Vaccine unit races against emerging infectious diseases

From her Iowa City office in spring 2013, Patricia Winokur, MD, cast a concerned eye to the east—the Far East—as a dangerous new strain of avian influenza emerged in China.

By Jennifer Brown
Illustration by LeeAnn Eddins
The H7N9 flu sickened 135 people, most of them after contact with live poultry. The majority of people had severe respiratory infections, and 44 died. Because this strain had never circulated in humans, immune systems were not primed to respond. If the virus acquired the ability to spread from human to human, the world population would be very vulnerable, potentially facing a pandemic of high mortality.

It was a familiar scenario to Winokur, professor of internal medicine and director of the Vaccine and Treatment Evaluation Unit (VTEU) at the University of Iowa. Winokur is a veteran of clinical trials testing vaccines against newly emerging pathogens, including the H1N1 “swine flu,” which caused the last worldwide flu pandemic in 2009. So she was not surprised when the call came in late August that launched the UI VTEU’s test of a vaccine against H7N9—a ticking time bomb that, if not diffused quickly, had the potential to become a new pandemic.

On Aug. 31, Winokur phoned colleagues across the university, coordinating the checklist of financial, regulatory, and human safety requirements that must be in place before any clinical trial can start recruiting participants. She contacted the therapeutic committee to initiate its review of the experimental vaccine; hospital billing and the central university finance office to establish appropriate payment for the trial; and the Institutional Review Board, which ensures safety and ethical treatment of clinical trial participants, to review and rule on the protocol. This trial would consume a huge amount of her clinical team’s time, so she also reallocated work on other trials and added six staff members to her study team.

On Sept. 20, an email went to the UI’s nearly 45,000 students and employees, describing the trial and inviting them to consider participating. Fliers were posted around campus and throughout the community, and announcements were made through university communications channels and via local media in an effort to mobilize people willing to roll up their sleeves and be vaccinated.
By Sept. 23, Winokur had the vaccine from Sanofi Pasteur along with an adjuvant from Novartis Vaccines and Diagnostics designed to boost immune response to the H7N9 antigens. By Oct. 11, the UI site was fully enrolled with 176 participants, and immunization and data collection had started. By early 2014, the UI portion of the trial was complete, and Winokur expected lab results in one to two months.

In the meantime, more new cases of H7N9 were being reported in China, reinforcing the need to get data on the vaccine as quickly as possible. "We and the other VTEUs are the go-to sites for these very important, urgent trials," says Winokur. "The H7N9 trial is a good example of a situation where the government needs data on the safety and efficacy of a vaccine urgently and asked us to really push the timeline, because they needed this data fast."

**Tradition of success**

The clinical research expertise, the infrastructure, and the collaborative cross-campus relationships that facilitated the H7N9 vaccine trial at the UI have evolved over several decades, a period in which Iowa has developed a reputation for exceptional success in vaccine trials.

In the early 1990s, Jack Stapleton, MD, UI professor of internal medicine and microbiology, and associate director of the VTEU, established a clinical research team focused on finding treatments for HIV, the virus that causes AIDS. Stapleton’s group participated in various trials for anti-viral therapies and vaccines through the National Institutes of Health-funded AIDS Clinical Trial Groups. Over the following decade, Stapleton expanded the scope of his team’s work into vaccine trials for other viruses, including hepatitis A, herpes simplex, and human papillomavirus (HPV).

“Our team was very successful,” he says. “In particular, we developed a reputation for high-quality work and strong enrollment and retention of study participants.”

In 2002, in the wake of 9/11, when the NIH needed clinical sites to rapidly test vaccines against potential bioterrorism agents, the UI HIV clinical trials group was tapped to participate in a trial for smallpox vaccine. Stapleton asked Winokur to help manage the UI portion of the trial.

In keeping with its track record, the UI site was among the most successful—enrolling more subjects more quickly than other sites—for the smallpox trial, which determined...
that the stockpiled vaccine could be diluted up to five times and still retain its potency, automatically multiplying the number of available doses.

In 2003, Winokur and colleagues in the Departments of Internal Medicine and Microbiology, including Michael Apicella, MD, leveraged the UI’s success in vaccine trials with its long-standing expertise in bacterial pathogens to obtain a seven-year, $22.2 million contract from the National Institute of Allergy and Infectious Diseases (NIAID) to establish a Bacterial Respiratory Pathogens Research Unit for developing and testing vaccines and treatments against bacterial respiratory infections in humans.

