Effect of Rapid Respiratory Virus Testing on Antibiotic Prescribing Among Children Presenting to the Emergency Department With Acute Respiratory Illness: A Randomized Clinical Trial

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Abstract

**IMPORTANCE** There is high usage of antibiotics in the emergency department (ED) for children with acute respiratory illnesses. Studies have reported decreased antibiotic use among inpatients with rapid respiratory pathogen (RRP) testing.

**OBJECTIVE** To determine whether RRP testing leads to decreased antibiotic use and healthcare use among children with influenza-like illness (ILI) in an ED.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized clinical trial among children aged 1 month to 18 years presenting to an ED with ILI from December 1, 2018, to November 30, 2019, was conducted. Data were analyzed March 23, 2020, to April 2, 2021. All children received a nasopharyngeal swab for RRP testing and were randomized 1:1 to the intervention group or control group (results not given, routine clinical care). Results were available in 45 minutes. Intention-to-treat analyses and modified intention-to-treat (clinician knows results) analyses were conducted using multivariable Poisson regression.

**INTERVENTIONS** Rapid respiratory pathogen test results given to clinicians.

**MAIN OUTCOMES AND MEASURES** Antibiotic prescribing was the primary outcome; influenza antiviral prescribing, ED length of stay, hospital admission, and recurrent healthcare visits were the secondary outcomes.

**RESULTS** Among 931 ED visits (intervention group, 452 children and control group, 456 children after exclusion of those not meeting criteria or protocol violations), a total of 795 RRP test results (85%) were positive. The median age of the children was 2.1 years (interquartile range, 0.9-5.6 years); 509 (56%) were boys. Most children (478 [53%]) were Hispanic, 688 children (76%) received government insurance, and 314 (35%) had a high-risk medical condition. In the intention-to-treat intervention group, children were more likely to receive antibiotics (relative risk [RR], 1.3; 95% CI, 1.0-1.7), with no significant differences in antiviral prescribing, medical visits, and hospitalization. In inverse propensity-weighted modified intention-to-treat analyses, children with test results known were more likely to receive antivirals (RR, 2.6; 95% CI, 1.6-4.5) and be hospitalized (RR, 1.8; 95% CI, 1.4-2.5); there was no significant difference in antibiotic prescribing (RR, 1.1; 95% CI, 0.9-1.4).

**CONCLUSIONS AND RELEVANCE** The use of RRP testing in the ED for ILI did not decrease antibiotic prescribing in this randomized clinical trial. There is a limited role for RRP pathogen testing in children in this setting.

(continued)
Abstract (continued)

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03756753

Introduction

Acute respiratory infections represent one of the most common reasons for pediatric emergency department (ED) and urgent care visits. It is estimated that in pediatric ED and urgent care settings, 55% to 57% of children are prescribed an antibiotic, despite the source of the infection mostly being viral. Unnecessary antibiotic prescribing can lead to adverse drug events, increased health care costs, and antibiotic resistance. Identification of the respiratory pathogen provides an opportunity to guide the evaluation and management of children with acute respiratory infection, with the potential to decrease antibiotic use, resource use, and health care costs.

Newer molecular-based platforms enable more rapid pathogen detection with enhanced sensitivity and specificity. Although some pediatric studies using these newer platforms have reported associations with decreased antibiotic use and hospital length of stay among inpatients, guidance regarding whether the same benefits exist for patients in an ED or urgent care setting is limited in the pediatric population. The objective of this randomized clinical trial was to determine whether knowledge of the pathogen associated with acute respiratory infection affects clinicians' decision-making regarding antibiotic prescribing and health care use in a pediatric ED setting. We hypothesized that there would be a decrease in antibiotic prescribing in the group in which results of rapid respiratory pathogen (RRP) testing were reported to the clinician.

