

Jeremy Farrar: When disaster strikes

Jeremy Farrar had not intended to be at the forefront of avian influenza research. But as the director of the Oxford University Clinical Research Unit in Ho Chi Minh City, the bird flu outbreak found him.

As of June 2008, there were 285 reported cases of avian influenza, of which 243 were fatal. Jeremy Farrar has been involved with most of the 35 cases reported in Vietnam. In addition to treating patients, he is part of a collaborative effort to prevent this devastating virus from reaching epidemic proportions.

Farrar's early work focused on infections of the brain (1). But like many clinical scientists in Southeast Asia, Farrar now works on a number of indigenous afflictions, including malaria, typhoid, dengue fever, and other emerging infectious diseases (2). In the last few years, Farrar has focused on the pathophysiology and treatment of avian influenza (3, 4). He is also exploring the cross-reactivity of memory T cell responses to influenza in hopes of creating a broadly protective vaccine for H5N1 (5).

THE CALL

Do you remember what you were doing when you first heard that the bird flu had hit Ho Chi Minh City?

Yes, I remember vividly. It was a moment I'd been dreading. It was late at night during the Vietnamese New Year in January 2004.

I got a phone call from a friend who was a doctor in the hospital. There had been a group from the WHO visiting Ho Chi Minh City. They'd been in Hanoi, where the first case had been diagnosed a few days before. We had only just come through SARS and when the first case of influenza appeared, there was a huge fear that these new, unusual respiratory infections were a reoccurrence of SARS.

What happened?

The WHO team was visiting hospitals advising people to be watchful of unusual respiratory illnesses. During their

visit, the team and my colleague, Professor [Tran Tinh] Hien, who's the vice director at the Hospital for Tropical Diseases, went to see a child that the doctors were a little bit worried about. The WHO people—and this is not a criticism—decided it was unlikely that the child had SARS or avian influenza. They left, but Professor Hien stayed behind to talk with the child and her mum. The girl admitted that she had been quite sad in the previous days with the death of her pet duck. The girl and her brother had fought over burying the duck and, because of this argument, she had gone back, dug up the duck, and reburied it—probably so her brother wouldn't know where it was buried.

With that history, Professor Hien phoned me at home and said he was worried about the child. He took some swabs from the child's nose and throat and brought them back to the hospital. That night the laboratory ran tests on the samples, and they were positive for Influenza A. So we started treatment sometime after midnight, and the child survived. It's actually a lovely story because it shows you that in clinical medicine, taking a good history and being able to act quickly is still very important. As a result, the girl survived and is now a very happy teenager back in school.

This must have been terrifying if you've remembered it so well.

It was. This was a year or two after SARS. Everybody across Asia was frightened of this disease reappearing, and it was particularly frightening for medical staff because SARS had been so infectious between people. In fact a good friend of mine, Carlo Urbani, who was the WHO representative in Hanoi, died of SARS as a result of identifying patients and then ensuring that the hospital was closed off. He stayed in the hospital for two or three weeks and didn't leave. His



Jeremy Farrar

actions probably prevented SARS from breaking out across Vietnam. It was an incredibly courageous thing to do.

And of course, when you have an unusual respiratory infection in a hospital—whether it's in Ho Chi Minh City or Jakarta or Beijing or London or Washington, DC—and you have no idea what it is, it creates a frightening environment. You're first a human being and second a doctor, and yes, it was frightening. That's why it's so etched in our minds, I think.

Do you still worry when you hear about new cases of avian influenza?

Now, in 2008, I'm less worried than I was in 2004. In retrospect you can say, "Perhaps we didn't need to be so worried." But at the time we didn't know that.

Now there is some consensus that H5N1 won't pass between humans. Is the attention it continues to receive from both the public and granting agencies exaggerated?

No, I think the world has been right to take this seriously. The chance of something terrible happening is small, but it's also not quantifiable. I can't tell you whether it's 1% or 5% or 0.001%. However if [human-to-human transmission] were to happen, it would be a cata-

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strophic event. One that's very difficult to cope with.

Also, some of the investment that has come about as a result of the outbreaks has been very well spent. The capacity for diagnosis, treatment, and disease surveillance has improved immeasurably in the past four years. It went from being nonexistent in many places across Asia to being infinitely better than it was.

SEARCHING FOR A QUICK FIX

When a patient comes in with avian influenza, is it clearly something different than a normal flu?

It's variable. For a few days there's coughing and a fever, gradually it gets worse, and by the time these patients seek medical attention, they are often extremely sick. And not just with an infection of the lungs like in normal human flu. We saw one patient, for instance, who seemed to have a brain infection. And others had an infection of the liver or the kidneys. The patients can get worse very quickly. That's why the mortality rate has been so high. Sixty percent of reported cases have resulted in death.

Have treatments for influenza improved since the first outbreak of H5N1?

Over the last 30 years influenza has to a degree been neglected. We have a single drug, oseltamivir [a neuraminidase inhibitor], which is widely available. But we currently have no drug that we can deliver intravenously. To have a single drug for an infection caused by an RNA virus is a huge risk. Resistance develops very quickly in RNA viruses, and combination therapies are needed to treat patients. I hope researchers will continue to work for better diagnostics, better drugs, and a better vaccine. It's an insurance policy against the tiny risk of a very major problem.

Thus far, antibody-based vaccines against avian influenza have had limited success. Do you think we know enough about the T cell response to influenza to develop a T cell-based vaccine in the near future?

No, I don't think we do. Understanding what mediates protection against RNA viruses like HIV or influenza, whether it is antibody-mediated, T cell-mediated, or both, has proven elusive.

In the end, my belief is that it's probably a false division. You may like to push the T cell response or the antibody response but, ultimately, for long-term protection, you're going to need both for a vaccine to be functional. In the case of the influenza vaccine, we are still dependent on a technology that was developed 40 or 50 years ago.

But that is changing. Many organizations are now investing in research to make better influenza vaccines that could be produced more quickly in response to threats. The world really does need more than a single drug and a system of making flu vaccines more quickly and effectively than we've done in the past. You could be a real optimist—as long you weren't one of those people who caught H5N1—and say that this has been a sort of wake-up call to the potential consequences of an influenza pandemic.

A SUSTAINABLE SOLUTION

A good portion of your research is done at the laboratory bench, so why in Vietnam?

In my view, I think a more equitable way of approaching international health is to move the center of gravity from the developed world and bring the research to the countries that are most affected by those illnesses, to allow the benefits of that research to be felt by the people in those countries. And there needs to be a critical mass of people dedicated to research. No matter how brilliant you are, you're totally dependent on your colleagues around you. One person can't make a difference. I think there's been a realization that [infectious disease research] has to shift to where the diseases are. And it's happening, but it needs to speed up, particularly in parts of Africa, Asia, and Latin America as economies develop and enlightened funding agencies see the need to make that shift.

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2. Farrar, J. 2007. *Nat. Immunol.* 8:1277–1279.
3. Hien, T.T., et al. 2004. *N. Engl. J. Med.* 350:1179–1188.
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5. Yong-Hwa Lee, L., et al. 2008. *J. Clin. Invest.* 118:3478–3490.

"Understanding what mediates protection against RNA viruses like HIV or influenza has proven elusive."



A man herds ducks in Tay Ninh, Vietnam.

STEPHEN BAKER