Flu mounts COVID’s bustling stage

Karen Titus

October 2020—Barely a half year into the pandemic’s presence in the United States, history has already begun pressing down on SARS-CoV-2 testing. Like an actor playing Hamlet, it’s been difficult not to feel the burden of past performances when preparing for the months ahead.

Now, at the start of fall, that also means readying for the return of influenza. Here, even longer experience has shown that each new season is, indeed, a new season.

As in the theater world itself these days, planning for what lies ahead feels tempest-tossed. Plans are being laid. Discussions continue. Creativity abounds, and hard work persists. The season shall unfold. But no one knows how it will look until the curtain—or whatever is passing for one this year—goes up.

Poor Hamlet is troubled enough to fill the stage for hours—it is, in fact, Shakespeare’s longest play. Yet he’s just one man. Laboratories this fall are absorbing the slings and arrows of two roles simultaneously. Can they prepare for both parts (think Richard II and III sparring on the same stage) with confidence? What will a pandemic-based flu season entail?

The influenza season is always unpredictable, says John Waugh, system vice president, Pathology and Laboratory Medicine, Henry Ford Health System. “And layering one respiratory illness on top of a pandemic illness is something that we haven’t seen before. So I think we’re all going to school on this one,” he says, using an especially apt metaphor. (When Waugh spoke with CAP TODAY, the University of Notre Dame was making headlines with its plans to return to in-person teaching. Waugh eyed the school’s confidence warily. “They have Touchdown Jesus,” he laughed, referring to the large mural visible from the football stadium. “Maybe that’s going to be a factor.”)

Dr. Bobbi Pritt at Mayo Clinic, with Matthew Binnicker, PhD (left), and Joseph Yao, MD, both clinical virologists in the Division of Clinical Microbiology. In addition to standalone COVID-19 testing, they’re planning to use multiplex platforms to test for SARS-CoV-2, influenza A, influenza B,

and in some cases RSV for patients who are at risk for more than one virus. [Photo: Matthew Meyer]

At Mayo Clinic, "We really are doing two things," says Bobbi Pritt, MD, chair, Division of Clinical Microbiology, and professor of laboratory medicine and pathology. First, she and her colleagues intend to offer standalone COVID-19 testing. Second, they're planning to use multiplex platforms to test for SARS-CoV-2, influenza A, influenza B, and in some cases respiratory syncytial virus for patients who are at risk for more than one virus.

Behind those offerings lie many conversations between the lab and their patient-facing clinical colleagues, she says. One Mayo task force has been meeting multiple times a week, involving top-level leaders in pathology, surgery, outpatient, inpatient—"you name it," says Dr. Pritt. "We're all trying to hypothesize what might happen this fall. None of us has the answers."

It may be helpful to consider COVID-19 and non-COVID respiratory illnesses separately as labs prepare, Waugh says, at least to start.

"I kind of have a clock in my head that says about Dec. 1 every year is when we should start looking for flu," he explains. "So we tend to line up testing supplies in the October/November time frame." At the very least, he says, they want to be ready for the start of flu season, regardless of how it might end.

The COVID situation has its own trajectory. "I think of it as kind of a roller coaster," Waugh says. "We went up a big hill and then came down, but then we've got the smaller hills"—the result of reopenings and closings, and the loosening and tightening (or sometimes start) of social distancing, restricted gatherings, and mask requirements. "We'll continue to see that as different parts of the country, different states, approach this differently."

The disease distinction is helpful only up to a point, however. "The great concern is the coexistence of COVID-19 with seasonal influenza," Waugh says. Will this be a relatively harmonious blended family? (If nothing else, the pandemic is giving observers a chance to trot out a lot of metaphors.) Or will this be a Montague/Capulet-type family gathering?

Dr. Ginocchio

As labs consider the tests they'll need, Christine Ginocchio, PhD, MT(ASCP), vice president, global medical affairs, BioMérieux/BioFire Diagnostics, sounds a note of caution. "You can't lump everything into one bucket." Testing done in the outpatient setting in a mildly ill patient will differ from testing patients sick enough to come to the ED or those being intubated.

At Mayo Clinic, physicians who work primarily with outpatients by and large prefer a multiplex test that detects SARS-CoV-2, influenza A, and influenza B, says Dr. Pritt. "RSV, to them, is not necessarily as important in all patients. Which is good, because some of the rapid tests performed in the outpatient setting don't include RSV," she says. RSV is important for children, of course, but most physicians are primarily interested in differentiating between flu and COVID-19 in adults, she says.

