broadly with respect to rethinking strategies. While the specific approach tested proved unsuccessful, the overall effort was very informative and valuable. I think it is a reminder for all of us to be as critical of our own ideas as we possibly can be while we seek to do the best science and try to advance scientifically meritorious candidates into well-designed studies that really critically test their potential to deliver the results they're designed to deliver.

The vaccine field was also influenced by the results of the RV144 trial in Thailand—the first to show any protection against HIV infection. This trial was, and maybe still is somewhat controversial among researchers. What are your thoughts on the outcome of RV144 and the cadre of follow-up studies that are now ongoing or planned?

I was one of the people who was skeptical of the RV144 study and was an author of an opinion piece in *Science* with many other partners in the HIV vaccine field who expressed concern about that trial. But since then, some very interesting scientific insights and leads have emerged. In particular, the RV144 study provided important clues about what might be a beneficial mechanism of antibody-mediated protection that was previously unappreciated. While additional studies to replicate and extend the RV144 study results are needed, the study investigators have provided the field with important data to frame testable hypotheses. In this regard, the RV144 results will be truly valuable if they can inform new approaches to induce the targeted immune response in the majority of vaccinated individuals, and if this response proves to engender protection from HIV infection in the follow-on study now being pursued.

The follow-up studies probing potential mechanisms of protection underlying the RV144 results have been very informative and the challenge now for the field overall is to use the insights from these studies to inform future vaccine efforts. This is on one hand a scientific issue but also an issue of how the field organizes itself effectively to test those hypotheses in a rigorous, strategic, and expeditious manner.

Most recently you led Merck's collaboration to expedite development of an Ebola vaccine candidate. Were there any lessons from that experience that are relevant to HIV?

For me, there were a number of very important lessons from the Ebola vaccine development experience. It was an unprecedented effort, not only in terms of the speed with which the candidate advanced through various stages of clinical trials—progressing from the first-in-human studies to evidence of vaccine efficacy in only 10 months—but also with respect to the number of independent studies done by different partners as part of the development program. It was really impressive to see so many private and public sector partners stepping up to address this pressing public health need and finding ways to align complementary expertise to get the job done in an accelerated way. That was not only what happened with the Merck program but also with other collaborations advancing alternative vaccine candidates. The clinical investigators in the various countries and their partners did a remarkable job launching complicated and high quality clinical trials in a very short period of time.

I saw very clearly just how sincere the interest of private sector partners, including large pharmaceutical companies as well as smaller biotechs, is in addressing important public health needs. It's very clear that success will only be realized when different stakeholders understand both the potential contributions and constraints that each of the partners face in order to maximize each organization's ability to contribute. We now need to find ways to foster even more effective multisector partnerships to address established public health threats like HIV and to proactively prepare for other infectious disease threats that will emerge in the future. I believe that we can do this, and that we must take the opportunity and responsibility to do so very seriously.

My own view, based on my experience over the past 11 years at Merck, is that the private sector is interested in addressing other global health challenges, including HIV, but there needs to be new models of collaboration developed so that they can partner with public sector entities in creative, more effective ways to maximize progress. I think there's tremendous opportunity here. With the Ebola crisis you saw how very different organizations from different sectors could find a way to work together when they had a shared commitment, and in that regard, it is the same as the challenge we face with HIV.

Unfortunately, public attention focused on HIV has waned because the pandemic has been around for so long—almost 35 years. Yet more people die each week from AIDS than have died of Ebola in the 2014 outbreak overall. The urgency to enable all HIV-infected people to get effective therapy and to develop effective approaches to protect at-risk individuals so that they don't become infected remain major imperatives.

After such a broad and varied experience at Merck, why return to HIV, and join IAVI in particular?

While I have worked on a number of diseases and that has been tremendously exciting from a scientific, public health, and personal perspective, my scientific heart and mind remained committed to doing something about HIV, or at least doing my best to help the overall effort be as successful as it possibly can. That was what I focused on through my career in academia and as a physician. That's why I went to work in the Office of AIDS Research. And that's why I went to Merck in the first place. Contributing to HIV control and hopefully elimination is really what I've always wanted to focus my career on.

My interest in coming to IAVI really grew out of what I have seen working in academia, government, and industry, and that is that I believe there are major opportunities for more effective collaborations between sectors than many people can imagine if they only work in one sector. There is all too often a misunderstanding between the different sectors and I think people don't fully appreciate the good intentions or the real constraints that exist in each sector. I believe that is a solvable issue, but one that will require innovative approaches to partnership and collaboration. IAVI worked hard under Margie McGlynn's leadership to become an ever more effective partner and I think there are opportunities to take that to an even more significant level if we understand how we can play the most effective, collaborative, enabling role for the field overall. That to me is a really exciting opportunity. I think there are opportunities to fill gaps, imagine new models of collaboration, and work in close partnership with others to set some powerful precedents in the HIV vaccine field.

My impression, having now been at IAVI for three weeks, is that everything I hoped would be true about the promise of IAVI to be that positive, collaborative presence in the field is true. The people who work here are incredibly dedicated to the goal of HIV vaccine development. They are

people who want to be the most effective partners and collaborators that they can be and I feel fortunate to have them as colleagues.

I also feel fortunate to be able to work with really great partners at USAID [United States Agency for International Development], the Bill & Melinda Gates Foundation, the National Institutes of Health, in academic and government laboratories, and a number of other partners including private sector entities and governments. All of these organizations share a common commitment and collectively we have the opportunity to figure out how we can best advance progress across the HIV vaccine field.

So what then is your vision for IAVI and how it can contribute to the goal of developing a preventive HIV vaccine?

Well, in many ways HIV vaccine development does share some of the fundamental aspects of the challenges of Ebola vaccine development. It requires looking for opportunities for different partners to work together in the most collaborative fashion and to have a strategic approach that enables the best science to be done efficiently and then expeditiously translated into informative clinical studies, wherein the most promising candidates can be advanced into efficacy studies in creative ways to get answers as quickly as possible.

When you have a disease like HIV or Ebola, for which either the commercial incentive doesn't exist or the scientific complexity or risk is too great, it's really going to depend upon models of collaboration between public and private stakeholders to achieve success. And that means we need to find ways of collaborating effectively and linking different sectors with each other in the most effective ways. And if there are opportunities for organizations like IAVI or others to help facilitate those collaborations, that would be a really important contribution. In addition, we also hope to make valuable contributions to advance and enable basic, translational, and clinical HIV vaccine research—ideally in collaboration with others and in ways that establish platforms for broader research benefit—and to strengthen research capacity in countries heavily impacted by AIDS in innovative and sustainable ways.

