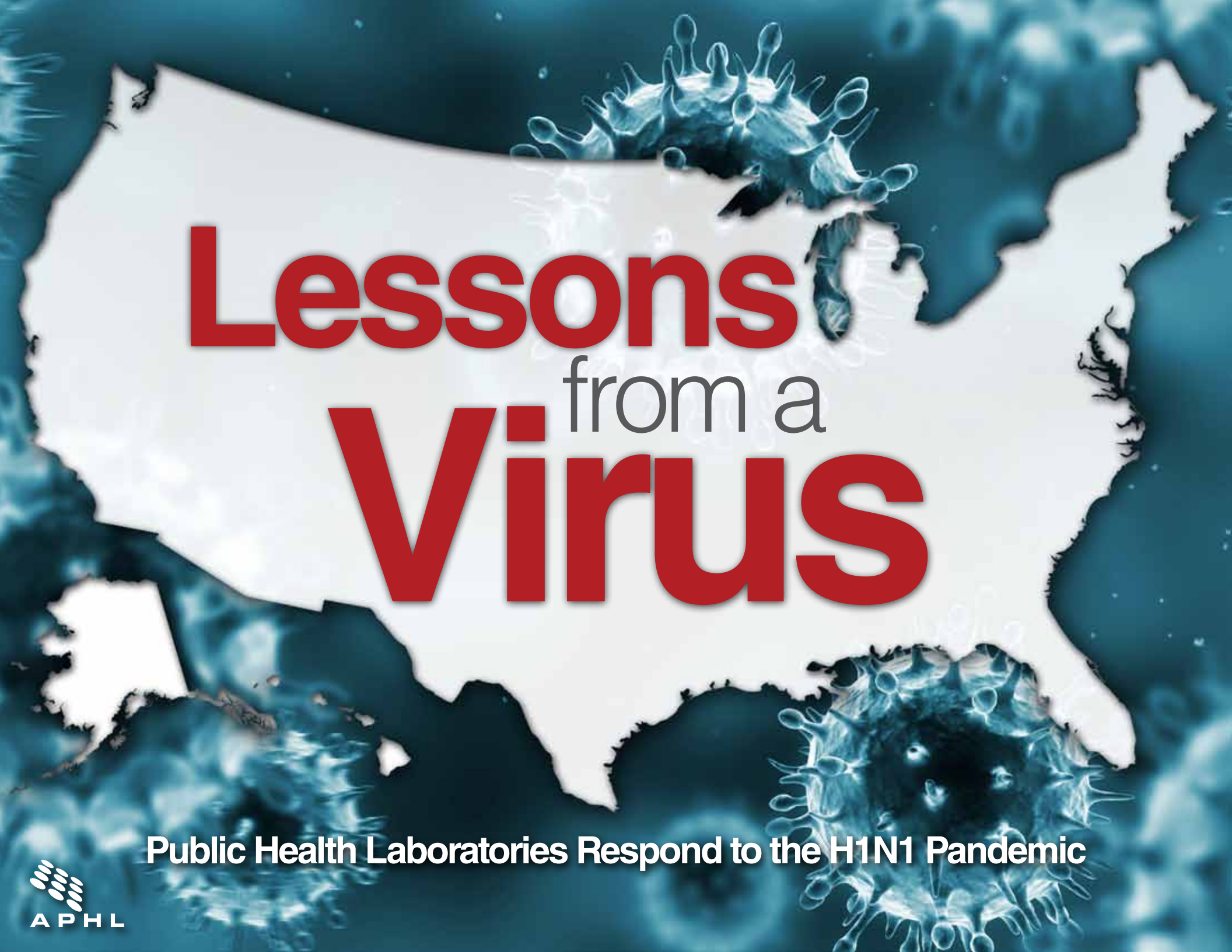
Lessons from a Virus
Public Health Laboratories Respond to the H1N1 Pandemic
APHL

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Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

Lessons from a Virus

Public Health Laboratories Respond to the H1N1 Pandemic

New York City public health lab during the H1N1 crisis./AP

Acknowledgments

Public health is intimately tied with human behavior; so communicating the experiences of a pandemic can be just as valuable as exchanging data.

In April 2011, a group of laboratory and influenza experts joined to share these stories in an expert panel meeting held at the Association of Public Health Laboratories (APHL) in Silver Spring, Maryland. The participants in the panel are listed in the back of this book. They spoke of the school nurse, the scientist who helped with logistics, the student fellow, and many more who had perspectives to share. APHL then mined the stories for guidance and meaning.

In addition to the expert panel, a core team from the CDC and APHL staff provided invaluable resources and guidance. From APHL: Rosemary Humes, Tricia Aden, Jane Getchell, Kelly Wroblewski; and from the CDC: Dan Jernigan, Joe Miller, Steve Lindstrom, Roy Johnson, Julie Villanueva, and Toby Merlin.

But the greatest acknowledgment needs to go to those working in the public health laboratories. APHL welcomes more of their stories, as together we continue to learn to shape effective responses to public health challenges.

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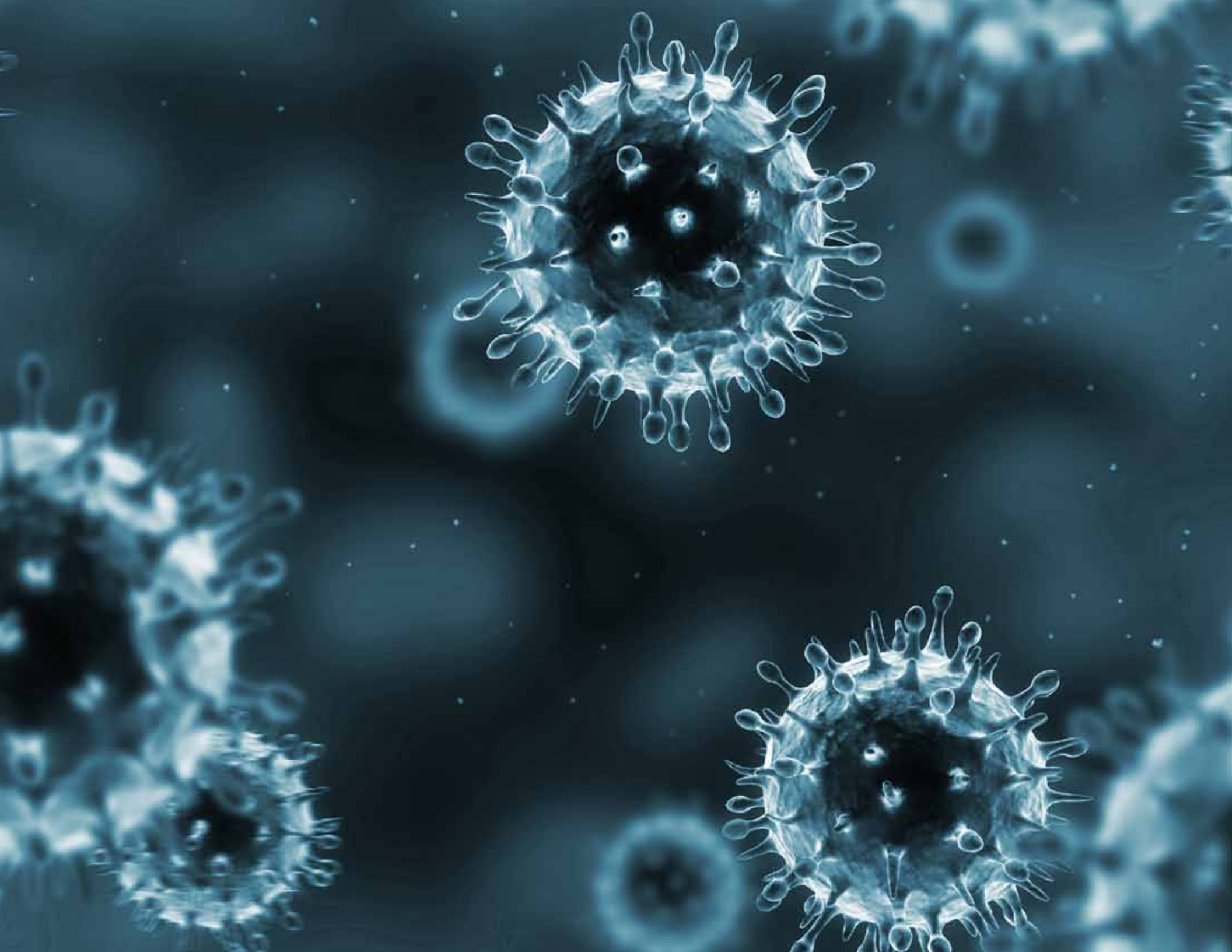


Chapters

A street in Mexico City at the height of the H1N1 pandemic./AP

Foreword

By Thomas R. Frieden, MD, MPH
Director, Centers for Disease Control and Prevention

The 2009 H1N1 influenza pandemic required rapid mobilization of public health laboratories around the world. The speed with which labs at the CDC and worldwide responded is a testament to how far we had come in just a few years. The H1N1 pandemic also highlighted areas where we need to improve so we can more effectively address the next global disease threat.

On April 15, while I was still serving as New York City's Health Commissioner, CDC labs detected the first case of H1N1 in California. About a week later and shortly after a larger number of cases of H1N1 were confirmed in Mexico, there was an outbreak of respiratory disease at a city high school. Given the large number of cases—more than 100 in just two days—and the knowledge of a possible global pandemic, we needed to know as quickly as possible whether H1N1 had arrived.

Within a day, the CDC confirmed that our cases were the same H1N1 pandemic strain circulating elsewhere. By the end of the month, the CDC developed diagnostic tests, which were quickly approved by the FDA and sent to labs throughout the country. Over the next week or so, testing kits were also sent to labs across the world. By the time I joined the CDC in June, this rapid laboratory response had established the foundation for dealing with the pandemic.

"Effective international pandemic response requires that all sectors of government and civil society be as prepared as possible. ... Labs will continue to be at the core of pandemic detection and response."

Thomas R. Frieden, MD, MPH, Director, Centers for Disease Control and Prevention

That same month, there were troubling reports from Europe that the H1N1 virus had mutated—always a major concern with any influenza strain. Our lab generated models of the impact of the mutation on the structure of the virus, facilitating analysis that accurately projected that the impact of this mutation, even if it spread, would be minimal.

There were limitations as to what labs were able to accomplish. For example, because commercially available rapid tests in use had a high rate of false negatives, many people with H1N1 may have been falsely reassured and gone untreated. CDC labs continue their research, including work to develop better tests.

Effective international pandemic response requires that all sectors of government and civil society be as prepared as possible; that all of these groups work in close partnerships that complement each other's strengths; and that communications among policymakers, health professionals, and the public be timely, accurate, clear, and consistent. Labs will continue to be at the core of pandemic detection and response. H1N1 revealed a general need to strengthen global public health lab systems so that they have the capacity and workforce able to act swiftly and decisively.

"I have never seen anything like it in my lifetime. … The rapid molecular characterization of a novel pathogen and the development and worldwide delivery of a molecular diagnostic has been widely recognized as a sea change in public health capability to respond to new infections."

Toby L. Merlin, MD, Director, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, CDC

Introduction

Public health professionals in the past 30 years have worked through acts of bioterrorism with the potential to kill hundreds in days. They have tackled emerging infectious diseases and antibiotic-resistant strains that could turn an airplane cabin into a deadly hazard. They have raced to apply detective skills to trace pathogens that threaten the food supply of entire regions.

So why do so many name the 2009 H1N1 influenza pandemic as their greatest challenge and finest moment in laboratory science?

In matters of morbidity and mortality, H1N1 took less of a toll on the United States than some seasonal outbreaks overall. Although the virus had a disproportionate impact on certain groups, such as those under 18 years of age—who experienced four to five times more flu deaths than in regular flu seasons—older Americans were largely spared the illness and deaths seen in past pandemics. Its duration could be considered most narrowly as one of a few weeks in April and May. *New York* magazine dubbed it "The 0.5 epidemic," adding, in a headline: "Relax. H1N1 is not going to be nearly as bad as you may have been led to believe … unless."

It is the "… unless"—what could have been—that gives the H1N1 response its unique impact. What the H1N1 pandemic meant to public health laboratorians could be summed up in two words: two weeks. This is the time it took

“I don’t know that I’ll ever do anything as meaningful in my career again. You knew every day that what you were doing was making a difference.”

Rosemary Humes, MS, MT (ASCP) SM, Biomedical Advanced Research and Development Authority, formerly Senior Advisor for Scientific Affairs, APHL

between the identification of the novel virus and the creation, emergency FDA authorization, manufacture, and distribution of a test capable of being used at public health labs in the United States and internationally.

This diagnostic was the *sine qua non* of every action in public health regarding the virus, from closing a neighborhood school to shutting down international flights. Effects near and far rippled from what the test could tell about the virus, and the test was a product of CDC scientists and a longstanding partnership among APHL, public health laboratories, commercial partners, and the CDC.

Years, even decades, of preparation, training, and capabilities were compressed into those two weeks. Patterns and procedures that might have emerged over months in other crises were adopted, attempted, and adapted in a matter of days. Every chit was called in; nascent partnerships advanced overnight; missing pieces were revealed in stark relief under the time pressure. Heroes, individual and collective, surprised even themselves by rising to the challenge.

By the time the second wave of the virus appeared, laboratorians knew what they had done right. They had seen how damage had been averted. And they knew what they needed to improve for the future.

This publication collects that knowledge—so that others can use it and so that the once-in-a-lifetime accomplishments of these public health science leaders won't be forgotten.

"It was pure luck. We were just doing due diligence. We got the message out: Every time there's something unsubtypable, call us."

Dr. Peter A. Shult, PhD, Director, Communicable Disease Division and Emergency Laboratory Response for the Wisconsin State Laboratory of Hygiene

Chapter 1

From RT-PCRs to Home Brews: The Centrality of Testing

The Wisconsin public health laboratory got a call April 9, 2009, from the Marshfield Clinic's Research Center with the news that as part of its study of a new influenza test, Marshfield had found a specimen that was "unsubtypable." By the end of that month, a pandemic would be declared, caused by this novel virus that would soon be identified as H1N1.

The network of the public health labs, other laboratories, corporate and academic partners, and the CDC made it possible to track and understand this virus, but at the center of it all was the test.

Molecular diagnostics, with its pinpoint accuracy and revolutionary speed, was in many ways the ideal process for the H1N1 pandemic. Without the ability to get to the genetic level, the rapid response on the part of public health labs would not have been possible. For the first time, molecular diagnostics, with all its complexities, was indispensable to a massive emergency public health effort.

The influenza diagnostic used primarily by public health labs today, reverse-transcription polymerase chain reaction (RT-PCR, often referred to as PCR), is a technique, not a test in itself, used to detect a myriad of infectious diseases. Labs adapt the technique to track down diseases as needed—developing an assay for pertussis, for instance. Labs and the CDC can create protocols that function much like recipes, with standardized procedures and reagents. Labs can also create "home brews," tests responding to individual needs, based on known genetic sequences. In the years following the H1N1 pandemic, such tests have proliferated through clinical creation and are also called lab-developed tests, or LDTs.

CDC Estimates of 2009 H1N1 Cases in the U.S.
(April 2009 - April 10, 2010)

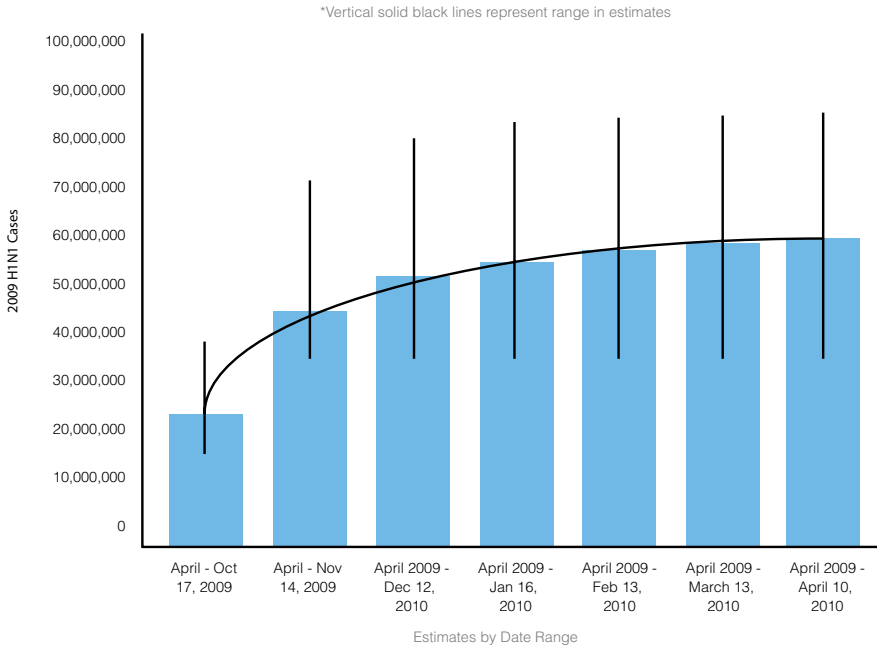


Fig. 1

CDC Estimates of 2009 H1N1 Deaths in the U.S.
(April 2009 - April 10, 2010)

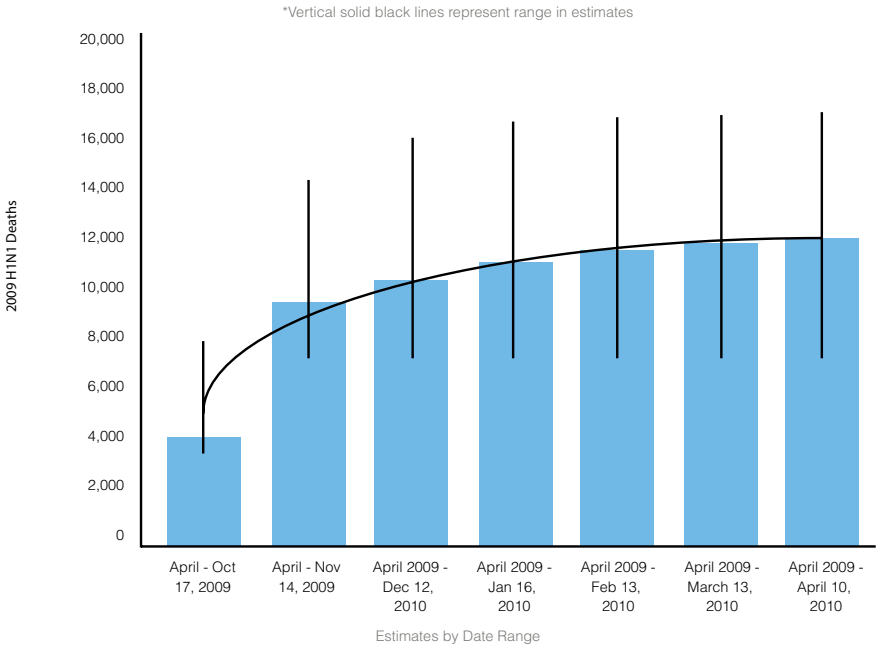


Fig. 2

CDC Estimates of 2009 H1N1 Hospitalizations in the U.S.
(April 2009 - April 10, 2010)

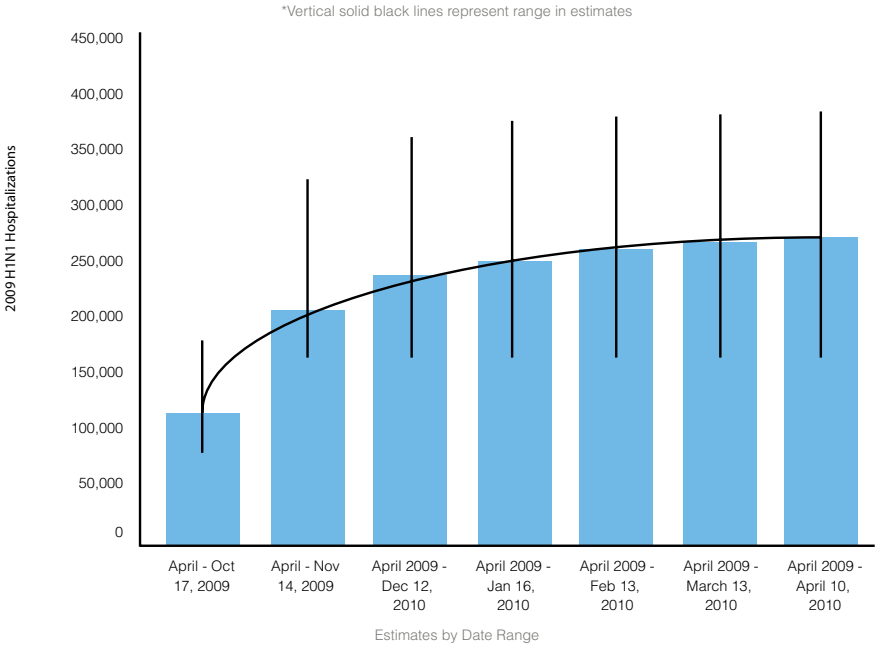


Fig. 3

H1N1 TAKES ITS TOLL

CDC estimates show that the greater number and impact of cases came in the fall wave of the pandemic—when more cases could be more quickly and accurately diagnosed.

Before H1N1 appeared, the CDC and public health labs—and the World Health Organization (WHO) and international policy—regarded avian and seasonal flu as the greatest threats. CDC scientist Stephen Lindstrom and his team developed what became known as the "five-target assay," a PCR test for five types of influenza, including avian and seasonal strains. Through APHL and CDC collaboration, public health labs tested specimens and collected data, essential for FDA clearance of the test. It was this kit that would be the foundation of the H1N1 test.

Something the Test Couldn't Identify

The CDC, diagnostics manufacturers, and academic labs are always seeking to create better tests—more accurate tests, easy to use at provider offices and in the field at any point of care. It was one of these development efforts, a joint project of Meso Scale Diagnostics, the CDC, and BARDA, the Biomedical Advanced Research and Development Authority at Health and Human Services, that led to the phone call from Marshfield.