The inpatient setting is different, Dr. Pritt continues, as is dealing with patients who are immunocompromised. RSV takes on heightened importance in those situations, so physicians "want all the options."

“Thankfully,” Dr. Pritt says, “we are seeing tests coming on the market that offer those different combinations. But, well,”—she pauses, then sighs, before continuing—“like everyone, we are not immune to the supply chain shortages.”

Standalone influenza tests come, like Instacart orders, in a variety of sizes and shapes, and often with the same uneasy anticipation. Some are point of care; the Roche Liat, for example, is a real-time, highly sensitive PCR assay that can be performed at the patient’s bedside in less than 20 minutes, says Dr. Pritt. Others allow 96 tests to be run simultaneously but require upfront RNA extraction and have four- to six-hour turnaround times. Specimens are usually batched, so TATs can extend to 12 to 24 hours. In between are tests that are considered relatively rapid but take one to three hours for results, including larger panels, such as BioFire’s respiratory panel, Dr. Pritt says, with its more than 20 analytes for viruses and some bacteria.

In the best-case scenario, Dr. Pritt says, laboratories could turn to any of these options as needed, but supply chain issues make that unlikely. “We’re all hoping we can get the number of kits and reagents we need,” she says.

“Usually you have one, maybe two tests for a given virus,” she adds. Trying to line up half a dozen tests would have had the makings of a French farce at the start of the 2019–2020 flu season, but now demand has outstretched what any one company can provide. “So we’ll do as much as we can with one manufacturer, but then we’ll have to bring in a test by another manufacturer to make up the difference.” Even small academic labs are running four or five tests. By the end of August, Mayo Clinic planned to implement its *eighth* test. “All for the same virus!” Dr. Pritt marvels.

Using multiple tests means more than shoehorning analyzers into tight spaces. (Though that, too, can be a challenge.) CLIA has its requirements. Staff have to be trained and evaluated for competency. “And we have to figure out how to do proficiency testing for all eight tests.”

Sample management requires new tactics, too. When Mayo initially began offering SARS-CoV-2 testing through its reference lab, clients were signed up for a specific test. But as reagents fell short, and clients were moved to a new test system, Dr. Pritt says, “we had to manually convert the original test order. That was just a nightmare.” Eventually the lab created a universal code for SARS-CoV-2 molecular testing, “but it just shows you how complicated this is.”

Mayo plans to use the Liat in its outpatient setting, although supply constraints will limit the number of patients who can be tested by the device. Dr. Pritt also anticipates using Roche’s multiplex Liat test that combines influenza A/B and SARS-CoV-2 and offers a similar TAT. “That’s an ideal test for that environment—you collect a single specimen, test it once, and you get three different answers.”

The test also has the potential to address supply chain concerns, one of which was foreshadowed years ago in “The Graduate,” as movie fans of a certain age might recall. A single test uses fewer reagents—and, of course, fewer plastics.

Stan Schofield has plenty to say on that matter (and others) from his perch as president of the regional laboratory NorDx, which is part of the Portland-based MaineHealth integrated health care system. “Everybody wants to go back to work or back to school, and we can’t get pipette tips. Can you imagine? I mean, a little piece of plastic and you’re crumbled. I can do a thousand more tests a day, if I could get the pipette tips.”

He has similar supply concerns about the Roche Liat, which he’s planning to use at each of his system’s hospitals. “I don’t know the availability of the cartridges,” he frets. “We have all the little machines. But without the cartridges it’s just a fancy toaster on the shelf with no bread.

“Early indications are we’re going to have a *very* tight allocation of cartridges,” Schofield continues, “which will not even come close to meeting the needs of my emergency departments on a daily basis. We might get 200 tests a week for 11 hospitals. One medical center can blow through that in a day.”

So as with COVID-19 testing, the NorDx core lab will remain the backbone for the majority of testing. By running

the lab 24/7, nearly all patients have been getting their COVID-19 results in less than 24 hours. “Flu will be the same,” Schofield predicts. The Liat cartridges will be saved for patients who show up at more distant hospitals at odd hours, well past the last courier run. If cartridge availability does increase, then the POC tests would play an expanded role in the hospitals.

Flu testing has its own short-ish history.