Likewise, a lot of great science is taking place in academic and government laboratories, but the people doing the science don't necessarily have experience in product development so they don't always have the vision of the end-to-end framework within which successful vaccine programs are developed in private sector entities. Similarly, they don't often have expertise in bioprocess, scale-up manufacturing, or regulatory issues. That is an area where IAVI has begun to play an important role—enabling the work of others to be translated from concept to hopefully proof of concept. I think that is an important contribution and an area where we can do even more. We can work to achieve the vision of being the facilitators of progress for different partners in the field and can hopefully help connect the dots between different stages of the vaccine development process.

What do you see as the greatest obstacles in HIV vaccine development?

There are many major scientific challenges. The virus establishes persistent lifelong infection that the immune system is unable to clear. No individual is known to have spontaneously eliminated the infection, which makes it fundamentally different from any infection we can now prevent with vaccination. There are remarkably informative studies that describe why HIV is such a difficult virus to contain immunologically in an infected individual, and prevent by vaccination in an uninfected individual. But we need far better understanding of what a truly protective immune response might be and an absolute need to understand how to elicit it in a robust and durable manner in vaccinated individuals.

That being said, there are very promising leads and very interesting ideas emerging from basic research studies. Success will only happen if we take those findings to the next step and ask if we can induce the kinds of immune responses that are hypothesized to be important—whether that is a type of antibody specificity or function, a type of cellular immune response, or some combination of immune protective mechanisms—by vaccination.

However difficult the scientific challenges are, and they are difficult, we also need a way of advancing products through the development continuum in an expeditious, strategic, thoughtful, and informative manner. That is really something that is within our control as a community of researchers working to develop an effective HIV vaccine. We each have to ask ourselves how we can best contribute to the most successful overall scientific HIV vaccine research effort. That is the question IAVI will be addressing when we look to the future: How can IAVI as an organization be the best contributor, facilitator, enabler, and expeditor of progress toward the essential goal of developing an effective HIV vaccine? ■

VACCINATING *the World's Poorest*

In the 15 years since its founding, Gavi, The Vaccine Alliance, has emerged as an important bridge between the companies that make and manufacture vaccines and millions of people in developing nations who have very little capacity to pay for them.

By Michael Dumiak

Last January Seth Berkley found himself once again mixing with the elite at the World Economic Forum in the Swiss resort of Davos. The energetic, most would say tireless, New Yorker is the chief executive of Gavi, the Vaccine Alliance and the former head and founder of the International AIDS Vaccine Initiative (IAVI). In Davos, Berkley was anxiously lining up the last missing pieces for Gavi's "replenishment" donor conference, due to be held a few days later in Berlin. The organization was trying to raise US$7.5 billion to support its activities for the next five years, with a goal of helping countries immunize 300 million children. This effort, they estimate, could save six million lives. Over the course of their now 15-year history, the Alliance reports immunizing 500 million children.

Worldwide, 73 countries with an annual per-capita income equal to or below $1,580 are eligible for Gavi support. The organization pairs its hefty donor resources with pent-up and guaranteed demand, making a marketplace for vaccines in the world's poorest places and creating an incentive for pharmaceutical executives to sit down and negotiate lower prices for this market. Gavi is successful at raising large sums of public and private money and acting as a buyer for 'Gavi-eligible' developing nations, accelerating introduction of new vaccines in the poorest countries. Gavi also requires participating countries to share in financing vaccine purchases, taking on part of the cost of new or underused vaccines. The Alliance further aims to strengthen the capacity of health and delivery systems within Gavi-eligible countries and to forge partnerships that can assist in the logistics of developing systems to deliver vaccines effectively, even in very difficult-to-reach places.

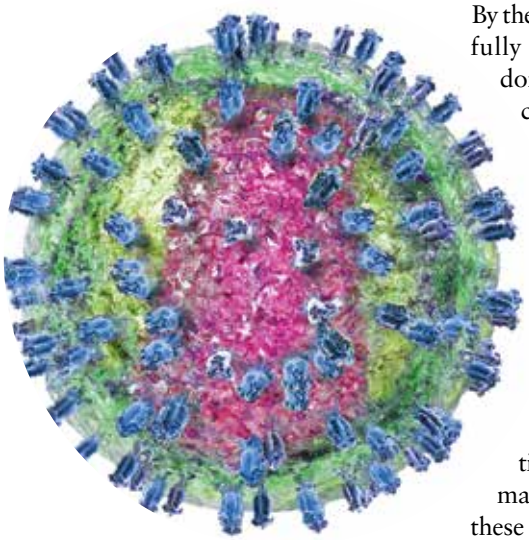
Despite its successes, Gavi still has its critics, and there are plenty of obstacles to vaccinating poor children that any organization would have difficulty overcoming. There are still many middle-income nations where—because of a lack of resources, conflicts, or the failure of governments to place a higher priority on health care—vaccines are still beyond the reach of large numbers of people. But the interplay between Gavi and its partners is worth close study as similar strategies may be used to get an eventual HIV vaccine, or those against other pathogens such as Ebola or dengue, to the vast number of people who will need them.

Beyond Davos

At 11am on Monday, January 26, the day of Gavi's replenishment conference in Berlin, the organization was still $250 million short of its $7.5 billion goal. Currency shifts were taking a toll. The euro had hit an 11-year low against the dollar. Donors were swinging in and out: Berkley was surprised by Japan, whose government decided not to pledge at all for the 2016-2020 period. But he still held some cards. "At the end we had some amazing people stepping up," Berkley says. Bill Gates took the stage that morning in Berlin and said he'd add an extra $50 million to the $1.5 billion he was already giving to Gavi.

Both Gates and Davos are instrumental to Gavi: Gates, as the Bill & Melinda Gates Founda-

tion was Gavi's first backer; Davos, because the premise of Gavi is to bend market forces and create new dynamics in vaccine economics. The World Economic Forum prides itself on its patina of movers and shakers trying out new ideas and this is where the idea for Gavi emerged. In March 1998 The World Bank convened public health, financial, and pharmaceutical industry leaders out of concern that children in poor nations were not gaining access to increasing numbers of new vaccines that were available to children in wealthy countries. The World Bank call led to Gates-hosted dinners in Seattle and another conclave in Bellagio, Italy, where the idea for Gavi first took shape. The Gates Foundation decided to back Gavi with an initial pledge of $750 million at Davos in January 2000.



By the time Berkley left Berlin, Gavi successfully raised its target $7.5 billion from donors. As a result, the Alliance will carry a certain amount of clout when it comes to negotiating vaccine prices and implementing its strategic plan over the next five years. Gavi-eligible countries may be poor, but they represent a very large number of people in parts of the world that do not currently use many pharmaceutical products. "Today, nobody thinks about launching a new vaccine without at least asking the question of what they will do about the Gavi markets," Berkley says. "If you can get these vaccines introduced there, eventually you are building new marketplaces. You are also going to have the biggest effect on disease because there is less likelihood of really good treatment strategies in these countries."

