The Journal of Infectious Diseases

MAJOR ARTICLE

Multiplex Respiratory Virus Testing for Antimicrobial Stewardship: A Prospective Assessment of Antimicrobial Use and Clinical Outcomes Among Hospitalized Adults

Makeda Semret,[1] Ian Schiller,[2] Barbara Ann Jardin,[2] Charles Frenette,[1] Vivian G. Loo,[1] Jesse Papenburg,[1] Shelly A. McNeil,[4] and Nandini Dendukuri[3]

[1]Division of Infectious diseases and Medical Microbiology, Department of Medicine and Laboratories, [2]Research Institute, and [3]Technology Assessment Unit, McGill University Health Centre, Montreal, Québec, and [4]Canadian Center for Vaccinology, IWK Health Centre and Nova Scotia Health Authority, Dalhousie University, Halifax, Canada

(See the editorial commentary by Branche and Falsey, on pages 923–5.)

Background. Respiratory tract infections are frequent causes of hospitalization and initiation of empirical antimicrobial therapy. Testing for a broad panel of respiratory viruses has been advocated as a useful tool for antibiotic stewardship. We conducted a prospective observational study to assess the impact of rapid viral test results on antimicrobial prescriptions and clinical outcomes among hospitalized adults.

Methods. Eight hundred patients admitted with respiratory symptoms were tested by a 12-virus respiratory panel (RVP) during 3 consecutive winters in Montreal, Canada. The primary outcome measure was change in antimicrobial prescriptions (ie, de-escalation of empirical antimicrobial therapy or commencement of new antimicrobial therapy) after RVP results were available. Clinical outcomes were also assessed.

Results. Influenza virus was identified in 53% of individuals in the study population, and other viruses were identified in 10%. Influenza virus positivity was associated with shorter duration of hospitalization and appropriate antiviral management. Antibiotic management was most significantly correlated with radiographic suspicion of pneumonia and less so with results of the RVP. Positivity for viruses other than influenza virus was not correlated with significantly different outcomes.

Conclusions. Physicians respond to results of testing for influenza virus when managing hospitalized adult patients but respond less to test results for other viruses. These data can inform the design of stewardship interventions and the selection of viral testing panels for hospitalized patients.

Keywords. antimicrobial stewardship; respiratory viruses; adult; respiratory virus testing.

Acute respiratory tract infections are common causes of infection-related deaths worldwide. Differentiating between bacterial and viral infections can be clinically challenging, frequently leading to empirical antibacterial therapy, which, in turn, contributes to the burden of antimicrobial resistance [1–3].

In recent antimicrobial stewardship implementation guidelines, rapid testing for broad panels of respiratory viruses was advocated as an important intervention to reduce the use of inappropriate antibiotics for respiratory tract infections (weak recommendation/poor quality evidence) [4]. Nucleic acid amplification–based tests are now the gold standard for laboratory confirmation of respiratory viruses [5, 6]; however, they can be costly, especially when targeting a broad array of viruses. In the absence of solid outcome studies specifically assessing their impact on antimicrobial use and hospital resource utilization, institutions face difficult decisions on the choice of tests and the patients most likely to benefit from testing [7]. Studies conducted among pediatric populations have shown that rapid viral testing generally contributes to reducing antibiotic use [8–10], but those among adult patients have yielded conflicting results. Small reductions in antibiotic use, shorter durations of hospitalization, and lower overall costs were noted in some studies when test results were communicated to physicians rapidly [11–14]. However, these were limited by small sample sizes, by comparisons only to historical controls, or by the fact that they only included outpatients—making it difficult to extrapolate their results to acute care hospital settings.

We introduced a laboratory-developed, real-time polymerase chain reaction–based 12–respiratory virus panel (RVP) in our institution in 2009. The RVP had an overall positivity rate (calculated using data from all seasons and for all patients) of around 30% and turnaround times of 6–24 hours and was quickly adopted by clinicians as a useful tool for analyzing patients presenting with acute respiratory syndromes. The objective of this study was to prospectively evaluate whether rapid viral test results lead to changes in antimicrobial prescriptions among adults hospitalized with respiratory

Received 4 April 2017; editorial decision 18 May 2017; accepted 11 June 2017; published online June 19, 2017.

Correspondence: M. Semret, MD, FRCP(C), 100 Decarie Boulevard, Glen Site Bloc E, E05.1616, Montreal, Quebec, Canada H4A3J1 (makeda.semret@mcgill.ca).

The Journal of Infectious Diseases® 2017;216:936–44

© The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/infdis/jix288

tract infections and whether these results can help predict important clinical outcomes. Data from this study will better inform the role of respiratory virus testing within antibiotic stewardship programs.

METHODS

Study Setting and Ethical Approval

The McGill University Health Centre (MUHC) is an 850-bed tertiary care center in downtown Montreal, Canada, with 2 hospital campuses for adult patients. Patients presenting with respiratory symptoms are tested by RVP at the discretion of the treating teams. Staff are reminded every winter season (via memos and posted notices) of the importance of respiratory virus testing, particularly for patients requiring admission for which appropriate infection control measures need to be implemented.