Methods

Study Design

We conducted a single-center, randomized clinical trial (Randomized Clinical Trial Assessing Point-of-Care Influenza and Other Respiratory Virus Diagnostics [RAPID]) of children aged 1 month to 18 years evaluated in a large pediatric ED from December 1, 2018, to November 30, 2019. Data analysis was performed from March 23, 2020, to April 2, 2021. The trial protocol and statistical analysis plan are available in Supplement 1. The Children's Hospital Colorado health system serves a 7-state region and comprises a primary academic ED, 2 community-based satellite EDs, and 3 urgent care facilities, evaluating approximately 170,000 children each year. Children with influenza-like illness (ILI) presenting to the primary academic ED were eligible for study participation. To minimize ascertainment bias, the research staff approached children and families for participation as soon as they wereroomed in the ED, before clinical evaluation. We defined ILI as a temperature greater than or equal to 37.8 °C and at least 1 of the following symptoms: cough, sore throat, runny nose, or nasal congestion for children aged 12 months to 18 years. For children aged 1 month to less than 1 year, we defined ILI as temperature greater than 37.8 °C or at least 1 of the following symptoms: cough, sore throat, runny nose, or nasal congestion. Children were included in the study if they were triage level 3 (stable, should be seen by a clinician within 30 minutes), 4 (stable, may be seen nonurgently by a clinician, requires minimal testing), or 5 (stable, may be seen nonurgently by a physician, requires no testing) based on the Emergency Severity Index to identify a population that would likely be evaluated at an urgent care facility. Children were excluded if they had experienced respiratory symptoms longer than 14 days, were seen in nurse-only visits, or had enrolled in this study within the previous 14 days. The study was approved by the Colorado Multiple Institutions Review Board. All participants' parents or legal guardians provided written informed consent, and children gave assent if aged 7 years or older and were not cognitively impaired. We provided financial incentives after all study procedures during the initial visit ($20) and following completion of a 10-day survey ($10).
waiver of consent was obtained for clinician surveys because these data were deidentified. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials.

The primary outcome was antibiotic prescribing (intravenous or enteral antibiotics either administered in the ED or hospital or as an outpatient prescription) during the ED visit. Secondary outcomes included influenza antiviral prescribing (either administered in the ED or hospital or as an outpatient prescription), appropriate antiviral prescribing (antiviral prescribing if results of influenza testing were positive), ED length of stay, hospital admission, recurrent ED visits, number of health care visits within 10 days of the index visit, clinician decision-making in the ED (ordering tests and treatments and making decisions regarding disposition), and patient/family acceptance of testing. Subgroup analyses included the exclusion of hospitalized children and restriction of the cohort to children with a bacterial pathogen or viral pathogen detected.

The study team obtained samples using nasopharyngeal swabs from all children enrolled in the study (FLOQSwab; Copan Diagnostics Inc), placed the swabs in Universal Transport Media (Copan Diagnostics), and conducted RRP testing using the BioFire FilmArray RP2 Panel (BioFire Diagnostics), which has an average turnaround time of 45 minutes and tests for adenovirus; coronaviruses HKU1, NL63, 29E, and OC43; human metapneumovirus; rhinovirus/enterovirus; respiratory syncytial virus; influenza A, A/H1-2009, A/H3, and B; parainfluenza virus 1, 2, 3, and 4; Bordetella pertussis and B parapertussis; Chlamydia pneumoniae; and Mycoplasma pneumoniae.

Results of RRP testing were provided to the ED clinician and families of children in the intervention group; the results were not given to clinicians and families of children in the control (routine clinical care) group. Children may have received clinical respiratory pathogen or influenza testing for the same pathogens (BioFire RP or GeneXpert, Cepheid; both with clinical turnaround time of approximately 2 hours) at the discretion of the clinician.

The unit of randomization was the ED visit. The study statistician (A.M.) randomized children 1:1 in permuted blocks of 6 in REDCap.16 Blinding of study investigators, clinicians, and families was not possible because of the nature of the diagnostic intervention.

We provided a letter to families in the intervention group with results of testing in the ED. For families discharged before receiving the results, we sent a text message with results (681 children had been enrolled by the time of this change). Second, clinical nurses obtained nasopharyngeal swabs for the study, but to improve efficiency, 3 months into the study, we trained our research assistants (D.S.-C., E.K., C.P., and I.F.) to collect swabs instead (307 participants had been enrolled by the time of this change).