Up until 10 to 12 years ago, Waugh recalls, physicians typically assumed flu was the culprit in patients with respiratory illnesses in the winter months. Testing for influenza A and B became more the norm with the advent of antiretrovirals such as Tamiflu and Relenza. Their widespread use in more vulnerable patients required fairly quick TATs, since the medications are most effective within 48 hours of symptom onset.

With COVID-19, the questions become harder for patient-facing physicians, says Dr. Pritt. Do they give Tamiflu? Enroll them in a clinical trial for COVID-19? Or is it a completely different story—does the patient have a bacterial infection that requires antibiotics?

Dr. Ginocchio frets that the presence of multiple illnesses will create “a huge diagnostic dilemma.” In patients coming to the hospital especially, “It’s going to be difficult to say specifically if this is COVID or not.”

Early on, because of the severe lung damage seen in many COVID-19 patients, “Everybody felt, *Well, a CT scan is super-diagnostic*,” Dr. Ginocchio says. Recent data now suggest a different story: CT scans appear to be only 75 to 80 percent accurate, she says. Without rapid SARS-CoV-2/flu tests, “If we do see flu reemerge, it’s going to be a really difficult diagnosis.”

Stepping back a bit, Dr. Ginocchio talks about how COVID-19 develops and the broader implications for testing. Most people who become severely ill from COVID-19 don’t do so until the second week. Most people head to the hospital around day seven or eight and land in the ICU around day eight or nine. So the rapid decline isn’t as sudden as it once seemed. Severe lung damage is indeed a tipping point, as are other, underlying comorbidities. Says Dr. Ginocchio: “As a result of having these secondary comorbidities, you develop a secondary, bacterial superinfection at home, which is what pushes them to the emergency room, to the ICU, and then to intubation.” Five to 10 days into mechanical ventilation, a second group of patients may develop another infection, such as ventilator-associated pneumonia. “And sepsis is very, very common.”

Given all these factors, says Dr. Ginocchio, “Syndromic testing is so critically important in this patient population.” BioFire’s pneumonia panel covers bacteria, viruses, and resistance markers, but, she adds, “I’m not saying this as a manufacturer; I’m saying it as someone who would think clinically, *What do we need to do to treat our patients correctly?*” Although the data are variable on coinfections, emerging studies suggest that up to 30 percent of patients coming into the ICU to be intubated already may have a secondary bacterial infection, she says. “I think everyone, on admission to the ICU, needs to have a comprehensive pneumonia panel” to avoid inappropriate empirical treatment. “We want to target that initial therapy without guesswork.” In some cases—sepsis or a bacterial superinfection, say—therapy may need to be escalated. “You need to test them again the minute they show signs of a potential ventilator-associated pneumonia,” she says. But just as important, she adds, is using testing to deescalate therapy, if need be, to practice good antimicrobial stewardship to avoid *C. difficile* disease or other adverse events.

Long story short: In the hospital setting, “you need to know what they have when you admit them,” Dr. Ginocchio argues. “They don’t necessarily just have COVID.” Some studies from China report that 50 percent of COVID-19 patients had a secondary bacterial infection, she says, with high mortality rates in that group. “So much higher that we presume it adds to severity of the overall illness.”

SARS-CoV-2 testing alone may not be sufficient in communities where flu is circulating, Dr. Ginocchio says, though she acknowledges that “Some people will argue, ‘What’s the big deal? Just give them Tamiflu and send them home.’”

That might work in an outpatient environment. But that patient population can include those with complicating issues, such as chemotherapy, immunosuppression, transplants, chronic lung disease, or cystic fibrosis.

“So I think we have to be able to make that diagnosis,” Dr. Ginocchio says. “I’m a proponent of diagnostic stewardship—test the right patient at the right time.”

That’s why her company decided to incorporate SARS-CoV-2 testing into its routine respiratory panels. As of mid-August, it had an EUA for its RP2.1 panel with the SARS-CoV-2 addition; the company was working on adding it to its POC respiratory testing as well as its pneumonia panel. Not everyone will need comprehensive testing—“not everybody in the outpatient setting, absolutely not,” she says—but it needs to be available for patients who will be at risk if given a misdiagnosis.

