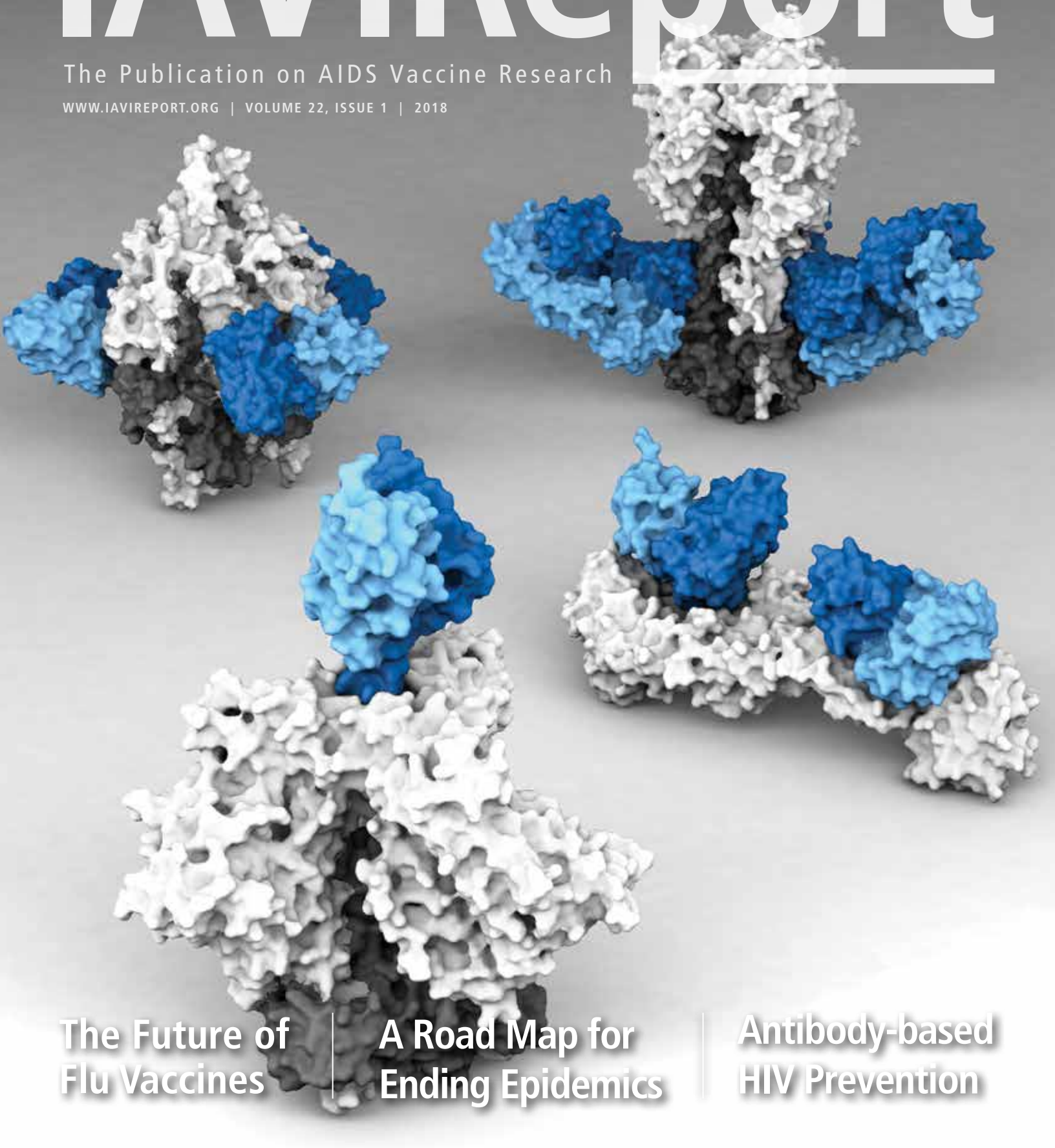
VOLUME 22, ISSUE 1

# IAVIReport

The Publication on AIDS Vaccine Research

WWW.IAVIREPORT.ORG | VOLUME 22, ISSUE 1 | 2018



## The Future of Flu Vaccines

## A Road Map for Ending Epidemics

## Antibody-based HIV Prevention

# EDITOR'S LETTER

This year's flu season was one for the books, and it swung the spotlight directly on vaccines. The predominant strain of influenza virus that circulated in the US, an influenza A subtype known as H3N2, was particularly virulent, leaving thousands dead and sending many more to the hospital. And the seasonal flu vaccine was only modestly effective against this particular strain.

One hundred years after the worst influenza pandemic in human history, there is growing concern about how effective annual flu shots are and whether or not the world will be prepared when another pandemic strikes. The answers to these questions are troubling. But if anything, this particularly severe flu season seems to be spurring researchers and public health experts to pay more attention to this threat than ever before.

Influenza is a highly variable virus. Though much less variable than HIV, there are still possible areas of overlap between the HIV and flu vaccine research efforts. We discuss these in an article that also explores the current state of research into developing both better seasonal flu shots and vaccines that could ward off a future pandemic strain (see page 6).

This issue also features an interview with Jonathan Quick, senior fellow at the non-profit Management Sciences for Health and author of the recently published book, "The End of Epidemics: The Looming Threat to Humanity and How to Stop It" (see page 12). In his book and in the interview, Quick balances the looming threat that many infectious pathogens pose with a sense of hopefulness about how everyone from average citizens to government officials can do their part to help limit or even eliminate these threats in the future. In doing so, he draws many lessons from the response to HIV/AIDS.

As for HIV vaccine research, this issue features a perspective piece authored by one of IAVI's own scientists, Devin Sok. He outlines advances in three areas of antibody-related HIV prevention research that were discussed during January's Keystone Symposia (see page 4).

On a more somber note, we also pay tribute in this issue to two dedicated and inspiring contributors to HIV research who passed away recently—David Cooper and Bonnie Mathieson (see pages 17 and 18). The legacies these two leave behind will continue to influence the field for a long time to come. *IAVI Report* recognizes their steadfast dedication to ending HIV/AIDS for all time. And though they did not live to see that shared vision become a reality, it will be because of their persistence and that of countless others that it will eventually be realized.

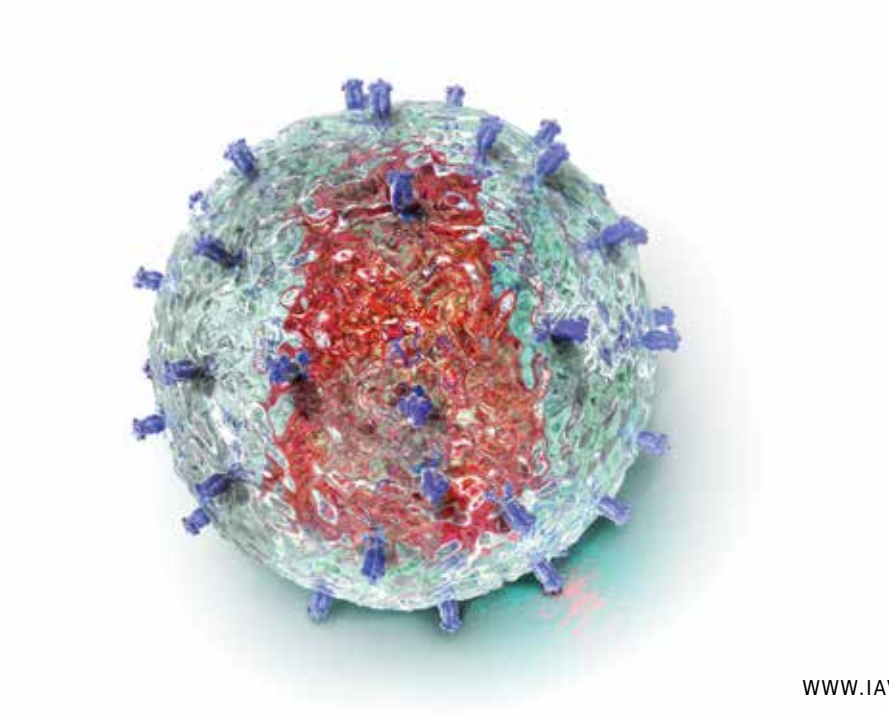
*– KRISTEN JILL KRESGE*



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.

