In late flu season, early signs of new tests' impact

Kevin B. O'Reilly

April 2016—The 2015–2016 influenza season is shaping up to be lighter than physician offices and hospitals have seen in recent years, with fewer flu positives reported, a lower death count, and a smaller share of flu-like illnesses among outpatients.

Last year's flu season, by contrast, was "very hectic," says MAJ Charlotte Lanteri, PhD, deputy chief of microbiology at Brooke Army Medical Center at Fort Sam Houston in San Antonio, Tex. It is not just the lower number of patients presenting with flu-like symptoms in the medical center's inpatient and outpatient settings that has made for a quieter season so far, she says. Also contributing to the peaceful, easy feeling at Fort Sam Houston—at least as regards the flu—is the medical center's implementation of a rapid molecular test for influenza A and B.

The decision to switch from a rapid antigen test to molecular using Roche's CLIA-waived Cobas Liat PCR system stemmed from a "two-pronged attack," says CPT Lindsey Nielsen, PhD, a Brooke Army Medical Center microbiology fellow who led the effort to validate and implement the new flu testing method. "One is we wanted to get faster, but also to have the results be accurate."

The speed versus accuracy tradeoff in flu testing is a thing of the past, say the laboratory professionals at Brooke Army Medical Center and other labs. Those implementing rapid molecular flu testing systems from Roche and Alere are seeing highly accurate performance and real-world turnaround times of less than half an hour. At least one laboratory has put together preliminary data that suggest the adoption of rapid molecular flu testing improves patient care while cutting health care spending.

Switching to the Roche rapid molecular test (which features an instrument time of less than 20 minutes) for influenza A and B has already saved countless hours on the part of medical technologists, Dr. Lanteri says. Outside the peak of the flu season, rapid antigen testing required confirmatory PCR testing on another platform with a 90-minute turnaround time.

"The patient's way down in the ER waiting for results for that long, and it's not clinically relevant at that point," Dr. Lanteri says. "The patient is sent home and presumptively treated based on signs and symptoms."

Now that confirmatory testing is superfluous.

"So this is good, from our selfish [laboratory] standpoint of just needing to relieve our techs of all these tests so they could focus on other assays we were doing that are of moderate complexity," Dr. Lanteri adds. "It's a real win-win from our laboratory perspective and from the clinical perspective of getting accurate, quick results."

Dr. Nielsen says that with the rapid antigen test, the medical center experienced a 30 percent rate of false-negatives, which "is higher than what's been published in the literature." The insert for Roche's Cobas Liat flu test lists 100 percent sensitivity for A and B, with 96.8 percent specificity for A and 94.1 percent specificity for B.

"We're very confident in the results," Dr. Nielsen says of the Cobas Liat flu test. "It's not only lived up to that [insert], but we have taken positive samples and submitted them to a surveillance program to do sequencing on them. And we've never had a sample that we've submitted as a positive that was rated as a false-negative."

"It's a definitive test," she adds. "Whether it's in the ED or the clinic, a negative is a negative and we're done."

So how does the flu season look so far in San Antonio?

"Compared to last year's flu season, this year is much slower," Dr. Nielsen says. "We've seen an increased percentage in the H1N1A subtype, and a higher percentage of influenza A."

Brammer

Nationwide, a similar pattern has prevailed, says Lynnette Brammer, MPH, lead for the CDC's domestic influenza surveillance team.

"It's been a much lighter year than the past three years," Brammer says. "The last season and the two years prior to that were both strongly H3N2 predominant, and the season in between was H1N1 pmd09 predominant. This year it's much more of a mix. If you look at the public health data, you can see it's H1 predominant, but not strongly H1 predominant. You see a strong amount of B and H3s circulating."