We surveyed families regarding sociodemographic characteristics, symptoms, sick contacts, and vaccination status to explore factors associated with the outcomes of interest and approached the families again before ED discharge regarding their experience with the nasal swab and the likelihood to have future testing. Families were notified of the randomization group after sample collection. Participants discharged before the second interview were contacted by telephone or text message the following day. We provided a memory aid to track the child’s symptoms and contacted families between 7 and 13 days after enrollment by telephone or email for a third interview regarding symptom duration, additional medical visits, and antibiotic or antiviral therapies. Study personnel asked clinicians treating children in the intervention group to complete a survey shortly after the clinicians received RRP test results regarding clinicians’ characteristics and changes in medical decision-making (testing, prescribing, and disposition) based on the RRP test results.

The study team collected sociodemographic characteristics and presenting symptoms of the children through self-report and medical record review and collected physical examination findings, diagnoses, and clinical outcomes data through medical record review. A research assistant (D.S.-C., E.K., C.P., or I.F.) verified data entered directly into REDCap by family members and, for the remaining questions, entered responses into REDCap via a handheld tablet based on the caregiver’s report. The research assistants or study investigators (K.G., D.S.-C., E.K., C.P., and I.F.) completed additional medical record abstraction after the study visit following standardized methods. A second
research assistant (D.S.-C., E.K., C.P., or I.F.) independently verified all data entered into REDCap from medical record review; the principal investigator (S.R.) discussed and corrected any discrepancies.

We used the same high-risk medical conditions associated with an increased likelihood of complications associated with influenza. In the intention-to-treat (ITT) analyses, we analyzed data based on the initially assigned study group at baseline. Children or caregivers who withdrew consent or had a protocol violation concerning eligibility were excluded from ITT analysis. In addition, we conducted modified ITT analyses whereby the intervention group comprised children whose clinicians knew the RRP test results (children in the intervention group with results given to clinicians and children in the control group whose clinician ordered clinical testing, confirmed by medical record review) and the control group comprised children whose clinicians did not know the RRP test results (children in the intervention group who were discharged before results were available and children in the control group whose clinician did not order RRP testing). We also conducted per protocol analyses, defined as children who underwent RRP testing and, if randomized to the intervention group, results were given to clinicians; if children were randomized to the control group, no clinical RRP testing was performed. We defined appropriate antiviral prescribing based on a positive test for influenza and the child received or was prescribed an antiviral and appropriate antibiotic prescribing based on a diagnosis of sepsis, rule out sepsis, shock, pneumonia, pharyngitis, and otitis media.

Statistical Analysis
We conducted analyses on an ITT, per protocol, and modified ITT basis. The primary outcome was antibiotic prescribing. We conducted descriptive analyses using frequencies for categorical variables and measures of central tendency for continuous variables. We compared sociodemographic and clinical characteristics of the intervention and control groups using Pearson $\chi^2$ tests for categorical variables and nonparametric tests (Wilcoxon rank-sum test) for continuous variables. Hypotheses tests were 2-sided, and significance was determined at $\alpha < .05$. For children enrolled in the study more than once, we included the first observation in the analyses. In ITT analyses, we compared intervention group by outcome using Poisson regression with robust error variance (binary outcomes) or log linear models (continuous length of stay outcome). The ITT analyses were also adjusted for a priori variables of high-risk comorbidity, age, and diagnoses classified by appropriate antibiotic therapy. In the modified ITT analyses, we used inverse propensity-weighted regression to adjust the main association between the clinician knowing the RRP test results and the outcome, because these groups were no longer randomized. Propensity scores were calculated as the likelihood of the clinician knowing the test results using multivariable logistic regression. Propensity covariates were selected a priori as high-risk comorbidity, age, and diagnoses classified by appropriate antibiotic therapy and also determined based on clinical relevance and significant differences in the bivariable analysis. Weights were calculated according to the inverse probability of receiving treatment. Covariate balance in the weighted cohorts was assessed using standardized differences, with absolute values less than 0.25 considered balanced. Weighted Poisson and log linear regression was performed to assess the association between the clinician knowing the test results and the primary and secondary outcomes. Outcomes are presented as risk ratios and geometric mean ratios with 95% CIs. Analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Using a 2-sided $z$ test for difference in 2 independent proportions, we determined that a sample size of 392 patients in each group would achieve 90% power at a $P = .05$ significance level to detect a relative risk difference of approximately 10% (from a baseline of 30%) for antibiotics prescribed (primary outcome) for the intervention group compared with the control group using data from a prior study in our ED. Assuming 20% attrition, we required 470 participants in each group.
Results