Meso Scale Diagnostics (now Meso Scale Discovery), a Maryland company, and the US agencies were experimenting with a new, rapid, point-of-care influenza test kit as part of a study at the Naval Health Research Center in San Diego, California. The kit was designed to detect three influenza subtypes—avian (A/H5) and seasonal (A/H1 and A/H3). On one specimen, the kit had detected an influenza that didn't fit into any of the known subtypes. It wasn't time for alarm bells to go off yet, but the specimen would certainly need further study.

"I knew there was a study going on, so early on, we found out that one of the reference labs confirming the testing was Marshfield," says Dr. Peter Shult, director of the communicable disease division at the Wisconsin state public health lab. "We've had a long association with them, even before the Laboratory Response Network was created.

H1N1 Diagnostics Basics

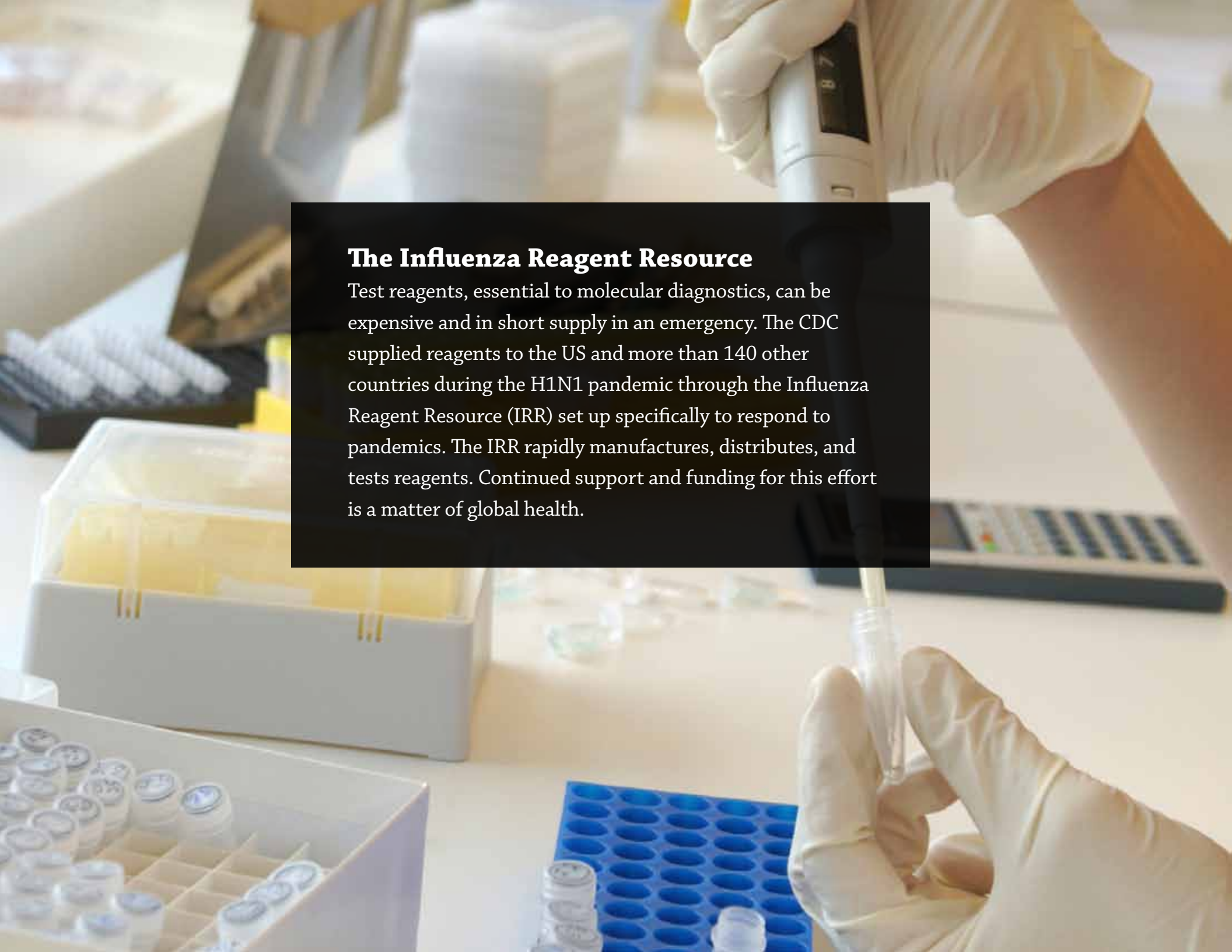
H1N1 was usually detected using one of four types of tests, each with its own benefits and drawbacks:

• Reverse-transcription polymerase chain reaction (RT-PCR, mostly referred to as PCR): The molecular diagnostic used by most public health labs in the pandemic. Great accuracy in a few hours; requires special training, equipment, and reagents to perform. Average test cost: $150. PCR techniques can be developed in labs or be part of a packaged test kit.

• Virus isolation for influenza: Common in public health labs before molecular diagnostics; accurate but can take two to four days.

• Rapid influenza diagnostic tests (RIDTs): Common in outpatient settings, less expensive, easy to use, can give results in as little as 15 minutes. Emerging data on the sensitivity of these tests in clinical practice indicated a range of 50% to 70%, leaving a large number of possible false negatives.

• Direct fluorescent antibody tests: Often used in hospital settings; can give results in several hours; less labor-intensive; less accurate than PCR.



The Influenza Reagent Resource

Test reagents, essential to molecular diagnostics, can be expensive and in short supply in an emergency. The CDC supplied reagents to the US and more than 140 other countries during the H1N1 pandemic through the Influenza Reagent Resource (IRR) set up specifically to respond to pandemics. The IRR rapidly manufactures, distributes, and tests reagents. Continued support and funding for this effort is a matter of global health.

"Whenever there are clinical labs doing testing, it's part of our work when they find something unusual to do appropriate testing and get them linked up with the CDC," Shult says.

Marshfield sent the specimen to the Wisconsin lab, and by Monday, April 13, the Wisconsin lab ran it through the five-target assay. No recognizable subtype. In effect, they knew the virus's surname, but not its first and middle names. They tried it again. Subtype still unknown. So they packed it up and sent it to the CDC. By the 16th, the announcement came from the CDC—a novel influenza virus was out there, and they had its fingerprints.

Labs across the country immediately started testing influenza specimens with the five-target assay, while the CDC worked to adapt the assay to detect the new virus. To develop a test, scientists work from the inside out: Determining the genetic makeup, then designing a test specifically shaped to detect it.

Swine flu viruses surface from time to time, Lindstrom says, usually as isolated cases in a person who has had contact with pigs—a youth raising pigs for a state fair, for instance. After launching the five-target assay, Lindstrom and the team had turned their attention to swine, to ensure these occasional cases didn't become bigger problems. In fact, their swine test was at the point where it was the subject of a poster presentation at a clinical virology conference shortly before the first H1N1 cases were reported.

"It was very odd timing," Lindstrom says. "Luckily, we did have an assay on hand. It was designed so that if there was a novel virus emerging, we could identify it with a red flag."

At first, it wasn't clear whether this novel virus was just another one-time occurrence. What made it different: The two cases sent from the Navy lab in California were from children who had had no contact with pigs, or with each other.

"Those were two red flags," Lindstrom says.

Flu View Map, Week 18

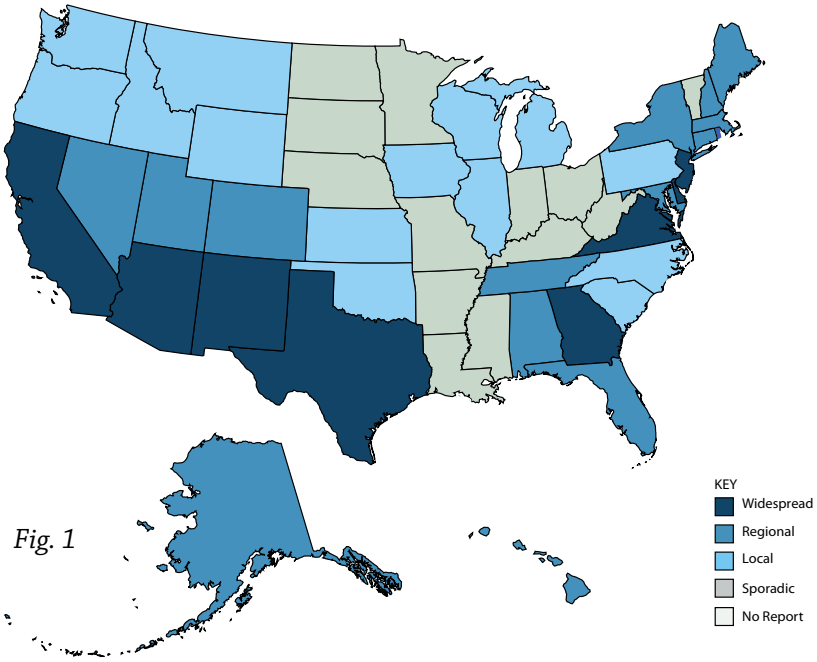


Fig. 1

Flu View Map, Week 20

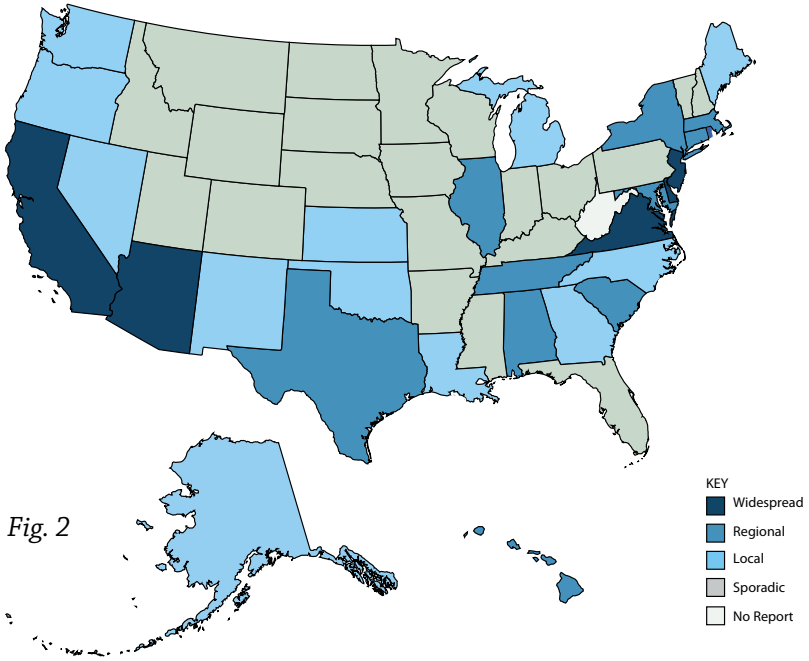


Fig. 2

Flu View Map, Week 25

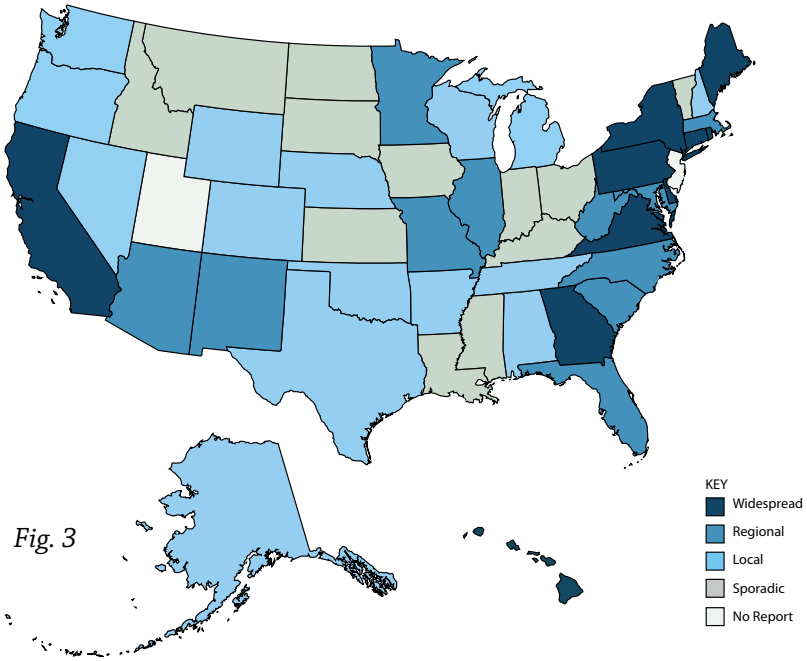


Fig. 3

THE VIRUS SPREADS NATIONWIDE

CDC maps show how the virus moved from concentration in the Southwest to the East Coast and other regions. The weekly Flu View reports were an important communications strategy, with updated news and statistics.

If the H1N1 test had been adapted from the five-target assay alone, Lindstrom says, it would have taken another two weeks to develop. As it was, "our advance work on swine helped us push it."

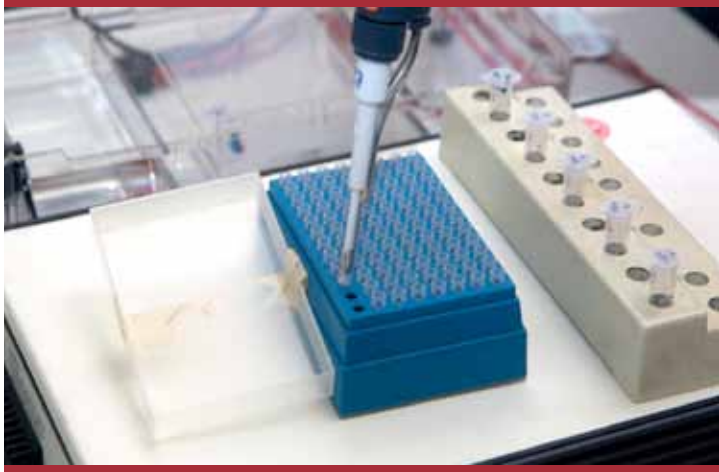
Public health labs opened their doors to let in specimens from clinical and other labs because they had the best test thus far, and they were eager to fulfill their surveillance mission. Within two weeks, labs were getting delivery of an accurate test kit for novel H1N1, authorized under an Emergency Use Authorization from the FDA. In the coming weeks, hundreds of specimens would come to individual public health labs daily.

The CDC opened the doors as well—posting the virus's full genetic sequence on public websites by April 27th. This allowed labs with molecular diagnostic capacity worldwide to create their own home-brew tests—at a speed previously unknown. Public health labs also served as reference centers to confirm results of less-accurate tests.

"We went from four or five sites capable of doing molecular testing to about 18," Shult says. "In the future, this increased capacity from H1N1 could take a lot of the burden for diagnostic testing off the public health lab system."

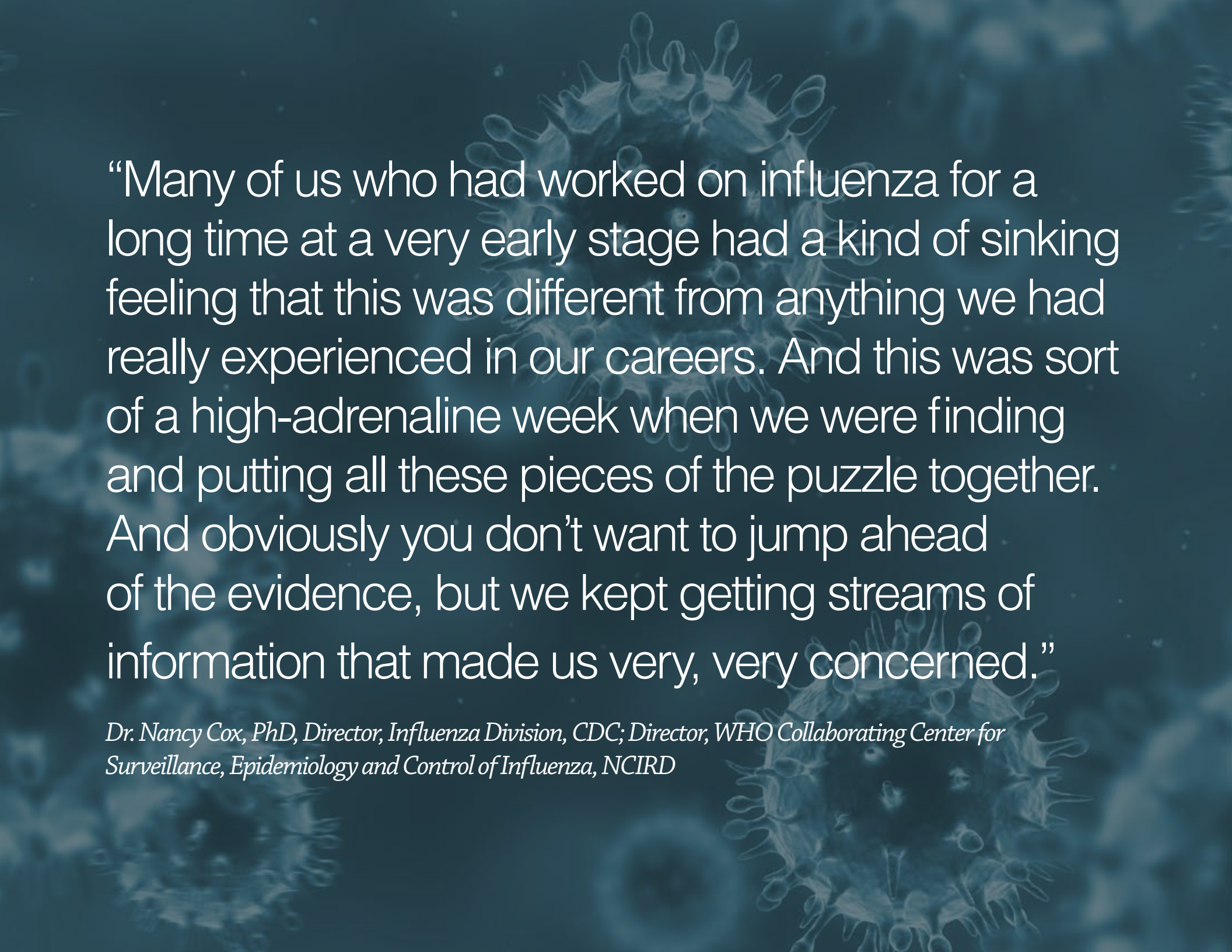
But the benefits of molecular diagnostics in a pandemic are matched by the challenges. As public health laboratory leaders have been saying for years, you can't just hire a molecular biologist off the street. The layers of quality assurance involved in validation add critical steps to the process. Specific, sophisticated instrumentation as well as expensive reagents are required. Lastly, regulatory clearance can add time to the process. These subtleties don't always translate well to the general public or its advocates and political representatives. For them, the gold standard is an immediate yes-or-no answer at the point of care.

Advancing Research and Development



Laboratory innovation requires consistent funding.

Established in 2006, the Biomedical Advanced Research and Development Authority (BARDA) jump-starts innovation for a wide variety of health threats. Because there is often little commercial market for preparedness and emergency tools, funding for this agency becomes critical—and influenza is one strong example of this situation. For instance, the Meso Scale Diagnostics point-of-care test for avian and seasonal flu—the test that led to the discovery of the first H1N1 cases—was developed under a BARDA agreement.



"Many of us who had worked on influenza for a long time at a very early stage had a kind of sinking feeling that this was different from anything we had really experienced in our careers. And this was sort of a high-adrenaline week when we were finding and putting all these pieces of the puzzle together. And obviously you don't want to jump ahead of the evidence, but we kept getting streams of information that made us very, very concerned."

Dr. Nancy Cox, PhD, Director, Influenza Division, CDC; Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, NCIRD

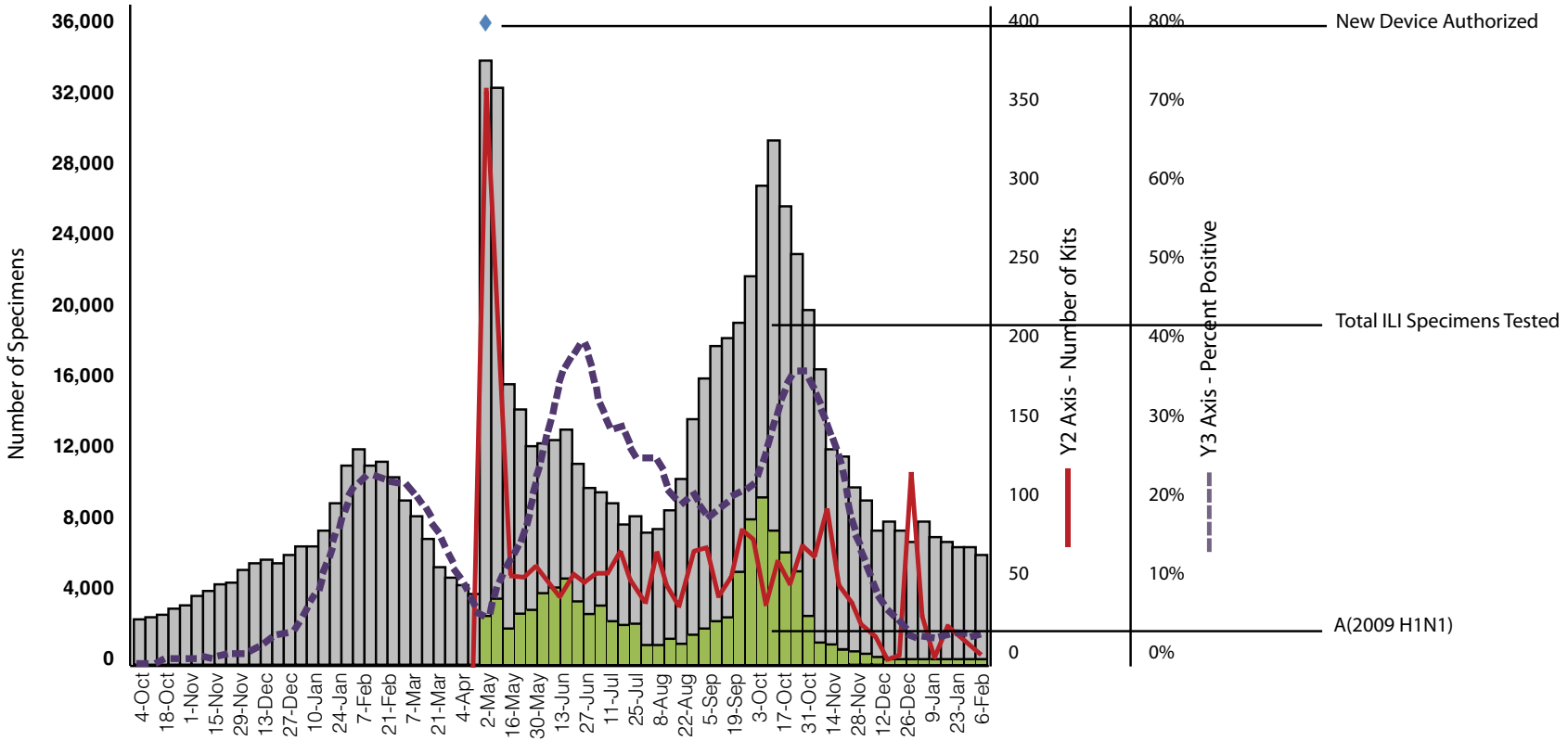
Future Issues

The clinical testing gap:

Molecular diagnostic techniques meant that armed with the genetic sequence and the right equipment and reagents, more labs could do more testing more rapidly than ever before. The problem pinpointed by most post-pandemic reports was the danger of the less-specific rapid tests being used on an outpatient basis: false negatives.

