In flu season management, POC molecular to the fore

Anne Paxton

May 2017— Stacked against some of the nation's previous bouts with influenza—such as the 2014–15 season—the 2016–17 flu season didn't break records for drama.

To be sure, every flu season is different, and regional variation was prominent. In Central Texas, some outbreaks appeared to start later than usual, but the dominant viruses were the same as last year's—H1N1, H3N2, and influenza B—says Bob Fader, PhD, chief of the virology and microbiology laboratory at Baylor Scott & White Health, Temple, Tex. The strains identified were a good match with this year's trivalent and quadrivalent vaccine. Testing volume was up, as were positive PCRs.

From her vantage point in the northeast, "I'd say this season was about average," says Donna M. Wolk, MHA, PhD, D(ABMM), system director of clinical and molecular microbiology for Geisinger Health System, Danville, Pa. "We had a diverse mixture of viruses throughout the entire respiratory season—nothing like two years ago when influenza predominated and the vaccine mismatch for flu strains was partly responsible for testing volumes five times that of our usual respiratory virus season."

In Southern California, the outbreak was more substantial. "We had a heavy flu season," says Omai Garner, PhD, D(ABMM), associate director of clinical microbiology and director of point-of-care testing for the UCLA Health System. "We counted a lot of positive PCRs this year, and our urgent cares and ERs were full. There were a lot of patients."

But there *was* something more dramatic to note about this flu season, Dr. Garner says: Influenza testing technology has taken a big step forward.

For most clinicians, "Before this year, if you weren't doing antigen testing for influenza, you were either using clinical discretion to diagnose, or you were sending the specimen to the lab and getting the result outside of the time frame that was clinically useful," he says. But the recent approval of new CLIA-waived molecular influenza tests has triggered a whole new ball game. "You can now have a very sensitive test at the point of care. Before this flu season, that didn't exist."

In his dual role, helping to lead microbiology and point-of-care testing at UCLA, Dr. Garner says, "We've been thinking about how to improve our infectious disease testing for a long time. We completed an in-house evaluation, and we think that waived molecular influenza testing is going to represent a great solution for us." The UCLA system plans to go live this fall with waived molecular testing in both of its emergency departments and most of its outpatient areas and study how it affects turnaround time and patient and physician satisfaction.

UCLA, which serves two 400–500-bed hospitals and 200 outpatient clinics, currently uses the Simplexa A/B & RSV PCR test in-house. "But in our very extended outreach network, we can't turn around same-day results, so in a lot of our outpatient areas, we're still using the poor antigen tests that are available." The clinicians don't trust them, and for inpatients they've been eliminated across the board.

Especially during the flu season, Dr. Garner notes, doctors' clinical diagnoses based solely on patients' presenting symptoms have a higher sensitivity than the antigen tests. "If it looks like flu during flu season, it's probably the flu. And the challenge is if you have a test with bad sensitivity, you may accurately think it's flu but the test tells you it's not. Then your sensitivity can drop below 50 percent, depending on how much flu virus is present." Given the rapid antigen test's potential for misleading results, he adds, "It's almost better not to test at all." The FDA has issued a reclassification for some influenza antigen tests amid serious concerns about their sensitivity, he notes.

In the past, antigen testing hit closer to the mark. "When the antigen test in influenza got its approval from the

FDA in 2005 or 2006, the tests were actually pretty good for the strains that were there. It's just that there's been so much antigenic drift that has gone on over time, the sensitivity gets worse and worse." During the H1N1 pandemic in 2014–15, the numbers showed antigen testing's worsened performance, Dr. Garner adds.

Dr. Garner

UCLA may or may not be ahead of the curve in moving to waived molecular testing. But it's had special cause to feel the need. "The reason waived testing is important is that we have a very large network of outpatient facilities, some of them 50 to 60 miles away from the microbiology lab." With Los Angeles' notorious traffic, that can be a 10- to 15-hour delay in specimen transport. "So because we have such a big outpatient footprint, we represent a key area where the waived technology can really come into play."