Michael Haydock, a vaccine analyst at the London firm Datamonitor, points out that Gavi invests in training health workers and educating communities about the benefits of vaccination. "This takes a lot of the onus away from big pharma. If they wanted to access these countries by themselves they would have to invest significant resources for minimal financial return," he says. "Partnering with Gavi also provides the opportunity to gain higher market share within developing markets, because Gavi-procured vaccines are then more likely to be used as routine vaccines of choice."

The resulting steady and predictable revenue stream is a boon for manufacturers. Gavi is not the only institution pooling demand to negotiate lower prices: the Pan American Health Organization, a public health agency which serves as regional office for the Americas of the World Health Organization (WHO), has used its revolving fund for 35 years in order to pool resources and procure vaccines at bulk prices for its member states. The United Nations Children's Fund (UNICEF) also has its 25-year-old Vaccine Independence Initiative, a relatively small kind of revolving credit line for Pacific island vaccine buyers, which brings them the added benefit of bundling demand for orders and using UNICEF procurement expertise and resources.

But it is Gavi that is now, by volume if not by margin, vaccine giant GlaxoSmithKline's (GSK) largest single customer. Both Pfizer and GSK made concessions in advance of the Gavi donor conference in Berlin. In the current vaccine market, Gavi does not really act as a price-setter, bargaining back and forth, walking away if the deals don't work. What it does is use its leverage to set a floor price and ensure supply of vaccines to remote and poor places.

Gavi's Aurelia Nguyen refers to this as 'market shaping.' In fact, Nguyen's job title is Director, Policy and Market Shaping. The idea is to introduce some countervailing forces into the vaccine marketplace to 'shape' it in a way that gets this valuable product to the largest amount of people possible, most of whom can't afford it. The way it works is this: Alliance representatives meet with officials from UNICEF, Gavi's procurement contracting agent, and set out a pricing strategy. Nguyen says this includes analysis and review of demand for the vaccine, setting target prices, and discussions on terms and length of contracting. UNICEF officials then write a tender requesting suppliers bid for volumes of vaccine (see UNICEF tenders by volume, here: http://uni.cf/1AwSPoy and prices for vaccines, here: http://uni.cf/1AwSWR4). Berkley describes the Alliance's role here as trying to create a 'monopsony,' a kind of market where there is only one buyer. Suppliers respond to the tender. The manufacturers are then awarded contracts for the volumes at hand.

Nguyen, who used to work for GSK, says Gavi is pursuing three conflicting aims. The first is to find a balance of supply and demand. Second is ensuring appropriate prices for vaccines in the world's poorest nations. Third is to get appropriate and innovative vaccines to the Gavi countries. "There's a fundamental tension we deal with," she says. "If you want to aim for the lowest cost, you may just want to buy from the cheapest manufacturer." But that could jeopardize a secure supply. A vaccine program with interruptions is no program at all. So, Ngyuen says, she may need

to settle for a higher price to find the lowest—but most sustainable—price at which Gavi can buy.

Gavi is described as a market innovator and a model that can spur the development of new vaccines, expand production of existing ones, and influence the market. As the Ebola epidemic raged last summer, for instance, Gavi was able to tell suppliers it would guarantee purchase to the tune of $300 million for a vaccine that doesn't yet exist.

The model Gavi uses to do this is rooted in market economics. But when it comes to vaccines, and for pharmaceuticals as a whole, the rules of how markets function get a little twisted. Basic market economics starts with supply and demand: higher supply, lower cost, and higher demand, higher cost. For vaccines it's different and more complex for a number of reasons.

"Supply and demand work only in the most approximate fashion in vaccine markets," says health economist Joel Hay of the University of California, Los Angeles, Center for Vaccine Research. "Vaccines are not a good like a mobile phone: it is really a product that is dependent on different psychological and social factors," says Sibilia Quilici, deputy director of health policy at Sanofi Pasteur MSD. One of these factors is what Quilici calls 'intertemporality:' the consumer gets something now, pays for it now, but the benefit is in the future and is hopefully something that never happens at all, i.e. getting sick. It is also more complicated on the demand side. "Vaccines are a health product. If you think about antibiotics, if you think about clean water, vaccines are among the products saving the most number of lives in the world. It is essential that access to vaccines is given to every person and every child in the world," Quilici says. "Knowing that, developing countries cannot afford a product at the same price that Europe or Australia or the United States can. The price has to vary, depending on the country, and has to be adapted to the capacity and the ability of the country to pay for it."

But how prices are determined for vaccines can be a bit of mystery, according to Amanda Honeycutt, a healthcare analyst at North Carolina-based think tank RTI International. "We don't have really good answers to how vaccine prices are determined. It's not really determined in the marketplace in the same way as other goods."

Quilici argues vaccines are unique. "It is more complex to set a price for a vaccine for many reasons. Vaccines are complex products. You can't find a generic to compete with it. It is really difficult to produce: they are live products, most of them, even if they are attenuated. A vaccine takes between six and 22 months to produce; 70 percent of that time in production is related to quality and safety. It's long, and complex, and within the production chain there are many uncertainties," she elaborates.

All of these factors make the process of negotiating vaccine prices for the poor—for Gavi, or any other organization that would emulate it—rather complicated. This is especially true now that the types of vaccines in development have changed so radically.

Increasing complexity, increasing cost

For decades there were a set of shots administered to babies to protect against what were the leading diseases of the day. These included vaccines against tetanus, measles, rubella, and others. Laboratory-produced vaccines have a 135-year history and even older roots, with most of these basic vaccines being introduced in the postwar years of the 20th century. The medical College of Physicians of Philadelphia, which operates the History of Vaccines website and its handy timeline (http://www.historyofvaccines.org/content/timelines/all) dates the contemporary "vaccine era" to the late 1950s when the combined diphtheria, tetanus, and pertussis vaccine took hold after introduction in 1948. These vaccines were highly effective and comparatively cheap.

> Developing countries cannot afford a product at the same price that Europe or Australia or the United States can. The price has to vary…
>
> *— Sibilia Quilici*

As the pharma industry entered a blockbuster-era in the 1980s and 1990s, vaccines languished and were considered unprofitable. It was not so long ago that academics wondered if pharma would give up vaccine production altogether. It's a little different now: the global vaccine business, Quilici says, is a $23 billion industry. Compared with global pharma's $300 billion a year, though, it's niche.

A big change, GSK's Thomas Breuer says, came nearly 15 years ago with the introduction of Prevnar 7. Breuer is a former physician and epidemiologist who has worked with the Robert Koch Institute, Germany's frontline public health body, and is now GSK's chief medical officer for its vaccine operation and a member of the company's management board.