That danger received national attention when in June 2009 in Utah, a woman who had tested negative for H1N1 three times, using a rapid test, died of complications from the virus. A fourth test, administered when she was in a hospital's shock and trauma unit, showed a positive result, but it was too late.

NEW DIAGNOSTIC INCREASES POSITIVES



Vaccines and the PHLs

In the complex process of vaccine development, the public health laboratory is often helpful in providing seed strains from which a vaccine is manufactured. Creating a vaccine requires a great deal of specimen material, and it must be the right material. While the public health labs are not actively involved in developing vaccines, in both their surveillance activities and in the collection of specimens for the CDC and WHO, the labs are critical. In the H1N1 pandemic, a vaccine was developed within the planned time frame of six months, but even this rate of speed wasn't enough to get ahead of the virus. Eventually, more than 81 million in the United States received the H1N1 vaccine. The CDC and partners are looking at ways to step up vaccine development and production in future influenza events. Public health labs continue to play a critical role, through finding ways to provide the best seed material the most rapidly.

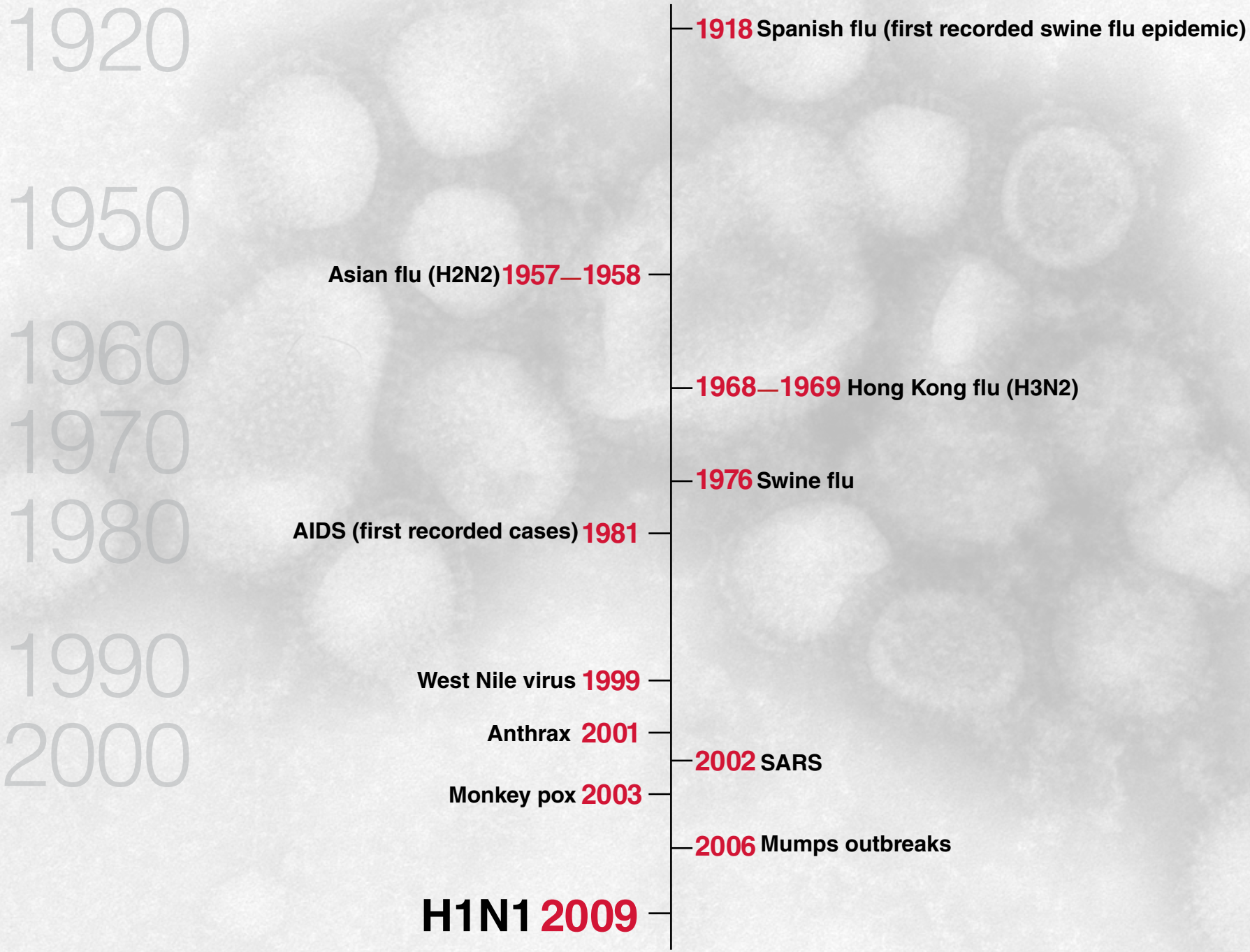
This was not the only case, nor the last, that went undetected, with fatal results. Is there a role public health laboratories can play in advancing readily available, rapid, and highly sensitive diagnostic tests that can be used in a clinical setting?

The CDC and partners are working continually on improved capabilities, particularly more rapid, higher volume, and point-of-care tests, as well as the instruments needed to execute them. The fast work on H1N1 modeled the kind of adaptation and regulatory innovation that advances today's efforts. But such tests lack a routine clinical value—making funding for development hard to come by—and getting regulatory agreement can be tough.

How will regulatory changes impact future lab-developed tests?

This is a question that H1N1 brought definitively into play. Just as there are multiple diagnostics, there are multiple points of view on how tests should be regulated. Some laboratory scientists feel regulation has the effect of stifling innovation, development, and rapid response. Others in the field express concerns about too many or too easily cleared tests being unneeded, a burdensome expense, or, at worst, dangerous. Many clinical and commercial partners are strongly pushing for lab-developed tests, and regulatory bodies are pushing back. With lab-developed tests becoming easier through molecular diagnostics, some factors limiting use and spread of new diagnostics are degree of need; cost and availability of equipment, training, and reagents; and regulatory issues. In considering this, laboratorians are as usual concerned with maintaining both emergency response capacity and quality and consistency.

Timeline of Emerging and Pandemic Infectious Threats



Chapter 2
Preparedness Assumptions and H1N1 Reality

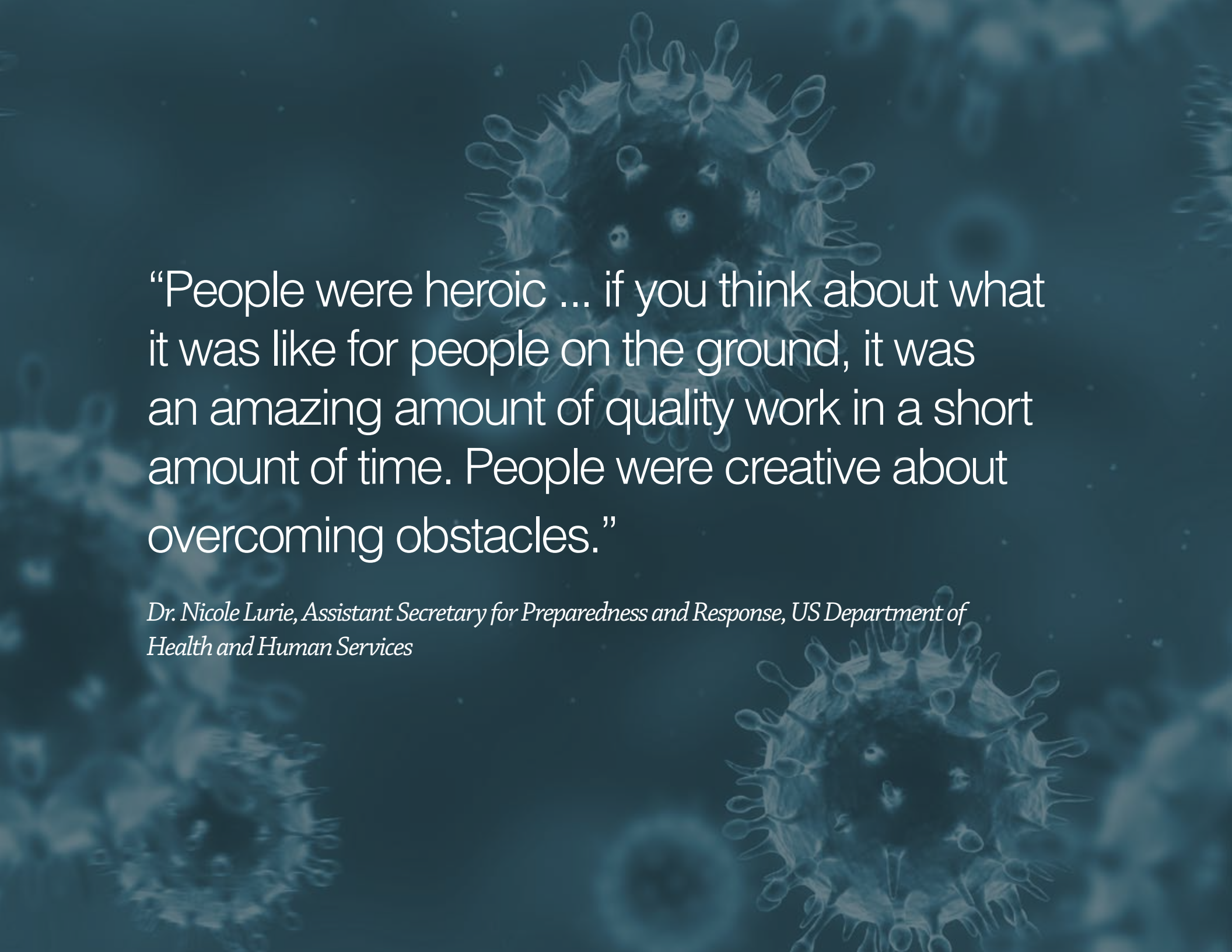
Preparedness made the difference in the public health laboratory response.

Over two weeks in the beginning of April 2009, scientists from 44 public health laboratories came to the CDC in a massive training exercise to learn to use a new test kit that had only recently received FDA clearance. Two groups of 22 labs each had a weeklong training session to learn how to use the five-target assay—formally, the Human Influenza Real-Time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel)—with the 7500 Fast Dx Real-Time PCR instrument made by Applied Biosystems, now part of Life Technologies. Together, the test kit and instrument could deliver results within four hours, as opposed to days, to target avian and seasonal influenza, considered the biggest, most likely threat to public health.

"Experts knew that other kinds of influenza could cause a pandemic, but on the world stage, avian flu was the focus," says Rosemary Humes, then APHL scientific advisor.

"We had some fairly extensive flu plans in place, but they were always geared on the assumption that we would have a few days," says Dr. Susan Neill, then director of the laboratory services section of the Texas Department of State Health Services.

"We thought it would be coming from Asia, and we thought it would be severe, and it was just not any of that," says Dr. Daniel Jernigan, deputy director of the Influenza Division at the CDC. "But the test itself actually couldn't care less what kind of flu it was. So we were able to pick up this unusual flu with a test that also could pick up bird flu, or seasonal, or whatever."



"People were heroic ... if you think about what it was like for people on the ground, it was an amazing amount of quality work in a short amount of time. People were creative about overcoming obstacles."

Dr. Nicole Lurie, Assistant Secretary for Preparedness and Response, US Department of Health and Human Services

Just days after the training ended, the first novel swine flu cases were detected. "That fast turnaround time from detection of H1N1 to the deployment of the public health labs—in the future, people will think this is usual," Humes says. "But it was only because of all the work done in advance that it was possible."

Long Road to Rapid Response

"You don't want to set up systems just for a pandemic," says the CDC's Jernigan. "You want to be able to use systems currently working and implemented. It's more about using an infrastructure and a warm base from a group doing work on a regular basis."

"The government was thinking there would be a private sector response—but we were concerned that the response from anthrax and SARS indicated that public health is going to be out in front—and if public health isn't ready, the nation is not ready."

So in effect, the advance work for the H1N1 pandemic began in 2004. Steve Lindstrom, now leader of the Diagnostics Development Team, Virus Surveillance and Diagnosis Branch, Influenza Division, at the CDC, had begun by simply transferring knowledge to public health labs on request; the process evolved to be more formal, with regular training sessions and responses to public health needs. The team worked with APHL to fund clinical studies, for instance, and to collect data to get FDA clearance for reagents.

With reagents being expensive and in demand, training was made part of the requirement for test clearance. "We wanted additional control for accuracy," Lindstrom says. "It helps us on the technical end, so if a lab is requesting reagents, we know they know how to do the test."

"The plan was always that this five-target assay would be the basis for developing testing for any future influenza strains," Humes says. This put additional importance on its development, regulatory clearance, and training. If the first step wasn't right, what followed wouldn't work in a crisis.

Keeping the Warm Base

"Warm base" is a concept borrowed from business and manufacturing, meaning that a factory or company will be primed and ready to swing into action when a product or service is needed.

In the labs, it means using strategies in training and equipment strengths already in place and adaptable to dealing with crises such as the sudden appearance of a novel influenza virus. It extends further to areas such as communication—being ready with messaging, for instance.

Public health can also have a warm base ready for manufacture of diagnostic test kits. Developing just-in-time contracting to be used when needed is another example. Even regulation can have this element—the FDA's Emergency Use Authorization can be seen as a warm base from which to quickly authorize use of novel devices.

Laboratory Response Network: From Bioterrorism to Influenza

In early April 2009, the Laboratory Response Network (LRN) had gathered at a national conference to look at its decade of emergency preparedness and response. A few weeks later, this preparedness resource would be put into use to connect public health labs during the H1N1 pandemic.

Founded in 1999 by APHL, the CDC, and the FBI to test for agents of bioterrorism, the Laboratory Response Network has evolved to become the nation's laboratory resource for response to emerging infectious diseases, toxic spills, natural disasters, chemical terrorism, and other public health threats.

LRN member laboratories conduct confirmatory testing of specimens referred by clinical laboratories, law enforcement agencies, the armed forces, and other partner agencies. The results of their analysis determine emergency response measures.

In an odd historical parallel, the LRN had its first challenge within two weeks of finishing nationwide training, in 2001—the appearance of anthrax spores in a Florida office building. "That day, the concept of a national, rapid response laboratory network proved its worth," remembers Scott Becker, APHL Executive Director.

During the H1N1 pandemic, laboratories leveraged the LRN infrastructure, such as linkages with sentinel clinical laboratories, trained staff, and equipment to provide a rapid response. By not reinventing the wheel, these laboratories saved precious time and quickly responded to the thousands of specimens coming into public health laboratories.

"The LRN was intended to respond to a situation like this," says Dr. Nicole Lurie, Assistant Secretary for Preparedness and Response, US Department of Health and Human Services. "Clearly, it's important for all kinds of events, some more serious, and some less."

The labs build on resources established through the LRN—but it works both ways. "We all understand that the most successful components are the ones that are built on day-to-day systems," Dr. Lurie says. "And there are components of the LRN that are part of the day-to-day systems in this country."

Completed in 2008, the kit had one more hurdle: The CDC had to push hard to get fast FDA clearance before the next flu season started. The kit was cleared in September 2008, but part of its FDA agreement was the requirement that lab workers be specifically trained in using it.

Also in 2008, APHL and the CDC had collaborated to perform laboratory capacity modeling, which aided in estimating quantities of reagent that would be needed if there were a pandemic, and this number was used to stockpile the Influenza Reagent Resource.

As soon as the kits were manufactured, by January 2009, APHL sent invitations through the National Laboratory Training Network to state and local public health labs to come to the CDC for training. The training network, a collaboration of APHL and the CDC, has a long history of working with public health labs nationwide, doing annual training sessions on influenza—another preparedness plus. And the training on the five-target test kit was based on past training laboratorians had in using the PCR methods. Without long-term institutional knowledge and continually updated training, the labs would have lacked the workforce "warm base" critical to tackling H1N1.

"The technical training and capacity aren't anything that can't be used for other pathogens," Lindstrom says. "In fact, what we were working on was an extension of what we were doing for bioterrorism."

Information keeps coming in—and influenza viruses, too, keep changing. As soon as one test would go out, the team would start moving again—looking for genetic mutations, designing for better performance. It is work that continues today.

Disasters and Drills

Multiple systems in preparedness intersected to allow the rapid H1N1 response: the National Laboratory Training Network, surveillance efforts, test development, the Laboratory Response Network, and more. The lesson for the labs was twofold: A strong affirmation that the struggles to develop and fund their preparedness programs were justified, and proof that adaptability must be part of any preparedness efforts.

Just a year before the pandemic, many public health labs had been able to beef up capacity through APHL and a CDC cooperative agreement. About 25 labs, all Public Health Emergency Preparedness grantees, got funds ranging from $9,000 to $18,000, using the money to do outreach and education for clinical partners. One creative use: The Tennessee Department of Health, Division of Laboratory

View of the Future from 2007

In 2007, the CDC, with participation from multiple other agencies, began implementing a strategy for improving global diagnostic preparedness for pandemic influenza. The list of priorities they developed reveals both how on-target these needs were for the 2009 pandemic and how much work needs to continue:

- Develop new diagnostic tests and improved diagnostic capabilities
- Improve surge capacity
- Implement proficiency testing
- Develop regulatory preparedness
- Improve access to viruses and reagents
- Provide guidance for clinicians
- Improve virologic surveillance

Services, brought software to enable an online learning program. Physician offices and clinical labs could log in securely to learn new lab techniques in flu diagnostics and surveillance.

The preparedness systems that enabled the fast H1N1 response were based on lessons learned, sometimes painfully, from crises ranging from anthrax to Hurricane Katrina. Other states ran incident drills.

"Planning was extremely helpful, but I think even more so than the planning was running drills and exercises to test the actual plans," says Dr. Kirsten St. George, Chief of the Laboratory of Viral Diseases at the Wadsworth Center in Albany, New York. The center designed drills to test surge capacity.

"We ran the lab drills for three days in a row," she says. "Having those three days was extremely important. A lab can do extraordinary things in one day. But by day three, all sorts of stresses would start to show."

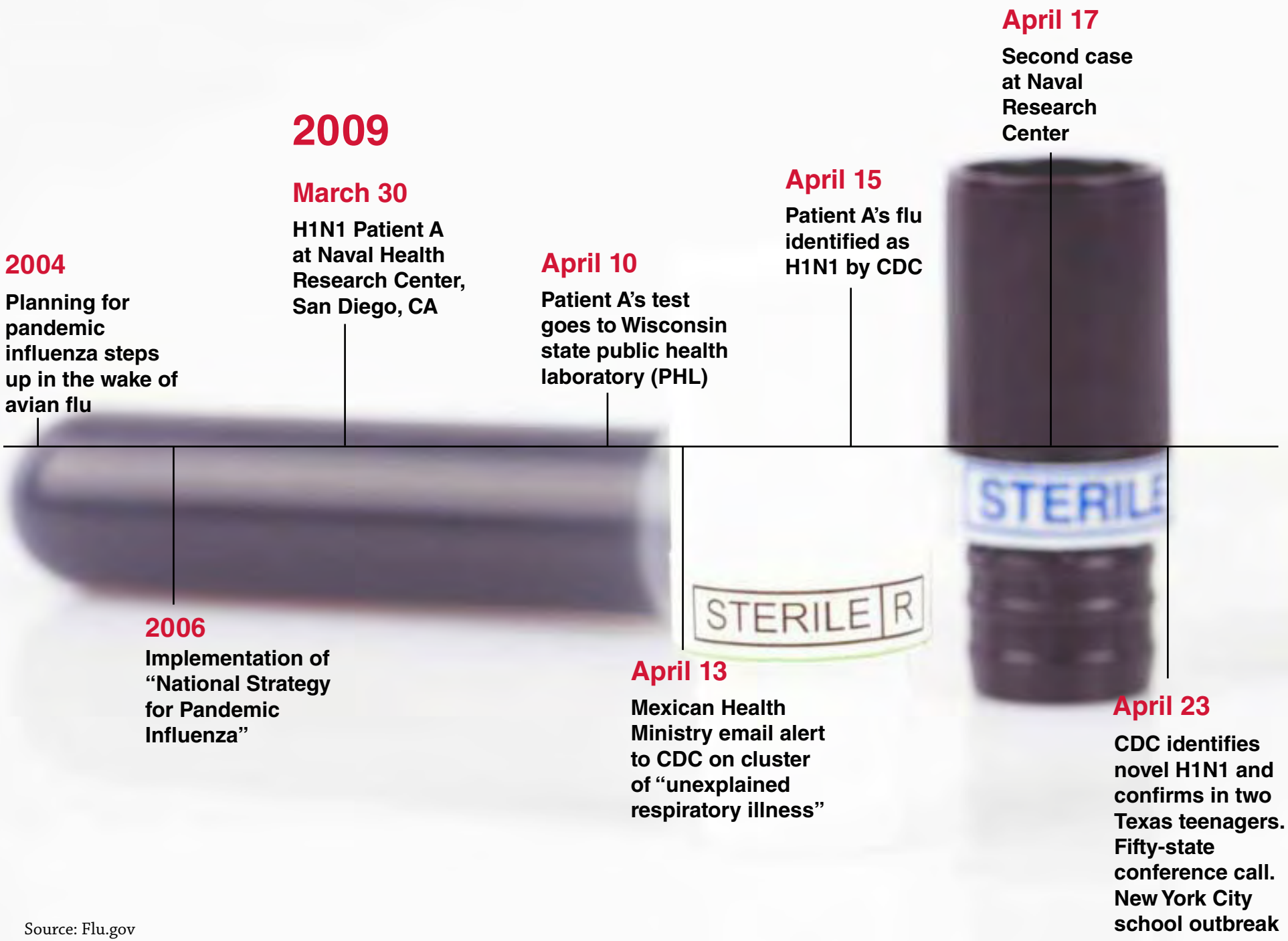
"Each of the labs ended up changing some aspect of its workflow design. ... As a result of testing those plans, we had much smoother systems in place once the pandemic hit," St. George says.