“Between the bacterial pathogens work and our vaccine trials, we assembled a pretty formidable and well-trained staff and well-funded research team,” Stapleton says.

In 2007, the UI received a seven-year, $23.7 million contract from NIAID to become an independent VTEU, under Winokur’s leadership—one of eight VTEUs at that time. The multimillion-dollar contract was renewed in 2013. There are now nine VTEUs, each of which can potentially receive funding up to $135 million per year over a seven- to 10-year period.

New grant, new roles

Throughout the VTEU program’s 50-year history its priorities have evolved to keep pace with emerging public health needs and concerns. VTEUs are now required to establish partnerships with infectious disease experts in developing countries to increase the network’s capacity to study infectious diseases where they are endemic. These partnerships will improve understanding of how and why new diseases emerge and expand the testing of new vaccines and therapies in populations most affected by these diseases.

Once again, homegrown expertise provided key connections and capabilities to help the UI VTEU fulfill this new goal.

Mary Wilson, MD, UI professor of microbiology and internal medicine, is an expert in leishmaniasis, a disease caused by infection with *Leishmania* parasites, which are transmitted by the bite of sand flies. The most severe form of the disease, visceral leishmaniasis, attacks internal organs and is fatal if left untreated.

Wilson has established several international partnerships focused on leishmaniasis, including one with Indian physician Shyam Sundar, MD, professor of medicine at Banaras Hindu University in India. Wilson and Sundar began working together in 2006—through a Tropical Medicine Research Centers (TMRC) grant from the NIH—to study the epidemiology, human genetics, and human immune responses to visceral leishmaniasis. The TMRC grant was recently renewed.

Sundar, who established a hospital in his home state of Bihar to treat patients with leishmaniasis, has developed some of the best clinical trials in the world for leishmaniasis therapies. His work led to the approval of liposomal amphotericin by the FDA for treatment of this disease, and to the approval of miltefosine for treatment in India and multiple studies of its efficacy in other countries.

“The VTEU collaboration gives us a way to look at immunological questions in humans that we would never be able to address otherwise.”

—Mary Wilson, MD

“Through Mary’s connections, we at the VTEU have been able to set up several international collaborations, including the one with Dr. Sundar and his unbelievably talented group in India,” Winokur says.

“I think collaboration with our international partners will be an exciting part of what is coming for us at the VTEU. I also think it will be a great opportunity to enhance our education options for UI infectious disease trainees, allowing them to visit these locations and see infectious diseases in other parts of the world,” she adds.

Although there currently is no effective vaccine for leishmaniasis, several trials are under way, including one started in spring 2013 at the
UI VTEU. This phase 1 trial of 48 participants will evaluate the safety, tolerability, and immunogenicity of a recombinant protein vaccine for visceral leishmaniasis, which was developed by the Infectious Disease Research Institute, a nonprofit in Seattle. The trial is one example, Winokur says, of how the UI is fulfilling another role of the VTEU sites: helping small companies bring products to market.

**Back to the bench**

Clinical trials often are seen as a final step in the process of translating basic science discoveries into approved treatments. But clinical trials can also serve as a starting point for new avenues of exploration.

The biological samples obtained during clinical trials conducted at the VTEU offer a unique opportunity for UI researchers to pursue more complicated immunological questions that may ultimately improve and advance vaccine research.

Using blood samples obtained from participants in the leishmaniasis vaccine trial, Wilson and fellow UI microbiologist Steve Varga, PhD, are investigating a fundamental question about human immune responses: How can you tell if a vaccine works?

The UI researchers are testing an idea that emerged from work in Varga’s lab suggesting that expression of two surface proteins on CD4 T cells may be a biomarker for the activation of these cells, which are important components of the adaptive immune response.

The vast majority of vaccines work by inducing protective antibodies. However, antibodies are not the protective agent against some pathogens, including microbes that live inside human cells such as *Leishmania*. In fact, Wilson notes, for certain diseases, including visceral leishmaniasis, there’s evidence suggesting that antibodies can exacerbate symptoms of the infection.