NorDx used its own laboratory-developed test for SARS-CoV-2, which served them well, Schofield says, given what he calls the scavenger hunt other labs went on to track down reagents and supplies. It intends to use a combination LDT when flu season starts. RSV will likely remain a standalone test, he says. “I’m not sure I want to put that in the combination. I’ll let my PhDs and medical directors chew on that a little bit.”

Schofield

COVID-19 will still be prevalent when flu hits, he says, so the combination test will be done automatically. “It’s just going to be the standard of care.” He suspects that will be the CDC’s recommendation. “You just can’t differentiate the clinical symptoms very well,” Schofield says. “It’s going to take the molecular differentiation.”

Most worrisome to Waugh are patients who are coinfected with SARS-CoV-2 and flu. “I’m very confident we will see those kinds of situations,” he says, particularly in patients with risk factors such as exposure, age, and immunosuppression.

Dr. Pritt has a related concern. Since COVID-19 tends to be top of mind for patients who present with any of the various, nonspecific symptoms, such as diarrhea, “Once you get that first lab result that shows a patient has COVID, it’s easy to focus on that” and use it to explain all the symptoms. “We have to continue to be careful and not get so hung up on COVID that we miss something else that’s also important.”

If the questions are becoming thornier for patient-facing physicians, the answers are also becoming harder for labs to provide. Says Dr. Pritt: “We’re often coming to the table with limitations, saying, ‘We only have these two tests.’ Or we say to them, ‘This is the test we have the most of—will that be sufficient?’ And if they want something else, we may not be able to provide that.”

Those hard decisions get made daily at Mayo Clinic, according to Dr. Pritt. She and her colleagues have established a command center in the lab for daily meetings with key representatives in various departments. “Every day we’re assessing how we’re doing with the supply chain. If we have shortages, how are we going to accommodate that? Are we going to perform one test versus another? Every part of the supply chain is vulnerable now.”

Mayo pathologists and clinical microbiologists are also serving on institutional boards to address such matters, including, in one instance, issues related to preprocedure/presurgical COVID-19 testing. The lab initially performed this testing using an assay Dr. Pritt says was highly sensitive, with a rapid TAT. Then “something happened with that test,” she says, “and the manufacturer all of a sudden wasn’t able to provide the kits they promised us.” It’s the perplexing, repeating, pandemic plot line. “So we very quickly had to shift gears and come up with a backup plan.” The new test is relatively fast, she says, but it did increase TAT slightly.

She fears similar scenes could play out with flu tests, with physicians forced to make equally tough, daily decisions. She uses the Roche Liat as an example. If the test is in high demand, what happens if there's a big outbreak elsewhere in the country and kits are sent to that spot instead?

"There are so many different reasons why all of a sudden supplies may not be available," Dr. Pritt says.

Schofield calls the ongoing supply chain problems "a disaster. It's almost criminal." As his system catches up in one area—reagents, say—it falls behind in another, as outbreaks in other parts of the country effectively commandeer supplies he'd been counting on. "Things that were on trucks disappeared—big pieces of equipment that I ordered a year ago were delayed *again*, because they got redirected to Houston."

While the national narrative continues to refer to the pandemic's "testing problem," laboratories tell a more nuanced tale: They actually have a *backup* testing problem.

It's a story devoid of cliffhangers. Yes, there will be supply chain problems. Again. Still.

Flu season will only add to the pain, Schofield predicts, as manufacturers shift from producing cartridges for SARS-CoV-2 testing alone to combination cartridges.

"In other words, if I needed COVID cartridges today," he says, speaking in mid-August, "I could probably get it. I don't think I could get it next month or the month after."

It remains a worldwide issue, Waugh says. Many of the products that will be in demand are made abroad, and, in manufacturing's version of sheltering in place, "They tend to stay in their home countries." Even if a product is manufactured in the United States, the parent company may be European-based, with obligations to ship product back to the country where it's headquartered. "So that creates constraint right out of the gate."

The pandemic has pushed everyone into a crash course on economic and manufacturing basics.

Ramping up production, for example, sounds easy but isn't.

"Factories take a year to build," Schofield says. "And the raw materials have not been worked out in a global-friendly way."

Despite the Herculean efforts of manufacturers, "Nobody can make enough tests," Dr. Ginocchio says.

She recalls a conversation with someone who asked her, *If we gave your company a couple million dollars, could you make a million tests a day?* "Well, we'd have to build a whole new building and new production lines. And we can't get raw materials. Everybody is trying their best, but you can't do the impossible."