Incident command structures, biosecurity training, occupational health training, advance risk communication strategies—these are all part of the labs' continuing preparation, and all were put to work in the H1N1 pandemic.

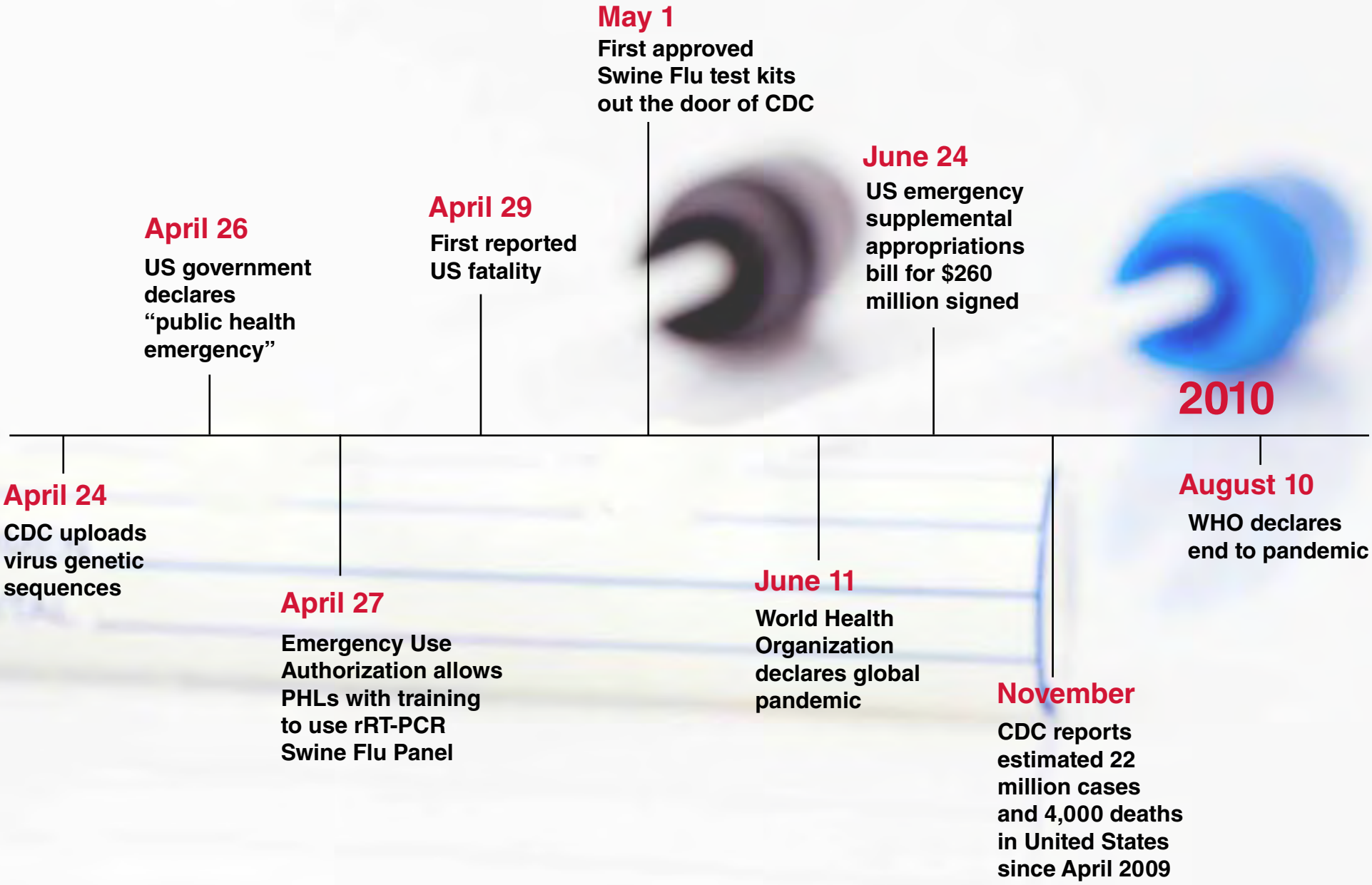
"The broader message is a maturation of our staff as first responders," says Dr. Peter Shult, of the Wisconsin lab. "When you compare how the lab functioned in anthrax versus pandemic, there was a vast difference. We had cross-trained; we had incident command structures in place. People were empowered to do things within that management structure.

"And it's been an evolution over the 10 years because many of our states had a number of outbreaks in the interim that have allowed us to evolve to be better prepared."

H1N1 Timeline



Source: Flu.gov


May 1
First approved Swine Flu test kits out the door of CDC
April 29
First reported US fatality
June 24
US emergency supplemental appropriations bill for $260 million signed
April 26
US government declares "public health emergency"
2010
April 24
CDC uploads virus genetic sequences
April 27
Emergency Use Authorization allows PHLs with training to use rRT-PCR Swine Flu Panel
June 11
World Health Organization declares global pandemic
November
CDC reports estimated 22 million cases and 4,000 deaths in United States since April 2009
August 10
WHO declares end to pandemic

Simulation Becomes Reality

In August 2008, APHL, the CDC, and a consulting firm offered labs an influenza pandemic model to test their capacity. Within the model, laboratories could insert information on personnel, equipment, workflow processes, and other variables.

"It would then tell you that you would be able to process X specimens in a day," says Dr. Jane Getchell, Senior Director for Public Health Programs at APHL and state laboratory director in Delaware during the pandemic. "I looked at the numbers the model predicted and thought 'this can't be right.' But as a matter of fact, nearly a year later, we did test almost exactly the number it predicted we could."

Delaware ended up under a particular burden because it was the site of the first major flu outbreak at a US college or university—so it tested the state's preparation. "After the simulation, we identified ways to speed up our processes," Getchell says, "such as getting another extraction instrument for our specimen processing."

Future Issues

The H1N1 pandemic showed clearly that preparation can be pressed into practice immediately. Lab scientists pointed to a few areas for today and tomorrow's preparation:

Multiple events:

"We're not always going to have the luxury of dealing with one event at a time," says Kentucky Laboratory Services Director Dr. Stephanie Mayfield. If an incident command structure is occupied with influenza, what happens if there is a foodborne outbreak simultaneously? If large populations are hospitalized, how can we stop hospital-acquired secondary infections?

What about contingencies?

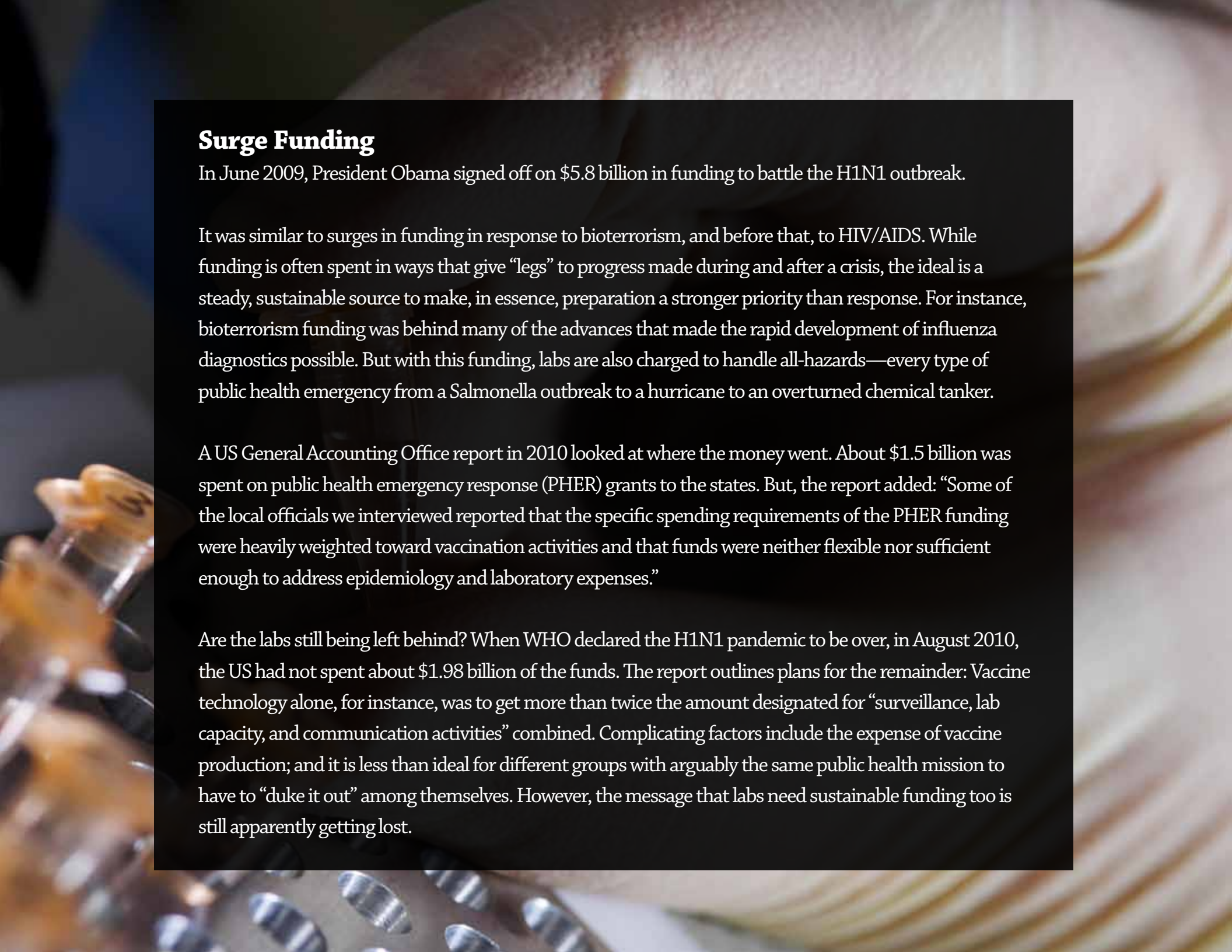
Many labs during H1N1 were frustrated at not having the proper equipment or technology to test and report results quickly. But getting the technology isn't the whole solution. "There are times during disasters where you're not able to access the technology you've come to depend on," cautions Dr. Nicole Lurie, Assistant Secretary for Preparedness and Response with the US Department of Health and Human Services. "Remember that you have to function in those environments as well." Power outages, satellite problems, and even food and water shortages can be part of labs' risk calculations and contingency planning.

Sustainable funding is critical:

At least once a year, the influenza virus changes slightly. It stays ahead of testing and research—and ahead of funding for testing and research.

The changing virus is one side of the equation. On the other side is the changing levels of funding.

Labs experience "roller-coaster" funding levels—a surge of money in response to a crisis and cuts when a crisis is behind. And H1N1 was no exception—emergency funds pouring in were welcome, but preparation funding was the better investment. The mass training of 44 labs,



Surge Funding

In June 2009, President Obama signed off on $5.8 billion in funding to battle the H1N1 outbreak.

It was similar to surges in funding in response to bioterrorism, and before that, to HIV/AIDS. While funding is often spent in ways that give "legs" to progress made during and after a crisis, the ideal is a steady, sustainable source to make, in essence, preparation a stronger priority than response. For instance, bioterrorism funding was behind many of the advances that made the rapid development of influenza diagnostics possible. But with this funding, labs are also charged to handle all-hazards—every type of public health emergency from a Salmonella outbreak to a hurricane to an overturned chemical tanker.

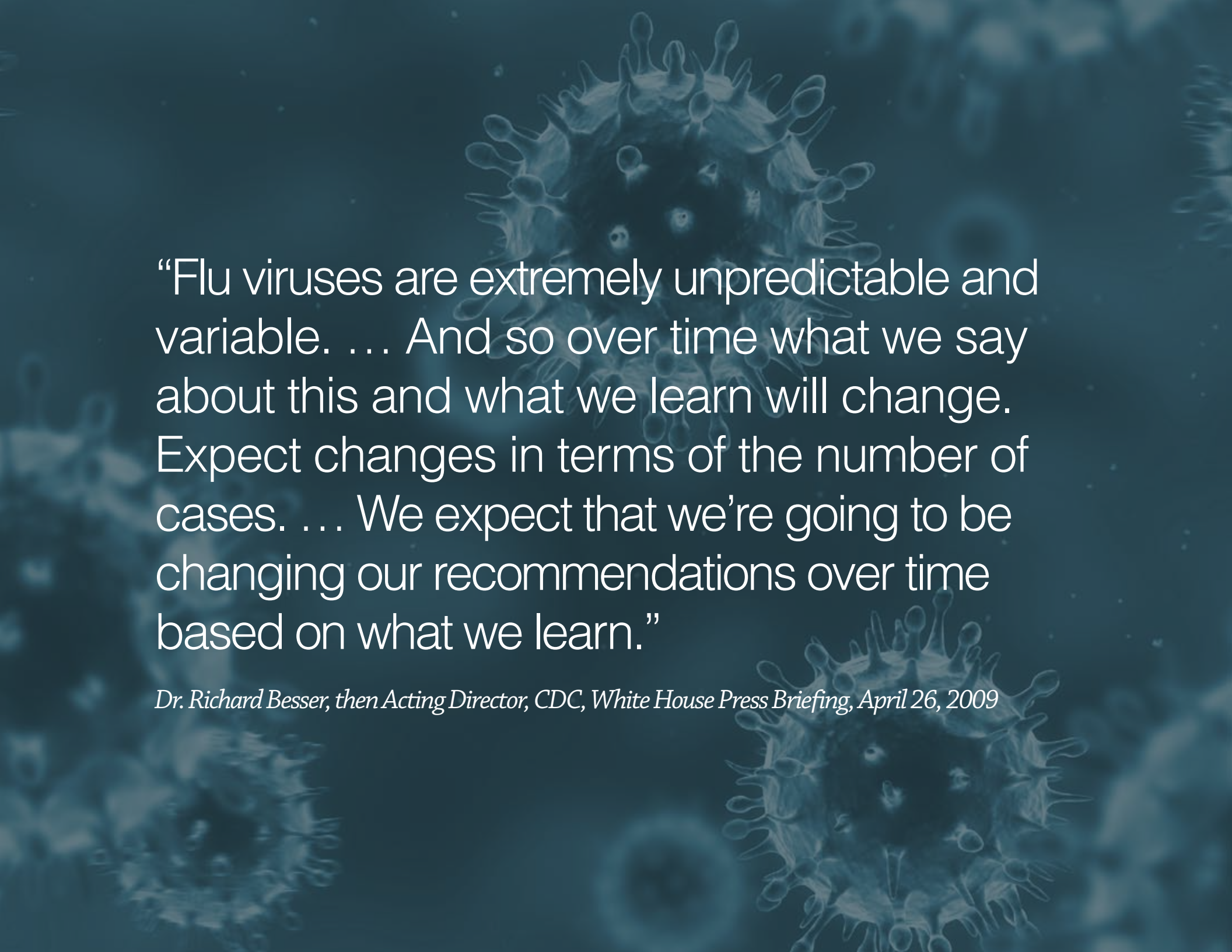
A US General Accounting Office report in 2010 looked at where the money went. About $1.5 billion was spent on public health emergency response (PHER) grants to the states. But, the report added: "Some of the local officials we interviewed reported that the specific spending requirements of the PHER funding were heavily weighted toward vaccination activities and that funds were neither flexible nor sufficient enough to address epidemiology and laboratory expenses."

Are the labs still being left behind? When WHO declared the H1N1 pandemic to be over, in August 2010, the US had not spent about $1.98 billion of the funds. The report outlines plans for the remainder: Vaccine technology alone, for instance, was to get more than twice the amount designated for "surveillance, lab capacity, and communication activities" combined. Complicating factors include the expense of vaccine production; and it is less than ideal for different groups with arguably the same public health mission to have to "duke it out" among themselves. However, the message that labs need sustainable funding too is still apparently getting lost.

for instance, would not have been possible after the start of the outbreak—resources would have been impossibly stretched by an effort to do training, diagnostic development, and actual testing and surveillance all at the same time.

"People think of a lab as a building—you build it and you walk away," Humes says. "But you need people who are trained, you need new equipment, you need to stay up-to-date with disease pathogens. Every year, the influenza virus changes just a little bit."

"People realize you don't just build a house and then you're done," Humes adds. "Yet they regard labs as a one-time expense."



"Flu viruses are extremely unpredictable and variable. … And so over time what we say about this and what we learn will change. Expect changes in terms of the number of cases. … We expect that we're going to be changing our recommendations over time based on what we learn."

Dr. Richard Besser, then Acting Director, CDC, White House Press Briefing, April 26, 2009

Chapter 3

"Expect Changes": The Public Communications Experience

As the first outbreak occurs, public communication and message coordination have an impact on everything from policy decisions to future practice—and public health labs are at the center.

At the beginning of the day on Thursday, April 23, 2009, at St. Francis Preparatory School in Queens, New York, a line of students complaining of fever and sore throats trailed out of the school nurse's office and into the hallways.

By Monday, more than 20 national and international TV crews were stationed outside the school. The story: H1N1 outbreak.

That Thursday, the school nurse, Mary Pappas, had known "something was going on." She had seen illnesses come and go—even been through an outbreak of whooping cough—but this was worse. Her two assistants were so overwhelmed with taking temperatures and calling parents that secretaries and an assistant principal had to help. Even a school security guard pitched in, taking temperatures and putting sticky notes with the results on children's foreheads.

It was her instinct that led her to call a supervising doctor with the city's school health bureau to report the unusual number of high fevers and other symptoms. He then contacted a nurse who works with the CDC.

"As soon as we had heard it was out west, we thought 'what can we do here to detect it right away," says Dr. Sara Beatrice, Assistant Commissioner of Health and Director of the Public Health Laboratory, New York City Department of Health and Mental Hygiene. "This nurse was able to very rapidly communicate her experience."

Mary Pappas served as school nurse at St. Francis Preparatory in Queens, New York, site of the first large outbreak./AP

It was instinct—and experience—that led Pappas to call the city's school health bureau to report the unusual number of high fevers.

The school collected lab samples that Friday, and the lab tested into the night. By 2 a.m., the lab called the CDC with the news that it had probables. The New York City lab immediately shipped samples to the CDC for further testing—and within 24 hours, the city had a confirmed outbreak.

The incident became the subject of several articles, not just in professional journals such as *Clinical Infectious Diseases*, but others such as this one in *New York* magazine, October 2009:

> "By Monday, more than two dozen TV field units—eventually including crews from Korea, Japan, and Ukraine—were camped outside St. Francis, which remained closed for a week."

It was the first major outbreak in the city and in the nation—and it would end up galvanizing the city's labs and public health structures. Communication would be key to avoiding panic or poor decisions—and it was part of the New York lab's preparedness planning.

Yet obstacles continue in communication in every lab. Communications can have the side effect of putting tremendous burdens on the labs—from raising expectations that labs would test everyone to making it necessary for labs to scramble to implement or improve public communication strategies.

Media themselves are changing rapidly—as many in public health pointed out, it's a different media environment than it was during the anthrax episodes, or even when dealing with SARS. Social media, online news, and the 24-hour news cycle mean a printed news release every few days, or even each day, won't do the job. Some lessons learned during earlier crises may no longer apply. What kind of communication lessons from H1N1 will survive?

Mixed Media Messages

Shortly after the outbreak began, the CDC received a long, rambling email: A woman and her boyfriend had been in Mexico and wanted to get tested for H1N1, but wanted the lab to mail them the five-target PCR test and let them do it themselves. They were also having some sort of problem with the mail at their current residence, so, she asked, could the lab please mail the tests to the McDonald's across the street?

Risk Communication and the Labs

When Dr. Richard Besser, a CDC veteran who had been tapped to serve as interim CDC director during the pandemic, would take the podium for news conferences, he would often have a laboratory scientist with him—usually Dr. Nancy Cox, CDC Influenza Division director. This was just one of the most visible ways in which public health communication—and communication of the labs' importance—took a leap forward.

"I would speak to the overall questions, but Nancy Cox was there to explain things in detail and show people what was involved," Besser says. "We tried to champion early on the efforts ahead of this outbreak for finding swine-associated flu, and then the ability to get out reagents and test kits quickly to state health departments."

While Besser, now an ABC News senior health and medical editor, got notice for his ease of delivery and "telegenic" presence, what earned praise among scientists and communications professionals alike was the top-down dedication to good quality in risk communication.

"Risk communication was not an afterthought here," Besser says. "We needed to engender public trust and let people know what we knew, when we knew it. And that would mean giving incomplete information, and updating information when we had it."

This basic strategy of risk communication—allowing uncertainty—is not a natural inclination to many in science when communicating with the public. But it's critical to developing a relationship of trust.

"There's a sense among lab scientists that you don't want to give any info until you have all the facts, until you've done that additional assay, that additional validation—and we didn't do that," Besser says. "Another thing that can be difficult for laboratory scientists and epidemiologists is that these are such technical fields. Often people default to their own technical language when speaking to political leadership, whether that's a governor, mayor, or the people in Washington."