## IN THIS ISSUE



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**[ ON THE COVER ]**

The cover image depicts the structures of four super antibodies, shown in blue, bound to their target antigens. Clockwise from the upper right is a crystal structure of the influenza virus group 1 and group 2 neutralizing antibody CR9114 in complex with influenza virus haemagglutinin (4FQI); a crystal structure of the Zika virus and dengue virus cross-neutralizing antibody C8 in complex with a soluble Zika virus Env ectodomain (5LBS); a cryoelectron microscopy structure of the broadly neutralizing HIV antibody PGT145 in complex with a recombinant HIV Envelope (Env) trimer (5V8L); a crystal structure of the respiratory syncytial virus (RSV) and human metapneumovirus cross-neutralizing antibody MPE8 in complex with a stabilized RSV prefusion fusion glycoprotein trimer (5U68).

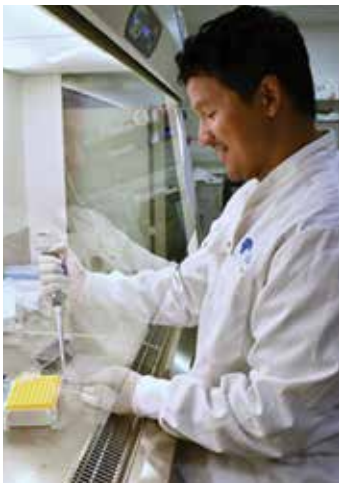
*Image provided by Christina Corbaci and Lars Hangartner at The Scripps Research Institute in La Jolla, CA.*

# Applying Innovative Approaches and Technologies to HIV Prevention

## By Devin Sok

Vaccines have contributed tremendously to preventing infectious disease. Yet three decades after the discovery of HIV, a vaccine against the virus remains elusive. Difficulty in achieving this goal lies primarily in the enormous antigenic diversity of HIV, and the virus's ability to cover its most conserved epitopes with sugars that are relatively invisible to the immune system.

Despite these challenges, investigators remain dedicated to the mission and are using innovative approaches and technologies to make significant strides toward developing a protective HIV vaccine. In keeping with structure-based rational vaccine design, researchers are collecting even more detailed information on the sole target for neutralizing antibodies: the HIV Envelope (Env) trimer. This information is helping to inform the design of a new generation of HIV vaccine immunogens intended to induce the types of broadly neutralizing antibodies (bNAbs) that have been described from chronically infected individuals. Following evaluation of these immunogens in animal models, several are now being readied for human clinical trials. Researchers are also making progress in understanding the role of antibody effector functions in protecting against HIV. These themes and other new findings were reported on at the Keystone Symposia in Banff, Canada, where two meetings were held in parallel: *Progress and Pathways Toward an Effective HIV Vaccine* and *Emerging Technologies in Vaccine Discovery and Development*.



While both Keystone meetings focused primarily on attempts to elicit protective antibodies through vaccination, exciting data were also presented on passive immunization approaches, which sidesteps the immune system and instead delivers the antibodies directly to achieve protection.

The lessons learned from HIV vaccine design and development are also being applied more broadly against other infectious diseases. At Keystone, several researchers discussed how innovations in antibody isolation and other vaccine-related technologies are fueling efforts to develop vaccines against influenza, malaria, and other infectious pathogens.

### Structure-guided vaccine development

Despite the enormous antigenic diversity of HIV, the discovery and characterization of bNAbs have enabled identification of the most conserved epitopes on the Env trimer. Our understanding of these epitopes has advanced further through structural studies using X-ray crystallography and electron microscopy, which provide high-resolution information on what these epitopes look like. This information can then be used by researchers to engineer immunogens that faithfully mimic these epitopes to elicit bNAbs by vaccination.

Typically, however, these structural studies only provide a snapshot of what the Env trimer looks like at a given instant. To provide more information on the dynamics of the HIV Env trimer, researchers are using different techniques to measure the distances between two sites on the protein. These measurements are very sensitive, so any changes in the distance between the two sites, through conformation changes for example, can be captured. Although there are disagreements on how these experiments are performed and what information can be gleaned from them, the results of these studies highlight important progress toward a more comprehensive understanding of the Env trimer. Indeed, achieving a detailed level of understanding of the HIV Env protein structure and its dynamics would allow researchers to design the best epitope mimics to effectively elicit bNAbs through vaccination.

Meanwhile, structural studies are also guiding efforts to design vaccines for other viruses. At Keystone, researchers presented the results of structural studies for respiratory syncytial virus (RSV), human metapneumovirus (hMPV), coronaviruses, Ebola virus, and malaria, all of which will greatly inform vaccine design efforts for these infectious diseases.

Armed with structural information on the HIV Envelope trimer, investigators have designed several immunogens to try to elicit bNAbs. To test this new generation of engineered immunogens, we rely on animal models to evaluate their immunogenicity as part of an iterative design and evaluation process. Many different immunization experiments have been performed to date, including studies in transgenic mice, which are engineered to express human antibodies, as well as in a variety of other animal models including rabbits, guinea pigs, rhesus macaques, and even cows. These experiments have been important for answering specific hypotheses, but much more remains to be learned once these results can be compared to data emerging from future clinical trials with the same immunogens. There are currently plans to evaluate several of these rationally designed, next-generation vaccine immunogens in human trials, including the native-like trimer BG505 SOSIP.664 Env trimer (see *IAVI Report*, Vol. 21, No. 2, 2017) and the engineered outer-domain nanoparticle mmunogen (eOD-GT8; see *IAVI Report*, Vol. 21, No. 1, 2017).

## Other antibody functions

Besides the many efforts to elicit bNAbs through vaccination, there is a continued focus on the role of non-neutralizing antibodies and/or effector functions at mediating HIV protection.

Previous studies with the first-generation antibody b12 showed that there was a reduced level of protection when mutations were introduced to the antibody to eliminate its Fc receptor effector functions. But follow-up studies with one of the new generation of bNAbs, PGT121, indicate that the same mutation did not affect the antibody's ability to block the virus. These results suggest that the role of effector functions for mediating protection against HIV is likely antibody dependent, and/or virus dependent. Data were also presented at Keystone that emphasized how differences in assays designed to measure antibody-dependent cellular cytotoxicity (ADCC; the ability of a virus to trigger killing of a virus-infected cell), might lead to different interpretations. For example, the choice of HIV Env used in the assay is important as certain mutations in Env could lead to greater susceptibility to antibody-mediated ADCC activity. Overall, despite differences in the assays, bNAbs consistently offered higher specificity for killing HIV-infected cells than non-neutralizing antibodies.

## Passive antibody administration

Despite the progress in designing HIV vaccine candidates, several challenges need to be overcome before an efficacious product can be affordably administered around the world. In the meantime, many researchers are pursuing passive vaccination strategies, which involves directly delivering bNAbs over one's lifetime, similarly to how people with diabetes need to take insulin throughout their lifetime.

HIV bNAbs are currently being evaluated in proof of concept clinical trials to test their efficacy both prophylactically, as well as for HIV treatment or even potential cure for those already infected with the virus. Indeed, several next-generation antibodies are at different stages in the clinical pipeline, including some that are altered so that they have much longer half-lives than the original parent antibody. In addition to these modifications, other innovative approaches are being explored to reduce the number of antibodies that needs to be delivered to be effective. For example, one set of investigators have developed a bi-specific antibody, created by combining two antibodies (10E8 and ibalizumab) into a single construct, whereas other investigators have designed a tri-specific antibody that combines three antibodies (VRC01, 10E8, and PGDM1400) into a single construct. Both of these molecules show remarkable breadth and potency and are scheduled for evaluation in Phase I clinical trials in upcoming years. While vaccine research efforts continue, the development of HIV bNAbs for prevention could achieve public health impact in the interim.

Although the road to an HIV vaccine has been and will likely continue to be arduous, many agree that a preventative vaccine will achieve the highest impact in reducing the incidence and prevalence of HIV/AIDS. Investment in both HIV vaccine research and in antibody discovery and development for HIV prevention will not only benefit millions of people affected by the disease, it can also contribute significantly to the development of effective prevention products for other infectious diseases. ■

*Devin Sok is Director of Antibody Discovery and Development at IAVI.*

Electron microscopy reconstruction depicting antibodies attached to the HIV Envelope glycoprotein trimer at several sites of vulnerability shown in different colors. The areas of antibody attachment are the conserved epitopes that are currently being used by vaccine researchers as targets to design next-generation immunogens. Image courtesy of Andrew Ward and Christina Corbaci at The Scripps Research Institute.