For this study, we performed secondary analyses of data collected in the context of surveillance for serious influenza illness and vaccine effectiveness, sponsored by the Serious Outcomes Surveillance Network of the Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network [15], and received ethics approval by the institutional review board of the MUHC.

Data Collection

We prospectively identified potential study participants from the laboratory logs of RVP testing during 3 consecutive winters (November–April 2012–2013, 2013–2014, and 2014–2015). After cross-referencing data to the hospital information system, we screened RVP-tested patients who were hospitalized (for ≥24 hours), for potential enrollment. Eligibility criteria included acute respiratory tract infection (ie, pneumonia and influenza-like illness), exacerbation of chronic obstructive pulmonary disease (COPD) or asthma, unexplained sepsis, and influenza-like symptoms (eg, fever, dyspnea, cough, sore throat, and myalgia). Subjects were excluded if they were tested for respiratory viruses >7 days after onset of symptoms (since detection of viral nucleic acids in these cases might not be correlated with active infection), if infection was considered acquired in hospital, or if their reason for admission was clearly unrelated to a respiratory tract infection.

Trained clinical research monitors extracted the following data from medical records on all enrolled patients: age, sex, comorbidities, frailty scores for patients aged >65 years (scores were defined on a scale of 1 to 9, with 1 denoting very fit and 9 denoting terminally ill [16]), radiographic suspicion (by any physician) of pneumonia at the time of admission, complications (eg, thromboembolism and *Clostridium difficile* infection) during hospitalization, and hospitalization details, including intensive care unit (ICU) admission, antibiotic and antiviral prescription data, duration of hospitalization, and death. The study monitors sought informed consent to interview patients for detailed vaccine and healthcare utilization information in the context of the vaccine effectiveness study. Subjects who did not provide consent were excluded from the vaccine effectiveness analysis but not from the current study because only deidentified clinical data obtained from chart reviews were analyzed.

The principal investigator (M. S.) reviewed all data and an external auditor monitored data quality yearly.

RVP

Nasopharyngeal swab specimens were collected from patients by treating teams upon the orders of the physician, placed in a universal transport medium, and sent to the laboratory the same day. The testing panel targeted influenza A and B viruses, respiratory syncytial virus (RSV) A and B, rhinovirus/enterovirus, parainfluenza virus 1–3, adenovirus, human metapneumovirus, and coronavirus OC43 and 229E. The RVP assay developed at the MUHC was validated as having lower limits of detection for all viruses, compared with those for direct fluorescent antibody and culture [14].

RVP testing was done 3–4 times per day on weekdays (early morning, afternoon, evening, and overnight runs) and 2–3 times per day on weekends, depending on the volume of specimens. The minimal analytical testing time was 4.5 hours, and turnaround times ranged from 6 to 24 hours (median turnaround time from specimen collection to final verification was 8 hours 51 minutes for the hospital in which the laboratory is situated and 15 hours 4 minutes for the second hospital, situated 2.5-km away). Results of RVP were faxed to the ward and were also immediately available electronically on the hospital laboratory information system; additionally, to avoid delays in management, treating teams were notified by telephone of all positive test results labeled as "preliminary," even before the final report was issued.

Outcome Measures

We analyzed antibiotics prescribed for presumed respiratory tract infection or unexplained sepsis (ceftriaxone, doxycycline, azithromycin, piperacillin-tazobactam, imipenem, meropenem, intravenous vancomycin, moxifloxacin, and levofloxacin) as per our institution's guidelines for empirical therapy and did not include antibiotics prescribed for other infections (eg, cefazolin and oral vancomycin). The only antiviral used in our institution for treatment of influenza was oseltamivir.

Our main objective was to evaluate whether rapid availability of RVP results had an impact on antimicrobial use in hospital; specifically, we evaluated whether knowledge of the RVP result led to a change in antimicrobial prescription. To define a change in treatment, we first distinguished between patients who were treated before testing and those who were not. Because it was not possible to determine precisely when the treating physician became aware of the test result and on the basis of a turnaround time of <24 hours, we made 2 assumptions. First, antimicrobials prescribed on or before the date

of test collection (day 0) were started before testing. Among these, change was measured in terms of discontinuation of treatment with the antimicrobial on day 1 or 2 after testing (eg, discontinuation of antibiotics if the RVP detected a virus). Second, among patients who were not treated before testing, change was measured in terms of commencing antimicrobial treatment on day 1 or 2 after testing (eg, commencing antiviral if the RVP detected influenza virus). We hypothesized that a positive test result for influenza virus would be associated with the continuation or commencement of antiviral treatment and that a detection of any virus by RVP would result in a greater likelihood of discontinuation of antibiotics, particularly in patients for whom there was no radiographic suspicion of pneumonia.