Prevnar 7 protects against *Streptococcus pneumoniae,* which causes the bacterial form of meningitis and several other diseases from pneumonia to bronchitis. The '7' in its name refers to the seven serotypes of pneumococcal bacteria against which this multivalent vaccine is effective. While a multivalent vaccine against pneumococcus had been on the market since 1977, it wasn't terribly effective and did not protect infants under two from invasive pneumococcal disease. With Prevnar, researchers took advantage of a new wave of boosters and adjuvants to increase the vaccine's potency. Prevnar is a conjugate vaccine—the vaccine antigens are attached to an engineered carrier protein, in this case a diphtheria protein, which is intended to increase the immunogenicity of the vaccine. The first conjugate vaccine was introduced against *H. influenzae* type b in 1987. Prevnar took advantage of further developments of conjugate technology to boost antibody response to the vaccine, increasing its effective duration and overall potency.

Breuer says that Prevnar 7 changed more than the way vaccines were developed and manufactured. Pfizer, which acquired the vaccine when it bought the developer, Wyeth, introduced a new way to price vaccines with Prevnar 7. This new vaccine was priced comparably to other products in the pharma portfolio, even to high-margin items like the cholesterol-lowering drugs known as statins. "They did real health economic modeling and cost-effective analysis to bring home the value of their vaccine," Breuer says. "This was largely adopted by companies, including GSK." This made Prevnar 7 able to hit the market at about $58 a shot.

There are now several multivalent vaccines on the market: more and better pneumococcal conjugate vaccines (PCV) that protect against 13 strains of the bacterium (Prevnar 13), for instance. Other specialized new vaccines also made their mark in the last decade, such as those against human papilloma virus (with two vaccines on the market: Gardasil from Merck and Cervarix from GSK) or rotavirus, (with two vaccines on the market: Rotarix, from GSK and RotaTeq, from Merck). Many of these newer vaccines are now part of the basic immunization package recommended by national health agencies in many countries.

Quilici says vaccines are an exciting field. "You have preventive vaccines, you have more and more therapeutic vaccines, and they're working more and more on how they are administered," she says. "Today we have a needle, but maybe in two years we have a patch, or an orally administered dose that is safer, less painful, with fewer side effects. We have vaccines against infectious diseases but hopefully we'll have a vaccine against HIV and against cancers."

But as vaccines that have more complex development and production processes, and therefore higher price tags, join the slew of other routinely administered shots, the total vaccination costs are increasing exponentially. The US health care system has its own troubles with vaccine pricing, as outlined by Elisabeth Rosenthal in *The New York Times*. Rising vaccine prices, as Rosenthal explains, are putting increasing pressure on doctors, patients, and public health budgets. Now, consider the poorest countries in the world. "Vaccines are a great buy," says Robert Steinglass, Immunization Team Leader for the United States Agency of International Development's Maternal and Child Health Integrated Program. "But the perception of their relative expense obviously depends on the context of the local economy into which they are introduced."

In the last decade the price for the basic set of immunizations, according to figures from Médecins Sans Frontières (MSF), ballooned in Gavi-eligible countries by 2,700 percent to $38 in 2011 for a package against 11 diseases, up from $1.37 in 2001 for a package against six diseases—tuberculosis, polio, measles, diphtheria, tetanus, and pertussis. But the most recently developed in the original package of six vaccines was the combined diphtheria, tetanus, and pertussis shot approved in 1948. The newest vaccines for pneumococcal infections and rotavirus account for 70 percent of the overall cost, MSF says.

"There is no such thing as an expensive vaccine unless you specify the parameters against which expensive or cheap would be defined. Vaccines must give value for money judged against criteria of cost effectiveness," says David Salisbury, former director of immunization for the UK

Health Department and an analyst for the think tank Chatham House. "If they are cost effective, then the price is almost irrelevant—the health and wider economic benefits outweigh the costs."

Philip Jacobs, an economist in the University of Alberta's department of medicine and author of "Economic Evaluations in Vaccine Policy Decisions," argues that vaccines are less cost effective today and says the initial price for vaccines introduced to cover new pathogens and illnesses will continue to increase, often drastically. "Vaccine manufacturers and public health people used to call vaccines the best bargain available in health care. I don't think you would hear that argument today. The market has been growing, but the vaccines are less cost effective."

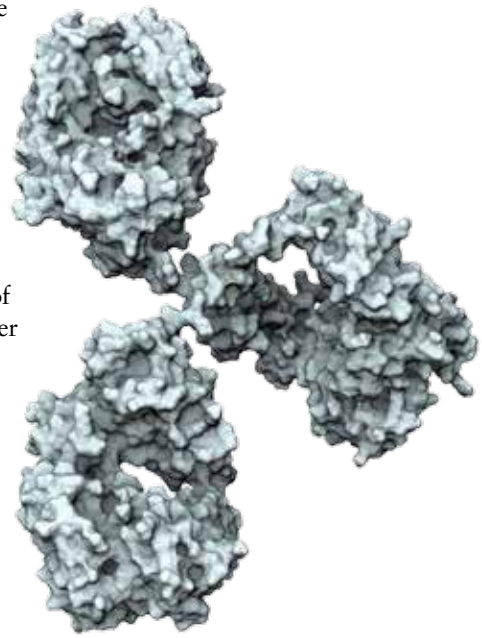
But Quilici says any pharma product on the market has to prove that it is at least in some way cost effective. "It is a new era for vaccines. They are not working in the same way as the ones developed in the 20th century," she says. "They are more expensive because of that. There is always a balance with the cost of the disease itself. Prices may be expected to increase but they will stay in balance with the cost of the disease that you want to prevent. For our system, it is always like that: how much are we willing to pay to avoid having to pay for damage in terms of disease."

Researchers working to develop even newer vaccines, like those against HIV and multi-drug-resistant TB, could potentially face even higher development and production hurdles. Oxford postdoc Gareth Betts at the Nuffield Department of Surgical Sciences, who has published research on the potential for using multiple viral vectors in new tuberculosis vaccines, says pursuing such a multi-vector strategy could produce more robust and powerful shots, reducing the need for multiple injections, but would also drastically increase manufacturing costs and therefore also price (see *Making it to Manufacturing*, *IAVI Report*, Vol. 18, No. 2, 2014).

Gavi strikes a balance

What Gavi seeks to do is to bridge the gap between the supply and demand for newer, more complex vaccines. On the supply side, there's a highly researched, engineered, complex, and effective product that can save a human life; a limited supply source; high research, development, and production costs; and private-sector pressures. On the demand side, there are 45 million babies born every year in poor countries who could benefit from new life-saving vaccines, but who have no ability to afford the product. The Alliance does this in part by negotiating lower prices for vaccines in poor countries, but also by encouraging even very poor governments to co-finance vaccine purchases.

