H5N2 strain, says David Swayne, director of the U.S. Department of Agriculture's Southeast Poultry Research Laboratory in Athens, Georgia.

First confirmed in poultry on U.S. soil on 3 January in samples collected from Washington state, the virus began infecting birds across the Pacific Northwest, mainly in backyard flocks. By early March, it had infected commercial turkeys in Minnesota's Pope County, presumably carried there by wild birds. From there, it cropped up across the Midwest, hitting 12 states in total. Avian flu outbreaks normally slow as temperatures warm, but this time spring brought no reprieve. Nor do investigators understand why the virus is ravaging turkey farms, threatening so many birds that some industry observers have warned of a turkey shortage this Thanksgiving. Bird flu typically infects chickens more readily, Bender says. But the transmission route is the most troubling mystery.

Some scientists initially guessed that the virus was entering farms on wild bird feces stuck to equipment or workers' clothing. "We were fairly clear that we were seeing point introductions," says Beth Thompson, assistant director of the Minnesota Board of Animal Health in St. Paul. "These sites weren't connected in any way." Lately, the virus has spread more rapidly through nearby turkey farms, suggesting that it is windborne. "It could be a plume-related effect," Osterholm says, in which a gust carries feathers or dust long distances. Other hypotheses for the virus's spread include lapses in biosecurity and rodents tracking it onto farms.

Animal health officials have implemented stricter biosecurity measures like having workers wash boots and change clothes before entering a barn and mapped 10-kilometer-radius response zones around affected farms for surveillance and testing. Here in Minnesota, the state with the largest number of infected sites, scientists are searching for the virus in wild bird feces, dead birds reported by the public, and wild turkey carcasses felled by hunters.

The Animal and Plant Health Inspection Service, UMN, and the turkey industry are also joining forces on a massive case control study to understand how H5N2 is spreading. Researchers will soon fan out to at least 30 affected turkey farms and an equal number of farms that haven't been hit by the outbreak. They will take stock of farm management practices, the type of feed and equipment used, the presence of wild birds, and the farms' proximity to roads and waterways, among other factors.

The Southeast Poultry Research Laboratory is now testing a candidate poultry vaccine. The U.S. Centers for Disease Control and Prevention (CDC) in Atlanta is also developing candidate vaccine viruses for use in humans in case the disease spreads to people, as some avian flus have in the past. But CDC is "cautiously optimistic that we will not see any human cases" because the virus does not currently have genetic markers associated with increased severity in people, CDC's Alicia Fry said at a 22 April press conference.

Another unknown is whether the virus will stick around in wild birds after the outbreak burns out, posing a continuing threat to flocks. "Maintenance of a high-path avian flu virus within wild birds is unprecedented," says David Stallknecht, an epidemiologist at the University of Georgia, Athens. But H5N2 already has a track record of confounding expectations. "We have to keep an open mind," Osterholm says. "The greatest enemy we have right now is dogma." ■

Flu in the coop

Though no humans have been infected, the current outbreak is the largest in decades of a highly pathogenic bird flu virus.

PERIOD	STATES INVOLVED	VIRUS	NUMBER OF AFFECTED BIRDS
1924	Connecticut, Indiana, Illinois, Michigan, Missouri, New York, New Jersey, Pennsylvania, West Virginia	H7 strain (then referred to as "fowl plague")	600,000 (New York City only)
1983–84	Pennsylvania, Virginia	H5N2	17 million
2004	Texas	H5N2	6600
2014–2015	Arkansas, Idaho, Iowa, Kansas, Minnesota, Missouri, Montana, North Dakota, Oregon, South Dakota, Washington, Wisconsin	H5N2	30.7 million

DATA: USDA APHIS

INFECTIOUS DISEASES

Ebola survivors fight back in plasma studies

Trials hope to show whether antibodies from recovered patients can save lives

By **Martin Enserink**, *in Conakry*

Jean Pé Kolié came down with Ebola on 22 March 2014, the day after a French lab had confirmed that Guinea had been struck by the virus. A medical student, Kolié thinks he got infected 4 days earlier, when he saw a very sick patient at the emergency room of the Kipé hospital, here in the Guinean capital. Kolié, 29, made a full recovery. More than 2300 Guineans did not.

In February of this year, Kolié was the first Ebola survivor to climb into a massive, bright blue bus parked in front of the National Center for Blood Transfusion (CNTS). It was his chance to fight back against the disease. The $350,000 bus, a gift from the Bill & Melinda Gates Foundation, is a sophisticated mobile plasmapheresis center, in which blood plasma is collected from survivors and processed to be given to new Ebola patients as an experimental therapy at the nearby Donka treatment center, run by Doctors Without Borders (MSF). Teeming with antibodies to the virus, the plasma may help boost their defenses. "I hope that my plasma can save the lives of my compatriots," says Kolié, who is encouraging other survivors to board the bus as well.