Everyone is scuffling up the same mountain. The diagnostics companies share suppliers, Dr. Ginocchio explains. Even if manufacturers can lock in backup suppliers, those suppliers "may not be capable of making it in the same vast amounts as your primary supplier." And it may not be reasonable, business-wise, for smaller suppliers to gear up for a massive demand that could vanish in a year.

Companies have been through the same economic challenges as everyone else, Waugh says, including different degrees of lockdowns in various states. They've also had to ensure worker safety, such as reconfiguring work spaces/production lines and perhaps offering COVID-19 testing. These are solvable problems, but they've "introduced some level of delay and caution," Waugh says.

And while companies are working quickly to develop SARS-CoV-2/flu tests, Waugh says, they won't scale up for mass production unless they have a very high level of confidence that they're going to get EUA approvals. Otherwise, if the FDA requires change, "now they've made too many of the wrong product."

There's nothing new about the process, and most companies are savvy about how it works. But it is an added step, made more fraught by the pandemic.

Moving too quickly has its own perils, Dr. Ginocchio says, citing the FDA bulletins with alerts that a test is not performing correctly or will have its EUA revoked. “You can’t blame the manufacturer,” she says. “Everybody’s doing their best, quickly.”

She extends that praise to the FDA, which, she says, “has been doing an amazing job. I cannot give them enough credit. And I feel bad, because they’re always going to get blamed. They’re working 24/7 to get tests approved, constantly upgrading guidelines and protocols.” She anticipates fewer roadblocks in obtaining EUAs, “simply because the FDA has worked out its own kinks.”

All of this will doubtless make for a series of interesting case studies at Harvard Business School one day. But labs don’t have the luxury of time.

The manufacturer of one multiplex test Dr. Pritt is interested in says it hopes to have it available by October. “But none of that is guaranteed,” she says. And even if the test is ready on time, “we don’t know for sure that they’ll have enough to give us.”

Dr. Waugh

Waugh isn’t worrying about delays, but he and others note that EUAs were taking longer to come through. “Initially the FDA had a very, very open policy on emergency use authorization,” Waugh recalls. EUA wasn’t spoken quite like a four-letter word, but many labs came close as they dealt with the fallout. “Once they opened the door we frankly had a lot of bad product that came into the U.S. and other parts of the world.

“The FDA has seen that,” he continues. “They know it, and they’ve heard from others, and there have been publications that have cautioned about products that have had poor performance characteristics or that were minimally tested, and now they are taking a more studied look at these.” He sits in on a weekly FDA call where these matters are discussed. His colleagues at diagnostic companies are a little surprised by the slower pace, he says, but no one is feeling a sense of urgency.

Ordering physicians may feel otherwise, especially with “flu season creeping closer to us all the time,” Waugh says. “Everybody would like the largest multiplex system that will give them the fastest results. Everybody wants to be in the express lane.”

But labs need to remain agnostic, says Waugh, given that they’ll be leveraging multiple systems with multiple supply streams of varying reliability. “We don’t want to steer them, or let them steer themselves, toward a specific test. We have worldwide constraints for these products, and the ones that are the most comprehensive and the quickest are the ones in heaviest demand.” That also creates internal constraints for large systems like Henry Ford that have multiple emergency departments and urgent care areas.

Demands for COVID-19 testing aren’t slowing down, either. “Everybody wants to be tested,” Schofield says. “For free. Yesterday.”

Much of the demand he’s seeing is coming from schools, corporations, and surrounding states. One asked about testing three counties’ worth of nursing homes, totaling 700 patients a day. “From a business standpoint I’d love to be able to do that,” he says. “From a being-able-to-deliver-the-goods standpoint, I’m very worried.”

Schools are contacting him about testing students. Each has its own algorithm (“It’s going to be fascinating to see what works and what doesn’t,” he says), each with a different demand for test kits, TATs, etc.

Tempting as those offers are, Schofield can't lose sight of others in need of testing: the 1,400 MaineHealth patients a day who are symptomatic or need preprocedure/presurgical testing. "I can't tell them to go away," he says.

It's possible two other approaches—pooling and antigen testing—could help ease pressure. Quest and LabCorp have EUA for pooling, Waugh says, and other organizations are likely to take their case to the FDA for consideration as well. "Just to have that in their back pocket if they need it."