# A Mean Flu Season SWINGS A SPOTLIGHT on Vaccines

**Influenza, like HIV, is a highly variable menace. A particularly bad flu season has researchers seeking ways to make a better vaccine, and in doing so, there may be lessons from, and for, HIV vaccine research.**

## By Michael Dumiak

As this particularly severe flu season winds down in the Northern hemisphere, parents, doctors, and scientists are once again reminded just how serious this bug can be. Imagine it 50 million times worse. It was once so: this year marks the centennial anniversary of the H1N1 Spanish flu pandemic, which lasted from January 1918 to December 1920. That flu infected 500 million people and killed more people in a single year than in four years during the worst outbreak of the Plague.

While public health officials are rattled by this flu season, they remain haunted by the specter of another pandemic. It is not a matter of if another pandemic will strike, but when, and how ready we can be.

"The influenza pandemic potential is 100 percent. It is going to happen," says Michael Osterholm, director of the University of Minnesota's Center for Infectious Disease Research and Policy (CIDRAP) and author of the recent book "Deadliest Enemy." "These date back to Hippocrates and, like earthquakes, tsunamis, and hurricanes, they are going to occur."

The looming threat of another pandemic and the inadequacy of seasonal flu shots suggest a truly effective vaccine against this perennial troublemaker would offer great benefit. Many experts argue that the best solution would be a universal shot effective against all of the existing and potential future strains and types of the virus. Such a vaccine would replace the annual jabs that aim to prevent infection or severity of illness from the seasonal flu, while also protecting against an emerging pandemic strain. Tackling the diversity of flu strains with a single vaccine echoes challenges HIV vaccine researchers face. It may be that the two fields can inform each other.

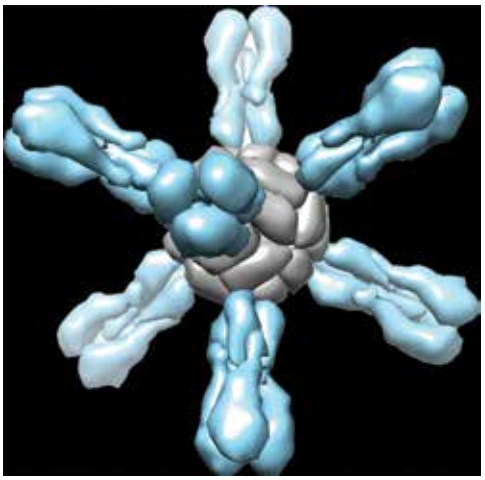
### Why so bad?

US Centers for Disease Control and Prevention (CDC) data indicates that the 2017-2018 flu season is among the most—if not *the* most—severe in the last 10 years. In mid-February, the agency was recording a higher hospitalization rate from flu than ever recorded at that point in the season in the US, well above 2014-15 levels, when the flu killed about 56,000 Americans and hospitalized more than 700,000. A high hospitalization rate speaks to the severity of the bug.

One of the factors making this flu season so bad was that this year's vaccine formulation is up against a particularly difficult subtype—influenza A, H3N2—which for a variety of reasons is harder to protect against. Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID), says H3N2 is notorious for mutating more rapidly and leading to

more complications in high-risk groups, such as the elderly or people with underlying debilitating diseases. Fauci says on top of that, this year's vaccine is also not particularly effective against the H3N2 subtype.

As this flu season progressed in different parts of the world, different rates of vaccine protection emerged. In Australia, the 2017-18 vaccine's overall efficacy was about 10 percent. In Canada, it reached 17 percent. In the US, overall vaccine effectiveness was measured at 36 percent in mid-February, and a slightly lower 25 percent against H3N2. Last year's vaccine was about 48 percent effective overall in the US. The adjusted overall effectiveness of the seasonal flu vaccine, according to the CDC, has not been higher than 60 percent in the last 15 years. Still the vaccine is recommended widely. Even if it doesn't protect against infection, it can often ease the symptoms of flu and its duration.



**Flu self assembly.** When ferritin (gray) is fused with the influenza protein hemagglutinin (blue), it self-assembles into a sphere with eight protruding spikes from its surface. Image courtesy of NIAID.

## Directing traffic

Influenza virus bears some resemblance to HIV, though it is not a retrovirus. It is an RNA virus protected by a shell, or lipid envelope, which, like HIV, is covered in protein spikes. These spikes, carrying the proteins haemagglutinin (H) and neuraminidase (N), are the virus's fusion engine: they are what allow influenza to dock to and board a host cell. They are also highly mutable. As with HIV, flu's rapid ability to mutate presents a constant challenge to the human immune system and to designing vaccines against the virus. It is also why, as with HIV, there are so many strains and subtypes of flu in circulation around the globe.

There are four types of influenza viruses that the CDC recognizes: A, B, C, and D, with types A and B being the ones behind the seasonal waves of infection. Scientists further differentiate influenza types into subtypes and strains. Subtypes for A take their nomenclature from the virus's H and N protein spikes, creating subtypes such as H1N1 and H3N2. Type B influenza, still harmful but lacking the powerful punch of its cousin, is broken down into lineage and strain, with currently circulating influenza B being either of lineage B/Yamagata or B/Victoria.

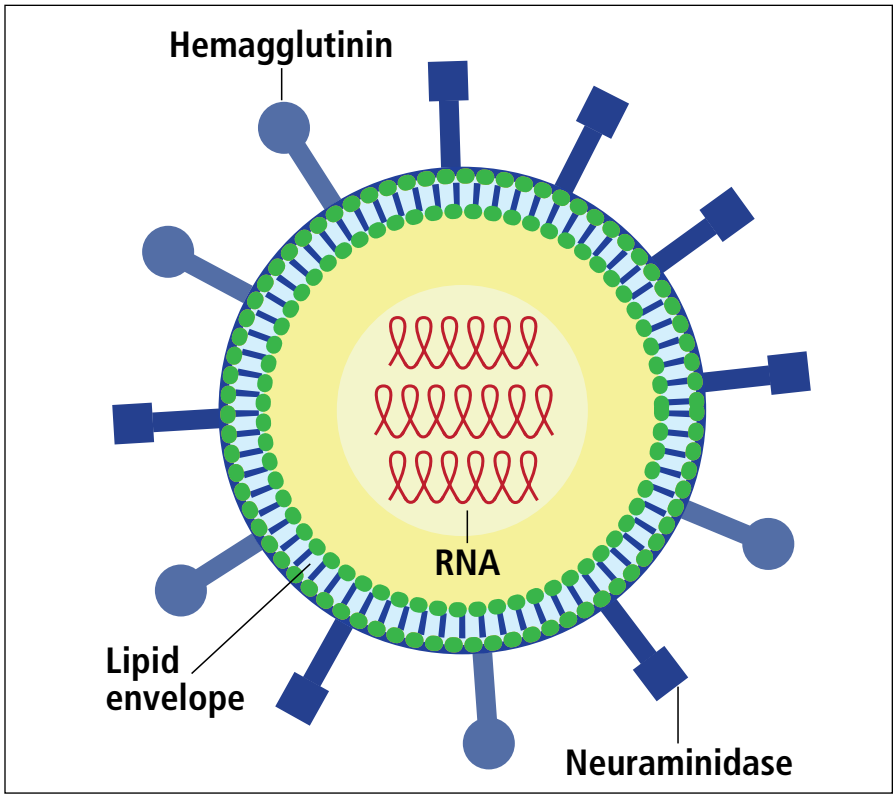
Most people develop immunity to influenza from previous exposures to the virus and from previous vaccinations. But new strains of flu can arise when viruses from animal populations (pigs and birds are the most common) recombine with human strains to form novel combinations to which few if any people have immunity against. These are the most dangerous. They can spread rapidly, with the potential to ignite a highly deadly pandemic. While the most recent flu pandemic happened in 2009 and the worst in recent history in 1918, there were also pandemics in 1968 and 1957. It is a mystery to scientists when a pandemic will happen, or what novel combination is most likely to occur.