Statistical Analysis

We classified patients according to their RVP findings: influenza virus positive, positive for viruses other than influenza virus (hereafter, "other virus positive"), and virus negative. Patients who tested positive for influenza virus and another virus were analyzed in the influenza virus–positive group. We compared clinical characteristics of the patients by calculating differences in means (for continuous characteristics) or proportions (for categorical characteristics) with associated 95% confidence intervals (CIs). For differences in proportions, we calculated a confidence interval by using the Wilson method.

To study the impact of the RVP finding on the outcome measures, we stratified patients by whether they began treatment before testing and by (suspected) pneumonia status. Among patients who began treatment before testing, we calculated the percentage of patients who discontinued antimicrobial treatment for each of the 3 categories defined by the RVP result. Likewise, for each of the 3 categories of findings yielded by the RVP, we calculated the percentage of patients who commenced antimicrobial treatment after testing. Results for antiviral and antibiotic treatments were analyzed separately.

To adjust for confounding variables, we fit Cox proportional hazard models of the main outcome measures that included RVP findings, age, Charlson index (a comorbidity index based on the number of preexisting chronic conditions present on admission and validated to predict mortality in longitudinal studies [17]), and suspicion of pneumonia as independent variables. Patients whose antimicrobial treatment was discontinued because of death or hospital discharge were treated as censored. Patients who began treatment before testing and had received antivirals for 3 days on the date a specimen was collected for analysis by the RVP (therefore would have completed 5 days of treatment within 2 days of testing) were dropped from these models.

All analyses were performed using SAS, version 9.3 (SAS Institute).

RESULTS

Study Population

A total of 1093 adult patients (tested by RVP during the study period) were screened for enrollment; of these, 800 were hospitalized and met eligibility criteria and, therefore, were included for detailed analysis (Figure 1).

Over the 3 winters, 425 study patients (53%) had influenza virus–positive results (342 tested positive for influenza A virus, and 83 tested positive for influenza B virus), and 81 (10%) had other virus–positive results. The viruses other than influenza virus that were detected most frequently were adenovirus and RSV (3.6% and 3%, respectively) (Table 1). Two or more viruses were detected in 25 patients (3%).

The 3 groups of patients (influenza virus positive, other virus positive, and virus negative) were comparable in terms of sex distribution, age, and Charlson index (Table 2). Influenza virus–positive patients were frailer than other virus–positive patients (difference, 1.4 [95% CI, .8–1.9]) and virus-negative patients (difference, 1 [95% CI, .6–1.3]), but their duration of hospitalization was lower than for the other 2 groups (difference, –2.4 [95% CI, –4.71 to –.03]; Supplementary Table 2).

A total of 322 patients (40%) had radiographic suspicion of pneumonia at admission. A suspicion of pneumonia was least

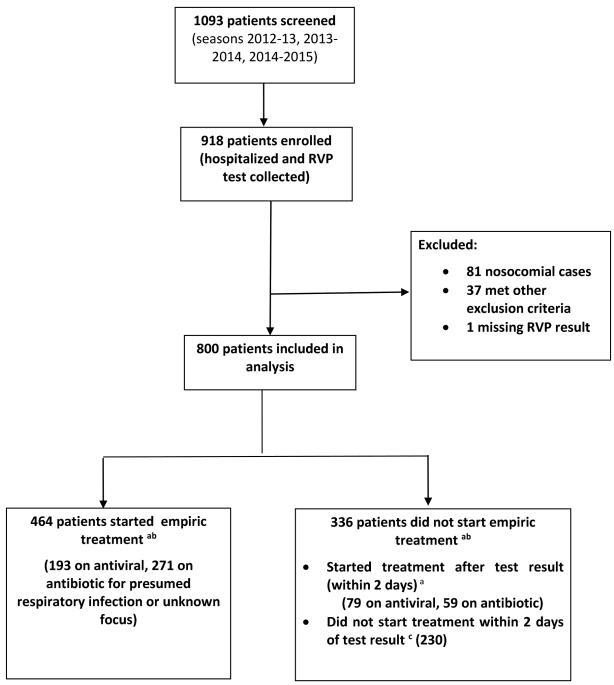

Figure 1. Flowchart describing selection of patients for analysis.[a]Treatment with antivirals (oseltamivir) and/or antibiotics for a respiratory tract infection or unexplained sepsis. [b]Patients who initiated treatment prior to testing and were receiving treatment on the day of specimen collection for respiratory virus panel (RVP) testing. [c]Patients who were treated after RVP findings were available (all started treatment ≥1 day after specimen collection for RVP testing), patients who were not treated, patients who started and ended treatment prior to testing, and patients who received an antibiotic for a nonrespiratory illness.

