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COMMENTARY

Impact of Rapid Molecular Detection of Respiratory Viruses on Clinical Outcomes and Patient Management

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ABSTRACT To determine if rapid molecular testing for respiratory viruses in patients with respiratory illnesses can provide advantages to patients and hospitals, rigorous investigations on the impacts of using these assays are required. Well-conducted studies are needed to inform decisions about implementation of new rapid assays to replace standard molecular testing or to initiate testing in laboratories that are currently not doing molecular tests for respiratory viruses due to the complex nature of standard panels. In this issue of the *Journal of Clinical Microbiology*, N. Wabe et al. (J Clin Microbiol 57:e01727-18, 2019, https://doi.org/10.1128/JCM.01727-18) report the results of their evaluation of the impact of using a rapid molecular test for influenza A/influenza B and RSV on outcomes for adults hospitalized with respiratory illness. The median time from admission to test result of the rapid test was 7.5 h compared to 40.3 h for the standard PCR assay. Compared to the use of the standard molecular assay, use of a rapid test significantly shortened time in the hospital and reduced the number of other microbiology tests performed. The authors concluded that rapid PCR testing of adults hospitalized with respiratory illnesses could provide benefits to both the patients and the hospital. Patients were able to leave the hospital earlier and a greater proportion of them had received their test results before discharge, which would allow appropriate treatment to be provided more quickly.

Respiratory tract infections include both upper tract infections, such as the common cold, and lower tract infections, such as pneumonia, bronchitis, bronchiolitis, and exacerbation of asthma. Lower respiratory tract infections cause substantial morbidity and mortality and are a leading cause of hospitalization, especially for infants, the elderly, and immunocompromised individuals (1–4). Respiratory tract infections are caused by a wide variety of pathogens, which include several viral and bacterial agents. Although the specific viruses responsible for illness differ according to season and age of patient, symptoms and seasons are similar for many respiratory viruses (5, 6). Therefore, early and accurate laboratory diagnosis to identify the etiologic agent of a respiratory infection is important to ensure appropriate antimicrobial therapy and for the effective implementation of isolation precautions and patient cohorting.

In the past decade, the conventional diagnostic methods of culture and antigen detection assays have been replaced by molecular assays for diagnosing respiratory tract infections. Laboratory-developed and commercial multiplex real-time PCR assays, which detect a large number of different pathogens, have been developed and implemented for routine diagnostic application. These assays are highly sensitive and specific (7–11). However, they are complex to perform, involving several testing steps, including nucleic acid extraction prior to amplification and analysis, and require a laboratory turnaround time (TAT) of five to six hours. Consequently, for routine diagnostic use, these methods are best suited for batchwise testing once or twice during a laboratory shift.

To decrease the time to result and enable random access testing, rapid sample-to-

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result assays have been developed. These assays combine nucleic acid extraction, PCR amplification, and detection into a single step (12–14). Several utilize test cartridges for each sample that are suitable for decentralized or point-of-care testing, with a time to result of 20 min to 2 h (15, 16). Several commercial panels are available for detection of influenza A (FluA) and influenza B (FluB) and/or respiratory syncytial virus (RSV), while other products can detect 11 or more respiratory viruses and bacteria. The short TAT of these rapid assays provides several potential advantages. Patients may spend less time waiting for results and could be provided with a proper antimicrobial agent in a timely manner, usually before they leave the emergency department or hospital. Quicker diagnosis of inpatients could help determine patient isolation protocols, reduce the length of hospital stays, and decrease the number of other microbiology laboratory tests performed. A large retrospective study of the impact of rapid antigen testing for influenza on clinical care in emergency departments concluded that influenza diagnosis made in association with a rapid antigen test resulted in fewer tests and antibiotic prescriptions and more frequent use of antivirals (17).