Pooling could help with lengthy TATs, though "it's not a first option for us," he says. In areas with low prevalence—maybe three or four percent—"pooling can extend the supplies you do have." But it's not an everyone-into-the-pool scenario. In addition to well-known concerns about loss of sensitivity, pooling triggers a separate set of sample management steps. And when prevalence starts to creep up, it becomes less attractive.

Antigen testing could fit into the flu picture if it can be done on automated systems. "Because then it becomes sort of the parallel of the antibody testing environment," Waugh says, "where you're leveraging chemistry automated analyzers able to handle large numbers of samples." That could work for testing larger populations of people, such as schools, universities, businesses, and sports teams.

Those tests were still in development when Waugh spoke with CAP TODAY in mid-August, though he expects them to be available by the start of flu season. "And those will be another tool in the toolbox for some of these mass screenings."

The tests may run into the NP swab supply problems that have dogged the pandemic response from the start, though, which has some eyeing tests that use saliva samples.

The same late-August day Dr. Pritt spoke with CAP TODAY, Illinois' governor was hailing a University of Illinois-developed saliva-based test as a game-changer that would help students return safely to campus. When such tests make a media splash, says Dr. Pritt, "All of our colleagues are calling us: *When are we going to get this?*

"And then you have to educate them that it's not that simple, and it may not be a good test for us, and here's why. It's a little frustrating," she says. "Every time there's a news headline, then things get a little blown out of proportion." Though the saliva-based tests are easier for patients, "it hasn't made testing any easier," Dr. Pritt says. It's still a three-hour test. And even if a new test is inexpensive, running it still requires staff and overhead. "Labs are still going to charge the normal price for it."

Nor are samples foolproof. "You just don't know from person to person what the full utility of a saliva sample is going to be," Waugh says. "That's why nasopharyngeal has stayed in first place as a sample of choice."

Dr. Ginocchio has her qualms about antigen testing in general. In what situations do you trust a negative test, she asks. Likewise, repeat tests increase the chances of catching positives. But is it practical? Dr. Ginocchio has her doubts. "People won't understand that: *I had a COVID test, and it was negative—I'm fine*. And to have people return two and four days later for repeat tests, I think is going to be quite difficult."

There are no good markers for beliefs or behaviors, with their sometimes corrosive, sometimes ameliorating effects.

At Notre Dame, Touchdown Jesus did not appear to help suppress the virus, and the school—along with others since—had to shift, at least temporarily, to remote instruction after early COVID-19 outbreaks. And at the University of Illinois, the comprehensive and well-regarded testing plan took a hit when students continued their risky behavior even after testing positive; some tried to circumvent the app designed to vouch for negative results, reported *The New York Times* in September.

Human actions have become de facto pre- and post-behavior variables. "We're never going to be able to meet the demands of people who want to get tested every day," Dr. Pritt says. "We're not going to have enough supplies for that. We hope we have enough to test all of our sick people and at-risk people. But it's a limited resource, so we need to protect it. And to do so we need help from the public to prevent infections that are easily preventable."

“I’ve had a lot of conversations about testing, limitations of testing, different approaches—should we use pooled specimen testing, should we use antigen testing,” she continues, running through the same questions labs have always tried to answer. “But one thing I always come back to is if everyone wore masks and socially distanced, the COVID outbreak would go away. We have very good data now that wearing masks prevents transmission. We know they’re effective. We need to continue that message of how important it is to wear a mask.”

Dr. Ginocchio puts it even more bluntly. “We don’t want to waste testing.”

The tail end of the last flu season offers encouraging information about how thoughtful behavior might affect the upcoming one.

Looking back, Waugh says, “When we went into COVID season, we had been on a seasonal flu protocol.” As SARS-CoV-2 testing got underway, “Our initial position in the February/early March time frame was let’s rule out flu first,” Waugh recalls. For those who tested negative for flu A/B but were symptomatic, SARS-CoV-2 testing was the next step.

As March began its free fall, providers decided it made more sense to look for SARS-CoV-2 infections first. “We essentially declared an end to flu season when we started seeing more flu B than flu A,” he says.

Dr. Ginocchio cites emerging data that tell “a fascinating story” regarding that time. Respiratory virus testing positivity rates can be as high as 60 to 65 percent in the peak winter months, she says, with flu between 20 to 35 percent of the positives. Respiratory viruses still circulate in the summer months, but overall positivity rates drop to about 30 to 35 percent.