Table 1. Respiratory Virus Panel Findings

Virus	Positive Test Results, Patients, No. (%)
Influenza A and B virus	425 (53)
RSV A and B	24 (3)
Parainfluenza virus 1–3	4 (0.5)
Rhinovirus/enterovirus	6 (0.8)
Adenovirus	29 (3.6)
CoV OC43 and 229E	11 (1.4)
Human metapneumovirus	13 (1.6)

Abbreviations: CoV, coronavirus; RSV, respiratory syncytial virus.

common among influenza virus–positive patients, compared with other virus–positive patients (difference, 16.1 [95% CI, 4–28]) and virus-negative patients (difference, 15.2 [95% CI, 8–22]). The proportion of patients admitted to the ICU was not significantly different between the 3 groups; however, the need for supplemental oxygen was more common in the other virus–positive group, compared with the influenza virus–positive group (difference, 16.7 [95% CI, 4–27]) and the virus-negative group (difference, 13.1 [95% CI, 1–24]). Of the 3 deaths in this group, 1 patient tested positive for RSV, and 2 tested positive for rhinovirus.

Patients Treated Before Versus After Testing

A total of 464 patients (58%) initiated antibiotics and/or antivirals before testing (Table 3). A suspicion of pneumonia was more common in this group, compared with those treated after testing (difference, 25 [95% CI, 19–32]; Supplementary Table 3), but clinical outcomes (death, ICU admission, and complications) were similar in frequency.

Change in Antimicrobials After Availability of RVP Findings

Among influenza positive patients without radiographic suspicion of pneumonia, oseltamivir was continued in 79% (Table 4). After censoring influenza virus–positive patients who died, were discharged, or had completed 5 days of oseltamivir within 2 days of testing, oseltamivir was discontinued in 15 (6 with and 9 without a suspicion of pneumonia); renal

Table 2. Demographic and Clinical Characteristics of Study Population, by Respiratory Virus Panel (RVP) Results

Variable	Overall (n = 800)	Influenza Virus Positive (n = 425)	Other Virus Positive (n = 69)	Virus Negative (n = 306)
Age, y				
Mean ± SD	70.1 ± 18.0	71.2 ± 18.2	67.6 ± 15.5	69.2 ± 18.3
Median	73.0	76.0	67.0	72.0
Charlson index				
Mean ± SD	2.9 ± 2.5	2.7 ± 2.4	3.0 ± 2.5	3.2 ± 2.7
Median	2.0	2.0	2.0	2.0
Frailty scale				
Mean ± SD	5.15 ± 1.9	5.6 ± 2.0	4.2 ± 1.6	4.6 ± 1.8
Median	5.0	6.0	4.0	5.0
Length of stay, d				
Mean ± SD	13.4 ± 16.4	12.4 ± 15.6	13.8 ± 21.4	14.8 ± 16.1
Median	8.0	7.0	7.0	10.0
Female sex	427 (53.4)	225 (52.9)	36 (52.2)	166 (54.3)
Admitted to ICU	95 (11.9)	53 (12.5)	9 (13.0)	33 (10.8)
Received mechanical ventilation	66 (8.3)	38 (8.9)	4 (5.8)	24 (7.8)
Received BiPAP therapy	54 (6.8)	34 (8.0)	7 (10.1)	13 (4.3)
Received supplemental O_2 therapy	480 (60.0)	243 (57.2)	51 (73.9)	186 (60.8)
Radiographic suspicion of pneumonia				
Yes	322 (40.3)	141 (33.2)	34 (49.3)	147 (48.4)
No	459 (57.4)	270 (63.5)	33 (47.8)	156 (51.3)
Unknown	19 (2.4)	14 (3.3)	2 (2.9)	3 (1.0)
Death				
Overall	64 (8.0)	39 (9.2)	3 (4.4)	22 (7.2)
Unrelated to infection	22 (34.4)	5 (12.8)	0 (0.0)	17 (77.3)
Directly related to infection	25 (39.1)	23 (59.0)	1 (33.3)	1 (4.6)
Indirectly related to infection	16 (25.0)	11 (28.2)	1 (33.3)	4 (18.2)
Missing cause	1 (0.2)	0 (0.0)	1 (33.3)	0
Complication				
Yes	324 (40.5)	172 (40.5)	22 (31.9)	130 (42.5)
No	448 (56.0)	235 (55.3)	44 (63.8)	169 (55.2)
Unknown	28 (3.5)	18 (4.2)	3 (4.4)	7 (2.3)

Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: BiPAP, bilevel positive airway pressure; ICU, intensive care unit.

Table 3. Characteristics of Empirically Treated Versus Non–Empirically Treated Patients