To determine if rapid molecular testing for respiratory viruses in patients with respiratory illnesses can provide these advantages, rigorous investigations on the impacts of using these assays are required. Studies are needed to inform decisions about implementation of new rapid assays to replace standard molecular testing or decisions to implement rapid assays in laboratories that are currently not doing molecular tests for respiratory viruses due to the complex nature of standard panels. Studies are also needed regarding the type of assay that will provide more advantages, i.e., smaller panels detecting FluA and FluB and RSV or complete panels detecting many common viruses and bacteria.

Wabe et al. (18) report the results of their evaluation of the impact of using a rapid molecular test for detecting respiratory viruses on outcomes for adults hospitalized with respiratory illness. Their major finding was that use of a rapid PCR test for detection of FluA, FluB, and RSV viruses significantly shortened time in the hospital compared to the use of the standard molecular assays. Additionally, the use of the rapid test reduced the number of other microbiology tests performed. The preimplementation part of their study, conducted during six months in 2016, included an intervention group that received a standard commercial multiplex PCR assay for detection of up to 16 respiratory viruses. The median TAT for the standard test was 27.4 h. The postimplementation part of their study, conducted during the same six months in 2017, included an intervention group that received a rapid PCR for detection of FluA, FluB, and RSV. The median TAT for the rapid test was 2.3 h. Both parts of the study included a matched control group of patients who were admitted for respiratory illness during the same time periods but not tested by the respiratory virus PCR panels. The median time from admission to test result of the standard PCR assay was 40.3 h compared to 7.5 h for the rapid test. In addition to the shorter amount of time required to perform the rapid test in the laboratory, part of the overall time difference was due to placing the rapid test in two of the three study hospitals. This reduced the time that had previously been required to transport the samples to the one referral laboratory at one of the hospitals that had performed the standard assay. Another difference in time to result was due to the random-access nature of the rapid test. Each sample was tested individually, and the test could be started when the sample was delivered to the laboratory. Compared to the standard test, in which batch testing was performed one or two times each weekday and once a day on weekends, the rapid test was available 24 hours, seven days a week.

For all adults with positive results for FluA, FluB, and RSV, the use of the rapid test was associated with a statistically significant 21.5-h decrease in median hospital length of stay (LOS). In addition, the subset of patients who received their results while still in the hospital, regardless of the test result, had a significant 25.5-h reduction of LOS. There was also a significant reduction in microbiology test use, including blood cultures, sputum cultures, and bacterial and viral serologies, compared with that in patients who received standard testing. The authors concluded that rapid PCR testing

of adults hospitalized with respiratory illnesses can provide benefits to both the patients and the hospital. Patients were able to leave the hospital earlier, and a greater proportion of them had received their test results before discharge, which would allow appropriate treatment to be provided more quickly. The hospital would have experienced economic benefits due to shorter LOS and lower test and procedure utilization.

The study was limited by the use of a rapid test that detected only FluA, FluB, and RSV. Twenty percent of patients in the rapid group had the standard multiplex test ordered after receiving rapid test results that were negative. This group of patients had a median LOS almost 1 day longer than that of patients in the rapid group who did not have a subsequent standard test ordered. The results of the study were also limited by comparing implementation group data acquired in two different years. A reduction in LOS when the rapid test was used could have been due to factors present during 2017 that were not present in 2016. For example, the respiratory viruses circulating in 2016 may have been more pathogenic compared to those circulating in 2017, resulting in longer hospitalization for patients infected in 2016. However, there was no significant difference in median LOS between the 2016 and 2017 control groups. Unfortunately, the authors were not able to evaluate any differences in antimicrobial use between the two groups.

