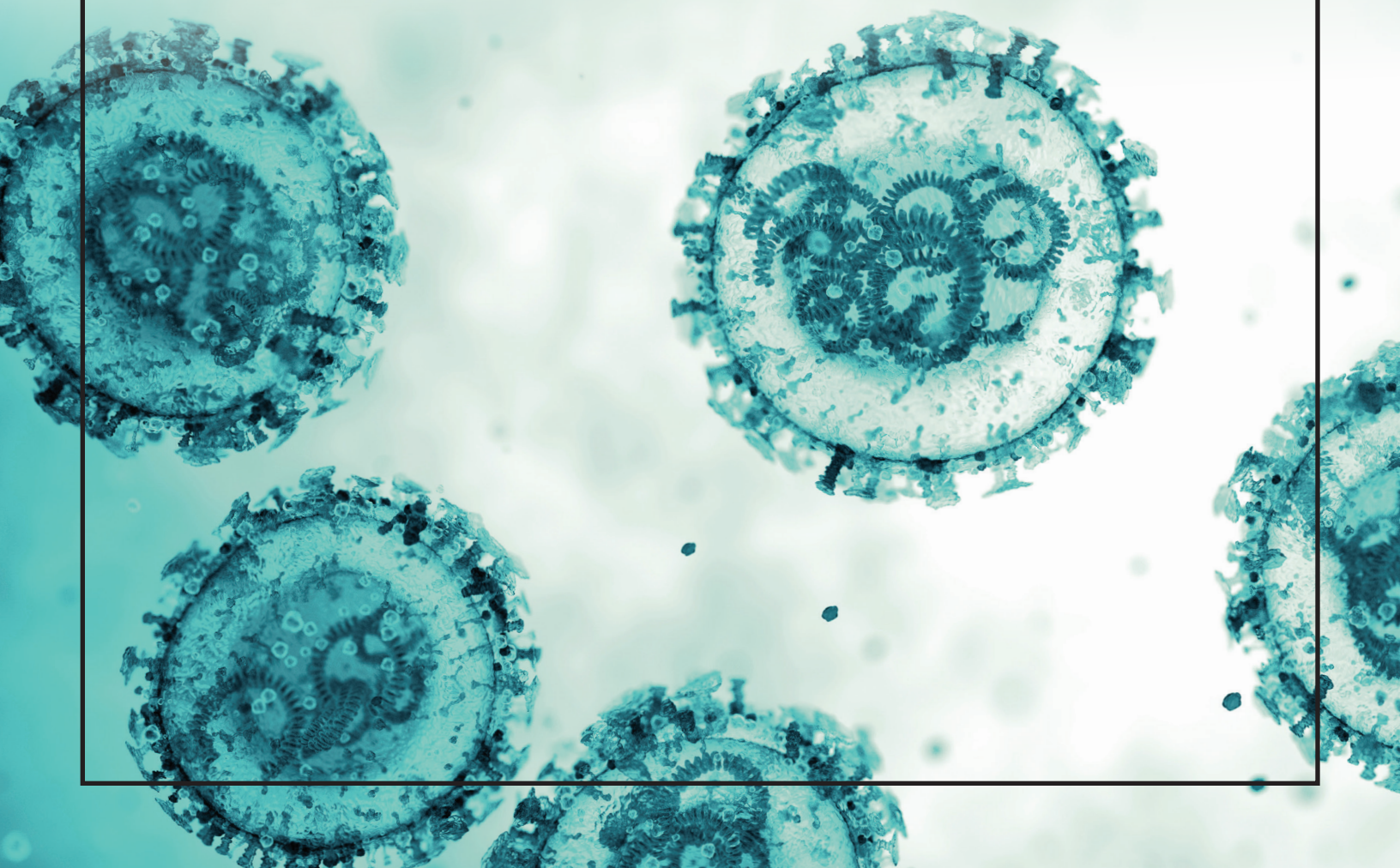




Genes, Planes, and Automobiles: How the Nebraska Public Health Laboratory Developed a Hantavirus Assay in 72 hours



Introduction

On the morning of Friday, May 8th, Emily McCutchen's heart was racing. Though she planned to take the day off, she had just received a call from the National Quarantine Unit (NQU)—a specialized infectious disease facility located on the nearby University of Nebraska Medical Center campus—warning her that a plane with American citizens was inbound, each potentially infected with a form of Hantavirus that is rarely seen in the United States. The visitors were coming from the M/V Hondius cruise ship, on which several passengers had fallen ill with the Andes strain (Orthohantavirus andesense) of Hantavirus.¹ This strain is the only one of its genus known to spread from person to person and brings with it an alarmingly high mortality rate.^{2,3}

Whether any of the incoming visitors had the virus was unknown. They would need to be tested as soon as they arrived at “o’dark thirty on Monday morning,” McCutchen recalls. As the then Deputy Director of the Nebraska Public Health Laboratory (NPHL), it was now on McCutchen and team to ensure that infected and presymptomatic patients could be rapidly identified, thereby enabling their transfer to a more secure biocontainment facility if needed.