The global response to influenza has evolved into a routine but imperfect science. More than 100 flu centers in 100 nations conduct year-round surveillance of the virus, receiving thousands of flu samples from patients and testing them. These data are funneled into five global healthcare institutions, among them the CDC, London's Francis Crick Institute, and Tokyo's National Institute for Infectious Diseases. Based on their data analysis, best forecasts, and deliberation, officials at the World Health Organization (WHO) make recommendations every February and September as to which strains and types of viruses should be included in the annual seasonal influenza vaccines. They are then produced by large pharmaceutical companies and their subcontractors and distributed months down the road, with anywhere from eight to 18 months' lead time. A lot can happen in the time between when the strains are chosen for the vaccine and when people start getting immunized. When the flu emerges, it is not always perfectly matched to the vaccine. Even if it is, the virus can mutate, making the vaccine less effective.

## Hatching a vaccine

Flu vaccines are manufactured in three ways: by far the most common is the method in use for the past 70 years, in which lab-grown influenza virus vaccine candidates are injected into fertilized chicken eggs. The eggs are incubated over several days. Then, the viral fluid is removed and the viruses are either killed or attenuated before purification and manufacturing. It takes about six months to make the first of a batch of vaccine, and the entire run can take longer. The whole killed vaccine variant is delivered by injection; the attenuated, via nasal spray. Sometimes, as during this season, US health experts recommend against the spray because its effectiveness against the more virulent H3N2 flu virus is in question.

In either case, if 100 million doses of killed influenza virus are needed, it means using 100 million chicken eggs. There are other methods for manufacturing flu vaccines. One is cell-based production, in which the flu is cultured in mammalian cell lines, such as those from dog kidneys. Another is recombinant production, in which manufacturers isolate a wild-type flu protein, combining it with portions of another flu virus grown in cell lines derived from a kind of caterpillar known as armyworm.




**Influenza up close.** The main proteins, lipid, and RNA genome that comprise the flu virus particle.

There are advantages to getting away from egg-based production: speed is one. It takes time to grow and incubate eggs. Also, as researchers from The Scripps Research Institute found, a key mutation in the flu virus that occurs as it grows inside eggs can hamstring the antibodies made against it, weakening them by 1,000 times (*PloS Path* **13**(**10**), e1006682, 2017). This is especially true against H3N2, the subtype causing such havoc in this most recent flu season.

But implementing cell-based or recombinant approaches would require new production facilities for seasonal flu vaccines. While there are manufacturers engaged in this, it is a lengthy and very costly enterprise, and there is no guarantee that the vaccine will be any more effective than if it were grown in an egg. It will only have failed faster.

Currently the big flu vaccine producers are the French multinational Sanofi and UK-based GlaxoSmithKline, with relative newcomer Sequirus, an Australian manufacturer that acquired Novartis's influenza business, getting into production of cell-based flu vaccines. Fluzone, FluLaval, and Fluvirin are the larger names on the market: they are all administered in either single or multi doses, are multivalent, and are manufactured using eggs.

"Anyone who has an easy answer today—a better selection for strains, or getting the eggs out of vaccine production—is presenting a really naïve view of how to take care of the problems here," Osterholm says. There are much bigger issues at hand and the threat of pandemic flu is the biggest.

## Old roads, new directions

Some years ago the WHO revised guidance for how to prepare for a future influenza pandemic after, in 2009, the virus compelled the organization to coordinate supply for 78 million doses of new vaccine. The experience exposed flaws in the international response to pandemic flu. But as the pandemic faded from view, so did the sense of heightened concern. Experts expressed warnings nonetheless. Interviewed for a WHO bulletin during the 2012 flu season, Gary Nabel, who at the time was heading NIAID's Vaccine Research Center, made a plea for a universal flu vaccine. "We need to do more than prepare for future viruses based on existing strains," he said.

Nabel is now chief scientific officer at Sanofi, which puts him, and the big French pharma, in position to do something about it. But it will be no cakewalk. As with HIV, pursuit of a universal vaccine for flu is a potentially high-risk, high-

reward affair, for which funding can be fraught.

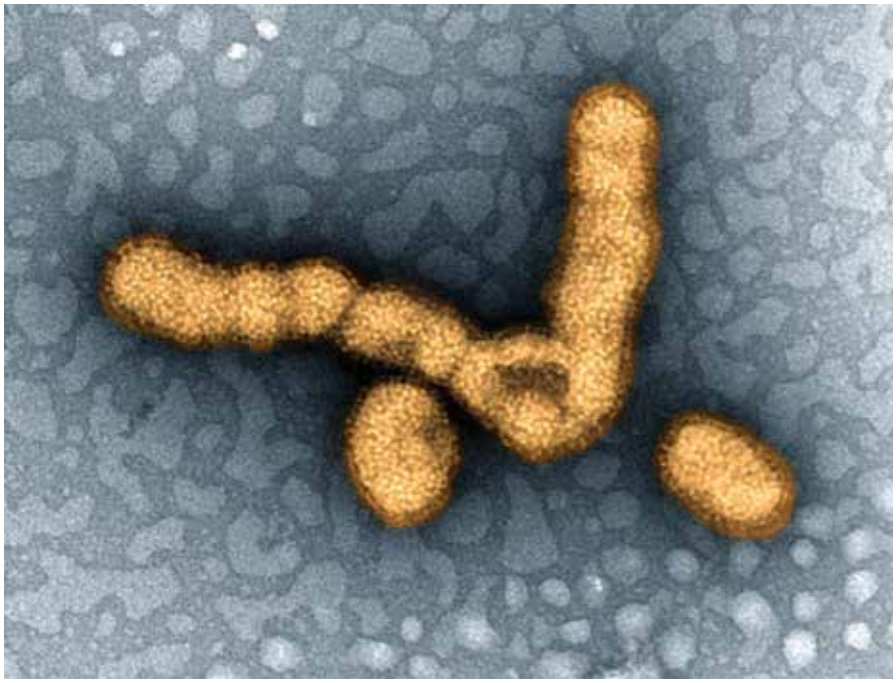
"One of the things people often ask me is, 'Why are you banging this old drum again? The universal vaccine has been tried in the past.' And they can point to clinical trials in the 1990s that failed," says Derek Gatherer, a computational biologist and virologist at Lancaster University in the UK.

But Gatherer, and many others, are undeterred. "We know a lot more about the human immune system now because of the human genome project and because of all the other genetic technologies now available: transcriptomics, and proteomics, and so on," he says. "There is greater expansion of sequencing and the 2009 pandemic really shot flu to the forefront of the biological research agenda. We now know a lot more about influenza than we did in the '90s, so there is a justification, I think, for taking a fresh look at the new approaches to universal flu vaccines which are not based on the old chestnut of, we'll see if we can elicit some antibodies against a less quickly evolving part of the flu virus, which doesn't have a very good track record."

The National Institutes of Health (NIH) is currently supporting several potential universal flu vaccine candidates. One employs a technique where the mutating head region of the hemagglutinin protein is removed and the conserved stem region fused with a nanoparticle. The institute is also experimenting with a virus-like particle cocktail of inactivated H1, H3, H5, and H7 flu virus subtypes, as well as an intranasal live-attenuated candidate. Fauci says while there has been discussion of universal flu vaccine over the years, new technologies emerging such as structure-based vaccine design didn't exist yet. "It's almost a new day. You have to look at it with fresh eyes."

Last summer NIAID held a two-day workshop billed as "Pathway to a Universal Influenza Vaccine." This led to a detailed plan for boosting universal flu vaccine research efforts (*J. Infect. Dis.* doi: 10.1093/infdis/jiy103). The goals it sets are for a vaccine to be at least 75 percent effective against symptomatic disease caused by all group 1 and 2 influenza A viruses, with the B type a secondary target; for protection to last at least a year, and ideally much longer; and to be applicable to all age groups.

Fauci says the first step is to increase the breadth of the flu vaccine. Developing a vaccine that is effective against all versions of H3N2 would alone be a great leap forward, he says. "Once you get that, then you increase your durability." The plan calls for answering fundamental questions about influenza and the body's response to these viruses as well as developing specific vaccine candidates. Fauci says this would create a progressive pathway to a universal vaccine, one that would protect against seasonal flu and be effective in the case of a pandemic. "When you talk about a universal flu vaccine, you don't talk about today we don't have it, and tomorrow we have a home run." This will come as no surprise to HIV vaccine researchers, who have had their own struggles with increasing the breadth and durability of immune responses induced by vaccines.