Training in risk communication as well as leadership is an investment that should be made in all areas of public health, Besser says: "It's important to have good lab people who can talk to the media."

And that doesn't mean learning how to "spin" information, as some believe. "It's learning to speak clearly and effectively to people who are stressed because of crisis. This is not about putting a good face on things, but communicating in a clear way that's actionable."

For instance, in response to a question about deaths, a spin answer might be: "It's too soon to say," or "If we're lucky, we'll have no deaths." Instead, the message regarding H1N1 acknowledged the risks and possible dangers, and conveyed steps being taken to minimize these.

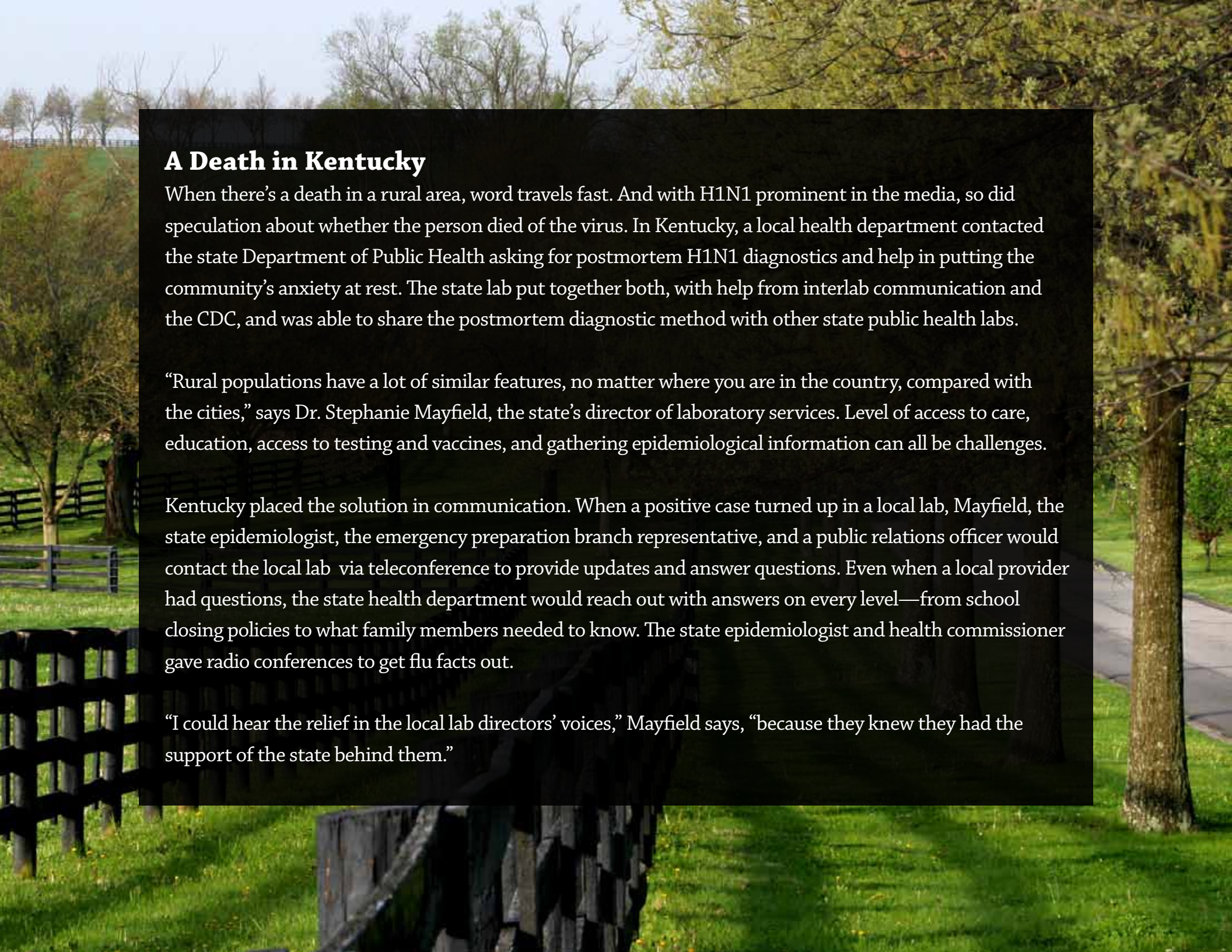
It gave the lab a laugh, but it had a serious side: "People were panicking," says Program Manager Julie Villanueva of the CDC's Influenza Division. "Some people can't simply go to their doctor and ask. I really felt for the people who didn't have health insurance and were hearing these stories and didn't know what the consequences would be."

Media reports about testing may have helped provoke the rush on testing that overwhelmed some labs. People had questions about testing and confirmation of results, and news outlets asked the questions. Public health did a good job of explaining the process. But reports sometimes left an impression that diagnostic testing, which can be a multilayered, intricate process performed by professionals, was simple, straightforward, and clear, every time—simple enough that you could do it yourself.

"In our state, every time a headline ran, we'd have policymakers at our back door asking us for a statement on our response," says Troy Leader of Washington Public Health Laboratories in Washington State. "You can't always plan for that anxiety, but you do know that there are going to be these spikes in how the public gets their information, and you have to respond to that expectation."

Good communications made clear to the public some of the differences between the rapid testing and PCR testing, in the interest of transparency and letting people know uncertainties. However, this sometimes became a case of a little knowledge being a "dangerous" thing. After media reports about the different types of tests, there were reports that some schools and businesses were accepting only PCR-confirmed negatives. The notion of a PCR confirmation took on a life of its own, say lab directors, becoming of outsize importance in decision-making for schools, for instance. People demanded to be tested—even when mass testing wasn't the best or most needed course of action.

For instance, pressure in Texas was greater: With every report from Mexico, people assumed there was a greater degree of threat waiting very close by. The Texas labs found that media reports set up a cycle of demand for testing. Residents wanted an immediate response from political representatives, who then turned to public health for immediate action. "Everybody wanted to know: Have I been exposed?" says Dr. Susan Neill, former state laboratory director at the Texas Department of State Health Services.



A Death in Kentucky

When there's a death in a rural area, word travels fast. And with H1N1 prominent in the media, so did speculation about whether the person died of the virus. In Kentucky, a local health department contacted the state Department of Public Health asking for postmortem H1N1 diagnostics and help in putting the community's anxiety at rest. The state lab put together both, with help from interlab communication and the CDC, and was able to share the postmortem diagnostic method with other state public health labs.

"Rural populations have a lot of similar features, no matter where you are in the country, compared with the cities," says Dr. Stephanie Mayfield, the state's director of laboratory services. Level of access to care, education, access to testing and vaccines, and gathering epidemiological information can all be challenges.

Kentucky placed the solution in communication. When a positive case turned up in a local lab, Mayfield, the state epidemiologist, the emergency preparation branch representative, and a public relations officer would contact the local lab via teleconference to provide updates and answer questions. Even when a local provider had questions, the state health department would reach out with answers on every level—from school closing policies to what family members needed to know. The state epidemiologist and health commissioner gave radio conferences to get flu facts out.

"I could hear the relief in the local lab directors' voices," Mayfield says, "because they knew they had the support of the state behind them."

The state needed to cleave closely to CDC messages in order to cut through the media-created expectation that everyone would be tested, and quickly. Its communication focus, therefore, was on easing fears and stressing that the worst-case scenario was not the likely one.

"When it starts in your backyard, the political response is different, and the expectations become different," says Neill. "I think now that we have seen that testing everyone just doesn't work, we will be able to put those plans in place to appropriately respond."

Changing the Questions

In New York, daily meetings involving the lab in a primary role helped keep communications clear. "Tom Frieden kept the process focused and under control," Beatrice says of the city's then Commissioner of Health. Each day, the stakeholder group would ask: What's the most important public health question that needs to be answered today?

New York City also had daily meetings with major news representatives, with all the city health department information officers included. The mayor held news conferences at least once a day, occasionally twice. Not only health officials, but also law enforcement officials and politicians were part of communications and planning.

Consistent, regular meetings also helped several labs avert one of the effects of the rapid-change environment—different messages coming from different sources. With no mechanism in place to track the various and sometimes conflicting facts and directives from different departments and agencies, labs can get stuck in the middle. Face-to-face or conference call meetings helped keep everyone on track and provided a place where questions could be raised and conflicts could be resolved.

As a side effect, the New York City lab was featured in both a *New York Times* article and a *New York* magazine story—which helped more people understand the role and importance of the labs.

Created from *New York Times* H1N1 overview article using Wordle.

Public Perceptions, Public Health

From looking at general news reports, in the main, the public health labs appear to have been perceived neutrally or positively by the public. While there was some concern in the early days about testing, most negative public perceptions coalesced around later problems with vaccine supply, a process in which the labs were not involved. The basic public health approach to the pandemic was, in the end, regarded as a success, with a few lessons that could be learned. A *New York Times* overview article on H1N1 from 2010 encapsulates this:

> "American health officials took a more cautious approach, which observers now credit with containing the pandemic with minimal disruption to the economy. For example, in the early days, they ignored advice to close the Mexican border and pre-emptively shut school systems. … To alert the public without alarming it, a stream of officials—from doctors in the navy blue and scrambled-eggs gold of the Public Health Service to a somber President Obama in the White House—offered updates, at least twice a week for months."

Future Issues

Warm base for communications:

During an event, there's a very short window in which to communicate. Putting in advance time to sharpen communications capacities and strategies, working with CDC officials and with state public information officers, is an investment that paid off for many labs, and one that should continue.

Changing media:

The nature of the media changed even in the time from SARS and anthrax crises to that of H1N1. The 24-hour news cycle, the rise of independent media and unvetted blogs, and

By Any Other Name

The naming of the novel influenza virus presented another communications challenge. The virus changed names several times through its appearance and initial outbreaks.

It's obvious why names such as "Mexican Flu" and "North American Flu" were inappropriate. But the first name to get widespread use, "swine flu," also caused problems. In the rural United States, communities and corporations were concerned that people would believe that working with pigs or eating pork could spread the flu. The name also set up a confusing conflict with a 1976 US flu outbreak. Naming the virus according to its genetic components was a more accurate option.

By July, the World Health Organization had named the virus 2009 Pandemic Influenza A(H1N1), and it was being generally referred to as H1N1. A nomenclature component should be part of communication plans for future incidents—and labs can be aware of possible public confusion related to nomenclature.

The PIO's View

One night in April 2009, Heidi Truschel-Light got a call: She would need to report to the University of Delaware campus the next morning at 6 a.m. There were media reports that the university was experiencing an H1N1 outbreak—the first such outbreak on a university campus—and as a public information officer for Delaware's Division of Public Health (DPH), it would be Truschel-Light's job to help manage the flow of communication to the media and a concerned public.

"It took me all day to get to the university clinic because I kept stopping on campus to talk to reporters," recalls Truschel-Light.

Eventually, the university would test more than 1,000 students—and find 24 confirmed cases. During the outbreak (between approximately April 26 and May 2, 2009), Truschel-Light and the rest of the communications team worked to provide accurate information to the public. "There was this enormous divergence of information," she says. "On the ground level, we were seeing kids who barely thought they needed medical attention. Then the WHO is saying that we have one of the most profound health crises in decades."

"People wanted results, results, results—and they wanted them immediately," says Dr. Jane Getchell, state laboratory director in Delaware during the pandemic. "The public information officers were priceless in calming people and helping them to understand."

The state set up a screening area in a gym, with more than 100 health workers giving tests. More than 250 students showed up for testing—some who felt ill, but others just worried about having traveled in Mexico. At that time, there was great confusion among colleges on decisions about whether to close. Decisions at colleges and universities had to be weighed against the problem of students having to travel home over long distances using public transportation.

The university worked in close conjunction with the DPH and so was able to give good reason for its ongoing decisions on staying open, including sharing probable and positive diagnoses and illness severity levels of those affected. The next fall, in anticipation of a second wave of infection, the school gave an H1N1 student information session, which was "standing-room only," according to a campus publication.

Truschel-Light says there were some key communications takeaways from the H1N1 outbreak. Chief among these is getting all parties on the same page so the public health labs, epidemiologists, and others aren't giving conflicting information. Communicating that information will change often over the course of the outbreak is also important.

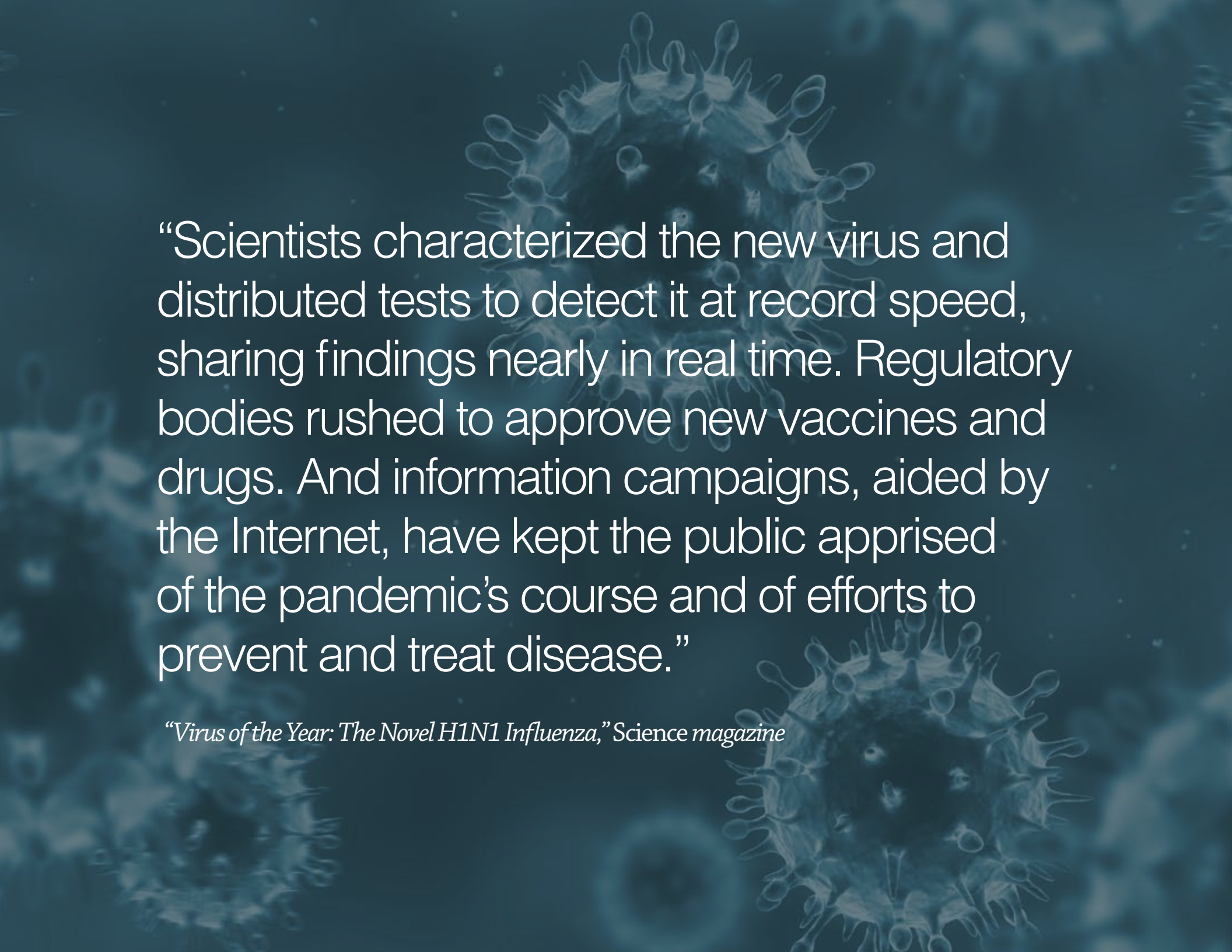
"Finding out after the fact that [lab] statistics were getting disputed a day or two after we released them was a problem," she says. "You've got to have solid ground every step of the way. Once people start to form a conclusion—and in the case of H1N1, that conclusion was 'college students are at risk'—it's hard to go back and correct that information, because people have ruled themselves out of risk."

While the communications methodology is in place for all health crises, Truschel-Light said each crisis is different and will involve different solutions. But communication between all parties involved is imperative every time.

a plethora of new media outlets that work in the hybrid areas between information and opinion are just a few of the factors that make keeping the message consistent, simple, and direct the only route to successful dissemination.

Social networking:

Social networking has become a powerful communications force that circumvents media outlets. The door that's open to more direct exchange also allows in more misinformation and possible manipulation of information. The H1N1 pandemic inspired CDC social media action that has been applauded and won awards for its usefulness, timeliness, and positive "viral" possibilities. Going by the principle that the best way to counter misinformation is to strengthen and disseminate accurate information sources, the CDC offered free widgets, buttons, badges, mobile information, online videos, and more. CDC's Facebook friend list felt the effects, going from about 3,000 before the outbreak to more than 50,000 by the summer of 2010. The three Twitter accounts used by the CDC to share H1N1 information grew to more than 1.25 million followers. A CDC YouTube video on the flu posted early in the pandemic had more than a million viewers.



"Scientists characterized the new virus and distributed tests to detect it at record speed, sharing findings nearly in real time. Regulatory bodies rushed to approve new vaccines and drugs. And information campaigns, aided by the Internet, have kept the public apprised of the pandemic's course and of efforts to prevent and treat disease."

"Virus of the Year: The Novel H1N1 Influenza," Science *magazine*

Chapter 4
Life in the Labs

Internal communication, workforce challenges, and relationships among labs and public health partners revealed personal strengths, major leaps forward, and weaknesses in systems.

"The H1N1 pandemic really put our lab to the test," says Patricia Blevins, bioterrorism lab coordinator, San Antonio Metro Health District (SAMHD).

The problem was volume. The lab was at a flashpoint for H1N1, as a border area of a border state. Then came the equipment failure at the State Health Lab in Austin.

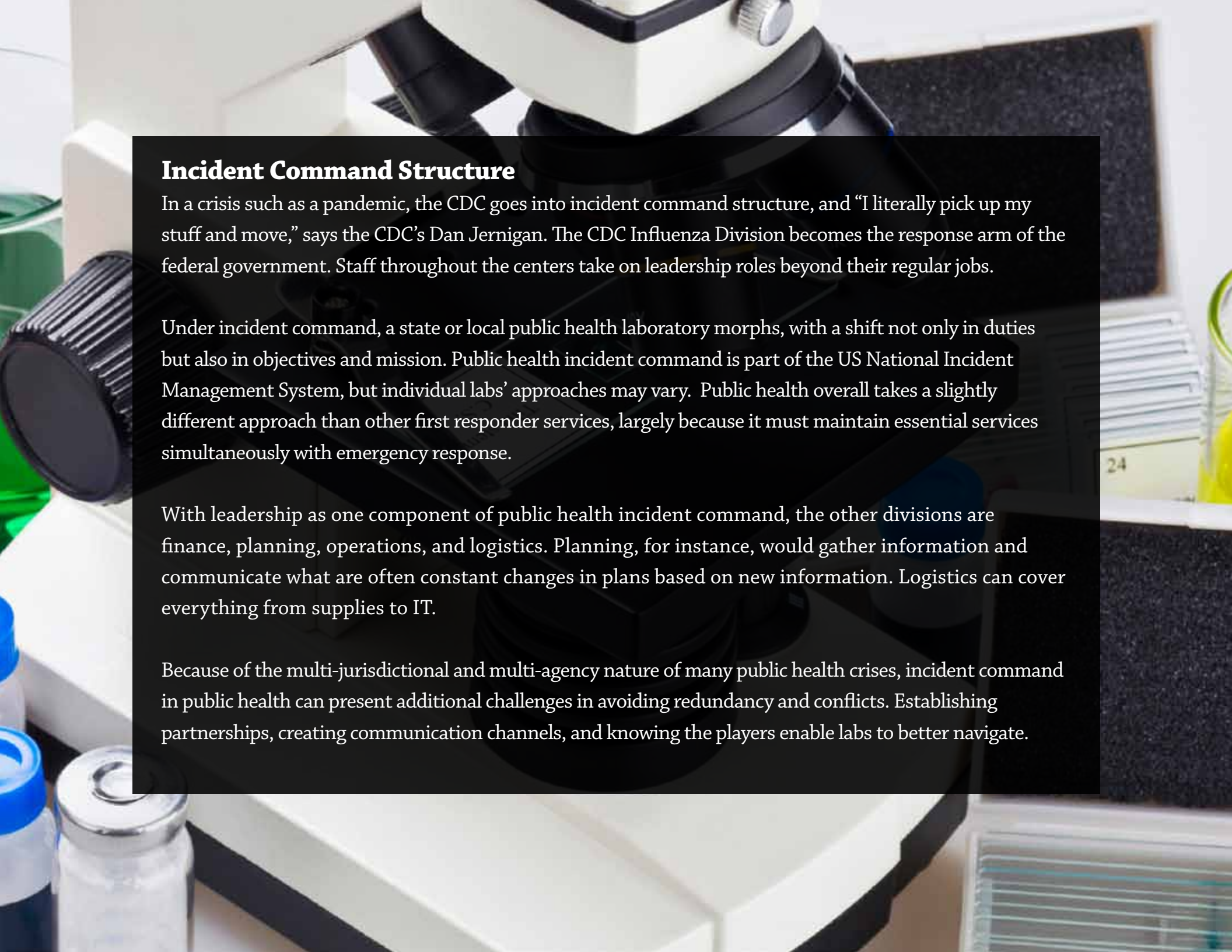
"Fortunately, we'd participated in a flu subtyping pilot through the state health department, so training wasn't an issue."

"I'd been in on the conference calls since the H1N1 news first broke," Blevins says. "We were hearing about the first cases in California and the deaths in Mexico, and we were getting updates from the state epidemiologists."

On Friday, April 24, when something popped up close to home—right in San Antonio—Blevins was assured the state lab would handle it. "So I relaxed and thought: This will be a great learning experience."

Then the phone rang. The testing equipment was down in Austin, and samples were on their way. It was 8 p.m.