After screening children during 1415 visits for eligibility, we approached 1372 families for enrollment. We enrolled 913 children into the trial (931 visits). Of these, 457 children (466 visits) were randomly assigned to the intervention group, and 460 children (465 visits) to the control group. Eleven visits were excluded (not meeting study criteria) or withdrawn from the study (protocol violations), leaving 452 children in the intervention group and 456 children in the control group. After excluding more than 1 visit for 5 children, 908 children were included in the ITT and 907 in the modified ITT analyses (Figure 1). Follow-up at day 10 was completed for 314 children (69%) in the intervention group and 306 (67%) in the control group.

There were no clinically significant differences in demographic and clinical characteristics between the intervention and control groups (Table 1). The median age of the children was 2.1 years (interquartile range, 0.9-5.6 years), 509 were boys (56%), and 399 were girls (44%). Most children were Hispanic (478 [53%]), 688 (76%) received government insurance, 314 (35%) had a high-risk medical condition; 146 (16%) of the children in the cohort were hospitalized. Positive RRP test results were obtained in 795 of 931 visits (85%). The most common pathogens were enterovirus/rhinovirus (n=295), influenza (n=180), respiratory syncytial virus (n=162), and adenovirus (n=115) (children may have had ≥1 pathogen). Results were invalid in 2 patients. Pathogens were similar in frequency between the control and intervention groups (Figure 2).

In primary ITT analyses, children in the intervention group were more likely to receive antibiotics than children in the control group (relative risk [RR], 1.31; 95% CI, 1.03-1.68) and to have a diagnosis in which antibiotics would be indicated (risk difference, 8.6; 95% CI, 3.2-13.8). In the
secondary analyses, there were no significant differences in antiviral use, ED length of stay, recurrent ED visits, or hospitalization. In adjusted ITT analyses, children in the intervention group were more likely to receive appropriate antivirals (RR, 2.5; 95% CI, 1.5-4.2), had longer ED length of stay (RR, 1.6 95% CI, 1.5-1.7), and had higher hospitalization rates (RR, 2.0; 95% CI, 1.5-2.7) compared with children whose clinicians did not know the RRP test results. Antibiotic prescribing was not significant (RR, 1.1; 95% CI, 0.9-1.3) in the adjusted analysis. (Table 2). Clinical outcomes of children grouped by clinicians knowing the RRP test results compared with not knowing the RRP test results (modified ITT analyses) are reported in Table 2. Children whose clinician knew the RRP test results were more likely to receive antivirals (RR, 2.6; 95% CI, 1.6-4.5), be admitted to the hospital from the ED (RR, 1.8; 95% CI, 1.4-2.5), and have longer ED length of stay (RR, 1.6; 95% CI, 1.5-1.7) (Table 2). Antibiotic prescribing was not significantly different between groups (RR, 1.1; 95% CI, 0.9-1.4) in the modified ITT analysis.