At the start of last March, Dr. Ginocchio says, respiratory virus positivity rates were at their expected winter levels, with the typical, gradual decline evidently underway.

Then COVID-19 hijacked the health care system, and quarantines, social distancing, and masking took hold. “By the end of May,” Dr. Ginocchio says, “our detection rate for all respiratory viruses was down to less than 10 percent, which is incredibly low. We don’t even see that in the summer.”

It’s not that the viruses took a hike. “They’re always there,” she says. “It’s just that transmissibility went away. You *should* wash your hands.”

Dr. Ginocchio has her own version of phase one, two, three, etc. Unlike the governors who mark these as steps for reopening their states, she uses her version to get a handle on coinfections.

Phase one, in this scheme, describes the emergence of COVID-19 in the months of March and April. SARS-CoV-2 was low in most areas, but other viruses were circulating at their normal levels for this time of year. Coinfection studies at the time saw 20 to 25 percent of non-SARS-CoV-2 viruses circulating among patients with and without COVID-19 infections.

Phase two describes the massive influx of COVID-19 disease, as seen in New York in early spring. “The number of other viruses coinfecting COVID-positive and COVID-negative patients was two to three percent—really, really low,” Dr. Ginocchio says.

“Testing may have been biased at this time with a focus just on COVID-19, but also quarantine, lockdown, better hygiene played a major role. If you do not transmit COVID-19, you do not transmit other respiratory viruses.” She saw a marked decrease in gastrointestinal viruses also during this time.

Phase three covers more recent history, where COVID-19 positivity rates are trending up as reopenings expand. Each part of the country, and its inhabitants’ behavior, varies. “People are tired of being on lockdown,” Dr. Ginocchio says. “So we’re starting to see the reemergence of other viruses also, but less than normal.”

She expected clues to be seen by early October with the start of the rhinovirus season. That could be a good indicator, she says, of what might lie ahead. “And then RSV, which usually starts to come in drips and drabs around

October/November, and then really goes up in December and January."

"Usually" being the key word. This year, such norms might be as bankable as a Confederate dollar.

"We really don't know," Dr. Ginocchio concedes. For the traditional viruses, "I think the numbers won't be what we normally expect, because people are being respectful of social distancing," though, as she and others point out, this is partly geographic-dependent.

Waugh says that people "who want to be safe" have accepted social distancing and masks, and are avoiding oversized gatherings. "Of course, you have contrarians who go the other way," he says.

And for himself? "I'm careful. I think about which way I'm pointed," he laughs, "and who's pointed at me."

Australia, with its jump-start on winter, offers a ray of hope for the season ahead. Its influenza rates have been historically low, Dr. Pritt says, likely the result of behaviors that took aim at SARS-CoV-2 transmission. The same thing could happen in the United States, she says, leaning heavily on the word "if"—*if* people continue/start to mask, distance socially, and so on.

It's not a given. "We have to prepare for the fact that people might be so burnt out, they might stop all those helpful measures," she says. "Then we could see a really steep rise in cases."

Dr. Pritt worries about what that could mean not only for testing, but for her already stretched-thin staff, who also are vulnerable to flu and COVID-19. It's a headache that bedevils Schofield, too. "Adequate personnel is my number two worry, behind supply chain issues," he says.

With a COVID-19 vaccine in the works but likely unavailable for the foreseeable future, physicians are emphasizing the importance of the flu vaccine this year. Some providers have mandated vaccinations; Mayo is using an opt-out approach.

Such approaches could boost vaccinations. On the other hand, with more employees now working from home, office sites may not offer the easy, widespread flu shot delivery they have in the past. "Good point," says Dr. Pritt. Perhaps there will be drive-through vaccines at clinics, similar to the drive-through collection sites for COVID-19, she says.

The human behavior wildcard, mixed with vaccine skepticism in general, could also affect vaccination rates. "Although if the pandemic hasn't motivated people to get a flu vaccine," Schofield says, "I don't know what's going to."

With more than enough "don't knows" to go around, labs aren't taking anything for granted.

Says Dr. Pritt: "We continue to prepare for the worst, hoping we won't need to be in that worst-case scenario."

Dr. Ginocchio agrees. "We have some very challenging times coming ahead of us. We're just going to have to take it step by step." And surge by surge, supplier by supplier, test by test by test by test.

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