Variable	Treated Empirically (n = 464)	Not Treated Empirically (n = 336)
Age, y		
Mean ± SD	71.1 ± 17.1	68.7 ± 19.3
Median	75.0	72.0
Charlson index		
Mean ± SD	2.8 ± 2.4	3.1 ± 2.7
Median	2.0	2.0
Frailty scale		
Mean ± SD	5.1 ± 2.0	5.1 ± 1.7
Median	5.0	5.0
Length of stay, d		
Mean ± SD	12.7 ± 15.0	14.3 ± 18.2
Median	8.0	8.0
Female sex	246 (53.0)	181 (53.9)
Admitted to ICU	63 (13.6)	32 (9.5)
Received mechanical ventilation	44 (9.5)	22 (6.6)
Received supplemental O_2 therapy	309 (66.6)	171 (50.9)
Radiographic suspicion of pneumonia		
Yes	236 (50.9)	86 (25.6)
No	222 (47.8)	237 (70.5)
Unknown or missing data	6 (1.3)	13 (3.9)
Death		
Unrelated to infection	40 (8.6)	24 (7.1)
Directly related to infection	8 (20.0)	14 (58.3)
Indirectly related to infection	21 (52.5)	4 (16.7)
Missing cause	10 (25.0)	6 (25.0)
Overall	1 (0.2)	0 (0.0)
Complication		
Yes	195 (42.0)	129 (38.4)
No	253 (54.5)	195 (58.0)
Unknown	16 (3.5)	12 (3.6)
RVP finding		
Influenza virus positive	266 (57.3)	159 (47.3)
Other virus positive	33 (7.1)	36 (10.7)
Virus negative	165 (35.6)	141 (42.0)

Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: ICU, intensive care unit; RVP, respiratory virus panel.

Table 4. Change in Management of Antivirals and Antibiotics After Respiratory Virus Panel (RVP) Testing Among Patients Treated Empirically (Before Testing), by RVP Result

Treatment, Pneumonia Suspicion	Influenza Virus Positive	Other Virus Positive	Virus Negative
Antivirals			
Suspicion			
Patients	47[a]	4	18
Antiviral continued[b]	37 (79)	0 (0)	1 (6)
No suspicion			
Patients	100[a]	5	12
Antiviral continued[c]	81 (81)	1 (20)	6 (50)
Antibiotics			
Suspicion			
Patients[d]	57	15	90
Antibiotic continued[e]	35 (61)	12 (80)	63 (70)
No suspicion			
Patients[d]	53	7	42
Antibiotic continued[f]	21 (40)	1 (14)	26 (62)

Data are no. or no. (%) of patients.

[a]Excludes 3 patients because of unknown pneumonia status.

[b]Among patients for whom antivirals were discontinued, 5 (4 influenza virus positive and 1 virus negative) either died, were discharged from hospital, or had completed 5 days of oseltamivir therapy within 2 days of testing.

[c]Among patients for whom antivirals were discontinued, 10 (all influenza virus positive) either died, were discharged from hospital, or had completed 5 days of oseltamivir therapy within 2 days of testing.

[d]One influenza virus–positive patient and 1 virus-negative patient are excluded because of unknown pneumonia status.

[e]Among patients for whom antibiotics were discontinued, 6 (1 influenza virus positive and 5 virus negative) either died or were discharged from hospital within 2 days of testing.

[f]Among patients for whom antibiotics were discontinued, 10 (7 influenza virus positive, 2 other virus positive, and 1 virus negative) either died or were discharged from hospital within 2 days of testing.

failure was cited as the reason for discontinuation in 7 cases. Univariate regression analysis confirmed that discontinuing oseltamivir after availability of RVP findings was significantly less likely in the influenza virus–positive group as compared to the influenza virus–negative group (odds ratio [OR], 0.12 [95% CI, .06–.22]; Table 6). Among patients who initiated antibiotics before testing and had laboratory confirmation of influenza virus infection, antibiotics were discontinued in 37% of those with and 47% of those without a suspicion of pneumonia (Table 4). Antibiotic discontinuation was significant in the univariate analysis (OR, 1.59 [95% CI, 1.03–2.44]; Table 6). After laboratory confirmation of another virus, antibiotics were discontinued in 20% of patients with and 57% of those without a suspicion of pneumonia.

If treatment was not started before testing, an influenza virus–positive result led to starting oseltamivir in 24% of patients with and 44% of those without a suspicion of pneumonia. Among patients with a suspicion of pneumonia, antibiotics were prescribed to 22% in the influenza virus–positive group, 38% in the other virus–positive group, and 23% in the virus-negative group (Table 5).

Impact of RVP Findings on Clinical Management

Results of multivariate Cox proportional hazards models appear in Table 6. An influenza virus–positive test result was very significantly correlated with oseltamivir use: influenza virus–positive patients who were not receiving antivirals before testing were 9 times as likely (OR, 9.38 [95% CI, 4.48–19.61]) to initiate oseltamivir after laboratory confirmation of influenza virus infection, compared with virus-negative patients. Similarly, among patients who were receiving antivirals before testing, influenza virus–positive patients were 0.1 times as likely to have their antivirals discontinued (OR, 0.1 (95% CI, .05–.20]), compared with virus-negative patients.