### Table 1. Sociodemographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intention to treat</th>
<th>Modified intention to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 908)</td>
<td>Intervention (n = 452)</td>
</tr>
<tr>
<td>Age, median (IQR), mo</td>
<td>25.8 (10.7-67.3)</td>
<td>26.1 (11.4-64.6)</td>
</tr>
<tr>
<td></td>
<td>Control (n = 456)</td>
<td>25.6 (9.7-70.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total (N = 907)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinician knows results (n = 340)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinician does not know results (n = 567)</td>
</tr>
<tr>
<td>Primary insurance status</td>
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<td></td>
</tr>
<tr>
<td>Private</td>
<td>187 (21)</td>
<td>94 (21)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>688 (76)</td>
<td>338 (75)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>28 (3)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Season of enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring (March-May)</td>
<td>413 (45)</td>
<td>207 (46)</td>
</tr>
<tr>
<td>Summer (June-August)</td>
<td>121 (13)</td>
<td>60 (13)</td>
</tr>
<tr>
<td>Fall (September-November)</td>
<td>100 (11)</td>
<td>49 (11)</td>
</tr>
<tr>
<td>Winter (December-February)</td>
<td>274 (30)</td>
<td>136 (30)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>509 (56)</td>
<td>252 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>399 (44)</td>
<td>200 (44)</td>
</tr>
<tr>
<td>Child race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>185 (20)</td>
<td>91 (20)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>134 (15)</td>
<td>68 (15)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>479 (53)</td>
<td>229 (51)</td>
</tr>
<tr>
<td>Other</td>
<td>90 (10)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (2)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Influenza vaccination status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated (at least 1 vaccine)</td>
<td>461 (51)</td>
<td>242 (54)</td>
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<tr>
<td>Unvaccinated</td>
<td>397 (44)</td>
<td>187 (41)</td>
</tr>
<tr>
<td>Do not know</td>
<td>49 (5)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>High-risk medical condition</td>
<td>314 (35)</td>
<td>157 (35)</td>
</tr>
<tr>
<td>Time ill before enrollment, median (IQR), d</td>
<td>3.0 (2.0-5.0)</td>
<td>3.0 (2.0-5.0)</td>
</tr>
<tr>
<td>Underwent clinical testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza PCR</td>
<td>57 (6)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Respiratory pathogen panel</td>
<td>72 (8)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>None</td>
<td>775 (86)</td>
<td>391 (87)</td>
</tr>
<tr>
<td>Child attends daycare or school</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daycare</td>
<td>163 (18)</td>
<td>91 (20)</td>
</tr>
<tr>
<td>School</td>
<td>296 (33)</td>
<td>141 (32)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (3)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Neither</td>
<td>411 (46)</td>
<td>200 (45)</td>
</tr>
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</table>

Abbreviations: IQR, interquartile range; PCR, polymerase chain reaction.

* Because clinician survey data were incomplete for 1 participant, that participant was excluded from modified intention-to-treat analyses.
Per protocol analyses demonstrated similar findings to the modified ITT analyses (eTable 1 in Supplement 2). Children had a higher risk of receiving antibiotics in the intervention group compared with the control group (RR, 1.4; 95% CI, 1.1-1.9), but this outcome was not significant in adjusted analyses (RR, 1.1; 95% CI, 0.9-1.3). Children in the intervention group were more likely to receive antivirals (RR, 2.3; 95% CI, 1.2-4.3), had a longer length of stay in the ED (RR, 1.4; 95% CI, 1.3-1.5), and were more likely to be admitted to the hospital (RR, 1.6; 95% CI, 1.2-2.2).

In modified ITT analyses comprising 285 of 452 children (63%) in the intervention group and 55 of 456 children (12%) in the control group whereby clinicians received the RRP test results clinically, children with RRP test results known to the clinician were more likely to have a diagnosis in which antibiotics would be indicated (sepsis, rule out sepsis, shock, pneumonia, pharyngitis, otitis media) than those without RRP results (risk difference, 6.0%; 95% CI, 0.4% to 11.6%). Children with a viral pathogen detected were significantly less likely to receive antibiotics than those with a negative test result (153 [20%] vs 40 [30%]; P = .01). When restricting analyses to children with a bacterial pathogen, there was higher antibiotic prescribing by clinicians who knew RRP test results vs those who did not, but these findings were not statistically significant (risk difference, 16.2%; 95% CI, −19.4% to 51.9%). Sensitivity analyses were conducted excluding hospitalized patients, with similar antibiotic and antiviral prescribing and ED length of stay noted in ITT and modified ITT analyses (eTable 2 in Supplement 2).

Family surveys were completed for 620 visits (68%) in both groups and clinician surveys were completed for 435 visits (96%) in the intervention group. Caregivers were more likely to have private

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**Figure 2. Pathogens Identified for Children Enrolled in the Randomized Clinical Trial Assessing Point-of-Care Influenza and Other Respiratory Virus Diagnostics (RAPID) Trial**