**H1N1 influenza virus particles.** Colorized transmission electron micrograph showing H1N1 influenza virus particles. Image courtesy of NIAID.

Gatherer and his colleagues also have two universal flu vaccine candidates that are in stasis, awaiting a development partner. In January the UK biotech Vaccitech, a spinoff from Oxford University's Jenner Institute, made news by landing a significant round of funding from Google's venture arm, Sequoia China and Oxford Sciences Innovation in order to continue testing its flu vaccine candidate, among other products. Vaccitech has already carried out human safety trials and is running a Phase IIb trial for which it is recruiting 2,000 volunteers from the British National Health Service. This candidate uses a poxvirus vector to target two proteins in the core of the

influenza virus that are non-mutating, but hidden from the immune system.

The concept, says Oxford University's Sarah Gilbert, is to stimulate the immune system's production of influenza-specific T cells rather than relying upon antibody generation. Vaccitech would like the candidate to be effective against all type A viruses. Chief Executive Officer Tom Evans says researchers are pursuing a two-pronged goal: one is to boost and improve upon the seasonal flu shot, and the other is to develop it for use as a standalone in the face of a pandemic. Gilbert echoes Fauci's perspective that increasing the breadth of the response of the flu vaccine is the first step. "Universal refers to breadth of coverage, not duration," she says. "A vaccine could protect against all strains of influenza A but still need to be given every year. First we need to test for improved breadth, then we can move on."

Sanofi is also pursuing vaccine candidates with expanded breadth. The company is working with the University of Georgia microbiologist Ted Ross, who is employing a computing-intensive technique called COBRA (computationally optimized broadly reactive antigen). According to a description given by Ross to *Science News*, COBRA computes and compiles all possible genetic iterations of a particular flu type, homing in on the haemagglutinin mutations, which researchers can then combine into one molecule. A Sanofi spokeswoman says this effort furthers more than a decade's worth of research.

But these candidates do not fill the need for a universal vaccine that could ward against all potential pandemics in Osterholm's mind. "The ultimate goal is this game-changing flu vaccine which would make seasonal flu vaccine obsolete," he says. "There is a hell of a challenge getting people vaccinated every year. We are realizing vaccine user fatigue that comes with that. We see rates of vaccine use going down, not up." A broader vaccine that still requires annual shots, to Osterholm, is still a problem. "It's better, but not universal to me. More breadth means what? If you have to get it every year, it defeats the very purpose."

CIDRAP's 2012 *Comprehensive Influenza Vaccine Initiative* report calls for a universal vaccine that protects against all HA subtypes, with at least minimum protection against H1, H2, H3, H5, H7, and H9, that is quickly scalable in the event of a pandemic, and provides a decade more of protection. It's a more ideal goal, but it remains to be seen if it can be reached. Vaccine and research technology is advancing quickly, but the question, is how quickly can it be applied?

## More novel approaches

One big difference between influenza and HIV is that people get the flu all the time and recover. No one has ever naturally recovered from HIV. But as the immune response to one flu strain is certainly not protective against all strains, similarly to HIV, a flu vaccine needs to induce a better immune response than occurs in natural infection.

"We get the flu over and over again, so it surely says we don't develop an immunity that is universal. It's not like when you have the measles one time and now you are protected against measles for the rest of your life," says Osterholm. This may have something to do with the mutation rate of the influenza virus. But it may be even more complicated than that. It turns out your immune system may be programmed in its response to flu by the first influenza virus it comes across. "When you are a child, whatever first looks you have at flu viruses may predetermine your ability to respond for the rest of your life," Osterholm says. "It means you have to overcome this. Whatever vaccine you are going to use, it's got to be able to elicit the kind of neutralizing immune response to the virus now—not to the one you had 25 years ago. It's a different virus."

What Osterholm is describing is called immunological imprinting, and further understanding it is a goal of Wayne Koff, chief executive of the Human Vaccines Project (and former chief scientific officer at IAVI). He and others as part of the Universal Influenza Vaccine Initiative are investigating how immunological imprinting might (or might not) affect responses to seasonal flu or even to influenza vaccines. Koff thinks understanding this is vital to overcoming challenges to the rational design of a universal flu vaccine. The Human Vaccines Project is working with James Crowe, Jr. and Buddy Creech at the Vanderbilt University Medical Center to design clinical trials to explore what happens in the hours after a person is immunized against flu and to map how the immune system sees the influenza vaccine. "If we could understand what are the correlates of protection and understand immunologic imprinting, it would give us the tools to optimize vaccine candidates to induce what you want to induce to create a vaccine that would work for all people."

Gatherer says the vast, broadly accessible databases of epitope and protein structures available for use in designing vaccine candidates are also going to open possibilities for new directions

in research. This may be one area where there could be cross-pollination between flu and HIV vaccine efforts.

Scripps researchers are using the combinatorial display libraries and single B-cell isolation screening that led to the isolation of broadly neutralizing antibodies currently energizing HIV vaccine research to bear against flu. Scripps structural biologist Ian Wilson and his team, along with Janssen Research and Development, have built artificial peptides that bind to the lower stem groove of the flu viral spike, blocking the ability of the virus to infect other cells, at least in Type A group 1 flu viruses in the lab. In designing the small-molecule peptides the group made use of imaging technology to map the atomic structure of the highly variable protein spikes on influenza.

Wilson's colleague, immunologist Dennis Burton, says the increasing ability to isolate and then produce broadly neutralizing antibodies against influenza could well open up alternative strategies to stopping flu, including passive immunotherapies employing "super-antibodies." Burton thinks researchers are at an inflection point in the use of antibodies and that even passive administration—directly injecting antibodies—could be a viable strategy for protecting against flu. Studies of this approach are already happening for HIV.

"One way of countering a suddenly emerging pandemic flu would be to have ideally a universal flu vaccine that would protect against anything," says Burton. "Another is to have stockpiled antibodies—that were very broadly neutralizing—that would target a pandemic strain. Even if you couldn't prevent infection, you could at least prevent maybe the worst symptoms and disease. Vaccines are always better with passive antibodies because then they're effective for much longer, and they're much cheaper, and so on and so on. But absent a vaccine, then the antibodies have a role."

Direct functional screening approaches have also led to the discovery of potent super-antibodies to other viruses besides flu, he writes in *Nature Reviews Immunology* along with Toronto biotech Adimab's senior scientist Laura Walker. This kind of screening produced a pan-influenza neutralizing antibody called F16, isolated by filtering through 104,000 plasma cells from eight immune donors. This is the antibody Wilson's team used to build its experimental peptide.

## Low fuel for flu effort

But Osterholm warns that the clock is ticking. "There's a number of candidates out there. The problem is they're all in the early stage."

In his view, it's vital that the flu vaccine effort pick up the pace, and that means better resources. Annual funding for flu vaccine this year was about US$32 million at the NIH, with another $40 million with a defense-related part of the federal government, the Biomedical Advanced Research and Development Authority. This is compared to about a billion dollars in funding for HIV vaccine research. "We don't compete aircraft carriers versus tanks. You need both," Osterholm says. "This is really about national security. The infectious diseases are against all of us. And this is one where we really, as a global community, need to come together and say, what is it that we need to do that is necessary to hold off, if not get the upper hand against these microbes?" The funding levels as he sees it are a measure of priorities. "Don't tell me the US government has made this a major priority when we're investing about $72 million."

This may be poised to change. At the end of February, eight Democratic US senators introduced a bill called the Flu Vaccine Act calling for a total investment of $1 billion for flu vaccine development over the next five years. Aside from it being a senate bill sponsored by Democrats, it will take more than money to get the job done, at least in Osterholm's perspective. "This is going to take really comprehensive coordination, and it's going to take the private sector being involved," he says. "This has got to be a comprehensive initiative that includes academic researchers, the government, nonprofit organizations, and industry. This bill has none of that, and basically puts the NIH in charge."