At the peak of the 2014–2015 flu season, about 27 percent of samples tested positive for one or more flu strains. This year's peak has seen about 23 percent of samples test positive for flu. And while 148 flu-associated pediatric deaths were reported during last year's season, only 30 had been reported to the CDC through March 19, 2016. On the outpatient side, during the 2014–2015 peak about six percent of visits were for flu-like illnesses. At this year's peak, the share of outpatient flu-like visits was under four percent. The latest influenza data are available at www.cdc.gov/flu/weekly.

Back at Brooke Army Medical Center, 12 Cobas Liat devices are on hand. In addition to flu, they also are used to run rapid tests for Streptococcus group A. The emergency department has two of the machines, there are three in the main hospital laboratory, and the five outpatient clinics have one or two depending on patient volume. Each can process one specimen at a time.

"The training checklist is very simple, so it's not been difficult to implement in that regard," Dr. Nielsen says.

The clinician reaction has been enthusiastic: "You say it's PCR with equal or faster turnaround times, then everyone's bought in right there."

The rapid molecular flu test costs "a few dollars more" than the rapid antigen test the army medical center had been using, Dr. Nielsen says. But she believes that extra cost is well worth it given the comparable turnaround time and greater accuracy.

Dr. Lanteri says the plan, once the flu season is complete and can be compared with the 2014–2015 experience, is to mine LIS data and "link up the pharmacy data, doctors' orders, and see whether physician prescribing practices were affected by the results."

Information about the cost effect of adopting rapid molecular flu testing is trickling out. Glen Hansen, PhD, director of clinical microbiology and molecular diagnostics at Minneapolis' Hennepin County Medical Center, presented preliminary data on the hospital's experience during the 2014–2015 flu season at last year's annual meetings of the American Association for Clinical Chemistry and the Association for Molecular Pathology.

Dr. Hansen and his colleagues linked physician ordering and treatment decisions with surveys of the doctors and their patients presenting with flu-like symptoms. Upon ordering flu testing, physicians were surveyed about their differential diagnosis based on history and physical, as well as the initial care plan. They were surveyed again after receiving the results to gauge their satisfaction and to understand how the new information influenced clinical decisions. Retrospective chart review was used to verify patient management changes.

"As laboratorians, we know that the data provided by our laboratory is used for patient care," Dr. Hansen tells CAP TODAY. "But there need to be more studies out there to show the impact of what these tests can do, not only the

effect on patient care but on all these actions that have dollar signs attached to them. . . . Our experience, at least in an emergency department setting, clearly indicates that access to flu data is one of the things that can affect clinical decision-making."

Dr. Hansen

From February to April 2015, the full pre- and post-test survey was administered in 150 potential flu cases in Hennepin County Medical Center's emergency department. Consistent with previous research, Dr. Hansen found that the ED physicians did not excel at correctly predicting which of their patients had the flu. Among patients with a fever, they achieved a 30 percent sensitivity. For patients without fever, the doctors' sensitivity rate was 27.5 percent.

Given those data points, it should come as little surprise that the rapid molecular flu results using the Cobas Liat system led to a documented change in patient management nearly 60 percent of the time. Of the cases in which the results changed clinical decision-making, 61 percent of the time it was because of negative results. The remainder of the treatment changes were made in cases in which patients tested positive for the flu.

In 53 percent of cases, there were documented changes in antiviral or antimicrobial prescribing, while 17 percent of the time there were changes in admission or discharge orders.

With negative test results in hand, physicians discontinued oseltamivir prescriptions in 33 cases. At about $100 per five-day course of the antiviral, that adds up to $3,300 in averted health spending. But the big savings is in keeping patients out of the hospital. At Hennepin County Medical Center, there were 15 cases in which doctors discharged patients based on negative rapid flu test results. Drawing on federal data on the average cost and length of stay for patients with pneumonia, Dr. Hansen estimates these faster, more reliable flu test results may have helped avoid $150,000 in medical spending.