Next year, Dr. Garner says, waived instruments will occupy the space where the clinics are now performing rapid antigen testing. He estimates that 50 to 75 of the 200 clinics could end up with a molecular platform for flu testing. Those available are the Alere i Influenza A & B, the Roche Cobas Liat Influenza A/B, and Cepheid's GeneXpert Xpress test; BioMérieux's BioFire is now promoting an FDA-approved, CLIA-waived panel, the FilmArray Respiratory Panel EZ, as well.

He expects the cost per testing instrument to be between $1,000 and $10,000. "And paying for that will represent a struggle in the outpatient area because it used to cost $15 to $20 a test for a lateral flow test that has no instrumentation with it whatsoever. But it depends on your perspective," Dr. Garner says. "In the laboratory, all the instrumentation costs far more than $10,000, but for point of care, where a dipstick reader is usually $500 to $1,000, the price for dozens of rapid molecular test instruments is going to mean a much more sizable up-front investment than is customary."

In some conversations about cost, he has steered physicians to look at the bigger picture: "Think about what you've been paying for the antigen test that hasn't been able to provide you with relevant clinical information."

Some companies may find a way to make their antigen test more sensitive, Dr. Garner says. "But projecting over the long term, if I had to predict, over the next three to five years I'd say the molecular testing will take over, at least for infectious diseases such as flu and RSV."

Still, he cautions, there's no comparison between what the laboratory can perform and what the platforms at the point of care can do. "With waived testing, you do one test in about 20 minutes. In the lab we can perform, in an hour and a half, 400 to 500 tests. That's why you have to be a bit judicious about a rollout of waived testing." So if a site is within a certain distance of the central microbiology lab, "it still makes sense to run the tests in the central lab, from a batching and efficiency perspective."

UCLA is different from systems like Cedars Sinai and Kaiser, Dr. Garner points out. "They build localized hospitals where you go for health care, so you don't have this issue of clinics operating 75 miles away from the laboratory. That's the reason that at UCLA we're trying to get on board with waived testing as fast as possible. But the way health care systems are expanding, with the direction of health care right now, I think more point-of-care waived testing will be the solution, especially because the FDA has changed the way it looks at point-of-care testing. I do think you're going to see an expansion of waived molecular testing."

Patients are becoming more savvy, he says, but not about everything. "More patients understand the difference between a viral infection and a bacterial infection. But if you're the treating physician and you don't have proof that a patient has a virus, then potentially the pressure is higher to prescribe an antibiotic."

Laboratory directors try to provide the most accurate data points possible, but ultimately it's up to the clinician to diagnose disease, and a lot of other factors may come into play. Often, Dr. Garner says, "I do know [using the antigen tests] they're now getting a data point of a negative that isn't truly negative. I try to give them as much data as possible that's correct, and then if they want to call the microbiology lab and are asking about follow-up testing, we love to make that clinical consultation. But again, that's difficult too, if we don't have solid data."

He doesn't know how many others are considering large rollouts of waived molecular testing for flu, but he predicts it's coming, regardless of institution. "Antigen testing is on its way out the door," he asserts.

Dr. Fader is not quite convinced that antigen testing will become a relic of the past anytime soon. Recent rapid growth in the Baylor Scott & White Health system has left influenza testing in a transitional phase, he says. "We have a huge system here. Just within Central Texas, we have more than 100 outpatient clinics and 13 hospitals. A lot of our outpatient clinics are still with the rapid EIA tests that are waived and can be done in clinical doctors' offices."

The system's hospital-based labs have switched to molecular testing, and some of the smaller hospitals may follow, but many of the labs are in a holding pattern. "We're kind of waiting to see on a couple of things." The price of the molecular instrumentation is an obstacle. "At a huge organization like this, we can't go out and buy a BioFire for every hospital or every clinic. So we kind of let everybody decide what testing modality they want to use during the course of the year."