We noted a trend to discontinue antibiotics after an influenza virus–positive test result in the univariate analysis, but

Table 5. Initiation of Treatment for a Respiratory Illness or Unknown Diagnosis ≤2 Days After Respiratory Virus Panel (RVP) Testing Among Patients Who Were Not Treated Empirically, by RVP Finding

Pneumonia Suspicion, Treatment	Influenza Virus Positive	Other virus positive	Virus Negative
Suspicion			
Patients	35	15	36
Antiviral started ≤48 h after testing[a]	10 (24)	0 (0)	4 (9)
Antibiotic started ≤48 h after testing[b,c]	9 (22)	6 (38)	10[i] (23)
No suspicion			
Patients	115	20	102
Antiviral started ≤48 h after testing[a]	54 (44)	1 (5)	4 (4)
Antibiotic started ≤48 h after testing[c]	18 (15)	3 (14)	11(10)

Data are no. or no. (%) of patients. Denominators exclude 13 patients because of missing pneumonia status.

[a]Excludes 6 patients because of unknown pneumonia status.

[b]Excludes 2 patients because of unknown pneumonia status.

[c]Data are for patients receiving antibiotics for a respiratory-related illness or an unclear diagnosis only.

this was no longer significant after adjustment for potential confounders (OR, 1.38 [95% CI, .89–2.16]). Only a radiographic suspicion of pneumonia on admission was correlated with continuation of antibiotics treatment among patients treated before the availability of test results or with commencement of antibiotics among those treated after the availability of test results.

DISCUSSION

Our goal was to assess whether rapid testing for a broad panel of viruses would be a useful tool for antimicrobial stewardship efforts, particularly in the early management of adults requiring hospitalization, and whether viral detection leads to different clinical outcomes. We hypothesized that knowledge of influenza virus positivity would lead to institution of appropriate antivirals and de-escalation of antibiotics and that positivity for other viruses would lead to cessation of oseltamivir and antibiotics.

Our patient population consisted of moderately vulnerable or frail, mostly elderly patients already at significant risk of death within 1 year (based on Charlson indexes corresponded to predicted 1-year mortality rates of 26%–52% [17]), the majority of whom started antimicrobial therapy for presumed respiratory tract infection upon presentation, before RVP results were available. Over 3 consecutive winters, influenza virus was detected in 53% of study patients; this frequency was significantly higher than the overall rate of influenza virus detection in the community. Based on results from our laboratory, influenza virus was detected in 9%–16% and other respiratory viruses in 21%–39% of all nasopharyngeal specimens (including those from children and ambulatory patients) during the study period, suggesting that influenza virus was a major cause of admission for respiratory tract infections among adults in our institution. One study from a setting similar to ours, in Quebec, Canada, reported higher relative contributions of viruses other than influenza virus among their patients, but these contributions were variable from year to year, accounting

Table 6. Findings of Univariate and Multivariate Logistic Regression

	Empirically Treated (Before Testing)		Not Empirically Treated	
Variable	Antiviral Discontinued After Testing	Antibiotic Discontinued After Testing	Antiviral Started After Testing	Antibiotic Started After Testing
Univariate				
Age	1.01 (.99–1.02)	1.02 (1.00–1.03)	1.00 (.99–1.01)	1.00 (.99–1.01)
Charlson index	1.07 (.95–1.19)	1.00 (.92–1.09)	0.96 (.88–1.05)	1.00 (.91–1.10)
Radiographic suspicion of pneumonia	2.61 (1.44–4.72)	0.61 (.41–.93)	0.64 (.36–1.15)	2.20 (1.30–3.72)
Influenza virus test result				
Negative	Reference	Reference	Reference	Reference
Positive	0.12 (.06–.22)	1.59 (1.03–2.44)	8.38 (4.03–17.44)	1.19 (.67–2.09)
Other virus positive	1.46 (.65–3.31)	1.18 (.53–2.65)	0.99 (.21–4.66)	1.92 (.90–4.07)
Multivariate				
Age	1.00 (.98–1.02)	1.02 (1.00–1.03)	1.00 (.98–1.01)	1.00 (.98–1.01)
Charlson index	1.05 (.93–1.18)	1.01 (.92–1.10)	0.98 (.90–1.07)	0.98 (.89–1.09)
Radiographic suspicion of pneumonia	1.99 (1.05–3.75)	0.59 (.39–.90)	0.68 (.38–1.22)	2.30 (1.35–3.90)
RVP finding				
Virus negative	Reference	Reference	Reference	Reference
Influenza virus positive	0.10 (.05–.20)	1.38 (.89–2.16)	9.38 (4.48–19.61)	1.21 (.68–2.15)
Other virus positive	1.95 (.82–4.65)	1.33 (.59–2.98)	0.52 (.07–4.18)	1.60 (.73–3.51)

Data are odds ratios (95% confidence intervals).

Abbreviation: RVP, respiratory virus panel.

for 25% of infections one year and only 16% the next [18]. In our study, nearly half of other virus–positive patients had radiographic suspicion of lower respiratory tract infections, and the majority required supplemental oxygen therapy, suggesting that these viruses were likely implicated in lower respiratory tract infections or COPD/asthma exacerbations. However, positivity for viruses other than influenza virus did not appear to be an important determinant of significant clinical outcomes, such as duration of hospitalization.