Gavi started with high expectations. The organization originally expected that in just a few years it could speed vaccine price decline through its use of volume purchases to levels that eligible countries could afford to purchase them on their own, says Helen Saxenian at the Results for Development Institute in *An analysis of how the GAVI Alliance and low- and middle-income nations can share costs of new vaccines*, written with Gavi colleagues for *Health Affairs*. But price drops didn't happen as quickly as expected. "Some of the newer-generation vaccines in particular, such as pneumococcal conjugate vaccine, might not reach the price points of the older vaccines, such as yellow fever vaccine, precisely because of their complex technology—which is something that the GAVI Alliance did not fully appreciate at its start. Some of the newer vaccines are also more expensive because of limited competition among a small number of manufacturers," the team writes. Co-financing, at least theoretically, the team writes, is an accepted part of Gavi eligibility because it helps build country ownership of the vaccine effort and raise awareness of the value of vaccines and of investing in health care at large. Over the years, Gavi has refined its calculus for what eligible countries can pay in order to distinguish among the poorest of the poor, for example the Democratic Republic of the Congo or Liberia, and more prosperous nations like Cuba, Azerbaijan, and Armenia.



Gavi's logistical efforts and moves to help shore up domestic health care systems also help keep the markets open that it strives so diligently to create. Bill Gates, in Berlin for Gavi's conference, seemed most gleeful when talking about a new vaccine delivery mechanism—a kind of high tech thermos that could keep vaccines cold. He even imagined the thermos being used to deliver vaccines to remote parts of the world on the backs of camels.

But the reason Gavi is so prominent is because of its negotiations with manufacturers. "Obviously, Gavi would not exist if the price of vaccines were not a problem for poor countries," says Stanley Plotkin, an executive advisor to Sanofi Pasteur and a physician who played a role in discovering

the vaccine against rubella. By pooling funding and quantifying and organizing the demand for a vaccine, Gavi creates a market for vaccines in poor countries. The market is negotiated among manufacturers, payers, and government agencies in order settle on a lower price for vaccines in poor countries than what is charged in wealthy countries, but a higher price than can be afforded by the poorest countries themselves. This is an example of what the global pharma industry calls tiered pricing. Gavi didn't invent tiered pricing, but it has used it incredibly effectively.

> The price difference can be more than 10 times, but it's the same vaccine. We don't have different vaccines for different parts of the world.
>
> *— Thomas Breuer*

"Before Gavi the offer for vaccines was at such a low price that manufacturers, and there are not that many manufacturers, decided to leave the market," says Quilici. "Vaccines were at such a low price that the industry could not really afford to produce them anymore. That's when Gavi came, considered pricing, and the way to work between manufacturers and publicly discuss pricing. The system is now in such a way that there is a balance."

But tiered pricing has its critics. MSF argues that the original prices for vaccines are inflated and therefore the reduced prices for poor countries are still too high. Kate Elder, MSF's access campaign's vaccines policy advisor, is troubled by the lack of cost transparency. GSK and Pfizer both announced price cuts to their pneumococcal vaccines earlier this year, Elder acknowledges. "But these are all very nebulous definitions and descriptors. Everybody is having this discussion completely in the dark." She argues that tiered pricing strategies, even adjusted for rates in the developing world, are cover for industry charging as much as it can get away with.

But as Breuer outlines, vaccine pricing is a function of a few set factors: the cost of research, clinical development, infrastructure investment, and manufacturing. Companies must also have some ability to bear large-scale failure when a drug or vaccine in development doesn't work. Producing Synflorix, GSK's pneumococcal vaccine, takes 18 months' production time, Breuer says. Several hundred quality tests have to be performed before a batch can be released on the market. The hurdles faced by vaccine developers today are much greater than those in the mid-20th century. The process of passing these new vaccines through clinical trials with much higher safety standards also add to the overall difficulty of developing a new product. There are also basic business concerns. "We are a publicly traded company, so we have to pay back shareholders who have given us money. They want to see a certain return."

So, Breuer says, GSK considers tiered pricing as the only way forward. The concept is that each market is different, so prices are set differently (which also makes it more difficult to see a real "going rate" for a vaccine). Higher prices paid in wealthier markets subsidize the company's development costs and afford it the ability to charge lower prices in places where people can't afford the full cost. "The price difference can be more than 10 times, but it's the same vaccine. We don't have different vaccines for different parts of the world," Breuer says. "It's part of our business model to make vaccines available to whoever needs it. But this only works with this tiered-pricing approach."

MSF's Elder recognizes how effective Gavi is at negotiating lower prices for vaccines. "You can't contest that Gavi has brought prices down significantly. This is exciting. It has set the global floor for those prices." But for her that isn't enough. "I think it's therefore Gavi's responsibility now to make sure those prices continue to come down," Elder says. "And, now that they've introduced those vaccines, also to make sure prices are sustainable and affordable for the countries when they lose Gavi support."

This happens when countries exceed $1,580 in annual per-capita income. Twenty-four countries are due to graduate from Gavi support this year alone. Three years ago UNICEF tried to launch a 'middle-income' procurement project for countries like these. Its initial tender for HPV, PCV, and rotavirus vaccine went out in December 2012. Whether it will be successful long-term remains to be seen: according to UNICEF, only $12.5 million was awarded for procurement of PCV, rotavirus, and HPV vaccines in the tender so far.

This 'middle-income' issue will cause further complications in the near future, analysts say. Right now, there's no such player like Gavi to support immunizations in these graduated countries. "This is a concern for health care across the board. A lot

Continued on page 19

(How) Can NHP *MODELS ACCELERATE* Vaccine Development?

It is a question of "how" not "if" non-human primate studies should be used to elucidate mechanisms of protection against HIV.

By Alan Schultz

The world needs and wants an AIDS vaccine, and definitive HIV vaccine efficacy can only come from human trials. There is no argument about that. But there are different opinions on the best path to reach the goal.

Some believe that advancing more candidate vaccines into clinical trials will accelerate the process of finding one that is efficacious. But the results of the five efficacy trials mounted since the discovery of HIV in 1984 underscore the difficulty of the problem. Three trials showed no evidence of efficacy, and another suggested the vaccine candidate possibly enhanced risk of HIV infection. Only one trial, RV144, provided a modest 31 percent efficacy.

It is important to recognize just how difficult a pathogen HIV is and how steep the hill is that researchers must climb to reach the goal of developing an AIDS vaccine. By comparison, consider the situation with Ebola. In response to the recent outbreak, there was an immediate call for development of a vaccine to protect against the deadly virus. As researchers set about this goal they could take comfort from the fact that up to 50 percent of Ebola-infected individuals recover from this terrible infection on their own. This is because 20 million evolutionary years of T- and B-cell immunity gave the human immune system the tools to contain and eliminate this new virus, as well as many others. The immune responses mounted against the Ebola virus in 50 percent of cases happened spontaneously and fast enough to effectively eliminate the pathogen. This means that *further* accelerating that type of an immune response through prior vaccination should be effective at reducing death and morbidity and, in fact, some Ebola vaccine candidates already look very promising in clinical trials.

