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Clinical Utility of On-Demand Multiplex Respiratory Pathogen Testing among Adult Outpatients

Daniel A. Green,[a,b]* Letiana Hitoaliaj,[c] Brian Kotansky,[c] Sheldon M. Campbell,[a,b] David R. Peaper[a,b]

Department of Laboratory Medicine, Yale School of Medicine, New Haven, Connecticut, USA[a]; Pathology and Laboratory Medicine Service, West Haven Veterans Administration Hospital, West Haven, Connecticut, USA[b]; Pharmacy Service, West Haven Veterans Administration Hospital, West Haven, Connecticut, USA[c]

Multiplex tests for respiratory tract infections include up to 20 targets for common pathogens, predominantly viruses. A specific therapeutic intervention is available for individuals testing positive for influenza viruses (oseltamivir), and it is potentially beneficial to identify non-influenza viruses to avoid unnecessary antibiotic use. We evaluated antimicrobial prescriptions following respiratory pathogen testing among outpatients at a large Veterans Administration (VA) medical center. Results of the FilmArray respiratory panel (BioFire, Salt Lake City, UT) from 15 December 2014 to 15 April 2015 were evaluated among 408 outpatients, and patient medical records were reviewed. Differences in antibiotic and oseltamivir prescription rates were analyzed. Among 408 patients tested in outpatient centers (emergency departments, urgent care clinics, and outpatient clinics), 295 (72.3%) were managed as outpatients. Among these 295 outpatients, 105 (35.6%) tested positive for influenza virus, 109 (36.9%) tested positive for a non-influenza virus pathogen, and 81 (27.5%) had no respiratory pathogen detected. Rates of oseltamivir and antibiotic prescriptions were significantly different among the three test groups (chi-squared values of 167.6 [$P < 0.0001$] and 10.48 [$P = 0.005$], respectively), but there was no significant difference in antibiotic prescription rates between the non-influenza virus pathogen group and those who tested negative (chi-square value, 0; $P = 1.0$). Among adult outpatients, testing positive for influenza virus was associated with receiving fewer antibiotic prescriptions, but no such effect was seen for those who tested positive for a non-influenza virus. These data suggest that testing for influenza viruses alone may be sufficient and more cost-effective than multiplex pathogen testing for outpatients.

Respiratory tract infections are the most frequent cause of acute illness in developed countries, with an estimated incidence of 500 million non-influenza virus respiratory infections occurring annually in the United States (1, 2). The vast majority of respiratory infections are caused by viruses, the most common of which are rhinoviruses, coronaviruses, influenza viruses, respiratory syncytial virus (RSV), parainfluenza virus (PIV), human metapneumovirus (hMPV), and adenovirus (3). These infections account for a substantial proportion of outpatient medical visits and are associated with an estimated $17.3 billion in direct annual costs, including more than $1.1 billion spent on an estimated 41 million unnecessary antibiotic prescriptions for viral infections (2).

Diagnosis of respiratory infections is based largely on clinical signs and symptoms, since there are myriad viral etiologies that present with similar clinical features. Although influenza infections may be treated with oseltamivir, no targeted therapies are available for other respiratory viruses. The main challenge for health care providers is to distinguish cases of the uncomplicated "common cold" from influenza, bacterial community-acquired pneumonia, secondary bacterial sinusitis, otitis media, and streptococcal pharyngitis. Therefore, with the exception of testing for influenza viruses, the value of testing for other viruses is predicated on identifying a viral, nonbacterial etiology and avoiding unnecessary antibiotic usage. Techniques that have been used to identify specific viruses include viral culture, direct fluorescent-antibody (DFA) staining, rapid antigen determination tests (RADTs), and pathogen-specific PCR assays. However, each of these methodologies has significant limitations (4): viral culture and DFA staining are labor-intensive and require highly skilled laboratories, and culture results are not available in time to affect patient management. Although they produce results much faster, RADTs are relatively insensitive, and pathogen-specific PCRs can test for only a single viral etiology.