Observational data suggest that early initiation of oseltamivir is associated with improved overall outcomes and fewer influenza-related complications in hospitalized patients [19–21]. Our data confirm that clinicians use rapidly available results of influenza virus testing to guide appropriate appropriate antiviral therapy. If the RVP detected influenza virus, physicians were 10 times as likely to continue oseltamivir that was started empirically or 9 times as likely to start oseltamivir de novo than if the RVP had negative results. However, among patients who did not start therapy before testing, fewer than half were prescribed oseltamivir after confirmation of influenza virus, presumably because physicians deemed the delay was too long for the patients' benefit. The association between RVP positivity and de-escalation of antibiotics was of smaller magnitude: patients started on antibiotics before testing and were subsequently found to test positive for influenza virus were roughly 1.4 times as likely to have their antibiotics discontinued as compared to those who tested negative, but the association was not statistically significant after adjustment for potential confounders, such as age and comorbidity. The variable most significantly correlated with continuation of antibiotics started before testing was radiographic suspicion of pneumonia. Despite the well-established fact that chest radiography findings do not reliably differentiate between bacterial and viral lower respiratory tract infections, nor even between infectious and noninfectious illnesses, clinicians appear to be influenced more by radiographic findings than by viral test results when making antibiotic management decisions, probably because of concerns about bacterial coinfection. This was not only true for patients who started empirical therapy and presumably had more-severe illness at presentation—patients who were not treated before testing and were subsequently found to have a positive RVP result were just as likely as those testing negative for all viruses to start antibiotics within the first 2 days.

In agreement with our data, 2 retrospective analyses from Canada showed that influenza virus positivity led to increased use of antivirals, but test results did not correlate with overall antibiotic use [14, 22]. Also, 2 European studies found no association between test results and antibiotic use or overall costs [23, 24].

These findings have important implications for antimicrobial stewardship programs in adult acute care hospitals: merely providing access to rapid multiplex testing may not be sufficient to reduce antibiotic use, even during winter, when influenza virus and other viral pathogens are frequent. The ability to interpret positive results in the context of clinical illness and the legitimate concerns of bacterial coinfections need to be addressed. Some have proposed the use of procalcitonin-guided algorithms to predict bacterial infection [25–27], but this approach has yet to gain wide acceptance. A recent randomized controlled trial evaluating an algorithm combining procalcitonin measurement with viral testing noted a trend toward decreased duration of antibiotics in the subgroup with the lowest risk for bacterial infection, suggesting that physicians can respond to a combination of viral and biomarker data. However, that study excluded patients with radiographic suspicion of pneumonia, making it difficult to extrapolate the conclusions to other populations [28].

Our data also question the pertinence of panels targeting a broad array of respiratory viruses for hospitalized patients. While the ability to detect a wide range of viruses might be critical for immunocompromised patients, testing only for viruses commonly linked to lower respiratory tract infections (ie, influenza virus, RSV, and possibly adenovirus and metapneumovirus) might be more cost-effective and sufficient for the purposes of antimicrobial stewardship. Viruses typically associated with upper tract infections (eg, rhinovirus/enterovirus and parainfluenza virus) are indeed common in children and in ambulatory adults, and their detection is potentially useful for determining a viral etiology for asthma/COPD exacerbations. However, they are less frequently implicated in hospitalized adults, and physicians have legitimate difficulties interpreting the significance of their detection in clinical specimens.

Our study has a few limitations. First, we used a prospective but nonrandomized design, as this was our only option for comparing the impact of a change in management following availability of test results to a situation where no test was available. Such designs have been shown to be valid for diagnostic test evaluation; we used carefully defined selection criteria and adjusted for confounding variables to limit biases. Second, we restricted our analysis to antimicrobial use in the first 2 days after testing, because our objective was to assess immediate changes attributable to test result. It is possible that antimicrobial use over the course of hospitalization would have been lower among patients with positive RVP findings, but it is equally or more likely that antibiotics would have been given for additional indications, such as nosocomial infections. Third, we did not analyze microbiologic data, so it is possible that some of the cases were being treated for confirmed bacterial infection. However, results of microbiological testing (ie, cultures of blood and sputum specimens) are generally not finalized before several days, so it is unlikely that these factored much into the clinicians' early antimicrobial management decisions. Finally, the sample size of other virus–positive patients in our population was relatively small, making it difficult to draw definite

conclusions about specific patient outcomes for each virus. Although we prospectively tried to identify all patients tested with the RVP, patients with influenza may have been more likely to be included. Even if such a selection bias occurred, the effect of influenza virus positivity on antibiotic management was small, making it unlikely that such a bias impacted our conclusions significantly.

In conclusion, multiplex testing has enabled a better understanding of the burden of viruses in respiratory tract infections among adults. Influenza virus positivity is associated with shorter durations of hospitalization and leads to appropriate management decisions, including instituting antivirals and a trend toward antibiotic de-escalation. However, rapid testing for a broad array of viruses does not appear, by itself, to be useful for stewardship interventions among hospitalized adult patients, unless it can be combined with additional means of ruling out bacterial coinfections.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank Catherine Nesbitt and Donna McKinnon for their help with data collection and data management.