The work started as samples came in on Saturday morning. More samples arrived on Sunday. Still, the pace was manageable enough to allow the three-person virology team to get up to speed. "It was the quiet before the storm," Blevins says.



Incident Command Structure

In a crisis such as a pandemic, the CDC goes into incident command structure, and "I literally pick up my stuff and move," says the CDC's Dan Jernigan. The CDC Influenza Division becomes the response arm of the federal government. Staff throughout the centers take on leadership roles beyond their regular jobs.

Under incident command, a state or local public health laboratory morphs, with a shift not only in duties but also in objectives and mission. Public health incident command is part of the US National Incident Management System, but individual labs' approaches may vary. Public health overall takes a slightly different approach than other first responder services, largely because it must maintain essential services simultaneously with emergency response.

With leadership as one component of public health incident command, the other divisions are finance, planning, operations, and logistics. Planning, for instance, would gather information and communicate what are often constant changes in plans based on new information. Logistics can cover everything from supplies to IT.

Because of the multi-jurisdictional and multi-agency nature of many public health crises, incident command in public health can present additional challenges in avoiding redundancy and conflicts. Establishing partnerships, creating communication channels, and knowing the players enable labs to better navigate.

"By Monday, the floodgates were open," Blevins says. "The samples kept coming and coming." For comparison: During its five-month pilot project, the SAMHD lab had processed some 200 flu specimens. On one day, Monday, 165 samples came in.

There wasn't enough refrigerator space for them all. Testing reagents were in short supply. The lab soon ran out of specimen labels, testing vials, even printer ink. All the while, the phones rang off the hook.

Staff from hospitals, sentinel labs, physician offices, clinics, and local health departments all wanted to know how to collect samples, how to transport them, how long results would take, and how worried they should be.

Blevins pulled staff from other areas, including the lab's BioWatch team, for support. During peak volume, she tapped a dozen colleagues to help with everything from fielding phone calls to prepping paperwork to PCR testing.

"We were lucky that no one got sick," Blevins says. "We did a fever watch so everyone was checked before coming in for the day." Of course, concern was not just a practical matter. "We wanted to make sure our staff knew that we cared about their safety and the safety of their families."

The biggest challenge was yet to come—reporting. State health officials pushed hard for results: how many new cases were showing up and where. "The numbers were the craziest part," Blevins says. "We didn't have our own laboratory information management system (LIMS) so we were dialing into the state LIMS. It just wasn't efficient."

Future Catches Up with EID Fellow

As an Emerging Infectious Diseases Fellow, Tam Van had set up PCR processes before, but not for diagnostics. But she had to adapt her training quickly when the H1N1 virus hit.

Van was working on her fellowship in the Wisconsin state public health lab in the spring of 2009 when she ended up getting firsthand experience with a pandemic. She was at a clinical virology symposium when the meeting was interrupted for a quick bulletin. Soon, she says, "I was an extra pair of hands" in a lab swamped by specimens. "It was an interesting experience—it didn't scare me away."

"I knew public health wouldn't be all outbreaks," she says. "I like the everyday work, too."

After her fellowship ended, Tam took her PhD to the private sector for biotech research, but soon returned to public health when the opportunity arose: She now works for APHL as manager of HIV, Hepatitis, STD, and TB programs.

Safety and Occupational Health Specialist Becomes Logistics Guru

Laura Zambuto/CDC

High security, high priority, highly pathogenic—Safety and Occupational Health Specialist Laura Zambuto at the CDC had experience in all of the above. She knew how to work with select agents, how to get specimens in and out quickly and safely, how to engage assistance from groups ranging from emergency operations to pathology. This skill set put her at the center of the CDC diagnostic operation during the early H1N1 crisis, where her work was praised by those in public health labs around the country.

It also put her at the gates of the CDC at night, waiting for delivery trucks from FedEx, UPS, or World Courier to arrive. And at the airport at all hours, picking up specimens being flown in on the CDC plane, for instance.

"We were a 24/7 operation," Zambuto says. Because of her knowledge of regulatory and safety requirements in handling specimens, she ended up managing logistics for most specimens. Every request was an urgent one, and setting priorities was a tall order. But maintaining quality control, both to protect the integrity of specimens and to protect workers and the public, had to be first priority.

What was surprising, Zambuto says, is that the biggest problems had little to do with biosecurity knowledge. They were simple ones—empty boxes piling up in the hallways and data entry duties piling up next to computers. The CDC was also getting too many whole blood samples, fecal samples, brain samples—specimens that don't usually get sent in and are difficult to accurately test.

Communications made the difference: As soon as word got out to local and state labs of requirements for specimens and packaging, circumstances improved. Preparation that included networking and breaking down silos meant laboratorians knew whom to call to get things done quickly.

"I thought it was crazy here, but working at a state or local lab was much harder," Zambuto says.

Login delays, remote glitches, and protocol inconsistencies cost valuable time. "One day, I had two people from accounting who just printed reports for eight hours straight," Blevins recalls. "It took a minute or longer to print one report."

Coordination among labs was another challenge: One lab had not included essential CLIA coding numbers, and so its specimens could not be verified as having been done according to regulations. The only solution was to re-test every one in the batch.

San Antonio has already taken that lesson to heart. Thanks to the Public Health Emergency Response (PHER) grant, Blevins reports that the lab is implementing its own LIMS. Other post-H1N1 upgrades include two additional PCR instruments and state-of-the-art automated extractors.

So are they ready for the next time? "If it happened tomorrow," Blevins says, "we'd be much better off."

Data—its collection, reporting, and transfer—was one of the top bottlenecks reported by public health labs in APHL reviews of the pandemic. A complicating factor: Molecular diagnosis results in richer, more complex data to have to communicate. It's not only the total volume of specimens that overwhelms, but also each specimen's individual volume of specific information. Yet it is those bits of information that make the critical difference between a known virus and a novel—and possibly more dangerous—one. Maintaining the integrity of the information transferred is, in effect, a life-and-death issue—and labs need the capacity to quickly do so.

Out of the Silos, Into the Cafeteria

Similar scenarios to that in San Antonio played out in labs around the country. Trying to ensure that overwork didn't lead to a lapse in quality and accuracy was a major concern. One lab instituted a regular dinner hour in the cafeteria to get laboratorians to take breaks. Scientists did demographic data entry, took phone calls, and monitored the fax machine.

"When the labs came together to brief each other, there were discussions that people were working long hours, seven days a week, and there needed to be some mechanism for some relief," says Dr. Sara Beatrice, of the New York City lab. "Part of my job is to protect my staff—not only with safety protocols, but making sure they get rested and fed."

PHLIP: Can We Talk?

Labs were under intense pressure during the H1N1 outbreak, often testing hundreds of specimens a day. Paperwork became an issue as lab workers also had to focus time on recording results and sending information of unusually high volume to the CDC. Several labs were still using faxes; others were emailing spreadsheets of data. One lab was simply unable to file reports—it had no capacity.

But the Public Health Laboratory Interoperability Project (PHLIP) is helping labs get access to faster, more efficient, and more accurate data communication.

The PHLIP pilot program, launched in 2005, has the goal of establishing a streamlined data flow between the public health labs and the CDC labs, and between the public health labs with commercial and hospital laboratories and healthcare providers. Because of the pandemic experience, APHL has been able to bring 29 labs to production stage—the ability to send electronic test result messages directly to the CDC—in less than two years.

Users of PHLIP also share recognized data standards for the transmission of laboratory results, which helps to eliminate errors and redundancies. APHL encourages all public health labs to consider participating in this program now in order to ensure smoother testing during the next public health crisis.

"Instead of having one key player in all positions, we now try to have a structure that is four or five deep," she says. "At the senior level, we are training all of them to be able to cover emergency preparedness and response to back me up. But at the lab level, it's a little more difficult to do that."

Lab directors were faced with training staff to multi-task without losing focus on accuracy and devising ways to cover the routine lab work that was still coming in during the pandemic.

"The people who go into public health aren't asking, 'Will I get paid for overtime?' " Beatrice says. "Their mindset is, 'I'm making a difference to the whole medical community—and I want to do it as much and as long as I can.' It is a commitment that is remarkable to see."

Workforce Shortages Hit Home

Stepping up workforce to deal with a surge in demand isn't easy in a lab, where many jobs involve specialized training and certifications. Worker health protection is another complicating factor.

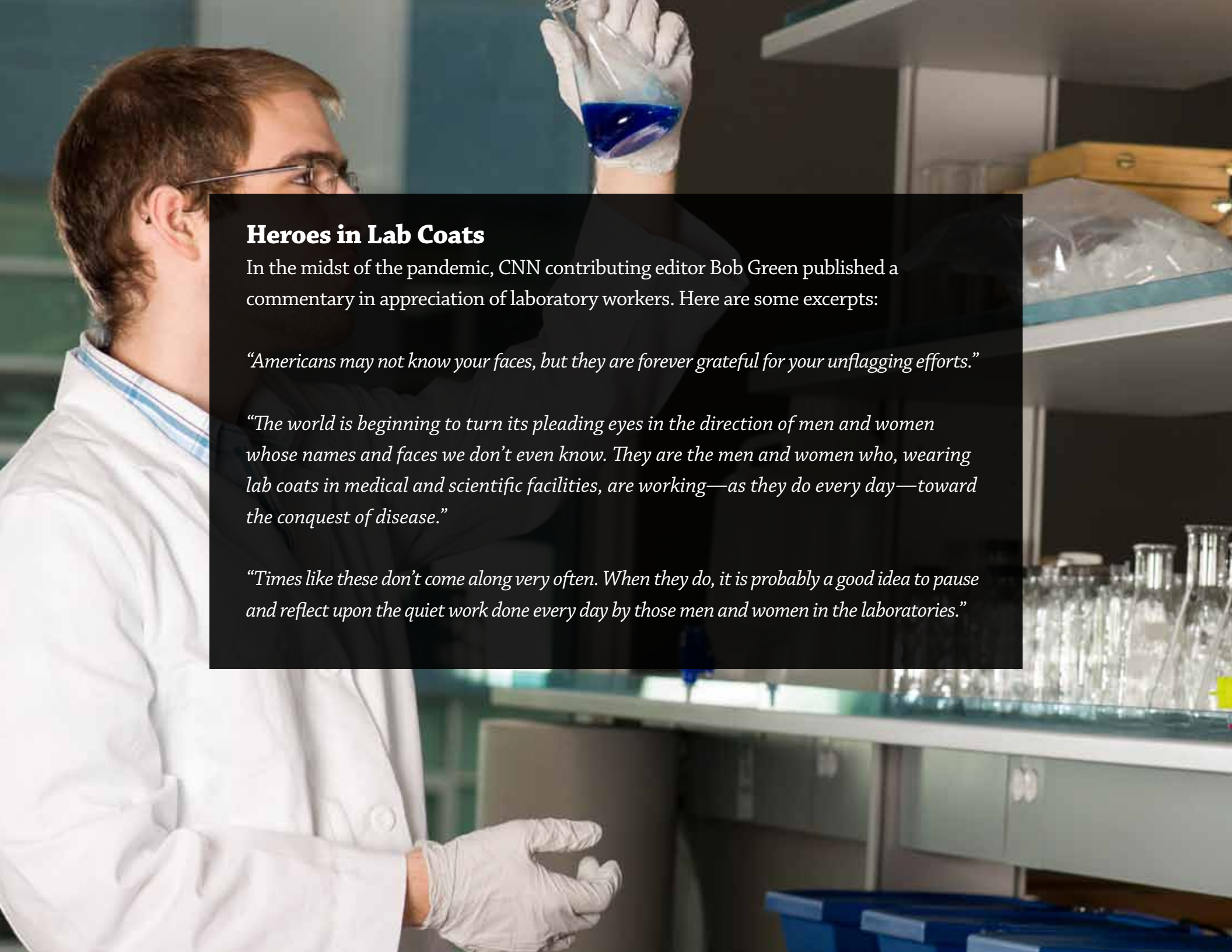
In Texas, for instance, the state lab trained more personnel in PCR testing and hired through a temp agency for shipping and similar tasks. Increasing workforce during a surge brings additional burdens to training, however—checking references and screening backgrounds and other hiring-related activities take time, the state lab pointed out in a lessons learned report on maintaining quality.

Being close to a university hospital system and technical knowledge center in Austin was a major plus for the Texas state lab; other labs looked to nearby partners for workforce help as well. At the public health lab in Nebraska, Tricia Aden, then a molecular microbiologist and now Manager of Influenza Programs at APHL, worked side-by-side with the Nebraska Medical Center molecular diagnostics staff during the pandemic.

Cross-Training to Manage Surges

Public health laboratorians today must often become skilled in several areas.

Several states had already been doing cross-training because of lab cutbacks, and this turned out to serve them well during the pandemic. Dr. Stephanie Mayfield, Kentucky's state lab director, swears by cross-training as a crisis management solution. "We survived by cross-training when I worked in a hospital, and I had always wanted to bring it into the lab," she says. "It's not just for more efficiency, but for more education and advancement opportunities. It's a win-win."



Heroes in Lab Coats

In the midst of the pandemic, CNN contributing editor Bob Green published a commentary in appreciation of laboratory workers. Here are some excerpts:

"Americans may not know your faces, but they are forever grateful for your unflagging efforts."

"The world is beginning to turn its pleading eyes in the direction of men and women whose names and faces we don't even know. They are the men and women who, wearing lab coats in medical and scientific facilities, are working—as they do every day—toward the conquest of disease."

"Times like these don't come along very often. When they do, it is probably a good idea to pause and reflect upon the quiet work done every day by those men and women in the laboratories."

"We asked them to come in after their day jobs and do RNA extractions and that sort of thing, training them in what we needed. They have great backgrounds, and they knew the platforms," Aden says.

"This is definitely something I think other labs could do—go to university medical centers and ask diagnosticians for a few hours of their time after work," Aden adds. "It worked well for us."

Future Issues

Who's watching the floodgates?

Labs would benefit by a gatekeeping mindset on the part of epidemiologists, lab scientists say. In some states, the epidemiologists took an aggressive approach to testing, and labs were overwhelmed in ways ranging from lacking staff to having shortages of reagents. Other states put the clamps down too soon on testing, creating a different set of problems in terms of surveillance, harming relationships, or creating negative public impressions.

Dr. Peter Shult of the Wisconsin lab is part of a current project working on "right-sizing" these efforts. One approach is to try pooling specimens in groups of five to 10 specimens at a time, rather than working with individual specimens.

Workforce leadership crisis:

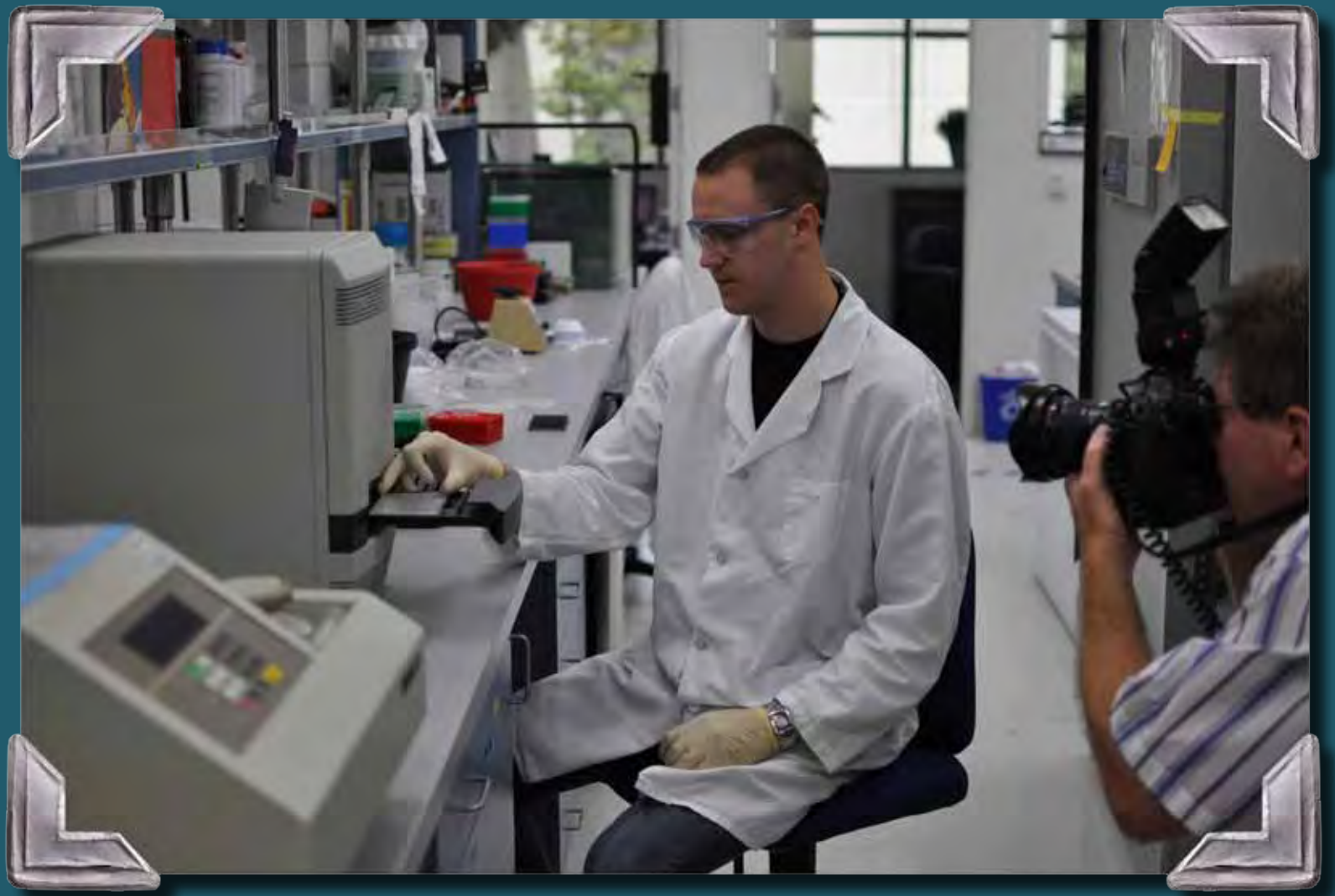
Public health labs have been facing a crisis in leadership for several years, with current lab leaders moving toward retirement and not enough choosing public health lab careers. Initiatives are developing solutions on several fronts:

- APHL has created leadership programs and training
- Advocates are seeking sustainable funding to make public health a more desirable career
- Association and corporate partners and others are exploring educational solutions from going into schools at the high-school level to offering online continuing education for laboratorians

Specimens on Wheels

One solution for rural or remote areas: Bring the laboratorians or specimen collection to the communities.

During the pandemic, Delaware enhanced services from its courier van equipped to pick up specimens. Couriers were lab staff, who took the van to collection points such as hospitals and made special runs when needed. It worked in large measure because Delaware is a small state, but the idea could be adapted for use on a regional basis.



The 7500 Fast Dx Real-Time PCR instrument was a critical part of the diagnostic and its approval./Life Technologies

Chapter 5
Staying Flexible as Imperatives Change

Fast response in the pandemic pushed boundaries in all directions for public health laboratories. Flexibility emerged as the most important quality for successful operation, especially in essential partnerships.

Approval or clearance of a typical in vitro diagnostic medical device by the US Food and Drug Administration is a process that can take a year or more.

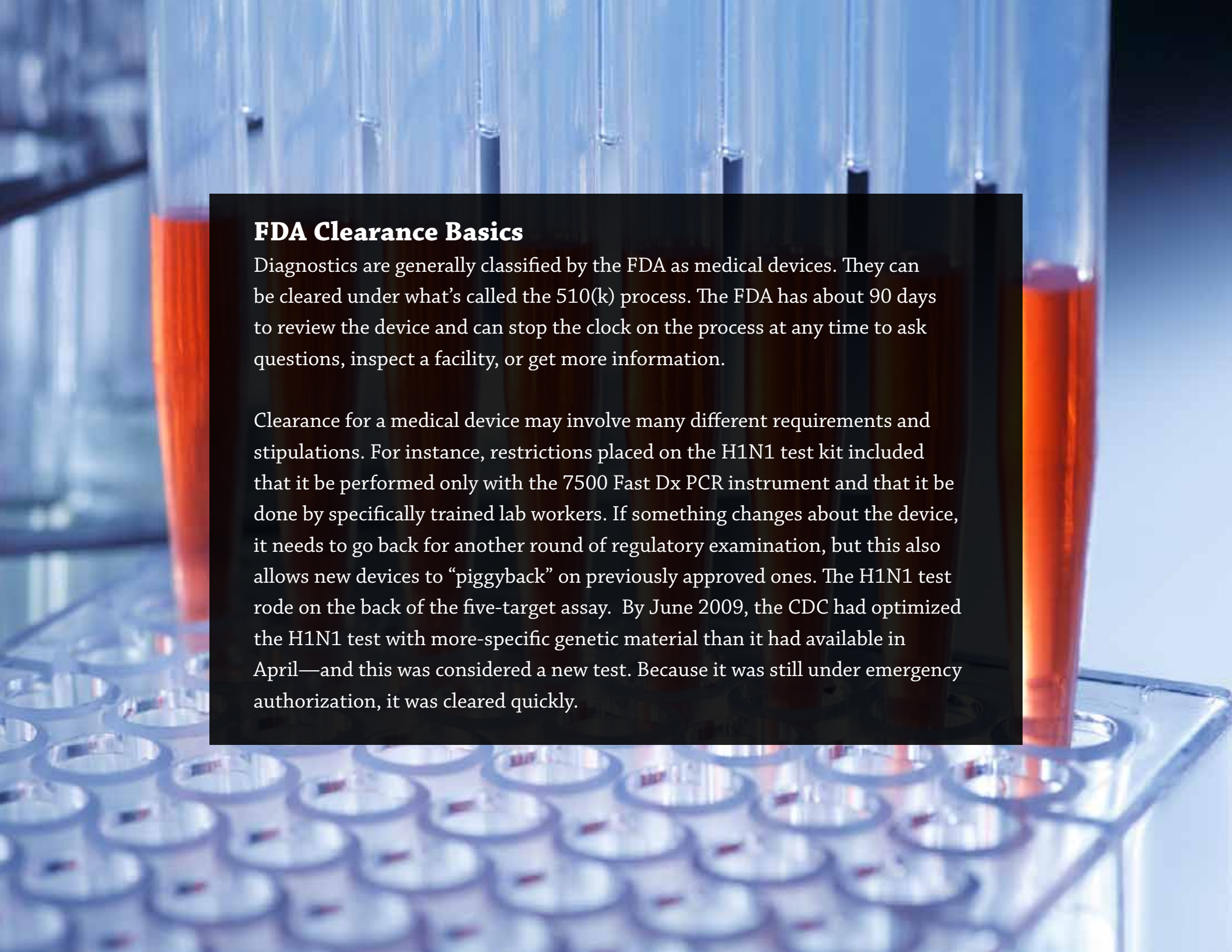
For the H1N1 test kit, it took four days.