Many of these limitations can be overcome with multiplex respiratory PCR panels, which are increasingly being used in the outpatient setting for patients with upper respiratory infections (URIs). These tests can be simple to perform, provide rapid results, and can assay for multiple organisms from a single sample. While the costs of these tests are significantly higher than those of previously used methods, the added expense may be justified if the results lead to improved patient outcomes and a reduction in overall expenses, especially a reduction in the overuse of antibiotics. Many sites that have implemented multiplexed respiratory virus testing use algorithms for testing inpatients, immunosuppressed individuals, and/or those with severe underlying medical problems. However, most antibiotics for respiratory tract infections are prescribed in the outpatient setting. Therefore, the aim of

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Address correspondence to David R. Peaper, david.peaper@yale.edu.

* Present address: Daniel A. Green, Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, New York, New York, USA.

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this study is to evaluate if the results provided by multiplex PCR testing affect outcome measures among adult outpatients, especially those related to therapeutic management.

MATERIALS AND METHODS

Testing. All multiplex PCR testing was performed on posterior nasopharyngeal swabs by using the FilmArray v1.7 respiratory panel (BioFire, Salt Lake City, UT). Testing was performed on demand by core laboratory personnel at the West Haven Veterans Administration (VA) Hospital (West Haven, CT) 24 hours a day, 7 days a week.

Inclusion criteria. Patients included in the study had specimens obtained by posterior nasopharyngeal swab at a Connecticut VA outpatient location, such as emergency departments (EDs), outpatient clinics, or urgent care clinics. Patients were excluded from the study if their specimens were not obtained from a posterior nasopharyngeal swab (e.g., bronchoalveolar lavage), if they were not seen at a Connecticut VA center (i.e., reference clients), or if testing was performed as an inpatient (hospital floor or intensive care unit [ICU]).

Sample size. Patients who met inclusion criteria were randomly selected to match enrollment in one of three groups: positive for influenza virus, positive for a non-influenza virus pathogen, and negative for all pathogens tested. Sample size calculations were performed to select for enrollment of 100 patients per arm, with the primary goal of detecting a 20% difference between groups using an 80% power calculation.

Chart review and data analysis. A retrospective chart review was performed on 408 outpatients who met inclusion criteria and were enrolled in one of three study groups. Patient demographic information was collected, including age, influenza vaccine status, order location, admission status, presence of underlying lung disease, immunosuppression, clinical syndrome, and testing for other respiratory infectious diseases. Immunosuppression was determined by criteria reported in Infectious Diseases Society of America (IDSA) guidelines for vaccination of immunocompromised hosts (5). Clinical syndrome was recorded based on International Classification of Diseases (ICD-9) codes and a careful review of provider notes. Therapeutic outcomes evaluated were oseltamivir prescription and antibacterial prescription rates. Clinical turnaround time (TAT) was the difference between the time of specimen collection and the time of the final result, and laboratory TAT was the difference between the time of specimen receipt in the laboratory and the time of the final result. All categorical data were analyzed by chi-squared analysis where indicated, and adjusted standardized residuals were calculated to identify significantly different cells. Clinical and laboratory TATs were compared by using a Mann-Whitney U test or Kruskal-Wallis test. A P value of <0.05 was considered significant for primary comparisons. For residual analysis, a P value of <0.01 was considered significant to correct for bias; this corresponds to a z score of 2.58.

Analysis was focused on the 295 patients who were seen in outpatient settings and were not admitted (i.e., continued to be managed as outpatients).

IRB approval. This study was approved by the Institutional Review Board of the West Haven Veterans Administration Hospital.