This is very different from the situation with HIV. Although the progression to death is much slower with AIDS (10 years on average, compared to three weeks for Ebola), there are essentially *no* survivors of AIDS; there is not a single documented case of an HIV-infected individual clearing the infection on their own†. The timetable may be slow, but without drug treatment, the uniform outcome of AIDS is death. Not only does this depressing fact deprive us of learning what the immune system could "do" to block HIV, it also implies that the human immune system is essentially ill-prepared to "handle" HIV. Though vigorous T- and B-cell responses ensue after infection, HIV easily mutates and stays ahead of them all. A successful HIV vaccine likely will need to direct human immune responses down a path different from the one they normally take.

That the number of HIV efficacy trials is meager is a simple consequence of this lack of survivors. What do we need the vaccine to "do"? What are the response(s) that are worth accelerating to combat HIV? We don't know. Without that knowledge, immunogenicity measurements in Phase I clinical trials tell us little about whether vaccine A will be more efficacious than vaccine B. This is why simply advancing more candidates into clinical testing is unlikely to provide a quicker path to an eventual vaccine.

† The tiny number of long-term survivors do not appear to mount strong immune responses against the virus but seem instead to be beneficiaries of unusual genetic resistances that provide no clues for vaccine development.

Given this, how can we be confident that a vaccine is good enough to incur the enormous resources required to conduct a large efficacy trial? Could correlates of protection that have been proposed from the modest efficacy of prime-boost regimen tested in the RV144 trial become the Phase I standard? Unfortunately, a prospective test of this hypothesis won't occur until completion of the upcoming efficacy trial of clade C ALVAC/gp120 vaccine candidates in South Africa, which is years away.

Developing vaccine candidates that can induce neutralizing antibodies against HIV is one clear pathway to an efficacy trial. Today's neutralization assays are high-throughput, reliable, and show there are antibodies that can neutralize HIV, but breadth of neutralization is very narrow. Though rare monoclonal antibodies that have impressive breadth of neutralization can be isolated, the track record of inducing them is poor. Some excellent scientists are vigorously testing a rational approach to this problem by developing various vaccine immunogens designed to guide the immune system to develop these highly specialized antibodies, but progress is agonizingly slow. We need a contingency plan to learn if something else can protect.

Modeling HIV infection in animal models and reversing the process is another alternative. Instead of optimizing the protective response—knowledge of which we lack—in human trials, multiple vaccine concepts can be tested by immunizing and then challenging the animals. Protection observed in NHPs has been used as evidence that a concept may be valid and deserves further development, but what is also needed from such experiments is a strong correlate that could be useful in Phase I clinical trials.

Unfortunately, animal models of HIV/AIDS are far from ideal. The only non-human species in which HIV replicates is the chimpanzee, but experimentation in chimpanzees was abandoned for several reasons: no disease endpoint existed, experiments in chimpanzees are extremely expensive, there is an insufficient number of available animals, and most recently, ethical concerns were raised about experimentation. Mice reconstructed to contain human immune cells, so-called humanized mice, are at present incomplete models. The best compromise is simian immunodeficiency virus (SIV) and its pathogenic sequelae in rhesus macaques, which replicates many important features of HIV infection. Chimeric SIV/HIV strains known as SHIVs, which substitute HIV's Env protein into SIV, allow for testing of HIV Env vaccines in non-human primates (NHPs). But as analog models, their relevance to predicting the outcome of HIV vaccine candidates in humans is unclear. Additionally, the first 20 years of SIV vaccine trials in macaques were largely unsuccessful, leading some to conclude that a vaccine simply couldn't be made and others to condemn NHP models as unproductive, unsuitable, certainly unvalidated, and therefore irrelevant to HIV vaccine development.

Three major developments in the last 10 years have changed the debate considerably. First, the vaccine concepts being tested actually have improved, and second, NHP models improved as well. New repeat-exposure mucosal challenge models use lower doses of virus capable of transmitting approximately one infecting particle, which is a much better model of human sexual transmission. Encouragingly, there are now several vaccine candidates that either significantly reduce per-exposure risk of infection or prevent establishment of infection in a large proportion of vaccinated animals. Thirdly, the RV144 trial was transformational. Though efficacy was short-term and too low to merit licensure, it established *in humans* for the first time that vaccination could prevent acquisition of HIV, and did so in the absence of neutralizing antibodies. Finally, vaccine correlates questions have become broader and more refined. Do antibodies need to neutralize to contribute to protection? Do innate responses affect the development of adaptive immune responses, and can they be modified by vaccination?

To improve these partially protective vaccines we must move beyond empiricism and begin rationally guiding vaccine development by thoroughly investigating and comparing these concepts in protected and unprotected NHPs. Invasive analysis of tissues available from NHP studies is ideally suited to uncovering the mechanism of protection, not merely imputing a "correlate," which may or may not be causative. What (and where) did the immune system do to intercept virus in these protected animals? While we wait for vaccines capable of inducing broadly neutralizing antibodies to be developed and for evaluation of the RV144 correlates from the follow-up trial in South Africa, redoubling efforts to analyze these partially protective vaccines in NHPs should be paramount. Despite their imperfections, NHP models remain the best way to make progress and intelligently guide HIV vaccine design. ■

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In BRIEF

New Global Goals and Guidelines Aim to Eliminate AIDS

September was a busy and ambitious time for global health. In less than a week's time, three organizations took bold steps intended to slow the spread of AIDS, if not end it entirely.

On September 25, the United Nations General Assembly (UNGA) adopted a sweeping set of 17 Sustainable Development Goals (SDGs), one of which relates to health and aims to end AIDS, tuberculosis, malaria, and neglected tropical diseases by 2030. These broad and ambitious goals, which also aim to end hunger and poverty and combat climate change among other things, replace the soon-to-expire millennium development goals (MDGs) that were adopted in 2000 with a 15-year span.

Two days after the SDGs were endorsed by the UNGA, US President Barack Obama urged world leaders to support the SDGs and announced plans to expand the HIV/AIDS treatment and prevention goals for the President's Emergency Plan for AIDS Relief (PEPFAR). The US government has already invested US$65 billion in PEPFAR, which now supports antiretroviral therapy (ARV) for about 7.7 million HIV-infected individuals in developing countries. By the end of 2017, PEPFAR plans to support ARV therapy for nearly 13 million HIV-infected individuals in its target countries—almost double the current number. PEPFAR also plans to provide 13 million adult male circumcisions to prevent new HIV infections, and to reduce HIV incidence by 40% among adolescent girls and young women in 10 sub-Saharan African countries with the greatest HIV infection rates by reallocating $300 million of current funding that was secured from improved program efficiencies. "An AIDS-free generation. This is not a distant dream—it is the extraordinary moment before us right now," said Ambassador Deborah Birx, the US Global AIDS Coordinator who oversees PEPFAR, in a statement.