Several studies have used a similar design to compare patient outcomes before and after implementation of a rapid PCR test that replaced conventional methods and/or standard multiplex PCR tests. Rappo et al. (19) tested adults in two consecutive influenza seasons using methods that included a mixture of conventional and standard PCR tests in the first year and a rapid multiplex PCR assay in the second year. They also found a shorter median TAT and a shorter length of hospital stay for the rapid test compared to the conventional and standard testing. In addition, when the rapid test was used, they reported significantly lower odds ratios for admission, duration of antimicrobial use, and number of chest radiographs. Another study evaluated antiviral use among hospitalized adults in two respiratory seasons before and after implementation of a rapid PCR assay (20). The time to result when standard PCR testing was used was 25.2 h compared to 1.7 h when the rapid test was in use. The median duration of oseltamivir use was significantly decreased when patients were tested by the rapid test. In a study of hospitalized children three months or older, in which the mean time to test result was 18.7 h for the standard test and 6.4 h for the rapid test, more patients received their result in the emergency department (51.6% versus 13.4%) when tested by the rapid test and the duration of antibiotic use was shorter (21). Patients with positive results by the rapid test also had shorter LOS and time in isolation compared to patients positive by the standard test.

Several other studies have examined the impacts of rapid detection of respiratory viruses on clinical outcomes and patient management, including hospital LOS, utilization of isolation facilities, and antimicrobial use and duration, by comparing patients tested by rapid and standard tests in the same season. One study tested patients with acute respiratory infections with both a rapid respiratory PCR panel and a standard laboratory-developed assay (22). This study found that the shorter time to result of the rapid test allowed isolation measures to be discontinued sooner in 14 of 30 patients and provided earlier results of approximately 1 day for patients receiving antimicrobial treatment. Andrews et al. (23) tested patients on alternate days in the same season by either a rapid or standard molecular test. The time from admission to test result of the rapid test was 19 h compared to 39.5 for the standard test. Use of the rapid test was not associated with changes in hospital LOS, readmission rates, or mortality, but was associated with a reduction in the median time to first dose of antivirals, allowing appropriate treatment to be given faster than when the standard test was performed. The authors noted that the study was limited by the relatively long time to test result for the rapid test. Brendish et al. (24) conducted a randomized controlled trial of adults presenting to the emergency department or acute medical unit of the hospital over two winter seasons to determine if the routine use of a rapid molecular test for respiratory viruses affected clinical outcomes compared to standard care with no testing. Patients

were randomly assigned to have a rapid molecular test or routine medical care. The use of rapid testing did not reduce the proportion of patients treated with antibiotics because many patients were started on antibiotics before test results were available. However, patients in the rapid testing group had reduced LOS and improved use of antivirals for influenza, and a higher proportion received single or brief courses of antibiotics compared to the control group. For many studies, significant reductions in the use of antibiotics may be difficult to achieve, as clinicians may not readily stop broad-spectrum antibiotics before bacterial cultures are available, even when a virus has been detected.

Studies on the economic impacts of implementing rapid PCR assays for respiratory virus detection, either to replace standard laboratory developed tests or as new testing, are also needed. One analysis showed that use of a rapid PCR test instead of a laboratory-developed standard PCR test for detection of influenza was likely to be cost saving in hospitals. Cost savings were realized by a reduction in waiting time for patients in the emergency department and decreased isolation time of hospitalized patients (25). In another study, the cost-utility of treatment based on the results of rapid PCR influenza testing compared to provider judgement or treating all patients with acute respiratory illness was evaluated for adult emergency department patients who were at high risk of influenza-related complications (26). The economic benefit of using rapid PCR testing for influenza detection depended on the influenza prevalence. Treatment according to a rapid PCR test for influenza was most cost-effective when prevalence was 3% to 7%. In all but the lowest prevalences, treatment according to rapid PCR testing resulted in improved outcomes compared to those with provider judgment.

The studies cited have consistently shown that rapid molecular tests have a significantly shorter TAT compared to that of standard tests. In some studies, faster results produced reductions in LOS, laboratory test utilization, and isolation measures. Earlier test results also allowed appropriate antimicrobials to be initiated and inappropriate antimicrobials to be discontinued in a timelier manner, especially for patients with influenza. These are promising results for the use of rapid molecular testing. However, it is difficult to generalize from the currently published studies regarding the impact of rapid molecular testing for detection of respiratory viruses because they are based on many different variables, including the study site, type of patients, type of rapid assay, and whether the rapid assay replaces a standard PCR assay or is a new test offering. A summary of the studies cited is provided in Table 1.