RESULTS

Demographics of admitted versus not admitted patients. Of the 408 study patients with testing originating in outpatient settings, 113 (27.7%) were admitted to the hospital, while 295 (72.3%) were managed as outpatients. There were significant differences between admitted and nonadmitted patients with respect to age, order location, pathogen detected, underlying lung disease, and clinical syndrome. There were no significant differences in laboratory and clinical TATs between these two groups. Residual analysis indicated that admitted patients were older, more likely to be seen in the ED, and more likely to have no pathogen detected. Among presenting clinical syndromes, admitted patients were more likely to have pneumonia or sepsis/systemic inflammatory response syndrome (SIRS) as visit ICD-9 codes and less likely to have ICD-9 codes associated with upper respiratory tract infection (URTI), cough, bronchitis, sinusitis, or pharyngitis. No information on gender was extracted, but patients were overwhelmingly male (Table 1). Among the 295 patients who were managed as outpatients, only clinical TAT and ICD-9-based clinical syndrome differed significantly between patients seen in the ED and those seen in other outpatient locations (see Table S1 in the supplemental material). When examined in greater detail, the differences in clinical syndrome were due to fewer being patients coded with URTI and related syndromes and more patients being coded with specific viral diagnoses. When admitted patients were examined in detail, there were higher rates of antibiotic prescriptions for patients with suspected infectious etiologies, and the therapeutic agents used were more likely to be broad-spectrum agents (data not shown).

Demographics of nonadmitted patients, grouped by respiratory pathogen PCR results. Among the 408 included patients, 295 (72.3%) received continued management in the outpatient setting. Among these 295 outpatients, 105 (35.6%) tested positive for influenza A virus ($n = 83$; 79.0%) or influenza B virus ($n = 22$; 21.0%), 109 (36.9%) tested positive for a non-influenza virus pathogen, and 81 (27.5%) tested negative for all pathogens (Table 2). Non-influenza virus pathogens that were detected were human rhinovirus/human enterovirus ($n = 33$; 30.3%), respiratory syncytial virus ($n = 25$; 22.9%), human coronavirus ($n = 23$; 21.1%), human metapneumovirus ($n = 13$; 11.9%), parainfluenza virus ($n = 12$; 11.0%), adenovirus ($n = 2$; 1.8%), and *Mycoplasma pneumoniae* ($n = 1$; 0.9%). There were no significant differences in demographic characteristics among the three result groups. Additionally, TATs did not differ among the three groups (Table 2).

Antimicrobial prescription rates among nonadmitted patients. Oseltamivir prescription rates were significantly different among the three groups (chi-squared value of 167.6; $P < 0.001$), with those testing positive for influenza virus having the highest prescription rate (81.0%) (Table 3). Antibiotic prescription rates were also different among the three groups (chi-squared value, 10.48; $P = 0.005$), with those testing positive for influenza virus receiving the fewest prescriptions (29.5%). There was no significant difference in antibiotic prescription rates between individuals who tested positive for a non-influenza virus and those who tested negative (48.6% and 49.3%, respectively, [chi-squared value, 0; $P = 1.0$]). The most commonly used antibiotics among outpatients were azithromycin ($n = 49$; 39.5%), moxifloxacin ($n = 38$; 30.6%), and amoxicillin-clavulanic acid ($n = 20$; 16.1%).

DISCUSSION

In this study, adult outpatients who tested positive for influenza viruses received significantly more oseltamivir prescriptions and significantly fewer antibiotic prescriptions than did those who tested positive for a non-influenza virus pathogen and those who tested negative for all pathogens. However, there was no significant difference in the antibiotic prescription rates for the latter two groups, suggesting that testing results for non-influenza virus respiratory pathogens did not affect the therapeutic management of these patients.

Multiplex PCR testing for respiratory pathogens offers significant advantages over other methods like DFA staining, viral culture, RADTs, and pathogen-specific PCRs. Commercial PCR pan-

TABLE 1 Demographics of included patients[b]