Source: UN in collaboration with Project Everyone

Capping these announcements, the World Health Organization (WHO) issued revised guidelines on September 30 for HIV treatment and prevention. The updated guidelines call for all HIV-infected individuals to start ARV therapy as soon as possible after their infection is discovered. The guidelines also recommend that high-risk, HIV-uninfected individuals be offered ARVs as a means of HIV prevention, a practice known as pre-exposure prophylaxis (PrEP). Previous guidelines were more limited for both treatment and prevention; viral load determined who received ARV therapy, and PrEP was recommended only for men who have sex with men.

Mitchell Warren, executive director of the global AIDS advocacy organization AVAC, who has been working in the AIDS field for 25 years, says we are entering the most exciting time in HIV science and policy. "But as exciting as the new goals and guidelines are, the gap of where we are and where we need to be is larger than ever," he acknowledges.

Chris Beyrer, a professor at Johns Hopkins Bloomberg School of Public Health and President of the International AIDS Society, considers the SDGs bold and visionary. "My only concern is that on health, they are very broad, and it may prove that they are too broad and general to serve as foci for advocacy, including around HIV/AIDS," said Beyrer. "The power of the MDGs was at least in part their specificity. The SDGS may be harder to advocate around."

And advocacy will likely be key, given the high price tag that accompanies achieving these goals. Governments, foundations, and public-private partnerships are already investing close to $19 billion a year in programs that provide ARVs in developing countries, and a recent report released by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and *Lancet* Commission estimates it will cost $36 billion annually to end AIDS by 2030.

If anything, the HIV-related MDGs, which called for halting the spread of HIV/AIDS by 2015 and achieving universal access to ARV treatment for all in need by 2010, illustrate how difficult it can be to reach the finish line. Earlier this year, UNAIDS reported that new infections have declined 35% and 15 million people in developing countries are now receiving ARV therapy. Yet ARV coverage still only accounted for about 41% of the 36 million people estimated to be living with HIV/AIDS, far short of universal access.

Still, Warren remains optimistic. He recalls the 2000 International AIDS Conference in Durban, South Africa, when doubts remained about whether there was enough money to fund ARV treatment outside the US and Europe. "Look what happened," he said. "Fifteen years later we have 15 million people on ARVs. In 2000, it was zero. The world can change." —*Mary Rushton*

Entering the Dark Zone: Scientists Recap Advances and Gaps in Understanding Germinal Center Dynamics

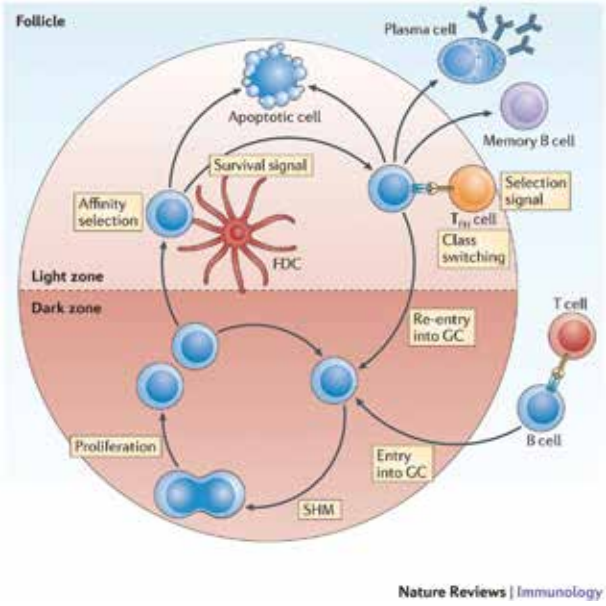
"We don't know much," said Barton Haynes, director of the Human Vaccine Institute at the Duke University School of Medicine and a director of the Center for HIV-AIDS Vaccine Immunology. Haynes was referring to the lack of knowledge researchers have about the complex processes and reactions that take place in germinal centers during the induction of broadly neutralizing antibodies (bNAbs) against HIV. Although they may not know much now, this topic is of growing interest.

On August 28, the US National Institute of Allergy and Infectious Diseases (NIAID) held a meeting to discuss the role germinal centers play in antibody maturation, and what strategies researchers can use to exploit this process to further HIV vaccine design and development. The meeting, "Germinal Center Dynamics and Antibody Affinity Maturation for Protective Immunity," was open only to invited guests but was recapped at a webinar sponsored by the Global HIV Vaccine Enterprise on September 25 (the webcast is available at http://www.vaccineenterprise.org/content/germinal-center-dynamics-and-hiv-vaccines). The main goals of the NIAID consultation were to identify gaps in knowledge, missing technologies, high-priority issues that need to be addressed by the HIV vaccine field, opportunities to promote multi-disciplinary basic immunology research, and suggestions for funders for short and long-range plans—what Shane Crotty, a professor in the vaccine discovery division of the La Jolla Institute for Allergy and Immunology and a panelist at the webinar, called "an ambitious but appropriate wish list."

Germinal centers are unique structures that form within peripheral lymphoid organs, including lymph nodes and the spleen, where activated B cells proliferate and diversify. It is in germinal centers that B cells undergo ongoing rounds of genetic mutation of the cell's variable region through a process known as somatic hypermutation. This is followed by the affinity selection process in which the mutated cells compete for binding to antigen. The end result of this two-step affinity maturation process is survival of B cells with the greatest affinity for the antigen (see Figure, this page). Germinal centers are also where mature B cells interact with follicular helper T (Tfh) cells—a specialized subset of $CD4^+$ T cells that play a critical role in the selection and survival of B cells and their differentiation into either plasma cells capable of secreting antibodies, or memory B cells that are a vital component of the desired immune response to vaccination. Tfh cells were only identified as a distinct type of T helper cell little more than a decade ago, but since then have become a burgeoning topic of study. These cells play an important role in germinal centers. "Tfh cells are required for