But this year's flu season, if anything, is making scientific voices more strident. "Our current vaccines are barely adequate, and the nation's drug regulators and science-funding agencies aren't doing enough about it," Stanford science and public policy fellow Henry Miller recently penned in the *Los Angeles Times*. "The fraught flu season of 2017-18," Miller writes, echoing voices in the scientific community following the 2009 and other recent bad flu seasons, "is a sign." ■

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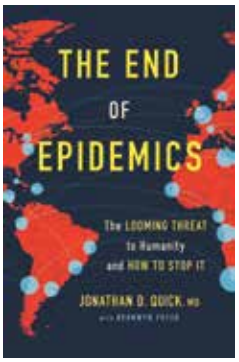
# Drawing Lessons from AIDS to *Prevent Future Epidemics*

**Jonathan Quick describes how the right mix of science, funding, leadership, and communication can come together to secure the world against future epidemics.**

## By Kristen Jill Kresge




**THE END OF EPIDEMICS**
**The Looming Threat to Humanity and How to Stop It**
By Dr. Jonathan D. Quick and Bronwyn Fryer
304 pages. St. Martin's Press.

The opening chapter of "The End of Epidemics: The Looming Threat to Humanity and How to Stop It," describes three of this century's most devastating bouts with infectious pathogens—the 1918 influenza pandemic, the AIDS epidemic, and the Ebola outbreak in West Africa in 2014. In chilling details, Jonathan Quick, senior fellow and former president and Chief Executive Officer at Management Sciences for Health and instructor of Medicine at Harvard Medical School, and his co-author Bronwyn Fryer describe how these epidemics gained footing and spread rapidly, together killing hundreds of thousands of people.

For influenza, it was a mutation to the seasonal strain that allowed this virulent virus to erupt in far-flung regions of the planet just as the end of the first world war approached. In the end it killed between 50 and 100 million people worldwide, making it the deadliest flu pandemic in history. The ongoing HIV epidemic was the result of a chimpanzee strain of a related virus that jumped species, crossing into the human population at least five times. The last time it occurred in Cameroon, the virus mutated, allowing it to spread rapidly among humans there, and then across the globe. Since then, 76 million people became infected with HIV and 35 million of them died. The most recent Ebola epidemic began with a two-year old boy playing in a tree

inhabited by Ebola-carrying bats in a small village in Guinea. Not long after this young boy died, the Ebola virus exploded in three West African countries, infecting nearly 30,000 people and killing more than 11,000 of them before it was snuffed out.

These three examples illustrate the deadly consequences that arise when a virus jumps from animals to humans, or mutates in such a way that humans have no prior immunity to it. It is scary stuff, and Quick and Fryer don't hold back from conveying an impending sense of doom. "Somewhere out there a dangerous virus is boiling up in the bloodstream of a bird, bat, monkey, or pig, preparing to jump into a human being. It's hard to comprehend the scope of such a threat, for it has the potential to wipe out millions of us…over a matter of weeks or months." This threat, they write, overshadows that posed by terrorism, future wars, or even the devastating effects of climate change. It may sound like the stuff of movies but it isn't. Infectious disease specialists that model disease outbreaks paint a grim reality. In the highly interconnected world in which we live, a new epidemic could spread and kill incredibly quickly—Quick reports that some models suggest a death rate of over 300 million people for some potential pandemics.

Given this stark reality, it is rather surprising that "The End of Epidemics" actually strikes an optimistic tone. "I refuse to accept that the inevitable local disease outbreaks will continue to explode into epidemics that kill thousands or millions," Quick writes. Rather than dwelling on dire statistics, he instead proposes a call to action for the planet, referred to as The Power of Seven. It involves implementing decisive leadership, creating resilient national public health systems, focusing on prevention, communicating effectively, pursuing innovative science, securing the necessary financial investment, and maintaining committed advocacy from all citizens. While this may sound like a lot to take on, Quick thinks the world is up to the task of achieving this seemingly impossible goal. "If we can eradicate smallpox, mount the largest public-health treatment effort in history as we did for AIDS, stop SARS [severe acute respiratory syndrome] in its tracks, and stop hundreds of outbreaks every year, then surely we can use The Power of Seven to end devastating epidemics."

For those who work on HIV, there are many familiar stories in "The End of Epidemics." Quick and Fryer chronicle the earliest days of the epidemic and how fear and stigma stymied an effective response to the virus. They also detail the role activism played both in the US and abroad in getting treatment to those infected. There is even a brief section on both the challenges and encouraging developments in HIV vaccine research. Quick is clear about the need for vaccines against intractable pathogens such as HIV, and others too. "As a doctor, I know that nothing can protect people against illness as effectively as a vaccine. It is the single most cost-effective public-health tool we have."

*IAVI Report* spoke with Quick about his book and an edited version of our conversation is below.

**It seems as though there is more attention being paid to epidemic and pandemic preparedness, precipitated at least in part by the most recent Ebola outbreak. Why hasn't it been more of a focus in the past?**

Well the reason it hasn't been a focus in the past is that there is this cycle of panic and neglect, or panic and complacency. We've seen it repeatedly. With the first new pathogen in the 21st century, SARS, there was a lot of panic. SARS came out of China in 2003 and rapidly spread to 27 countries and there was a huge outpouring of interest. Hundreds of pages of reports were done and a lot of promises were made. But a few years later, nothing much had changed. Then we had Avian Flu in the mid-2000s and then the 2009 Swine Flu. Each time it's been the same cycle of panic, lots of study, unmet promises of improved preparedness, and a slow drift back into complacency.

What I think has put pandemic preparedness back in the world's attention is the Global Health Security Agenda, which was a US-catalyzed global initiative that actually was launched in February of 2014, just before the Ebola outbreak. This was a really well conceived effort to attack the core reality that only one of out of three countries worldwide have the ability to prevent, rapidly detect, and quickly respond to outbreaks. Only one out of three countries! There is no mystery what should be done. The World Health Organization (WHO), through the International Health Regulations, has made it excruciatingly clear what is needed. Now the Global Health Security Agenda has 60 committed countries and a lot of supporters.

You then had Ebola, which really exploded at the end of 2014. There was a big horror fac-

tor associated with it that really got into the headlines. Ebola is actually not that contagious, and we saw how quickly it came under control once the people of West Africa understood what needed to happen. Then, a year later Ebola was followed by Zika, which is a virus that had been sleeping quietly in West Africa for 70 years. Then all of a sudden, a decade ago, Zika started moving eastward across the Pacific until in 2015 it exploded in Brazil. It was almost like one of these forest fires that gets going in the roots and then all of a sudden, poof—the whole forest is on fire.

So it was the Global Health Security Agenda that began raising the profile of epidemic and pandemic preparedness, and then Ebola, Zika, and now the ongoing Yellow Fever outbreak that were the main factors. It is also the hundredth anniversary of the Spanish Flu of 1918 that killed between 50 and 100 million people.

**So what could be done differently to be keep the focus on potential epidemics?**

Well if you consider the contrast between the response to SARS and Ebola, it is really striking. SARS was the first new pathogen of the 21st century and it was one plane flight away from getting into countries that couldn't control it. But it was wrapped up within six months because of the initiative taken by the then Director General of WHO, Dr. Gro Brundtland. When I asked what made her decide to build WHO's outbreak response capability and to be so decisive against SARS, she responded that people in positions of leadership have everybody coming to them with their issue. The reason she took action on infectious disease was that the responsible WHO team made a very strong case for stopping SARS.

We need to recognize that businesses and international organizations are very much victims of the "economics and the politics of now." And so, what we need to do at multiple levels is keep the bell ringing and really work on getting a broader base of support for these efforts. Not just in international organizations, but also within the business community. Businesses have the most to gain from getting this right, and the most to lose if we continue to leave ourselves vulnerable.

**You write in the book about how furious you are that the international community isn't investing sufficiently in preventing potentially devastating epidemics/pandemics, but rather choosing to spend an extraordinary amount of financial resources trying to control epidemics when they happen. As you say, "in both economics and epidemics, prevention always far surpasses even the best efforts at cure." Is this changing now?**

Well, I will say that following Ebola and with the Global Health Security Agenda, there have been some dramatic investments in building epidemic preparedness. The WHO partnership platform mapped out at least 20 governments, international agencies, and foundations that have made commitments and contributions. So there has been a good outpouring of support to accelerate preparedness efforts. There is also the Pandemic Emergency Financing facility that the World Bank established, and the commitment to CEPI [the Coalition for Epidemic Preparedness Innovations], which are really important investments and commitments. There's also been some notable contributions on the side of the private sector, especially by Unilever, Johnson & Johnson, and the members of the Private Sector Roundtable. I think it's a matter of sustaining those investments.