“Most efforts aimed at developing vaccines for these and other intracellular pathogens are focused on eliciting a cellular immune response—including activation of pathogen-specific CD4 T cells—because that’s what’s more protective,” Varga says.

However, unlike antibodies, which are easy to measure and quantify, it is very difficult to measure CD4 T cells responding to an infection or vaccination. It is even harder to determine whether the responding CD4 cells will protect humans from disease when they encounter the infectious organism at a later time.

Varga’s research on mouse cells suggests that expression of the two proteins—CD11a, CD49d—on the surface of CD4 T cells indicates that the cells have been activated by a pathogen.

The UI researchers want to see if expression of these cell surface markers can be used as a surrogate to identify protective immune CD4 T cells in human subjects receiving the leishmaniasis vaccine.

“What we hope to infer is whether the vaccine was successful,” Wilson explains.

Being able to determine if CD4 T cells are activated in response to a vaccine could provide a broadly applicable method to quantify vaccine success without needing to wait to see if vaccinated individuals are more protected from the disease than unvaccinated people.

“The VTEU collaboration gives us a way to look at immunological questions in humans that we would never be able to address otherwise,” Wilson says.

**H7N9 still ticking**

After the initial surge of more than 130 cases of H7N9 in April 2013, the virus died down during the summer months. However, the activity of avian influenza viruses tends to fluctuate seasonally, and as the weather turned cooler, the virus reemerged in China.

By early February, as *Medicine Iowa* went to press, more than 100 new cases of H7N9 had been confirmed, including 25 deaths.

“We are still watching this virus very closely,” Winokur says. “So far, H7N9 doesn’t appear to be capable of sustained human-to-human transmission, but there’s some indication from sequencing data that it has acquired some of the mutations it needs to spread between people. If that happens, an effective vaccine will be critical to prevent what could be a very dangerous pandemic.”
For as long as researchers have conducted vaccine trials at the University of Iowa, study participants have responded in great numbers and remained loyal participants—two hallmarks of the UI’s success.

Since 2007, the UI Vaccine and Treatment Evaluation Unit (VTEU) has enrolled nearly 2,200 volunteers into studies, for a total of 20,000 visits. The UI was a top-three enroller in 77 percent of the studies in which it participated and exceeded target enrollments in 65 percent of those studies. Over a seven-year period, only 23 participants did not complete their studies and less than 0.1 percent of study visits were missed.

“The Iowans who volunteer are such wonderful Midwestern people. They show up for all their appointments, which means we have superb retention and follow-through with our patients. For research studies, this is very important,” says Jack Stapleton, MD, UI professor of internal medicine and associate director of the UI VTEU.

“The individuals who volunteer for these types of studies are the backbone of our entire clinical trials program and they make Iowa an amazingly successful place to do this type of work,” adds Patricia Winokur, MD, professor of internal medicine and director of the UI VTEU.

“Honestly, antibiotic resistance is one of the things that scares me the most. Vaccines and other immunotherapies are going to be critical because we don’t have new antibiotics in the pipeline. To me, this is where infectious disease is hitting a critical era and vaccines may be an important way of buying us time until we can develop better antibiotics or methods of controlling these infections.”

—by Jennifer Brown
VTEUs were created in 1962 to conduct clinical trials of promising candidate vaccines and therapies for infectious diseases, especially for emerging public health concerns requiring rapid response, such as tuberculosis and anthrax.

Funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health.

Undertake studies that support product development, such as evaluations of novel investigational product delivery systems and reevaluation of current vaccine formulations and schedules of delivery.

- Baylor College of Medicine, Houston
- Cincinnati Children’s Hospital Medical Center
- Duke Medicine, Durham, N.C.
- Emory University, Atlanta
- Group Health Research Institute, Seattle
- St. Louis University
- **University of Iowa, Iowa City**
- University of Maryland, Baltimore
- Vanderbilt University, Nashville, Tenn.
Studies at the UI have evaluated vaccines for:

Herpes virus
Human papillomavirus
Influenza (including rare avian strains)
Leishmaniasis
Rotavirus
Shingles
Smallpox
Tularemia

The University of Iowa was awarded a 7-year, $23.7 million VTEU contract, which was renewed in 2013 with the potential for $135 million per year over 7 to 10 years.

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99.9% of study visits completed over a 7-year period.