Inside Germinal Centers

Naive B cells activated by an antigen travel to lymph nodes and the spleen where, together with helper T cells, they establish special structures called germinal centers (GC), pictured in the simplified schematic below. Within germinal centers, B cells multiply and undergo a process known as affinity maturation. Affinity maturation involves ongoing alternating rounds of somatic hypermutation (SHM), during which genetic mutations are introduced into the antibody gene of each cell, and affinity selection—a process through which the somatically mutated B cells compete with each other to bind with antigen that is presented on follicular dendritic cells (FDCs) and to receive signals from follicular T helper (Tfh) cells. Somatic hypermutation occurs in the dark zone of the germinal center, while affinity selection occurs in the light zone. The process of affinity maturation is "still an incredibly active area of research," said Michael McHeyzer-Williams, a professor at The Scripps Research Institute in La Jolla, CA. If the affinity of the somatically mutated B cell for antigen is weak, the cells will undergo apoptosis. B cells with the highest affinity for the antigen presented on FDCs then either re-enter the dark zone where they will undergo further rounds of expansion and somatic hypermutation, or exit the germinal center either as antibody-secreting plasma cells or as long-lived memory B cells. Researchers are now focusing on how this cycle can be manipulated to enhance the protection afforded by vaccines. *Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology, copyright 2014.*



germinal centers and therefore the bulk of B-cell memory as well as affinity matured antibody responses," said Crotty. While HIV vaccine researchers may not know precisely how antibody maturation in germinal centers unfolds, they know it is terribly important.

One major goal of HIV vaccine research today is determining what vaccine immunogens will induce antibodies that can neutralize a broad swath of the diverse strains of HIV in circulation, so-called bNAbs. Development of bNAbs is not favored—only a minority of HIV-infected individuals develop them and only after exposure to a rapidly evolving virus. "In every individual we've studied, the prerequisite for bNAb breadth is extraordinary virus diversification," said Haynes.

After isolating and closely studying what now amounts to more than 200 bNAbs against HIV, researchers realize that these antibodies are not just rare, they are unique. For one thing, these antibodies are almost all highly somatically mutated. To achieve this extensive level of somatic mutation, bNAb development must require optimized germinal center responses, according to Crotty. Given this, researchers are increasingly focusing on developing strategies to enhance germinal center dynamics to improve bNAb maturation. One area of investigation is how Tfh cells may enhance somatic hypermutation. Another is how adjuvants may drive germinal center dynamics. According to Haynes there is evidence from animal models that toll-like receptor (TLR) agonists can directly stimulate B cells. Data also indicate that Alum, an aluminum salt adjuvant that is the most widely used in vaccines, drives a slower accumulation of B-cell mutations than TLR agonists.

One hindrance to studying these processes is the difficulty in accessing germinal centers. In some ways when it comes to understanding the complex immune system interactions that occur here, scientists are groping in the dark. Hidden within lymph nodes, these compartments can only be analyzed by biopsy. Their location in germinal centers is one reason it took so long for Tfh cells to be classified. In non-human primates, researchers are now using a type of biopsy procedure referred to as fine-needle aspirates to study the immune responses that occur in response to different antigens.

Despite major gaps in understanding how germinal center reactions occur, "this has been a fantastically successful field of study over the past six years," said Crotty. He will serve as a scientific organizer of an upcoming Keystone Symposia on "T Follicular Helper Cells and Germinal Centers," which will be held from February 26 to March 1, 2016, in Monterey, CA; evidence of the topic's growing research prominence. —*Kristen Jill Kresge*

Continued from page 14

of middle-income countries have large, poor populations. Because they are classified as middle income, they see reduced international assistance. This means there needs to be government will to pick up the difference," says Mark Hollis, a health economist and life sciences analyst at IHS, a global industry consultancy and think tank. "We see this to some degree, but not across the board. Countries need to increase the amount they are spending on health care. You see them investing in nice shiny military technology but not in vaccines," Hollis says. But for countries that fall under their aegis, it is clear Gavi is effective in its dealings with vaccine manufacturers.

Others models to lower prices

There are also other factors at play that could bring about lower vaccine prices in the future. Financing tools such as advanced market commitments, which are long-term, single-purpose contracts aimed at bulk purchases or to encourage research and development for new vaccines, could be established and refined. Gavi organized one such commitment for the now-licensed pneumococcal vaccine, bringing in funding from Italy, Norway, Russia, the UK, Canada, and the Gates Foundation.

There are also new Chinese and Indian vaccine manufacturers that are producing vaccines. Berkley is keen to point out that Gavi started in 2000 by negotiating with five suppliers, all in the developed world. Industry consolidation squeezed that further. Now, however, 16 suppliers feed Gavi stocks, and the majority of those are in developing countries.

"What I think is greatly needed is a comprehensive study of the barriers to new vaccine development and introduction," says former US National Vaccine Program head Walter Orenstein, who is now associate director at the Emory Vaccine Center. He cites a call this summer in the *New England Journal of Medicine* by Plotkin, Princeton University molecular biology and infectious disease expert Adel Mahmoud, and Jeremy Farrar, director of the UK's Wellcome Trust, for a $2 billion global vaccine development fund to fill the gaps left by market inefficiency and public-sector inability or unwillingness to go further in targeting vaccines for infectious diseases.

New partnerships could change the economics of vaccines even further. Over the last 10 years, the international nonprofit organization PATH worked to hasten the delivery of a vaccine for Japanese encephalitis (JE). The organization also identified a Chinese vaccine supplier and worked with the WHO to advance the vaccine through clinical trials. PATH then bargained with the supplier to secure an affordable public-sector price.

On April 1, the southeastern Asian country Laos began an immunization program for JE with support from Gavi, UNICEF, the Bill & Melinda Gates Foundation, and PATH. The Chengdu Institute of Biological Products will supply the vaccine, marking the first time Gavi provided funding to a country to use a Chinese-manufactured vaccine.

Chengdu's price for its Japanese encephalitis vaccine for Gavi is 42 cents. That makes it cheaper than an American postage stamp. ■

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Upcoming HIV-Related Meetings

OCTOBER 2015

15th European AIDS Conference
October 21-24; Barcelona, Spain
More information: www.eacsociety.org/conferences/eacs-conference/conference.html

NOVEMBER 2015

International Conference on AIDS & STI in Africa (ICASA)
November 22-27; Tunisia
More information: icasa2015tunisia.org

3rd International Conference on HIV/AIDS, STDs & STIs
November 30-December 2; Atlanta, GA
More information: hiv-aids-std.conferenceseries.com

DECEMBER 2015

10th International Workshop on HIV Transmission
December 5-6; Atlanta, GA
More information: www.virology-education.com/event/upcoming/10th-hiv-transmission-workshop-2015

2015 National HIV Prevention Conference
December 6-9; Atlanta, GA
More information: www.cdc.gov/nhpc

7th International Workshop on HIV Persistence, Reservoirs and Cure
December 8-11, 2015; Miami, Florida
More information: www.hiv-persistence.com

2nd International Conference on HIV/AIDS, Women & Children
December 16-18, 2015; Shiraz, Iran
More information: ichawc2.sums.ac.ir/en

For a full list of meetings and their descriptions, go to www.iavireport.org/meetings.