Ninety people have so far been treated in the study, paid for by the European Union and coordinated by the Institute of Tropical Medicine (ITM) in Antwerp, Belgium, which makes it one of the largest treatment trials for Ebola ever undertaken. Results are due later this year. The study aims to recruit 130 patients, but enrollment has ground to a halt for a happy reason: The last Ebola patient in Conakry was discharged from the Donka center on 28 April. (There were only seven cases in all of Guinea last week.)

The World Health Organization (WHO) started pushing for studies of blood-based therapies in September, when the Ebola epidemic was exploding, experimental drugs like ZMapp and TKM-Ebola weren't ready, and there was a quickly growing pool of

Jean Pé Kolié was the first donor in Conakry's blue plasmapheresis bus.

Ebola survivors. Animal studies of similar therapies had yielded mixed results, and the findings of a 1995 human study in Kikwit, in what is now the Democratic Republic of the Congo (DRC), were ambiguous. Seven out of eight patients there who received survivors' blood survived themselves, but an analysis later suggested they were on the road to recovery anyway.

Early in the current epidemic, Sierra Leonean doctors treated 44 patients with whole blood from survivors, as had been done in Kikwit; the results have not been published. Three ongoing trials all use plasma instead of blood. This is technically more complex—plasmapheresis was never done before in Guinea, hence the imported bus—but it has several advantages. Survivors can donate every 2 weeks instead of quarterly, because their red blood cells are separated from the plasma and given back. Frozen at –30°C, plasma lasts at least a year, four times longer than blood. It also takes far less time to administer, a major advantage in Ebola treatment centers, where staff time is precious. (The Guinean trial is the largest of three plasma studies; hampered by a waning epidemic, its counterpart in Liberia enrolled only six patients, and the one in Sierra Leone just one.)

The Guinean team worried that recruiting donors would be difficult. "In Guinea, blood is sacred. You don't give it away," says CNTS researcher Alexandre Delamou. "And there were all kinds of rumors about MSF taking patients' blood and selling it in Europe." The study team kept a low profile in the media but worked hard to establish good relations with members of the Association of Recovered Ebola Patients in Conakry, in which Kolié is active. Carefully explaining that survivors might just be lifesavers can help convince people, Kolié says. Still, some donors keep their participation quiet out of fear of stigmatization.

Administrating the plasma brings its own problems. Because staff at Ebola treatment centers generally can't spend more than an hour wearing their suffocating biohazard suits, it takes four teams: one to explain the study and get written consent, a second to prepare the patient for transfusion, and two more to infuse two 250-milliliter bags of plasma—from different donors, to maximize the chances of success—and watch the patient for acute reactions.

MSF "initially wasn't all that enthusiastic about participating," Delamou says. "They were worried about the safety of their staff, which is understandable." Now, the collaboration is running smoothly, and every confirmed Ebola patient at Donka has so far agreed to participate.

The researchers acknowledge that results from the study will be difficult to interpret. The study has no control arm; both MSF and an ethical panel in Guinea considered it unacceptable to withhold a potentially lifesaving treatment from some of the patients. The team originally assumed that some patients would form natural controls because plasma of some blood types would not be available in sufficient quantities, but that hasn't happened.

The current plan is to compare patients in the study with those who came into the treatment center during the 3 months before it started. But that's far from an ideal control group: Those months included the peak of the epidemic in Conakry, when the center was stretched to its limits and treatment may not have been as good.

Even if the study does not show an overall effect on mortality, finer grained analyses could yield useful data. A lab in France will determine antibody levels in every batch of plasma to see if higher levels are correlated with a better outcome in recipients; investigators will also determine each patient's viral load right before the transfusion and 24 hours later to see if it drops. "We're probably not going to see a definitive answer from these studies," WHO's David Wood says, "but we will know what directions to pursue in the future."

> ***"I hope that my plasma can save the lives of my compatriots."***
>
> **Jean Pé Kolié**, Ebola survivor

If nothing else, the study has already shown that producing and safely administering plasma during an Ebola epidemic is feasible, says ITM's Johan Van Griensven—although it would be an even bigger challenge in, say, a remote forest village in the DRC than in this port city.

The big blue bus will stay in Conakry after the epidemic is over, says CNTS Director Nyankoye Haba, but what it will do isn't clear. Plasma, or components of it, can be used to treat some other infectious diseases and hemophilia, but a single plasmapheresis session costs about $85 in materials alone, Haba says. In a country where total spending on health per capita is about $67 per year, that price is almost certainly too high. ■

PHOTO: IDRISSA SOUMARE/AFREECOM