Parameter	Value for group		
	Not admitted	Admitted	Total
Total no. (%) of patients included	295 (100)	113 (100)	408 (100)
No. (%) of patients of age (yr) at testing ($P < 0.0001$)			
<40#	56 (19.0)	3 (2.7)	59 (14.5)
40 to 59#	82 (27.8)	12 (10.6)	94 (23)
60 to 79	131 (44.4)	61 (54.0)	192 (47.1)
≥80#	26 (8.8)	37 (32.7)	63 (15.4)
No. (%) of patients with order location ($P < 0.0001$)			
ED#	166 (56.3)	107 (94.7)	273 (66.9)
Outpatient#	71 (24.1)	4 (3.5)	75 (18.4)
Urgent care#	58 (19.7)	2 (1.8)	60 (14.7)
No. (%) of patients with pathogen type detected ($P < 0.001$)			
Influenza virus	105 (35.6)	29 (25.7)	134 (32.8)
Non-influenza virus pathogen	109 (36.9)	29 (25.7)	138 (33.8)
None#	81 (27.5)	55 (48.7)	136 (33.3)
Mean TAT (SD) (h)			
Clinical (NS)	3.2 (4.5)	2.3 (1.9)	3.0 (4.0)
Intralaboratory (NS)	2.0 (3.0)	1.9 (1.7)	2.0 (2.7)
No. (%) of patients with underlying lung disease ($P < 0.001$)			
Asthma	20 (6.8)	2 (1.8)	22 (5.4)
COPD#	40 (13.6)	29 (25.7)#	69 (16.9)
Other	8 (2.7)	9 (8.0)#	17 (4.2)
None	227 (77.0)	73 (64.6)	300 (73.5)
No. (%) of patients with immunosuppression status ($P = 0.003$)			
No	274 (92.3)	93 (82.3)	367 (90)
Yes	21 (7.7)	20 (17.7)	41 (10)
No. (%) of patients with clinical syndrome[a] ($P < 0.001$)			
Cough/URTI/bronchitis/sinusitis/pharyngitis#	162 (54.9)	13 (11.5)	175 (42.9)
Specific viral pathogen	53 (18.0)	20 (17.7)	73 (17.9)
Nonrespiratory syndrome	44 (14.9)	26 (23.0)	70 (17.2)
Other respiratory syndrome#	12 (4.1)	14 (12.4)	26 (6.4)
Pneumonia#	9 (3.1)	14 (12.4)	23 (5.6)
COPD	12 (4.1)	10 (8.8)	22 (5.4)
Fever/SIRS/sepsis#	3 (1.0)	16 (14.2)	19 (4.7)

[a] If multiple ICD-9 codes were used for a visit, only those most directly related to respiratory virus testing were extracted.
[b] All categorical data were compared with chi-squared tests. TATs were compared via a Mann-Whitney U test. For categories with significant differences, adjusted standardized residuals were calculated. # indicates an absolute value of the standardized adjusted residual of >2.58 for each row. NS, not significant; COPD, chronic obstructive pulmonary disease.

els are highly sensitive, produce rapid results (1 to 2 h), and can detect up to 20 pathogens in a single sample. In a variety of hospital settings, these tests can have a significant impact on infection control, hospital epidemiology, and patient management. Through rapid pathogen identification, patients can be quickly isolated or cohorted upon admission in accordance with hospital infection control practices, thereby mitigating the risk of nosocomial transmission (6). This practice may be especially important in preventing transmission to infants and immunocompromised patients, who have a higher risk of developing serious sequelae from lower respiratory tract infection (7, 8). In addition, identification of certain viral agents such as RSV may inform clinical decision-making and predict the disease course in children with bronchiolitis, as RSV is associated with a longer length of stay and more severe disease, including a higher likelihood of ICU care (9, 10). Similar findings have also been noted for hMPV infections (11–13). Unlike targeted PCR, multiplex testing can also identify patients coinfected with 2 or more viruses, which is associated with higher mortality rates in young children (14), although the clinical significance of coinfection is not fully understood. Identification of the underlying virus may also reduce the need for further diagnostic workup (15).

However, the value of performing multiplex PCR panels for respiratory viruses in adult outpatients is less clear, given that patients are less ill and isolation precautions are not needed. Among outpatients, the rationale for multiplex respiratory virus testing is 2-fold: to identify patients with influenza who will benefit from oseltamivir therapy and to confirm a viral etiology in patients with URI symptoms so as to avoid unnecessary antibiotic use. However, patients in this study who tested positive for a non-

TABLE 2 Demographics of nonadmitted patients, grouped by respiratory pathogen PCR results[a]