To date, Baylor Scott & White has not moved to the CLIA-waived molecular-based assays. "I know other places that have, and they've had good success." But Dr. Fader does see molecular testing steadily increasing. In the Temple hospital, the main hospital in Central Texas, for example, EIA is no longer performed on anyone over age 18. "That test gets reflexed to either the influenza PCR or the Luminex xTAG respiratory pathogen panel, which we use a lot."

The steep increase in cost is offset by the test's higher sensitivity, he says. "Although you're not getting results in 10 or 15 minutes, as you would with an EIA, you can get them in an hour or so. And some molecular assays are down to the 20- to 40-minute range."

Dr. Fader

Flu season always proves to be a test of the instruments' capabilities, Dr. Fader notes. At the peak of this season, between EIA and PCR assays, the Central Texas region was running 1,400 to 1,500 flu tests a week. "We end up with so many specimens coming in one at a time that if the molecular-based instrument runs only one and it's going to take 30 or 40 minutes, that's not going to be suitable for hospital-based labs."

"In those instances, we end up batching and doing probably two runs of the Luminex assay with anywhere from 30 to 60 specimens at a time, just to keep up with the demand." Baylor Scott & White also receives extra specimens from the CDC because it is one of five sites for a vaccine effectiveness study the agency is sponsoring.

The system's BioFire molecular instrument tests for a few more viruses and bacteria than the Luminex assay, but it runs only one specimen at a time, while the Luminex instrument handles multiple specimens at once and takes four or five hours to report a result. (Although prices vary by facility, at his system a BioFire instrument is running about $30,000 to $35,000, with a cost per test of about $110 to $140. The Luminex instrument is $40,000 to

$60,000 and the cost per test is $50 to $75.)

Perhaps signaling antigen testing's tenuous grip, the CDC recommends that if a negative EIA result is reported but the clinician still thinks the patient has the flu, the EIA result should not determine whether the patient is prescribed Tamiflu. Dr. Fader notes that at the peak of flu season, sometimes doctors skip the testing entirely. "They will just prescribe Tamiflu or other antiviral agents and not worry about doing the testing."

Nevertheless, he thinks the EIA test will remain a staple of flu testing for the next few years. "It's still very useful, especially for pediatric offices where the assays have a relatively high sensitivity, and specificity is very good for all flu assays." EIA tests are still the most user-friendly, he adds, though Roche's Cobas Liat and Alere's i Flu A & B molecular tests are easy assays to run as well.

Competition for patients among outlying clinics has tended to keep the EIA test in use for about 50 percent of the system's testing. "The clinic will say, 'If I don't offer this test, people will go to the other office that does offer the test.' Whether it's a good test or not, people will want it. So we're kind of stuck in that mode."

Dr. Fader considers this a temporary state of affairs. "We're in a transition time between the EIA assays and doing most of our testing by molecular methods, and as the cost of instrumentation comes down and more and more assays become CLIA-waived, people will see the benefits of spending the extra money and getting rapid molecular testing."

Geisinger Health System, where Dr. Wolk directs microbiology, has been one of the leaders in bringing molecular testing in infectious disease to the point of care. The system's FluWorks program is a laboratory-driven project that places PCR into the hands of Geisinger's rapid-response laboratories. "There's a lot of rapid cycle innovation going on in our system to design new care practices, and FluWorks is one of them," Dr. Wolk explains.

The system's extensive reach was one of the incentives for developing FluWorks. Geisinger covers 45 counties in central Pennsylvania and includes eight hospitals and eight rapid-response labs staffed by medical technologists who perform testing on site for larger regional physician office practices.

Geisinger's microbiology tagline, "Cutting-edge practices close to home," helped inspire FluWorks. "The strategy was to place the most accurate and fastest tests we could find into different geographical regions of our service area, so people can get the same care at any of the clinics or hospitals we serve. Another aspect is the ability to give noncritical patients more options, so they are not forced into emergency rooms when they don't need emergency care. Finally, we wanted to distribute the laboratory workload across our system, which better prepares us for future outbreaks or pandemics."