Financial support. This work was supported by the Serious Outcomes Surveillance Network funded by the Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network and by the Fonds Québec Recherche en Santé (Chercheur Boursier senior award to N. D.).

Potential conflicts of interest. M. S. and S. A. M. have received funding from Glaxo-Smith-Kline Biologicals and Pfizer through investigator-initiated collaborative research agreements. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Musher DM, Roig IL, Cazares G, Stager CE, Logan N, Safar H. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. J Infect **2013**; 67:11–8.
2. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med **2014**; 371:1619–28.
3. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA **1997**; 278:1440–5.
4. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clin Infect Dis **2016**; 62:e51–77.
5. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev **2008**; 21:716–47.
6. Ginocchio CC, McAdam AJ. Current best practices for respiratory virus testing. J Clin Microbiol **2011**; 49(9 Suppl): S44–S8.
7. Schreckenberger PC, McAdam AJ. Point-counterpoint: large multiplex PCR panels should be first-line tests for detection of respiratory and intestinal pathogens. J Clin Microbiol **2015**; 53:3110–5.
8. Rogers BB, Shankar P, Jerris RC, et al. Impact of a rapid respiratory panel test on patient outcomes. Arch Pathol Lab Med **2015**; 139:636–41.
9. Schulert GS, Lu Z, Wingo T, Tang YW, Saville BR, Hain PD. Role of a respiratory viral panel in the clinical management of pediatric inpatients. Pediatr Infect Dis J **2013**; 32:467–72.
10. Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. Pediatrics **2003**; 112:363–7.
11. Brittain-Long R, Westin J, Olofsson S, Lindh M, Andersson LM. Access to a polymerase chain reaction assay method targeting 13 respiratory viruses can reduce antibiotics: a randomised, controlled trial. BMC Med **2011**; 9:44.
12. Afzal Z, Minard CG, Stager CE, Yu VL, Musher DM. Clinical diagnosis, viral PCR, and antibiotic utilization in community-acquired pneumonia. Am J Ther **2013**; 23:e766–72.
13. Barenfanger J, Drake C, Leon N, Mueller T, Troutt T. Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. J Clin Microbiol **2000**; 38:2824–8.
14. Yee C, Suarthana E, Dendukuri N, Nicolau I, Semret M, Frenette C. Evaluating the impact of the multiplex respiratory virus panel polymerase chain reaction test on the clinical management of suspected respiratory viral infections in adult patients in a hospital setting. Am J Infect Control **2016**; 44:1396–8.
15. McNeil S, Shinde V, Andrew M, et al. Interim estimates of 2013/14 influenza clinical severity and vaccine effectiveness in the prevention of laboratory-confirmed influenza-related hospitalisation, Canada, February 2014. Euro Surveill **2014**; 19. pii: 20729.
16. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ **2005**; 173:489–95.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in

longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
18. Gilca R, Amini R, Douville-Fradet M, et al. Other respiratory viruses are important contributors to adult respiratory hospitalizations and mortality even during peak weeks of the influenza season. Open Forum Infect Dis **2014**; 1: ofu086.
19. McGeer A, Green KA, Plevneshi A, et al.; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis **2007**; 45:1568–75.
20. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet **2015**; 385:1729–37.
21. Muthuri SG, Venkatesan S, Myles PR, et al.; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med **2014**; 2:395–404.
22. Mulpuru S, Aaron SD, Ronksley PE, Lawrence N, Forster AJ. Hospital resource utilization and patient outcomes associated with respiratory viral testing in hospitalized patients. Emerg Infect Dis **2015**; 21: 1366–71.
23. Hernes SS, Hagen E, Quarsten H, Bjorvatn B, Bakke PS. No impact of early real-time PCR screening for respiratory viruses on length of stay and use of antibiotics in elderly patients hospitalized with symptoms of a respiratory tract infection in a single center in Norway. Eur J Clin Microbiol Infect Dis **2014**; 33:359–64.
24. Oosterheert JJ, van Loon AM, Schuurman R, et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. Clin Infect Dis **2005**; 41:1438–44.
25. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med **2011**; 9:107.
26. Bafadhel M, Clark TW, Reid C, et al. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. Chest **2011**; 139:1410–8.
27. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med **2008**; 36:941–52.
28. Branche AR, Walsh EE, Vargas R, et al. Serum procalcitonin measurement and viral testing to guide antibiotic use for respiratory infections in hospitalized adults: a randomized controlled trial. J Infect Dis **2015**; 212:1692–700.
29. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med **2005**; 352:1749–59.
30. Lee N, Lui GC, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis **2013**; 57:1069–77.
31. Lord SJ, Irwig L, Bossuyt PMM. Using the principles of randomized controlled trial design to guide test evaluation. Rockville, MD: Agency for Healthcare Research and Quality, **2009**.