It would appear obvious, from those early data, that rapid molecular flu testing could stand to save hospitals, patients, and payers quite a bit compared with the relatively small added cost of the new method. But Dr. Hansen offers a big caveat. Sometimes the negative result led to other expenses, as physicians tried to solve the diagnostic riddle. In 19 of the cases, physicians ordered another procedure, and in 10 other cases they ordered additional laboratory tests.

"Most studies on the economic impact [of diagnostic testing] only look at cases in which an intervention was made," says Dr. Hansen, who is also an assistant professor of pathology and laboratory medicine at the University of Minnesota School of Medicine. "We focus on both the negative and positive cases. . . . In the cases where it's negative, we had some cases where that led to more testing as physicians looked to see what tests could help give them more information. So you have additional interventions and additional costs."

That examination of the total cost impact of the rapid molecular flu testing method, when completed, could yield unpleasant answers, Dr. Hansen says.

"Administrators don't want to hear that testing resulted in more testing and more costs," he says. "So this cost analysis will be pretty powerful. . . . We are still working on it. We are trying to take a patient and walk through their whole ED visit and everywhere there's a clinician touch point add a dollar sign."

Despite that important caveat, Dr. Hansen says that "in these 150 patients you can see the level of cost deterrence is still pretty impressive. This still gives laboratories arguments they can use to make a strong cost

case for this better form of testing."

Arguments are unlikely to come from clinicians. At Hennepin County Medical Center, the ED physicians were satisfied with the new flu test's accuracy and timeliness in 95 percent of cases.

The other molecular flu test with a turnaround time of less than half an hour is Alere's i Influenza A and B test, which uses an isothermal nucleic acid amplification method, lists a 15-minute instrument time, and is CLIA-waived. Norman Moore, PhD, Alere's director of scientific affairs, infectious diseases, says "the negative is where a lot of the value is" in flu testing.

Dr. Moore

"In the wintertime, some doctors get into this habit where they start seeing influenza and then think every respiratory symptom is also flu without testing," says Dr. Moore, a member of the point-of-care testing committees of the CAP and the Clinical and Laboratory Standards Institute. "They get into that blind spot where it could be Strep pneumonia, and they think it's flu anyway. Well, they can run a test like this and when it's negative they may think, 'Let's take a pause here. It may be a different etiological agent that is responsive to an antibiotic unlike the antivirals.'"

"In the past," he adds, "rapids have had good specificity overall. You had confidence in a positive result, but not as much confidence in a negative result."

Dr. Moore believes the 15-minute instrument time is fast enough to influence clinical decision-making in urgent care and physician offices. So does Susan Spanos, M(ASCP), microbiology supervisor at Everett Clinic, which has 11 walk-in outpatient facilities in western Washington state.

Spanos

"There really isn't anything else on the market that is this fast," she says. "That's what it's all about, so that the physician can have the results quickly, make a decision, prescribe what they need to prescribe, and the patient's on their way. And patients want that as well."

Each clinic has at least one Alere i system, just a few steps down the hall from the exam rooms. Phlebotomists who are overseen by a medical technologist perform the tests, Spanos says. For influenza A, compared with culture, the Alere i test has a sensitivity of 97.9 percent and specificity of 86.2 percent, the company says. For influenza B, the test has a sensitivity of 92.5 percent and specificity of 96.5 percent.

Everett Clinic had used rapid antigen testing before it adopted the Alere rapid molecular flu test.

"The doctors were used to getting a result within 15 minutes. That's why they wanted to still hit that mark so they

could make real-time decisions about treatment," Spanos says. "But this is a much more sensitive test and we have picked up far more influenza than we did by rapid antigen."

When Spanos led implementation of the new flu testing method during the 2014–2015 flu season, she tracked test accuracy and clinical decision-making before and after the Alere test went live. Of 56 specimens tested for flu, 32 were positive by the Alere test while the rapid antigen method found only 11 to be positive.

In the period before implementing the Alere test, 18 of the 56 patients were prescribed antibiotics. But half of those patients, based on testing using the Alere and specimens sent to the state public health laboratory, were positive for influenza and thus got the wrong treatment.