Characteristic	Value for group			
	Influenza virus detected	Non-influenza virus pathogen detected	No pathogen detected	Total
Total no. (%) of patients included	105 (100)	109 (100)	81 (100)	295 (100)
No. (%) of patients of age (yr) at testing (NS)				
<40	24 (22.9)	19 (17.4)	13 (16)	56 (19)
40–59	27 (25.7)	29 (26.6)	26 (32.1)	82 (27.8)
60–79	42 (40)	55 (50.5)	34 (42)	131 (44.4)
≥80	12 (11.4)	6 (5.5)	8 (9.9)	26 (8.8)
No. (%) of patients with order location (NS)				
ED	55 (52.4)	66 (60.6)	45 (55.6)	166 (56.3)
Outpatient	29 (27.6)	22 (20.2)	20 (24.7)	71 (24.1)
Treatment room	21 (20)	21 (19.3)	16 (19.8)	58 (19.7)
Mean TAT (h) (SD)				
Clinical (NS)	3.2 (3.4)	3.4 (5.9)	3.1 (3.6)	3.2 (4.5)
Intralaboratory (NS)	2.1 (2.0)	2.2 (4.5)	1.8 (0.7)	2.0 (3.0)
No. (%) of patients with influenza vaccine status (NS)				
Not reported	48 (45.7)	38 (34.9)	29 (35.8)	115 (39)
Yes	57 (54.3)	71 (65.1)	52 (64.2)	180 (61)
No. (%) of patients with underlying lung disease (NS)				
COPD	12[b] (11.4)	12 (11)	16 (19.8)	40 (13.6)
Asthma	8 (7.6)	9 (8.3)	4 (4.9)	21 (7.1)
Other[c]	1 (1)	2 (1.8)	4 (4.9)	7 (2.4)
None	84 (80)	86 (78.9)	57 (70.4)	227 (76.9)
No. (%) of patients with immunosuppression status (NS)				
Yes	7 (6.7)	8 (7.3)	6 (7.4)	21 (7.1)
No	98 (93.3)	101 (92.7)	75 (92.6)	274 (92.9)

[a] Shown are demographics of all patients included for chart review. All categorical data were compared with a chi-squared test. TATs were compared via a Kruskal-Wallis test.
[b] Two patients with both chronic obstructive pulmonary disease and lung cancer.
[c] Other includes lung cancer and interstitial lung disease.

influenza virus pathogen did not receive fewer antibiotic prescriptions than those who tested negative. The FilmArray respiratory panel is one of the first assays to make testing for human rhinovirus/enterovirus (HRV/HEV) and human coronavirus (HCoV) widely available, while assays (including DFA staining, rapid culture, or species-specific PCRs) for hMPV, PIV, RSV, and adenovirus have been available for some time. Interestingly, when rates of antibiotic prescriptions were examined among these groups,

TABLE 3 Antimicrobial prescription rates among nonadmitted patients[a]

Characteristic	No. (%) of patients in group			
	Influenza virus detected	Non-influenza virus pathogen detected	No pathogen detected	Total
Total patients included	105	109	81	295
Antibacterial Rx ($P = 0.005$)				
Yes[b]	31 (29.5)	53 (48.6)[c]	40 (49.3)	124 (42.0)
No	74 (70.5)	56 (51.4)	41 (50.7)	171 (58.0)
Anti-influenza Rx ($P < 0.001$)				
Yes	80 (81.0)	6 (5.5)[e]	2 (2.5)	88 (29.8)
No	25 (19.0)[d]	103 (94.5)	79 (97.5)	207 (70.2)

[a] Shown are data for use of antimicrobials among nonadmitted patients. Rx, prescription.
[b] Includes patients with other infections identified (4 with flu, 2 with non-influenza virus pathogen, and 1 with no pathogen) and includes patients on antibiotics at the time of visit (1 with a non-influenza virus pathogen and 1 with no pathogen detected).
[c] Includes 3 patients given a prescription and told to wait for results and 1 patient with *Mycoplasma pneumoniae* prescribed azithromycin.
[d] Includes 11 patients with symptoms for >48 h; 2 patients were offered a prescription and declined.
[e] Includes 1 patient called to hold oseltamivir (Tamiflu) after RSV result was available.

fewer antibacterials were prescribed for patients with HRV/HEV or HCoV (see Table S2 in the supplemental material), which suggests that providers were less likely to prescribe antibacterials for patients with viruses that typically cause milder symptoms.