Yet, creating such a test is no small task. “Conceptually, it’s very simple,” explains Mike Wiley, McCutchen’s colleague and the Assistant Director of Genomic Epidemiology at NPHL, “but developing an assay that’s ready to be used in a patient setting is very difficult to execute on in such a short amount of time.”

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Clinical assays have to meet specific federal requirements (including those outlined in the [Clinical Laboratory Improvements Amendments of 1988](#)) which ensure robust testing quality across clinical laboratories. “There’s a whole slew of tests that, by federal law, I am required to put this assay through before we can ever even think about using it to influence patient care,” says McCutchen. “If I was told that we had a week to bring the assay up—that would be stressful, if not impossible,” she continues, “and here, we had less than 72 hours to do it.”

The challenge before them was not an intellectual one. Quantitative reverse transcription PCR (RT-qPCR) tests are common. McCutchen’s challenge lay in logistics. To synthesize and ship the necessary reagents would eat up precious time. Among the reagents needed was a synthetic segment of the Andes virus’ genome matching the strain circulating on the M/V Hondius, one that could serve as control material in critical assay benchmarking tests⁴.

“That’s when we called Twist and said ‘Help!’,” McCutchen recalls.

In just over 24 hours, Twist had synthesized and shipped the needed material. Despite a flight delay and an improvised 10-hour drive, Twist ensured the gene arrived ready for use late on Sunday night. With it, McCutchen’s team confirmed the test’s validity against the Andes strain that was associated with the cases on the M/V Hondius and, against all expectations, was ready when the cruise ship passengers arrived.

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Detecting Andes Virus

Just hours before McCutchen got the call that Friday morning, the first full genomic sequence from the M/V Hondius' strain of Andes virus had been shared online, giving the team a critical leg up in designing their test.⁵

"Early on, there was this global effort where you had researchers in Switzerland, Senegal, and South Africa rapidly sequencing passenger samples and making the data publicly available," Wiley explained. "Their efforts to get these sequences out in a public forum enabled the rest of the community to see exactly what was circulating and compare it to the assays that were already available."

Typically, when a rare pathogen outbreak occurs, laboratories will first look for established tests before attempting to build their own. However, the Andes virus rarely spills over into humans. When it does, it typically occurs in South America, meaning that no established test was clinically available in the United States.

"I called the CDC but they didn't have a clinical diagnostic molecular assay" says McCutchen. "We started calling everyone we know to try and get anything we could."

Significant help came from a virologist at the University of New Mexico, Dr. Steven Bradfute, who had previously studied the Andes virus. With his assistance, the NPHL team validated a RT-qPCR assay targeting the virus' M-segment. Like other Hantaviruses, Andes virus is a single stranded, negative sense,

RNA virus with a genome divided into three segments: L, M, and S. The M-segment codes for two glycoproteins needed for virus-host interactions and can be used to specifically delineate Andes from its relatives, including the Sin Nombre strain which is endemic to the United States.^{2,6,7}

To perform such a test, the team would need custom PCR primers and probes, as well as a sample of the virus' M-segment to act as a control. Neither the primers nor the probes could be synthesized and delivered in such a short amount of time. But Dr. Bradfute offered some help.

"Within hours of contacting him, he had aliquoted and shipped primers, probes, and some control viral RNA for us," McCutchen recalls. This meant the team would have the material they needed to start the assay validation process. However, the control RNA he shared had been collected in 1997 and differed slightly from that found in the M/V Hondius strain.

"We knew it was similar, but the available genomic sequences for the M/V Hondius strain suggested there was a single mismatch that fell within a primer binding site," says McCutchen. Small though it was, this mismatch concerned her because "you just never know how much that single mismatch can affect the sensitivity and the specificity of your primer binding."

To truly validate their assay, they'd needed a control sequence that perfectly matched the M/V Hondius strain's M-segment.

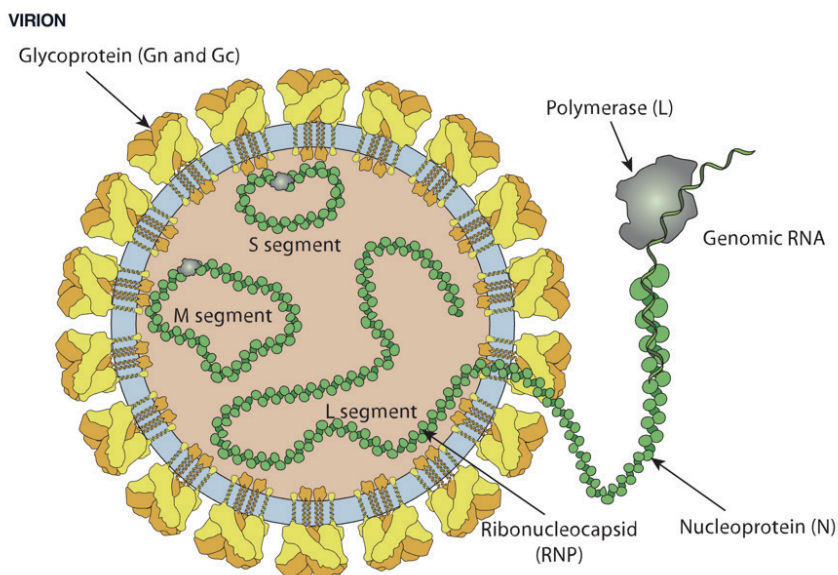


Figure 1. Orthohantavirus andesense. Here, the Andes virus can be seen with the three segments of its genome and their respective products. Image credit ViralZone, <https://viralzone.expasy.org/11847>