**Many experts predict that the next pandemic will likely be caused by influenza. If another flu pandemic is inevitable, why do you think there hasn't been more public and private support of better flu vaccines?**

First you have to consider the history of the flu vaccine. The first flu vaccine was developed in 1938 and was used in World War II to protect US military forces. Among the researchers who developed it was Jonas Salk, who later used his flu vaccine experience to develop the polio vaccine in 1952. The flu vaccine is 80 years old this year, and yet it's the least consistently effective vaccine that we have. You have to ask, why?

Influenza is a complex enemy but I think there was also complacency on the part of the scientific community and on the part of the broader public health community because flu was seen as just a seasonal irritant. We didn't really focus on the fact that it kills as many as 56,000 people a year in the US in the worst years.

I think another factor is that the seasonal flu vaccine is a steady market for the pharmaceutical industry and there is a huge opportunity cost of investing in a universal flu vaccine that will be tough to develop. So I think it's a really egregious example of both government and market failure that we do not have a better flu vaccine.

The good news is that there are probably a dozen different efforts going on now to develop a universal flu vaccine, which is really exciting. It's good that pharmaceutical companies and the US National Institutes of Health [NIH] are also supporting new methods of vaccine production, which will enable us to produce more vaccine, more quickly in the event of an overwhelming flu pandemic.

But I think we need to look back and ask why did it take us so long to wake up to the need for a more effective flu vaccine? Mike Osterholm from the University of Minnesota has been saying since 2011 that we need a billion dollars a year for flu vaccine research. There is finally a bill in Congress proposing that. So I hope it happens.

**Another topic you cover in the book is the role climate change and deforestation have on the emergence of infectious pathogens. You pose the question in your book of whether we might be entering the century of pandemics. Why?**

First, there is the fact that the current population of the planet is four times as big and twice as urban as it was 100 years ago, with 50 times as much international travel. So that's one dynamic. One of the ways that epidemics start is when humans come in contact with pathogens, viruses in this case, for which you don't have immunity. When people are going in to the forest and cutting it down, they disrupt the reservoirs for the virus, whether it is a monkey or a bat or whatever, and that's when you get outbreaks. So part of it is that deforestation creates greater proximity between humans and the viruses.

The other thing is that if you map places where the Anopheles mosquito that carries malaria, and the Aedes aegypti and its cousin mosquitoes that carry Zika, Yellow Fever, and dengue, are, you see that they are starting to appear over a much larger geographic area. And that will only continue with climate change. The Aedes and related mosquitoes are already in at least 30 US states. It's almost a certainty that there's another virus out there like Zika that's just been lurking out there, and if that new virus gets into those mosquitoes, it's a real concern.

**One of your seven recommendations to prevent future epidemics is to strengthen national health-care systems. I was struck that the number of ancillary deaths from the Ebola outbreak because of the breakdown in public health services was nearly as high as the death toll from Ebola infection—there were 10,600 reported deaths from AIDS, tuberculosis, and malaria, and more than 11,000 reported deaths from Ebola. What can be done to shore up health services to prevent this from happening again?**

When you actually look at the dynamic of what happened in West Africa, one of the critical things was that West Africa wasn't ready. They were living under two bits of received wisdom, both of which were wrong. One of them was that Ebola wasn't in West Africa. Of course it was in the textbooks and all, but nobody really learned about it. The other was that just five months before the case in Guinea that started the outbreak, the Oxbridge Biotech group classified Ebola as a "dead-end" event. That is, they concluded that if an outbreak occurred it would burn out so quickly it couldn't explode into a major epidemic. As a result, there were no practices in place to deal with this situation.

So when people with Ebola started flocking to facilities, and health workers were reassigned to handle Ebola, the health facilities became sort of no-go zones for people who needed primary care. As a result, you have stories of women delivering babies on the street. This is where better planning and a more integrated approach to early detection become really, really important. It's not just in countries with weak health systems where services are disrupted. An analysis done by the Department of Homeland Security in relation to a pandemic here in the US suggested we would have services closed and millions of people would be affected.

The key thing is you need to plan ahead. There need to be annual drills, particularly in health services, so you can review the chain of command and all your responses that so you can move quickly. You can't start doing the planning when you're in the middle of an overwhelming epidemic. You may not have a major event for five or ten years or whatever, but that preparation is necessary.

**What do you think is the best model going forward for epidemic preparedness? Is it partnerships between the public and private sectors? Or something like the recently launched CEPI?**

The foundation for epidemic preparedness is strong national health systems that are capable of preventing, rapidly detecting, and quickly responding to infectious disease outbreaks. This is where the continued commitment of national governments worldwide to the Global Health

Security Agenda is vital to make the world safer from major epidemics. I also think awareness on the part of the private sector can really be helpful. There are several private companies that have been champions of epidemic preparedness. Having strong individual champions is also important, such as Peter Sands, who comes out of banking, was very involved with the World Bank, then at Harvard, and is now head of The Global Fund to Fight AIDS, Tuberculosis and Malaria. He's a great champion. Having people such as Sands, Bill Gates, and the economist Larry Summers talk about these issues is really critical. You also need multi-organization alliances among non-governmental organizations, governments, and the private sector.

In terms of CEPI, I think it is a superb creation. CEPI begins with the end in mind. They look at the whole chain of activities from start to finish—every piece that needs to be put in place to get from a great idea to an effective vaccine that is widely available where needed. That perspective is really important. They've done the difficult task of priority setting and they have a pragmatic outlook on who can contribute and add best value at each step in the process. I think their biggest challenge is on the resourcing side. The ideal situation would be to have a billion dollars a year, which is actually not that much given the gaps that we have in vaccines and technologies.

**The first of the seven actions that you propose in your book is quick and decisive action by government and public health leaders. Given the proposed cuts to both the US Centers for Disease Control and Prevention and the NIH, do you think this type of decisive leadership on pandemic preparedness is realistic?**

I think it's a greater challenge, for sure. It always helps if you've got somebody who did what George W. Bush did for AIDS or Barack Obama did for global health security. It always helps if you've got a willing and enthusiastic champion. But when you don't, you can't just say, "Oh, well, we'll write off this half decade or this decade." You have to continue getting the message out there. Cutting the CDC's budget is just madness because there's no question in my mind that we're going to pay heavily—both in financial terms and in human lives—if in fact these cuts are made.

That's why 200 organizations and leaders came out with a strong letter saying this doesn't make sense. I also think that, again, having private sector leaders clearly send this message is important. This is something that Peter Sands argues for. There are a lot of different stakeholder groups that need to keep the pressure on when the current leadership is not getting the picture.

**Even though your book describes the devastating effects epidemics have, you also manage to strike an optimistic tone. Why are you hopeful?**

The reality is there will continue to be local disease outbreaks. There are also going to be regional epidemics. But I believe we can stop devastating epidemics and global pandemics. The scientific and public health community know what needs to be done. With the right leadership and strategic investments, we can do it. The difference between a local disease outbreak and a major epidemic is human action or inaction.

With smallpox, it wasn't until 1951—when Europe and North America had already proved that they could eradicate smallpox—that the conversation started at WHO on worldwide smallpox eradication. It took 15 years before the world's health leaders agreed to mount an eradication effort. But once that decision was made, it took only a decade to successfully eradicate the virus. The tragic part is that in the 15 years during which doubting health officials and Cold War politics were preventing decisive action, 30 to 40 million people died.

I'm also hopeful because when I look back, I've seen the impossible happen multiple times. We use the example in the book of when President Kennedy said that we would send a man to the moon and return him safely by the end of the decade. When they got working on that, they didn't have the technology to do it. Yet the leadership said we're going to the moon, and they did.

Look at what the picture was in 2000 with AIDS treatment. I remember those conversations. At a cost of US$12,000 per person per year, the majority of the global health community would have said it was impossible to mount large-scale treatment programs. Yet today we have approximately 21 million people on treatment.