Previous studies on the effect of respiratory virus testing on antibiotic usage have produced mixed findings. The detection of a known viral pathogen has been reported to decrease antibiotic usage in children with bronchiolitis seen in the ED or hospital (16–18). However, these data are not reproducible across all studies, and the effects of virus testing on antibiotic use are debatable (19–23). Some studies have shown no difference in antibiotic prescription rates but rather a decrease in the duration of antibiotic use or discontinuation of antibiotics after the result was made available (24, 25). Antibiotic duration could not be evaluated in our study, and this is an important limitation to consider. The conflicting and divergent nature of the evidence to date, however, indicates that virus testing alone is unlikely to alter antibiotic prescription rates and that entrenched provider practices likely play a larger role.

Another potential justification for outpatient multiplex testing is that the results might influence the decision about whether or not to admit a patient to the hospital. In our study, adults who tested negative for all pathogens had a higher rate of admission to the hospital than did those who tested positive for influenza virus or a non-influenza virus pathogen. However, these patients were older and more likely to have more severe illness based upon visit ICD-9 codes; thus, the higher rate of admission is unlikely to be directly attributable to the results of respiratory pathogen testing (Table 1).

The average clinical TAT for all patients in the present study was 3.0 h, with an intralaboratory TAT of 2.0 h. Achieving these TAT targets required substantial laboratory resources, but these times may still be longer than those for some ED or outpatient visits. A review of a random selection of 10% of the total charts revealed that results were available to clinicians before discharge in 47.4% of encounters. Additionally, results were available before 53.4% of anti-influenza virus or antibacterial prescriptions were written. These data present opportunities for laboratory improvement or even revised diagnostic algorithms, especially in outpatient clinics, where visits are typically shorter. In settings where the TAT will likely exceed the office visit time, targeted influenza virus PCR assays should be considered less expensive alternatives to multiplex PCR tests. There are multiple FDA-approved influenza virus A/B assays, some of which also detect RSV and many of which are also Clinical Laboratory Improvements Amendments (CLIA) waived. These assays provide equal or better TATs at a significant fraction of the cost.

Limitations of this study include the study cohort itself, which was comprised largely of older men, the majority of whom received care in the emergency department; these data may not fully represent the larger population of adult outpatients who seek care for URIs in the United States. Indeed, the clinical TAT was faster for patients seen in the ED, and results were more readily available to ED providers. Also, only a single respiratory virus season was evaluated. We did not compare rates of antibiotic prescriptions pre-FilmArray and post-FilmArray, but such an analysis could be skewed by the timing of assay implementation within a given respiratory virus season and also by test volumes. Additionally, we used ICD-9 codes to identify clinical syndromes associated with each visit; while there can be substantial variations in how visits are coded among providers and units, these codes still provide more readily extractable and reproducibly categorized information than do patient care notes. Finally, only 81 patients were enrolled in the group who tested negative for all pathogens, short of the target enrollment of 100 patients based on our power calculations. It is therefore possible that some differences in antibiotic prescription rates might have emerged had the target enrollment been met, but this appears unlikely, as the antibiotic prescription rates for this group and the group who tested positive for non-influenza virus pathogens were nearly identical (49.3% and 48.6%, respectively), and the inclusion of 19 additional patients in the former group would not have led to statistically significant differences, even if they all received antibiotics.

While the detection of known respiratory viral pathogens might be predicted to reduce antibiotic prescription rates, our study did not find such an effect unless patients tested positive for influenza virus. The additional benefit of performing multiplex virus testing instead of targeted influenza virus testing in outpatients is questionable, especially given the higher costs of commercial multiplex tests. Our data argue that targeted influenza virus testing alone may be a more cost-effective approach for adult outpatients with uncomplicated upper respiratory infections or that implementation of multiplex testing must be paired with provider education and antimicrobial stewardship to discourage the use of antibiotics for such patients.

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