For the first time, public health activated an FDA Emergency Use Authorization (EUA)—in effect, pulling a large regulatory fire alarm. The EUA was designed for use against life-threatening illnesses, particularly public health threats; it allows a product that fills an "unmet need" to be cleared quickly during an emergency.

"Could they really do it in a few days?" was the issue, remembers Dr. Joshua Sharfstein, then the FDA's principal deputy commissioner, now Secretary of Health and Mental Hygiene for the state of Maryland. "Teams from the FDA worked all weekend with the CDC, until 3 a.m., so that everyone could be ready on Monday."

The most intense work took place in about 48 hours, with the regulatory task force working in its own room in the CDC emergency operations center, where constant phone calls came in to and from the FDA.

What were they working on? Everything from the label to the instruction sheet; results, rationales, all the elements that go into making a case that this test was different, necessary, and worthy of activating the EUA.



FDA Clearance Basics

Diagnostics are generally classified by the FDA as medical devices. They can be cleared under what's called the 510(k) process. The FDA has about 90 days to review the device and can stop the clock on the process at any time to ask questions, inspect a facility, or get more information.

Clearance for a medical device may involve many different requirements and stipulations. For instance, restrictions placed on the H1N1 test kit included that it be performed only with the 7500 Fast Dx PCR instrument and that it be done by specifically trained lab workers. If something changes about the device, it needs to go back for another round of regulatory examination, but this also allows new devices to "piggyback" on previously approved ones. The H1N1 test rode on the back of the five-target assay. By June 2009, the CDC had optimized the H1N1 test with more-specific genetic material than it had available in April—and this was considered a new test. Because it was still under emergency authorization, it was cleared quickly.

"First, you have to demonstrate clinical utility, and that it is safe, because you're testing human specimens," says James Roy Johnson, program manager of regulated products at Battelle Memorial Institute, who works as a contractor with the CDC Influenza Division and was instrumental in the diagnostic development and authorization effort.

The test also needed "labeling." "It's not just the physical label, but documentation of all the claims you want to make," Johnson says. "What are the assay's limitations? You need to work through the language so you capture both the historical and current data for regulators, and also enough information for the end users."

Once again, preparedness sped the process. The key, Johnson says, was the ability to get the assay and the instrumentation cleared separately, but to be used together. The group, which included Dan Jernigan and Steve Lindstrom and others, had just come through the process of getting the five-target assay cleared—a tough process they had thought moved remarkably quickly. The H1N1 EUA process was like doing the same thing again—only faster and tougher.

"This was a new paradigm for a regulatory route," Johnson says. "The industry and government came together to mitigate the risk and come up with a solution. It opened the door for a more interactive process that really streamlines the communication and benefited both agencies, and public health needs," Johnson says.

"Both agencies can be a little cumbersome—that was realized—but we also realized the ability to interact and improve things together and to get this device out in record time," he adds.

As the pandemic went on, several diagnostics were authorized under the EUA, as well as equipment and instruments. In the future, says Jernigan of the CDC, it would be helpful to have more such exceptions, for diagnostic test development, manufacturing, and distribution.

Kits were created and rapidly shipped, in the US and internationally./CDC

While the EUA went through quickly, the results of the action are still continuing to raise debate. "What is the right level of regulation?" Sharfstein asks. "That's something the FDA is looking into. It's the intersection, again, of use and technology. The theory behind the test might be fine, but where are the results?"

The risks of authorizing a test that gives back false negatives are obvious—patient death and unchecked spread of influenza. The risks of authorizing a just slightly less-than-stellar or redundant test too quickly may not be immediately obvious to observers. But they exist not as test results but as unintended results: Wasted money, time, and effort that could have gone to effective solutions; setting poor precedents on which to build future technology; and certainly that being less than vigilant goes against the agency's mission. Regulations, also, are based on a "one-test, one-intended-use" paradigm, and in some ways genetic sequencing shatters that paradigm—because a sequence can be put to dozens of uses.

Sharfstein compares it with current debate over direct-to-consumer genetic testing. "It's the same concept—the regulatory challenge of finding the place between making things too restrictive and not making them restrictive enough."

He calls the success at getting the authorization "remarkable"—and adds that "it shows that the FDA knows how to move quickly."

Powerful Precedent

Until the H1N1 pandemic, the most challenging FDA approval push had been in 2008, for the five-target assay influenza test kit. The CDC, APHL, and Life Technologies (Applied Biosystems became part of the company in late 2008) had collaborated to quickly help arrange for everything needed to win approval and get the labs using the test

What Can Wait Until After the Pandemic?

In the midst of the pandemic, APHL got calls from some labs saying they were facing inspection under the Clinical Laboratories Improvement Amendments, a periodic check for lab quality compliance essential to continued operation. APHL was able to negotiate with the Centers for Medicare and Medicaid Services, which administers the inspections, and ask CLIA inspectors to be flexible—so labs could get the time—and energy-consuming process delayed until after the pandemic response was handled. CMS gladly complied, thus bringing them into the pandemic response "family."

immediately—confirmatory testing, funding for reagents, instruments needed, and more. FDA approval of the five-target assay made a powerful precedent when it came time for emergency authorization for the H1N1 test.

This iterative innovation process of building on precedents not only makes regulatory hurdles easier, but it also improves quality and can help protect safety. The lessons here: Build on what you have, and preparedness can have just as much urgency as emergency action—because what's being prepared for can quickly become a reality. "It goes beyond developing tests and devices to developing strategies, infrastructure, and support," Jernigan says. "That's what we learned."

Setting the Sequences Free

The CDC began in 2006 to release influenza genetic sequences, the genetic fingerprint of a virus that provides clues to its origin and is critical in identification and diagnosis. APHL gained support from all state laboratories to submit influenza samples to help in this process.

Molecular diagnostics put a new spin on regulatory and development areas, just as it had on the actual testing process. "Before, the federal government would have to make a lot of tests, and we'd send them out, and people would use them—that was the full process," Jernigan says. "With people being able to do their own PCR, we could put up the recipe and let people make that themselves. It's a much more robust approach for people able to ramp up testing for a novel pathogen. Globally, it's easier to respond because the capability is so expanded now."

While testers still need ancillary reagents, instruments, and training, they can in fact do their own validation, under CLIA regulations, by comparing results to a gold standard, Jernigan points out. "I think this helps the public health labs to not be as overwhelmed as they could have been, when academic and clinical labs can do their own testing."

But this freedom presents a regulatory difficulty. When the FDA was considering putting H1N1 tests under more control and scrutiny, the task force picked up the phone again. With demand for testing so high, it would have been a bad time to try to make an example out of the test.

Respond Now, Pay Later

Labs, corporations, and agencies alike needed to be flexible when it came to paying the bills. Lab leaders say the attitude on the part of corporations was enormously helpful—that they in effect simply asked who needed instruments or help, and provided it. "The vendors weren't asking for payment before they stepped up," Rosemary Humes, former APHL science advisor, says. Likewise for the CDC, which supplied reagents and other critical test components as needed during the emergency. The CDC also created a mechanism by which Public Health Emergency Response grant money could come to the labs, to cover some expenses.

Some in the regulatory area see it differently—their mission is to protect the public from bad tests. Some felt commercial and other labs were whipping up tests that weren't necessarily valuable or best quality and charging a high price, taking advantage of the concern about the virus. The wide-open field could set a poor precedent, they believed.

Soon after uncovering the virus's genetic profile, the CDC posted the sequence on the WHO website, where it could be used freely by anyone who wanted to develop a test or a vaccine. The release of the genetic sequence of the H1N1 virus required a different kind of flexibility—one that pivoted between science and commerce.

"What we did was stupid from a business standpoint," Jernigan says. "A pharmaceutical company would never give away the recipe for the test—you would make people license it from you. Our own technology transfer folks would have said not to give it away. But we're not in the business of trying to make money or have proprietary tests."

"The United States is a believer in patents and copyrights for a reason—we make sure software is protected and licensed, for instance," Jernigan says. "But when it comes to viruses, that's a model that doesn't work. Viruses are constantly changing, moving across borders."

"You have to see it in the context of what was happening with global virus sharing at the time," he says. Some countries were standing firm on not sharing virus sequences with the global health community unless they received vaccine benefits in exchange.

"We said, that's not a good model for rapid response ," Jernigan says. "Our model is very open. And it really paid off. Policies about virus sharing ended up in a different place after H1N1."

"Texas Two-Step"—Surveillance or Diagnosis?

Public health labs during the pandemic had to be flexible even about their own mission. Public health labs often take on a primary diagnostic role in the early days of an emergency. Much of the early HIV testing, for instance, was done through public health labs. As needs change and other labs develop capacity, the public health labs sometimes continue for some time to test specimens for hospitalized patients or those with acute complications. Eventually the surge capacity is scaled back to core needs such as surveillance and testing for resistance.

As with other circumstances surrounding H1N1, in 2009 and 2010 this process was accelerated. In Texas, the need to pivot between running hundreds of tests for diagnosis and analyzing hundreds of results for surveillance was so extreme that APHL Executive Director Scott Becker referred to it as the "Texas two-step."

Commercial labs clued in early to the way public health labs were being overwhelmed. This could have been because some were developing partnerships with labs, or because some were developing their own flu products. In any case, a clearly stated aim of companies such as Focus, a division of the behemoth Quest Diagnostics, was to develop tests in order to "offload a backlog" from public health laboratories and allow them to fulfill "priority public health surveillance needs."

Public health labs returned the consideration, offering key elements for commercial labs to validate and test their assays. Some commercial labs' tests were allowed under the EUA, and a few were cleared using the FDA 510(k) process.

Future Issues

What happens to the EUA-cleared devices?

After the EUA expiration in 2010, two diagnostics won 510(k) clearance—and one was the PCR developed by the CDC. Other companies were encouraged to apply for clearance. However, some test developers decided not to try for clearance because the market for H1N1-specific devices was not as strong and because new technologies for flu testing were becoming available.

Lab-developed testing conflicts:

A pressing issue for the FDA, enforcing regulations on lab-developed testing, could have major effects on testing conducted in clinical and public health laboratories.

But as H1N1 shows, public health labs' "home brews" can be critical in a crisis. Can they stand up to regulatory scrutiny—or can a response wait for a regulatory review? Public health labs may also find they have a role to play in validation as lab-developed tests seek review and confirmation.

Special instruments and advanced training are needed to perform molecular diagnostics—making preparedness before an emergency occurs imperative.

Chapter 6
Crossing Borders, At Home and Abroad

Relationships with international groups, corporate partners, military labs, academic labs, and clinical providers solidified as they became more critical in the pandemic—but left challenges for the future in their wake.

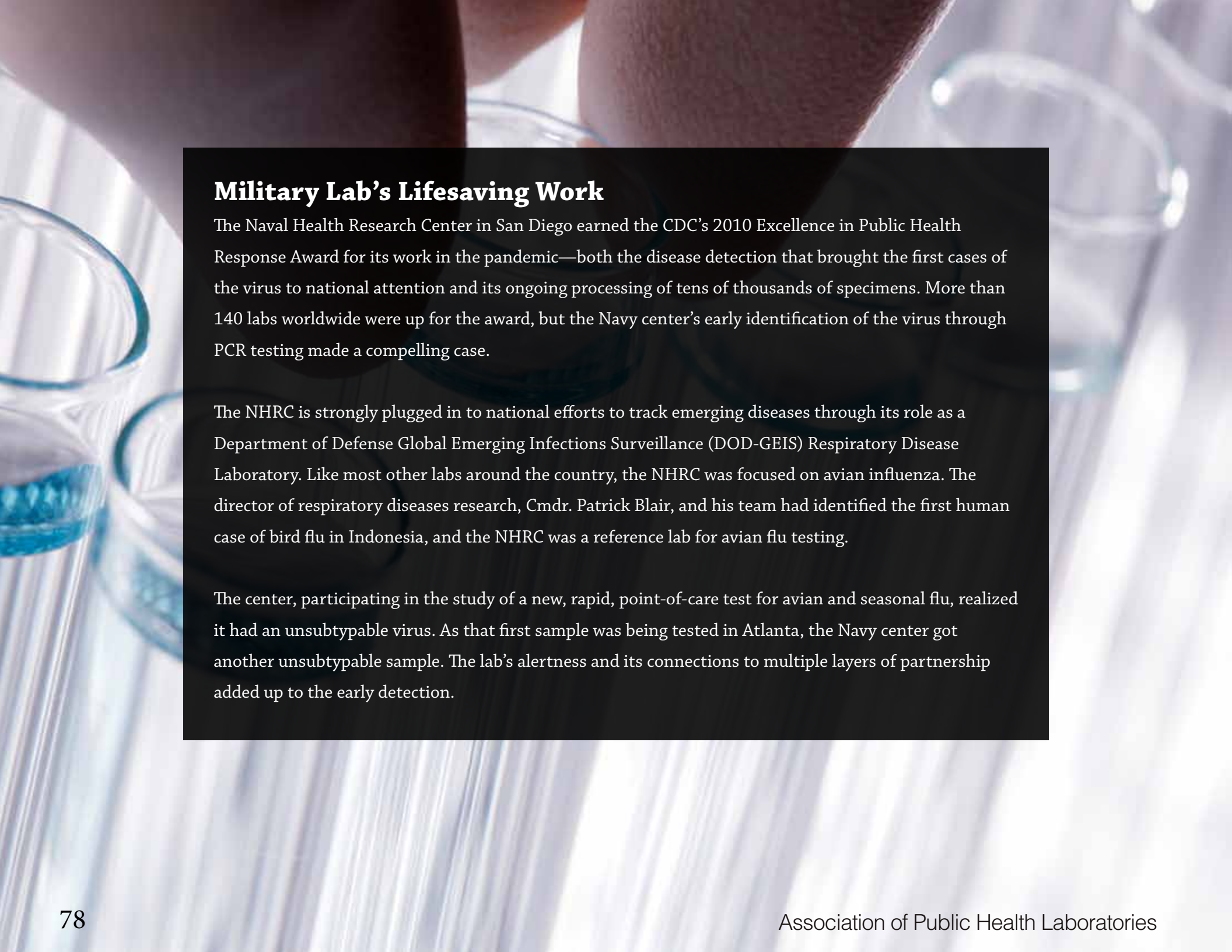
He had just come in to help in the CDC flu lab, on April 25. About 24 hours later he was being whisked through security and into an official car in Mexico City, to help as they set up a diagnostic lab at the H1N1 epicenter.

"I felt like Elvis," says Jonas Winchell, Team Lead, Pneumonia Response and Surveillance Laboratory of the CDC Respiratory Diseases Branch, of his rapid trip. "The next morning, I was in the lab. And I could see I'd be spending a lot of time there."

His prediction was accurate. For the next week, he would work 18-hour days to help get a lab up and running, train staff, and push specimens through.

The lab's freezers held more than 3,000 specimens that needed to be extracted manually—no automatic extractor. No clean rooms, to prevent cross contamination. No established protocols. Not enough reagents. And only one of the instruments essential for performing molecular diagnostics—and no one fully qualified to use it.

"They weren't prepared," Winchell says. "That said, I don't think many labs in any country would have been equipped to handle what was coming down."



Military Lab's Lifesaving Work

The Naval Health Research Center in San Diego earned the CDC's 2010 Excellence in Public Health Response Award for its work in the pandemic—both the disease detection that brought the first cases of the virus to national attention and its ongoing processing of tens of thousands of specimens. More than 140 labs worldwide were up for the award, but the Navy center's early identification of the virus through PCR testing made a compelling case.

The NHRC is strongly plugged in to national efforts to track emerging diseases through its role as a Department of Defense Global Emerging Infections Surveillance (DOD-GEIS) Respiratory Disease Laboratory. Like most other labs around the country, the NHRC was focused on avian influenza. The director of respiratory diseases research, Cmdr. Patrick Blair, and his team had identified the first human case of bird flu in Indonesia, and the NHRC was a reference lab for avian flu testing.

The center, participating in the study of a new, rapid, point-of-care test for avian and seasonal flu, realized it had an unsubtypable virus. As that first sample was being tested in Atlanta, the Navy center got another unsubtypable sample. The lab's alertness and its connections to multiple layers of partnership added up to the early detection.

The CDC, Steve Lindstrom's team, APHL, and others had been working to build capacity internationally through evaluation and assistance to labs for several years, but the challenges faced in Mexico's labs were no less than those found in many US ones.

The novel virus was taking a tough toll on Mexico, with more than 40 suspected deaths and more than 1,400 suspected cases. Schools and public buildings were shut down. Residents walked the streets in surgical masks, when they had to go out. And the lab continued to get 300 to 400 samples a day. People and government clamored for answers, and the "instant lab" was one way to help obtain these.

"The lab director and staff were great, but they needed a lot of rallying," Winchell says. He knew the diagnostic assay inside out, having helped in its creation, so this was something he could do. He got an assembly line approach started, established clean areas, helped set up a data management process, and divided lab workers into three shifts, keeping the lab open 24 hours. The lab suspended all other testing.

The instant lab creation relied on partnerships. Winchell called vendors he had worked with in the United States—and Life Technologies responded with more than 15 instruments and people to set them up. "The reps were great," Winchell says. "They had the right software, the right templates. They were bilingual, and they understood the science."

Canadian assistance was also on site in the international effort. Mexican government officials worked on laptops, crunching numbers. Lab workers soaked up the knowledge and began to take it back to their home states throughout the country, to train others. Eventually, the training in that one lab helped build capacity in 20 state labs around Mexico.

Corporate Partner Steps Up

Several APHL corporate partners moved quickly to ensure public health laboratories had what they needed to meet the surge in testing demand.

Serving a state bordering the H1N1 epicenter, the Texas public health lab was overwhelmed with samples to test—up to 1,500 per day. A longtime corporate partner that is also an APHL corporate member, Austin-based Luminex, stepped up to offer the lab its xTAG Respiratory Virus Panel, a molecular diagnostic that could detect several flu strains and could be used as a rule-out test for H1N1.

Corporate Partnership Evolves

A vital element in the diagnostic was the 7500 Fast Dx instrument—and the partnership with its manufacturer, Life Technologies, then known as Applied Biosystems. In 2009, Life Technologies had a strong relationship with the CDC through work on avian flu. The company's relationship with public health labs, however, was not so strong. Post-H1N1, with the rise in molecular diagnostics in public health labs, that situation changed.

"When the pandemic hit, we put at least three instruments in every public health lab. Some got more by the end; the labs in New York, Texas, and California got 10 or more instruments," says Dan Didier, Public Health Director at Life Technologies. Some labs got instruments even without approval to purchase them; "we just assumed we would get paid going forward," Didier says.

APHL helped arrange service contracts. "We had service engineers go into a lab on Friday, and come out on Sunday, and have the instrument up and running on Monday."

A round-the-clock Life Technologies task force made the hands-on effort. "It's a lot of turning the wheel," Didier says. "For FDA 510(k) approval, an instrument must meet strict standards and criteria—it's not something you just throw together in your garage."

BioWatch, the US early-warning bioterrorism network, as well as some research institutes had to wait for instruments—the pandemic came first.

"I've got to give a lot of credit to the CDC and the public health labs: They put a nice, firm protocol together," Didier says. In fact, the company says it didn't get many calls for help on the 24/7 hotline it had set up for public health lab questions. Data analysis was also made simple and seamless through the instrument.

"This brought the labs into the modern age of molecular detection and surveillance," Didier says. "We had a really good partnership between Life, the CDC, APHL, and the FDA. Now, the instruments are going to more county health labs. Being standardized on the instrument and on the protocol makes us prepared for the future."

Public health labs are using the instrument in other ways as well—for West Nile, dengue, and more diseases. "It's a workhorse instrument," Didier says.

"They were running 900 to 1,000 specimens a day by the time we left," Winchell says. "They were under an international microscope—and they did a fantastic job of turning the situation around."

Relationships and Reagents

Viruses cross borders. Commercial firms engineer the software that detects them. Academic centers research an even better way to do it. Hospital systems hold a wealth of surveillance data. In this interconnected world, public health laboratories increasingly need partnerships for their survival.

The discovery of the first two US H1N1 cases depended on partnerships. In the first case, a military lab, a clinical lab, and the CDC had partnered for a study, and the public health lab had plugged in to be sure it got surveillance data. In the second, an international partnership ensured a sharp eye on influenza.

"Part of the message of H1N1 was that those public health laboratories that do not have strong links with clinical and academic labs and rapid testing sites ought to do so," says Dr. Peter Shult of the Wisconsin state public health lab.

"There was an expectation after anthrax and the LRN that we would all develop these networks. If you didn't have them in place, the pandemic response had to be a lot harder."