Many choices must be considered when deciding to implement rapid testing. Several rapid commercial assays are available for detection of different respiratory pathogens. Some panels detect only influenza A and B, with or without detection of RSV. Some panels detect a larger number of respiratory viruses and bacteria, which provide a wider range of diagnoses. Most rapid tests are low throughput, which could cause delays during busy respiratory seasons. Impact studies need to consider not only the benefits to both patients and hospitals but also increased costs due to additional instrumentation, additional space to put multiple instruments to achieve higher throughput, staffing additional hours to achieve more rapid results, and reagent costs. Medicare reimbursement issues should also be considered. A recent local coverage determination ruling by a Medicare contractor determined that the use of small multiplex viral panels (3 to 5 targets) in susceptible populations (hospitalized, urgent care, or emergency department patients and those seen by infectious disease specialists) was reasonable and necessary, but that the use of highly multiplexed tests (6 or more targets) as front-line diagnostics was not justified and would not be covered (27).

In summary, some studies have shown benefits to patients and lower costs to health care facilities. The decision to implement a rapid PCR assay for respiratory pathogens, either as a new test or to replace current standard PCR tests, requires consideration of both clinical and economic factors. However, because factors used to determine these benefits are unique to each health care facility, the advantages reported by others may not be realized in all settings. This is an area that could benefit from well-designed and rigorously conducted multicenter studies to determine whether specific tests or pro-

TABLE 1 Summary of studies on the impact of rapid molecular detection of respiratory viruses on clinical outcomes and patient management

Reference	Rapid test	Patients	Design	Comparator	TAT (standard vs rapid [h])	Main outcome(s)
Wabe et al. (18)	FluA, FluB and RSV	Hospitalized adults	Same months in consecutive years	Standard multiplex PCR for 16 viruses	27.4 vs 2.3	Positive result associated with decrease in LOS; receiving results while in hospital associated with decrease in LOS; decrease in other microbiology tests
Rappo et al. (19)	Multiplex PCR for 16 viruses and bacteria	Emergency department and inpatient adults positive for respiratory virus	Consecutive influenza seasons	Conventional tests and standard multiplex PCR	7.7 vs 1.7	Influenza positivity associated with lower odds ratios for admission, LOS, duration of antimicrobial use, and no. of chest radiographs
Chu et al. (20)	FluA, FluB and RSV	Hospitalized adults	Consecutive influenza seasons	Standard PCR for FluA, FluB, and RSV	25.2 vs 1.7	Decrease in duration of oseltamivir use
Rogers et al. (21)	Multiplex PCR for 11 viruses	Hospitalized children $\geq$3 months	Same months in consecutive years	Standard multiplex PCR for 7 viruses	18.7 vs 6.4	Higher percentage received result in emergency department; decrease in duration of antibiotic use; positive result associated with decreases in LOS and time in isolation
van Rijn et al. (22)	Multiplex PCR for 16 viruses and bacteria	Patients in acute ward, intensive care, and pediatric ward	Samples tested by both assays in one season	Standard multiplex PCR for 18 viruses and bacteria	27.1 vs 3.4	Decrease in isolation days; oseltamivir started sooner
Andrews et al. (23)	Multiplex PCR for 16 viruses and bacteria	Inpatients and outpatients	Standard and rapid tests used on alternate days in one season	Standard multiplex PCR $\pm$ atypical serology	39.5 vs 19	Decrease in time to first dose of antiviral
Brendish et al. (24)	Multiplex PCR for 11 viruses and bacteria	Emergency department and inpatient adults	Randomized controlled trial over two winter seasons	Standard PCR for 8 viruses at clinician discretion	NA[a]	Decrease in LOS; higher percentage of influenza-positive patients received antiviral; higher percentage received antibiotics for $<$48 hours

[a]NA, not applicable.

cesses improve patient outcomes. Importantly, these studies should be designed using methods and standards that will allow others to use the results in evidence-based laboratory practice guidelines (28).

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