Dr. Wolk

The CDC recommends that clinicians treat patients with symptoms of influenza-like illness as soon as possible and within a certain window, Dr. Wolk notes. "But if you are going to prescribe antivirals to everyone with symptoms, then you will be treating a lot of patients with RSV or other viruses that you don't need to treat. And the treatment won't help; it will just add cost. The strategy to identify patients who really need antivirals quickly, perhaps on their way to the pharmacy, will allow our system to block use of antivirals for those who won't benefit from them."

Among hospital systems, this is not a common strategy, she adds. "Current urgent cares are performing antigen tests, which are only about 50 to 86 percent accurate. Results do occur in approximately 15 minutes, but for the

most part results can be as bad as flipping a coin to determine whether or not the test results are correct." Geisinger stopped performing antigen testing in 2013. "None of our laboratories are performing antigen testing, and we hold fast to that strategy, despite the pressure for a rapid, but perhaps inaccurate, result. There may be new antigen tests that might be more accurate in the future, but for now, we are holding on to molecular methods as our system's standard."

The system's laboratories complete moderate-complexity molecular flu tests in 60 minutes and hope to drop that to 20–30 minutes next year. In the physician office laboratory sector, "only a few players have launched molecular testing, mostly waived tests."

Molecular flu testing is quickly moving to the point of care, and Dr. Wolk has some fear about non-laboratorians performing molecular testing in small spaces, such as those found in urgent care clinics. "I am fearful that without the proper environment, cleaning processes, and continuous training, molecular samples could get contaminated with templates from other patient specimens or from nasal sneezing, etc., which could lead to false-positives. Protocols for point-of-care testing must have appropriate cleaning and processing procedures."

Waived molecular testing should be scrutinized, with prevalence monitored as a way to assess for potential contamination, Dr. Wolk notes. "If a spike in prevalence occurs, that would tip off staff to investigate for contamination."

It was because of the contamination risk that Geisinger decided to install the waived molecular testing not at the point of care but in an intermediate space. "We chose to move from a centralized molecular test to the next tier of laboratory support, which is the rapid-response labs." Now that it's going well there, "our approach will be to select a few smaller clinic practices to launch a waived test platform next year. We plan to monitor all sites for contamination, provide guidelines for cleaning between patients, and install apparatus for specimen processing."

Shortening turnaround time is their priority, Dr. Wolk says. The system plans to deliver flu results next year directly to patients, with information that describes when an antiviral will help and when it won't.

The whole effort has to be accompanied by an education campaign to get patients to understand the implications of a fast and accurate test that shows they don't have the flu. "With the flu program, our primary focus is engaging outpatients in understanding their disease processes and their options for treatment."

Dr. Wolk believes next year will be the turning point for molecular testing to displace antigen testing. From her perspective, the goal is not necessarily to have the test results at the same time the patients are in the office, encouraging them to wait and increasing the risk they'll spread germs among each other. Rather, with a 30-minute turnaround, patients can see their provider, have a sample collected, and get the result on their cell phone or other device when they're on their way home or to the pharmacy. "We are ready to launch this approach next year," she says.

Inpatients also benefit from rapid respiratory virus testing. With a median collect-to-result time of less than three hours, her laboratory documented that rapid respiratory virus testing supported improvements to mortality, length of stay, ventilator days, antimicrobials, antivirals, and total costs in the ICU population. "And we're in the process of studying other inpatient groups."

As this approach to flu testing and results reporting illustrates, the new testing technology may indeed dazzle, but that should not be the point, Dr. Wolk says. "Our whole goal is not technology for the sake of technology, but to get patients on the road to recovery as quickly as possible. With rapid molecular testing in hospitals and at the point of care, patients are our most important focus—if the technology doesn't inform or benefit the patient, we won't use it.

"What we're doing is driven by the technology," she adds, "but our aim has to stay patient-centric."

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