Future Issues

Cultivating worldwide capacity:

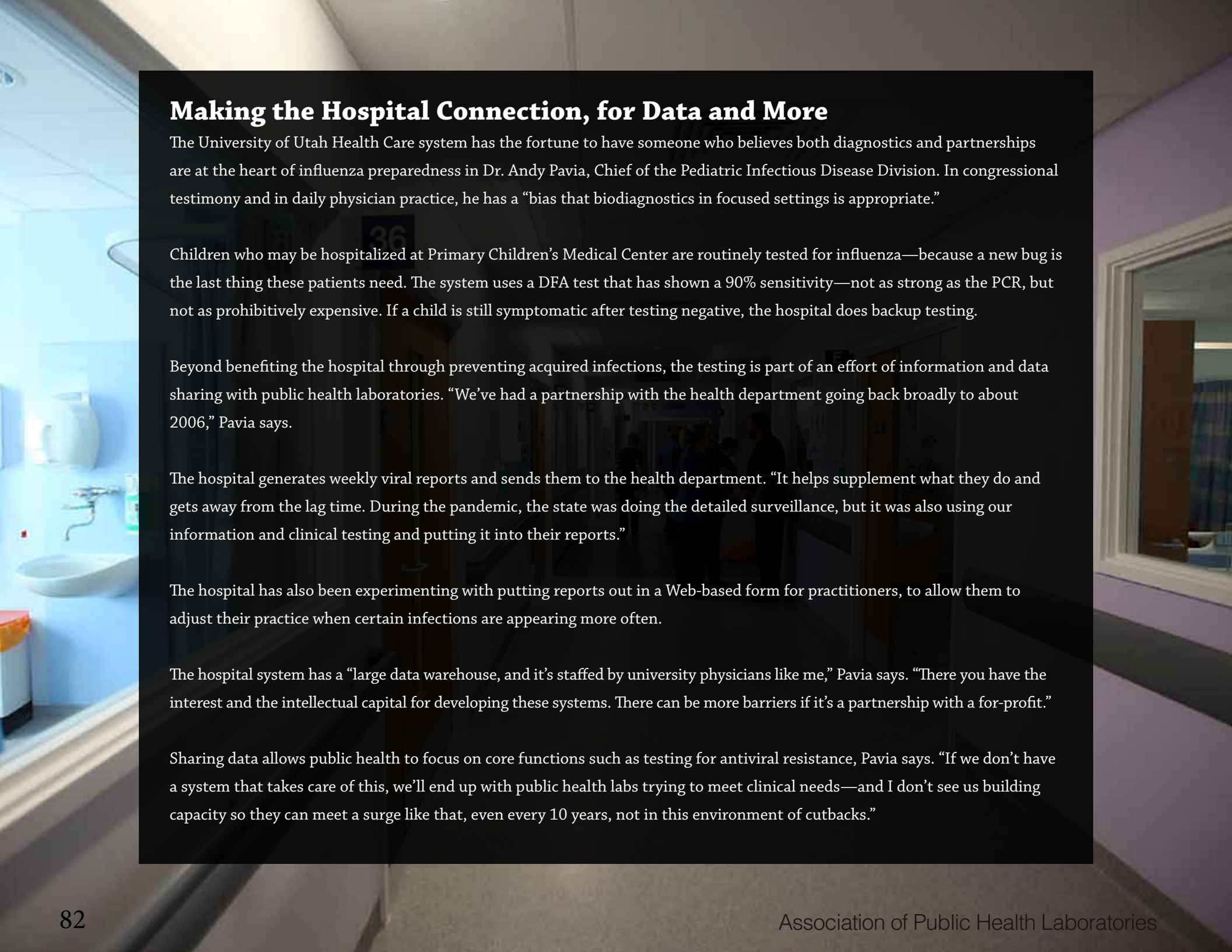
The situation in Mexico shows how strapped capacity in many countries can become under a pandemic. The CDC and APHL have teamed to conduct influenza surveillance training and increase capacity in other ways in Asia, Africa, and South America. Teams perform capacity reviews, from

Biosearch Beats the Deadline

Yet another partner went above and beyond: Biosearch Technologies in Novato, in Northern California, produces the Black Hole Quencher dye label used for probe technology in both the five-target and H1N1 assays. It increased production at the onset of the pandemic to meet US and international demand for test reagents.

Biosearch later produced a "dramatization" of this process for a YouTube video starring company employees—a light look at the company's seriously effective response. An employee answers a call from the CDC: "Seven days? OK, we'll get that going."

The company launches into production of "oligos" (oligonucleotides used to detect H1N1), explaining how it can ramp up capacity in an emergency, making enough probes per hour to stock 160 kits, each with 1,000 tests. The company worked around the clock, with its COO pressed into service as Chief Operating Tube Capper and the Director of IVD Oligonucleotide Manufacturing changing hats to become Director of Insert Folding. The result: The task was completed in four days—not seven.



Making the Hospital Connection, for Data and More

The University of Utah Health Care system has the fortune to have someone who believes both diagnostics and partnerships are at the heart of influenza preparedness in Dr. Andy Pavia, Chief of the Pediatric Infectious Disease Division. In congressional testimony and in daily physician practice, he has a "bias that biodiagnostics in focused settings is appropriate."

Children who may be hospitalized at Primary Children's Medical Center are routinely tested for influenza—because a new bug is the last thing these patients need. The system uses a DFA test that has shown a 90% sensitivity—not as strong as the PCR, but not as prohibitively expensive. If a child is still symptomatic after testing negative, the hospital does backup testing.

Beyond benefiting the hospital through preventing acquired infections, the testing is part of an effort of information and data sharing with public health laboratories. "We've had a partnership with the health department going back broadly to about 2006," Pavia says.

The hospital generates weekly viral reports and sends them to the health department. "It helps supplement what they do and gets away from the lag time. During the pandemic, the state was doing the detailed surveillance, but it was also using our information and clinical testing and putting it into their reports."

The hospital has also been experimenting with putting reports out in a Web-based form for practitioners, to allow them to adjust their practice when certain infections are appearing more often.

The hospital system has a "large data warehouse, and it's staffed by university physicians like me," Pavia says. "There you have the interest and the intellectual capital for developing these systems. There can be more barriers if it's a partnership with a for-profit."

Sharing data allows public health to focus on core functions such as testing for antiviral resistance, Pavia says. "If we don't have a system that takes care of this, we'll end up with public health labs trying to meet clinical needs—and I don't see us building capacity so they can meet a surge like that, even every 10 years, not in this environment of cutbacks."

equipment to workforce, conduct immediately useful training in techniques such as PCR testing, and evaluate future needs. This improves the global early-warning influenza system and helps wake leadership worldwide to the importance of the labs and influenza resources.

"Certainly molecular diagnostics have gone through the roof; tools and instrumentation have advanced rapidly," says Julie Villanueva. "But if we don't have strong communications, not only among our domestic but also among our international partners, we're nowhere.

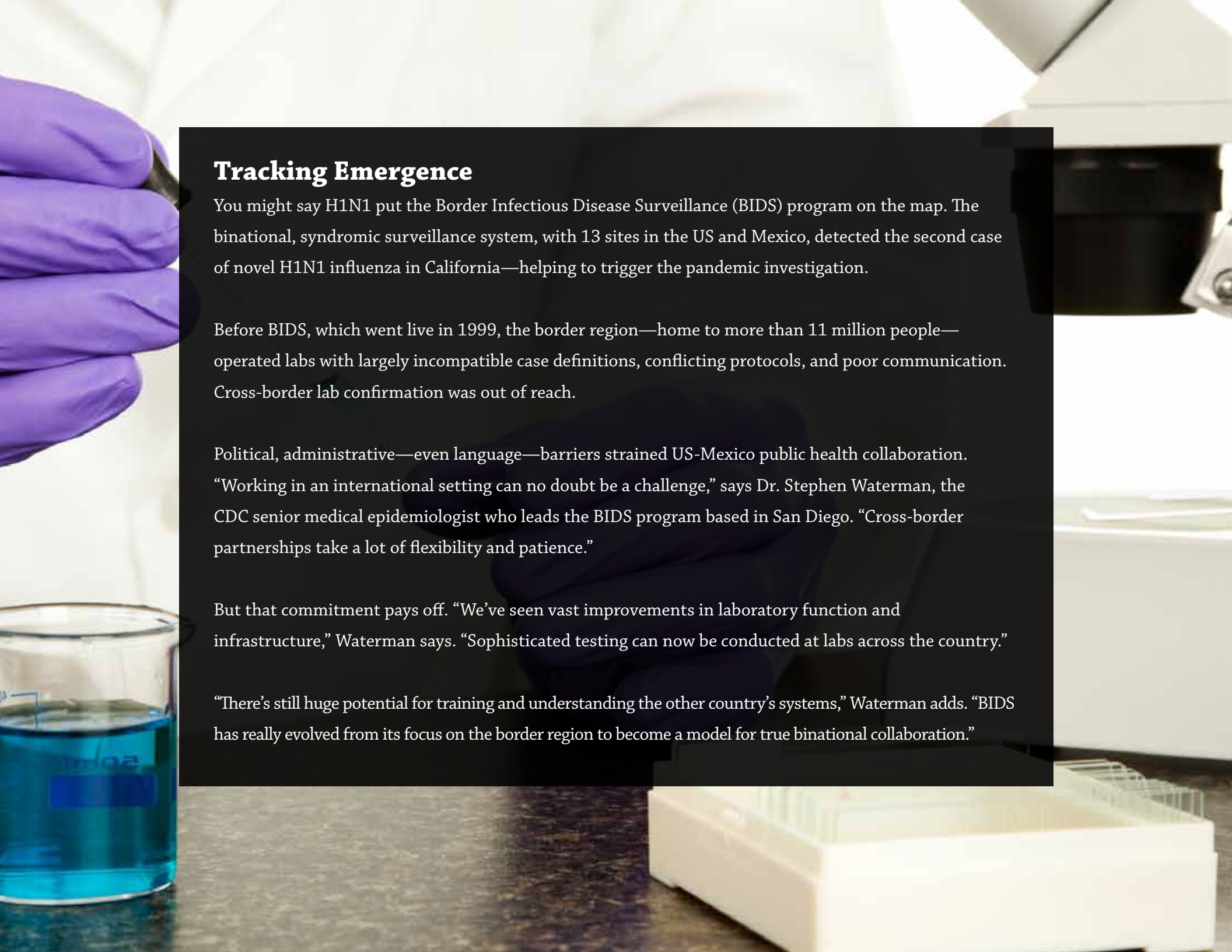
"I think communication could be a book in itself. We did well on a laboratory level, because we've worked well together for so many years. But we never really had a plan—and having a plan in place, domestically and internationally, is something we can do for the future."

Viruses as intellectual property:

During a potential global outbreak, a worldwide disease surveillance network is one of the most important components in battling a communicable disease. The outbreak of H1N1 in 2009 highlighted the ongoing debate over the benefits of sharing pathogen strains amongst countries. Strains are typically used for risk assessment and to develop treatments such as vaccines, and less wealthy countries have argued that they don't get the benefits that should come with making their pathogens available.

During the H1N1 outbreak, the United States and eight other countries responded to the concerns and agreed to give 10 percent of their vaccine stockpiles to countries selected by the WHO. However, the vaccine arrived in the United States after the peak, and the donated supplies also arrived in recipient countries late into their outbreaks.

The WHO has been in negotiations for achieving a consensus on benefit sharing for a number of years. In 2011, in part because of the events during the 2009 H1N1 response, The World Health Assembly reached an agreement among members on a resolution that addresses transparency in influenza virus surveillance, agreements for virus transfer, and access to vaccine manufacturing technology and affordable pandemic vaccines and supplies.



Tracking Emergence

You might say H1N1 put the Border Infectious Disease Surveillance (BIDS) program on the map. The binational, syndromic surveillance system, with 13 sites in the US and Mexico, detected the second case of novel H1N1 influenza in California—helping to trigger the pandemic investigation.

Before BIDS, which went live in 1999, the border region—home to more than 11 million people—operated labs with largely incompatible case definitions, conflicting protocols, and poor communication. Cross-border lab confirmation was out of reach.

Political, administrative—even language—barriers strained US-Mexico public health collaboration. "Working in an international setting can no doubt be a challenge," says Dr. Stephen Waterman, the CDC senior medical epidemiologist who leads the BIDS program based in San Diego. "Cross-border partnerships take a lot of flexibility and patience."

But that commitment pays off. "We've seen vast improvements in laboratory function and infrastructure," Waterman says. "Sophisticated testing can now be conducted at labs across the country."

"There's still huge potential for training and understanding the other country's systems," Waterman adds. "BIDS has really evolved from its focus on the border region to become a model for true binational collaboration."

Provider frustrations:

Information passages between public health in general and individual providers weren't always smooth. While public health looked to electronic means for getting the information out, one public health lab professional recalls a provider saying: "You can't expect me to look at the Internet every day." While establishing electronic information exchange among all health environments is a high priority, what information, when, and how it is transmitted is also important. Can innovations in health technology allow information to stream among public health, hospitals, and providers without compromising privacy or, when applicable, profit?

Global Laboratory Response

Established international networks allowed rapid performance of testing worldwide.

The Global Influenza Surveillance and Response System of the World Health Organization got a new name in May 2011—it was called the Global Influenza Surveillance Network during the pandemic. Its function of surveillance and control of influenza worldwide remains critical, with 136 National Influenza Centers in 106 countries, six World Health Organization (WHO) Collaborating Centers, four Essential Regulatory Laboratories, and 12 WHO H5 Reference Labs. With its help, the gene sequence for diagnostic design was posted April 25, the same day the pandemic was announced; it posted the first lab protocols three days later; and it shipped internationally the first test kit seven days later. By the end of the pandemic, more than 1,200 kits had been shipped to 151 countries, free of charge.

The APHL annual meeting in Alaska quickly shifted gears to become a hub for sharing knowledge and tactics for dealing with H1N1.

Conclusion

A Place to Learn Together

It was May 2009, just a few weeks after the H1N1 test had arrived in most public health labs and before the surge of tests had abated. Uncertainty reigned about the extent and severity of the pandemic.

Was it really the right time to take the nation's public health laboratorians and leaders away from their labs—and send them to Alaska?

Yes, decided APHL Executive Director Scott Becker and the rest of the association's leaders. It was the right time to bring laboratorians together. APHL would hold its annual meeting as usual—but with a few modifications.

"It was the toughest decision of my career in association management," Becker says. "Should we pull the plug on this because about 50 people can't be there? But the labs have a history of performing well under pressure." He sought advice from the CDC's Acting Director Richard Besser, who gave the APHL decision a thumbs up. So did colleagues from many other public health associations. Becker explains: "Public health work happens every day, everywhere. Our decision to hold the meeting just proved that once again."

The association worked to give those who could gather something of value. Some sessions were changed to influenza information sessions, such as an "Influenza Town Hall Meeting," which featured the acting CDC director, DHS personnel, and CDC lab leads. More chances to create partnerships and network were developed. Phone

“Public health work happens every day, everywhere. Our decision to hold the meeting just proved that once again. ... We felt like we were constantly awake. Mostly because we were.”

Scott Becker, Executive Director, APHL

conferences every day at 7 a.m. and an incident command structure on both coasts kept attendees plugged into the latest on the pandemic. APHL kept a response team at the conference in Alaska and at its Washington, DC, area office to further support members no matter where they were.

Becker remembers presenters backgrounded against a sun that never quite set, illustrative of the constant nature of the public health work, quickly conveying essential information to the group. "We felt like we were constantly awake," Becker says. "Mostly because we were."

What holding the meeting accomplished, beyond education and information, was giving APHL members opportunities to further develop precisely what was shown to be of the most value during the pandemic: partnerships, flexibility, forward-thinking for preparedness, best practices sharing, and communication. While for a few days they were not on the front lines in lab testing, they were building the foundation to tackle public health crises yet to come.

Dr. Richard Besser, then acting director of the CDC, provided information at several White House news conferences during the pandemic.

Participants & Resources

The following participated in the APHL expert panel on pandemic flu, were contacted for information, wrote articles or papers consulted, or gave presentations or testimony on H1N1 and the public health laboratories:

Tricia Aden, MT (ASCP), Manager, Influenza Programs, APHL
Sara T. Beatrice, PhD, Assistant Commissioner of Health and Director of the Public Health Laboratory, New York City Department of Health and Mental Hygiene
Scott J. Becker, MS, Executive Director, APHL
Richard Besser, MD, Chief Health and Medical Editor, ABC News; formerly Acting Director, CDC
Cmdr. Patrick Blair, PhD, Director, Respiratory Diseases Research, Naval Health Research Center, San Diego, CA
Patricia Blevins, MPH, BT Laboratory Coordinator, San Antonio Metropolitan Health District
Nancy J. Cox, PhD, Director, Influenza Division, CDC; Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, NCIRD, CDC
Dan Didier, Public Health Director, Life Technologies
Thomas R. Frieden, MD, MPH, Director, CDC; former Health Commissioner, New York City
Keiji Fukuda, MD, Assistant Director-General, Health Security and Environment, WHO
Jane Getchell, DrPH, Senior Director for Public Health Programs, APHL, formerly State Laboratory Director for Delaware and APHL member co-lead for influenza
Sally Hojvat, PhD, Director, Division of Microbiology Devices, Office of In Vitro Diagnostic Device, Evaluation and Safety, Center for Devices and Radiological Health, FDA
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Daniel B. Jernigan, MD, MPH, Deputy Director, Influenza Division, National Center for Influenza and Respiratory Diseases, CDC
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Kirsten St. George, PhD, M.App.Sc., Chief, Laboratory of Viral Diseases, Wadsworth Center, New York State Department of Health
David Schnurr, PhD, formerly of the Viral and Rickettsial Disease Laboratory, Division of Communicable Disease Control, California Department of Health Services
Joshua Sharfstein, MD, Secretary of Health and Mental Hygiene, Maryland; formerly Principal Deputy Comissioner, FDA
Peter A. Shult, PhD, Director, Communicable Disease Division and Emergency Laboratory Response, Wisconsin State Laboratory of Hygiene
Heidi Truschel-Light, Chief of Community Relations, Division of Public Health, Delaware
Tam Van, PhD, Manager, HIV, Hepatitis, STD & TB Programs, APHL
Julie Villanueva, PhD, PMP, Program Manager, Influenza Division, Virus Surveillance and Diagnostics Branch, CDC
Stephen H. Waterman, MD, MPH, Medical Epidemiologist, Quarantine and Border Health Services, CDC; Leader, BIDS Program
Jonas Winchell, PhD, Team Lead, Pneumonia Response and Surveillance Laboratory, Respiratory Diseases Branch, CDC
Kelly Wroblewski, MPH, MT (ASCP), Director of Infectious Disease, APHL
Laura Zambuto, MS, Safety and Occupational Health Specialist, Influenza Division, CDC

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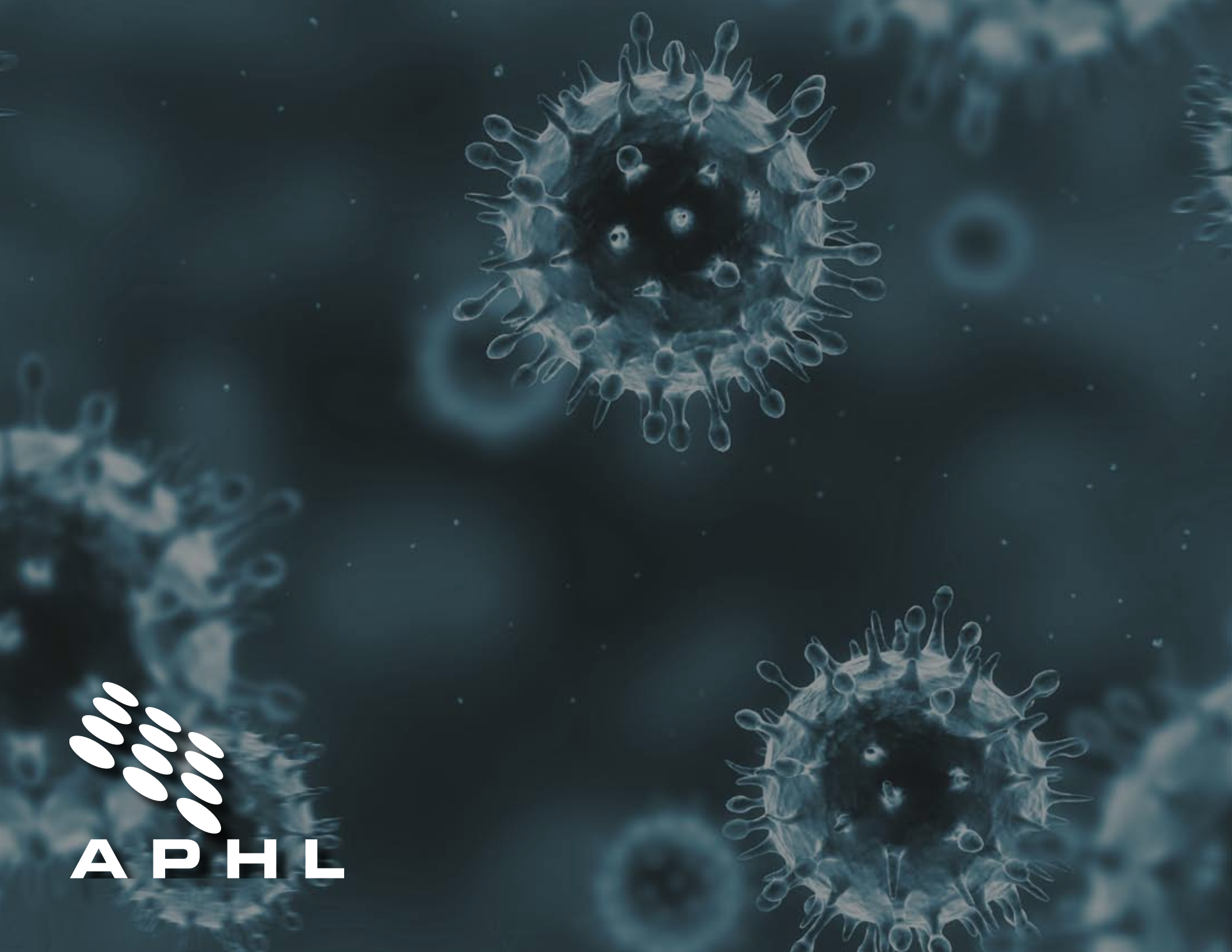
Association of Public Health Laboratories

The Association of Public Health Laboratories is a national non-profit located in Silver Spring, MD, that is dedicated to working with members to strengthen governmental laboratories with a public health mandate. By promoting effective programs and public policy, APHL strives to provide public health laboratories with the resources and infrastructure needed to protect the health of US residents and to prevent and control disease globally.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