Spanos also examined 53 patient charts from the period immediately after Everett Clinic went live with the Alere rapid flu test. Of those 53 patients, 12 were prescribed antibiotics and only four had a positive flu test. In each of those cases, there were other clinical factors that may have justified the antibiotic prescriptions, Spanos says.

No comprehensive cost comparison is in the offing, but Spanos and her colleagues believe the rapid molecular flu test makes financial sense.

"This test is more expensive than the rapid antigen test, as would be expected. But we had discussed this, and the tradeoff is better for patient care. And being able to know for sure that a patient has influenza, and that they can be treated, is a big deal considering that people die of influenza."

A third rapid molecular flu test will enter the market next year, pending regulatory approvals for Cepheid's new GeneXpert Omni point-of-care system. The Xpert Flu+RSV Xpress is expected to have a run time of around 30 minutes. A Strep A test also will be available on the menu for the system. The flu/RSV test already is available, and CLIA-waived, on the GeneXpert I system; it has an instrument time of 60 minutes.

Bishop

Cepheid CEO John Bishop says laboratories may want to wait on his company's product because, first, it offers simultaneous detection of RSV, which is vital for pediatric and geriatric patient populations. (Roche has submitted a flu/RSV POC test for FDA clearance and CLIA waiver, a company spokesman says.) Bishop adds that PCR is more accurate than the isothermal method employed in the Alere i. "At the end of the day, time to result is irrelevant if you're getting inaccurate results," he says.

A few minutes' difference in turnaround time may not mean much in real-world clinical practice, Bishop argues, noting the Omni system will feature wireless transmission of results. That means even if the patient is already out the door it will be painless to send the results to the patient and physician and enable the clinician to take quick action in changing the electronic prescribing order, if needed.

For clinicians who want to order a larger respiratory panel, a relatively new option available this flu season is Nanosphere's Verigene Respiratory Pathogens Flex. Called RP Flex for short, the panel was cleared by the FDA in September 2015 and allows for flexible ordering of 16 target respiratory pathogens with a 3.5-hour run time.

Northwest Community Hospital, located in the Chicago suburb of Arlington Heights, implemented the RP Flex in mid-February.

“A huge plus for us was the flexibility of it,” says Jason Weiss, DO, Northwest’s medical director of molecular and cytopathology. “As a community hospital, we have our own lab and we’re not affiliated with a large hospital group. . . . Our budget’s a little bit tighter because we’re a standalone hospital. But we wanted to provide the up-to-date care that the surrounding hospitals were.”

The hospital also uses the Alere rapid flu test.

“Our algorithm is that if these patients aren’t that sick, our clinicians look to see if they have the flu,” Dr. Weiss says. “We do the Alere and we get the results back very quickly. We have those at our [outpatient] treatment centers, and they are available for our emergency room patients too. And if the patients are really sick, ideally, we would like the clinicians to order the Nanosphere. Those patients are getting admitted anyway, so the more expanded menu of results helps in providing appropriate care for the patient.”

With the RP Flex, Northwest Community physicians can order in these combinations: flu alone, flu and RSV, the three *Bordetella* bacterial pathogens, or the rest of the respiratory pathogens as one order set. While the multiplex test simultaneously detects any of the 16 pathogens present in a sample, the results are revealed and interfaced only for those analytes the clinician requests. Between 10 and 15 percent of all the samples run on the RP Flex have been for the expanded respiratory panel, Dr. Weiss says.

Some laboratory professionals have raised ethical questions about the RP Flex, objecting to the quandary arguably created when the laboratory performs a test but does not share the result with the clinician because it was not actually ordered.

Dr. Weiss does not share that concern.

“If someone sends us a tube of blood, we could run every test in the book on it. We only run what you order,” he says. “Clinicians can always call us and unmask those results. The test isn’t finished, in my opinion, because the results aren’t available.”
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