Twist Synthesized Genetic Controls

That Friday morning, at 08:51am Pacific Time, Wiley emailed his contacts at Twist Bioscience with an unusually urgent request for a synthetic control sequence. Less than a half hour later, he'd heard back from Twist and was able to submit the M/V Hondius sequence for synthesis at 09:26am.

"By 12:50pm central time [10:50am PT], we had an email from Twist saying 'Our internal teams are now working on your order. We'll see the sample is shipped to the Saddle Creek address tomorrow [Saturday] afternoon for Sunday delivery,'" Wiley recalls. "The Twist team was amazing, partly because I never had to plead with them for this quick help—they just said okay, and sent the sequence."

Twist's DNA synthesis platform is among the best in the industry and is known for its ability to produce highly precise, customized sequences. Such precision is critical when generating controls—any variation from the desired sequence introduces a risk of disrupting primer binding and altering the assay's validity. Errors cannot be tolerated, which is why many researchers turn to Twist. Among other capabilities, Twist offers several predesigned [synthetic control sequences](#) but can also be enlisted for [custom gene synthesis](#) whenever needed.

Recognizing the gravity of the situation, Twist prioritized Wiley's request. Typically, the synthesis platform is running at all hours of the day, processing a long queue of projects. Twist prides itself on turning orders around quickly, but to get this sequence to NPHL in the time frame they needed, Twist prioritized Wiley's request in the synthesis cue. By moving with urgency, Twist was able to synthesize, package, and ship the control sequence to NPHL just over 24 hours after Wiley's first email.

Unfortunately, after leaving Twist's production facility in Wilsonville, Oregon, unforeseeable shipping issues caused the package to miss its connecting flight in Dallas, Texas. The resulting delay meant the controls would have arrived late on Monday, well after they were needed.

"We were just in awe at how much Twist stepped up—and how little input they needed from us—to get this material synthesized and delivered before our visitors arrived."

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To ensure the package arrived on time, Twist arranged for the control material to be driven from Dallas to the NPHL team in Omaha, Nebraska, a roughly 10-hour journey. Ultimately, the package arrived shortly before midnight on Sunday, providing McCutchen and Wiley with the material they needed to ensure the assay worked, just hours before passengers arrived.

"To be able to have that sequence in hand and know that we could test against the actual strain that was circulating was such a sigh of relief," explained McCutchen. "We were just in awe at how much Twist stepped up—and how little input they needed from us—to get this material synthesized and delivered before our visitors arrived."

Synthesis and Delivery Timeline (Pacific Time)

FRIDAY MAY 8TH

- 08:51am** – First email sent from Wiley requesting Twist's help
- 09:17am** – Twist responded, asking Wiley to send the sequence details
- 09:26am** – Control entered Twist's synthesis pipeline
- 10:50am** – Twist internal biosecurity review completed; Shipping pickup scheduled
- 11:00am** – Synthesis processes began

SATURDAY MAY 9TH

- 09:40am** – Quality check completed and control sequence dropped off at shipping facility in Portland, Oregon
- 04:10pm** – Package departed shipping facility, headed to Dallas, Texas

SUNDAY MAY 10TH

- 06:22am** – Twist team checked shipping tracker and found a delayed status; package missed connecting flight in Dallas, Texas
- 10:45am** – Twist team hired courier to drive package from Dallas to Omaha, Nebraska
- 09:25pm** – Package delivered by courier to Wiley's front door in Omaha, Nebraska

Research Tools, Ready When They're Most Needed

Twist has spent more than a decade becoming an industry leader in the DNA synthesis space. This means doing much more than synthesizing DNA with extreme precision at scale. It means being attuned to the industry's evolving needs; developing a platform that removes barriers for researchers and makes it easier to get the tools they need; and it means being prepared to help in times of crisis.

This is far from the first time Twist has played an important role in helping researchers quell an infectious disease outbreak. Around the same time that NPHL was mobilizing for Hantavirus, researchers in the Democratic Republic of Congo used [Twist's comprehensive viral panel](#) to confirm that a hemorrhagic fever outbreak was caused by the rare [Bundibugyo strain of Ebola](#) and obtained its full genomic sequence⁸

Whether it's by designing comprehensive target enrichment panels, synthesizing custom control material, or overcoming unforeseen transportation challenges, Twist is ready to help you get the tools you need, when you need them.

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