So I think there's no question we can make the world safer. For most pathogens, if we detect them early enough and institute good public health measures, we've shown they can be contained. For other pathogens, we need a combination of getting the right vaccines and other medical measures in place. I think we have to give it our absolute best shot. ■

# Remembering David Cooper: *A Great Leader in HIV Epidemiology, Treatment, and Prevention*

The battle against HIV/AIDS lost another great soldier recently with the passing of Australian immunologist and clinician David Cooper on March 18. Cooper was a pioneering scientist and champion for HIV treatment and prevention, and he left an indelible mark on the field he dedicated his career to. "He had a great skill in knowing the right questions to ask and then applied a creative and rigorous strategy to find the answer," recalls Sharon Lewin, director of the Peter Doherty Institute for Infection and Immunity in Melbourne. "It was a winning formula over a long and spectacularly successful career."

Cooper was involved with HIV/AIDS from the earliest days of the epidemic. He was a research fellow in cancer immunology at the Dana Farber Cancer Institute in Boston, Massachusetts, in the early 1980s when HIV was first observed in groups of young gay men in the US. From there, he returned to his home country where he diagnosed the first cases of HIV/AIDS in Australia in 1983 while at St. Vincent's Hospital at the University of New South Wales. Cooper went on to become the inaugural director of the Kirby Institute for Infection and Immunity in Society, the leading organization in HIV/AIDS research and epidemiology in Australia. But his reach extended well beyond his home country.

"David was a major global leader from the very beginning of the HIV epidemic—across Australia, the Asia Pacific region, and beyond," says Lewin. From 1994-1998, he served as president of the International AIDS Society (IAS). During his tenure, Cooper presided over the landmark 1996 IAS conference in Vancouver that ushered in combination antiretroviral therapy, transforming an HIV/AIDS diagnosis from a death sentence into a chronic, treatable disease for those who could access the drugs. He was a steadfast advocate for ensuring that these life-saving treatments became available more broadly, which began to happen in earnest four years later after the IAS conference was held in Durban, South Africa. "He was always highly committed to his patients and a major advocate for people living with HIV," Lewin says.

Cooper reflected on this remarkable achievement in an article published about him in *The Lancet* just two years ago (https://doi.org/10.1016/S0140-6736(16)32180-8). "The story of HIV is a modern medical miracle," he said. "From despair and tragedy, we have moved into an era of chronic treatable illness, in just 30 years." This article also notes that as a clinician, Cooper was involved in trials of every HIV medication on the market.

He was also adamant about the need for better HIV prevention, including a vaccine. "Although he is most well known for his extensive work on antiretrovirals and treatment strategies, he had a long standing interest in vaccines and was a firm believer that a vaccine was the only way to see the end of the HIV epidemic," according to Lewin.

He is remembered by colleagues for his caring nature, his determination, and the way he inspired others. "David Cooper was an early leader in HIV treatment and prevention, and an inspiration for so many people in the AIDS field, myself included," says Mark Feinberg, chief executive officer of IAVI. "David was exceptionally dedicated to the care of individuals living with HIV and so very thoughtful and generous with his colleagues. His passing is a loss not only to our field but to the many people who were encouraged by him in their efforts to combat AIDS."

*—By Kristen Jill Kresge*

# "She was the best of us"

## Remembering Bonnie Mathieson: A champion of young scientists

At the Annual Scientific Retreat in 2016 for the Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Design (CHAVI-ID), Bonnie Mathieson was invited to join its leader, Barton Haynes, and his guests, at his table for dinner. She politely declined and dashed over to sit at a table full of young investigators. Out of the corner of my eye I could see them all leaning in to hear what she had to say, while she listened intently to them. I reached for my phone, catching this photo of Bonnie at her best (see top photo, next page).

At the time, it seemed there would be countless opportunities for us all to hear Bonnie Mathieson's wise perspectives on how an HIV vaccine could be achieved. But on January 8th, Bonnie Mathieson left us all, without notice, just a week into her retirement.

Just a month before that CHAVI-ID meeting, Bonnie and her beloved husband, Don, celebrated their 50th wedding anniversary. Before their celebration, she had prepared a box of tiny pots filled with fragile cuttings from her wooded backyard, intended for my garden. She assured me: "These should be okay if you coax them a bit—just get them in the ground and give them some love." On a small bit of paper, informed by her botany education in the early 1960s at the University of Illinois, she had written: Blue bugloss, Liatris spicate, Mertensia virginica, Anemone nemorosa. Every spring, my yard blooms with hearty flowers cultivated by Bonnie, reminding me of her special spirit always so filled with hope.

Bonnie also constantly cultivated young researchers, all the while sharing her vast knowledge, wisdom, and fabulous sense of humor. Over decades, she "seeded" the HIV vaccine field by encouraging young investigators and coaxing them to become independent. She gave them confidence that they would thrive just as she envisaged the struggling green cuttings she chose for my yard would one day be well-established, vibrant, and beautiful. The field of HIV vaccine research will surely continue to be enriched by what Bonnie thoughtfully propagated over more than three decades.

At the recent Keystone Symposium on HIV Vaccines, where Bonnie was sorely missed, we started a memory book so others could share their sentiments directly to Bonnie and her family. As these thoughts convey, she was a source of scientific savvy and inspiration to many. What follows are just a few of the entries reflecting on what Bonnie meant to the cadre of scientists involved in the quest for an HIV vaccine.

*—By Margaret M. McCluskey,*
*Senior Advisor for HIV Vaccine Research at USAID*

*"At times when I was feeling discouraged, she sensed that and offered advice. Bonnie was a uniquely kind soul."*

*"Bonnie was always kind to a young, nervous PhD student who felt out of her depth."*

Bonnie with early-career investigators at a 2016 Duke CHAVI-ID retreat.

*"Bonnie was so easy to connect with. She was a mentor, a source of endless information and insights."*

*"She was so sincere, so generous with her time, so encouraging, and so interested."*

**"Bonnie's kindness, enthusiasm, and encouragement truly inspired me. I hope to someday look after young scientists in the same way."**

*"I appreciated how Bonnie listened to all voices, both loud and soft."*

Bonnie with Barton Haynes.

*"Her smile, warmth and generosity was only overtaken by her incredible mind and brilliant insights."*

**"I never met anyone so open, inclusive, and fun in so many ways — from the deeply scientific to the silly."**

*"You were kind and strong, a unique pairing in the world of science."*

Bonnie and colleagues at the 35th Annual Symposium on Nonhuman Primate Models for AIDS, August, 2017.

*"We were all big fans of you, Bonnie. And still are."*

**"This extraordinary woman was just about everything a person aspires to be: kind, intelligent, sensitive, focused, loving, loyal."**

# Upcoming HIV-Related Meetings


**APRIL 2018**

***2018 American Conference for the Treatment of HIV***
April 5-7; Chicago, Illinois, USA
More information: http://www.acthiv.org

***Keystone Symposia: HIV and Co-infections: Pathogenesis, Inflammation and Persistence***
April 15-19; Whistler, British Columbia, Canada
More information: www.keystonesymposia.org

***HIV & Hepatitis in the Americas***
April 19-22; Mexico City, Mexico
More information: http://hivhepamericas.org

**MAY 2018**

***14th International Workshop on Co-Infection – HIV & Hepatitis***
May 16-18; Seville, Spain
More information: http://www.virology-education.com/event/upcoming/14th-co-infection-workshop-2018

***16th European Meeting on HIV & Hepatitis: Treatment Strategies & Antiviral Drug Resistance***
May 30 - June 1; Rome, Italy
More information: http://www.virology-education.com/event/upcoming/16th-european-hiv-hepatitis-workshop-2018

**JUNE 2018**

***7th Asian Conference on Hepatitis and AIDS (ACHA)***
June 9-10; Beijing, China
More information: http://www.virology-education.com/event/upcoming/acha-2018

***22nd Asia Pacific AIDS and Co-Infections Conference (APACC)***
June 28-30; Amsterdam, Netherlands
More information: http://www.virology-education.com/event/upcoming/apacc-2018

**JULY 2018**

***10th International Workshop on HIV Pediatrics***
July 20-21; Amsterdam, Netherlands
http://www.virology-education.com/event/upcoming/10th-workshop-hiv-pediatrics

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