- **Adenovirus**
- **Coronavirus 229E**
- **Coronavirus HKU1**
- **Coronavirus NL63**
- **Coronavirus OC43**
- **HMPV**
- **Influenza A**
- **Influenza A H1/2009**
- **Influenza A/H3**
- **Influenza B**
- **Parainfluenza 2**
- **Parainfluenza 1**
- **Parainfluenza 3**
- **Parainfluenza 4**
- **Rhinovirus/enterovirus**
- **RSV**
- **Bordetella parapertussis**
- **Bordetella pertussis**
- **Chlamydia pneumoniae**
- **Mycoplasma pneumoniae**
- **Negative**
- **Inconclusive pathogen**

HMPV indicates human metapneumovirus; RSV, respiratory syncytial virus.
Table 2. Clinical Outcomes of Study Participants

<table>
<thead>
<tr>
<th>Outcome of Interest</th>
<th>Intention to treat</th>
<th></th>
<th></th>
<th></th>
<th>Modified intention to treat</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 908)</td>
<td>Intervention (n = 452)</td>
<td>Control (n = 456)</td>
<td>RR (95% CI)</td>
<td>Adjusted RR (95% CI)</td>
<td>Total (N = 907)</td>
<td>Clinician knows results (n = 340)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics prescribed/received</td>
<td>203 (22)</td>
<td>115 (25)</td>
<td>88 (19)</td>
<td></td>
<td>1.3 (1.0-1.7)</td>
<td>1.1 (0.9-1.3)</td>
<td>203 (22)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antivirals prescribed/received</td>
<td>56 (6)</td>
<td>31 (7)</td>
<td>25 (5)</td>
<td></td>
<td>1.3 (0.8-2.1)</td>
<td>2.5 (1.5-4.2)</td>
<td>56 (6)</td>
</tr>
<tr>
<td>Antivirals prescribed/received and influenza test result positive</td>
<td>48 (5)</td>
<td>25 (6)</td>
<td>23 (5)</td>
<td></td>
<td>1.1 (0.6-1.9)</td>
<td>2.5 (1.4-4.3)</td>
<td>48 (5)</td>
</tr>
<tr>
<td>ED length of stay, median (IQR), h</td>
<td>3.1 (3.0-3.2)</td>
<td>3.1 (2.9-3.3)</td>
<td>2.8 (2.0-4.5)</td>
<td>1.0 (0.9-1.1)</td>
<td>1.6 (1.5-1.7)</td>
<td>3.1 (3.0-3.2)</td>
<td>4.1 (3.9-4.4)</td>
</tr>
<tr>
<td>Admitted to hospital from ED</td>
<td>146 (16)</td>
<td>77 (17)</td>
<td>69 (15)</td>
<td></td>
<td>1.1 (0.8-1.5)</td>
<td>2.0 (1.5-2.7)</td>
<td>146 (16)</td>
</tr>
<tr>
<td>Additional hospitalization within 10 d (medical record review)</td>
<td>27 (3)</td>
<td>15 (3)</td>
<td>12 (3)</td>
<td></td>
<td>1.3 (0.6-2.7)</td>
<td>2.0 (1.0-4.2)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Additional ED visits within 10 d</td>
<td>58 (6)</td>
<td>29 (6)</td>
<td>29 (6)</td>
<td></td>
<td>1.0 (0.6-1.7)</td>
<td>0.9 (0.6-1.6)</td>
<td>58 (6)</td>
</tr>
<tr>
<td>Additional medical visits</td>
<td>161 (26)</td>
<td>85 (27)</td>
<td>76 (25)</td>
<td></td>
<td>1.1 (0.8-1.4)</td>
<td>1.1 (0.9-1.5)</td>
<td>161 (26)</td>
</tr>
</tbody>
</table>

Abbreviations: ED, emergency department; RR, risk ratio.

* Because clinician survey data were incomplete for 1 participant, that participant was excluded from modified intention-to-treat analyses.
* P = .31, inverse propensity weighted.
* P = .51, inverse propensity weighted.
insurance (143 [23%] vs 45 [15%]) and be non-Hispanic White (144 [23%] vs 44 [15%]). More families whose clinicians knew the RRP test results compared with those whose clinicians did not know the RRP test results (306 [96%] vs 402 [89%]) stated that they would be likely to undergo future testing if results were available in 45 minutes; these choices increased (312 [98%] vs 425 [94%]) if the results were available in 20 minutes. Knowledge of RRP test results would have prevented 24 of 303 families (8%) in the control group from seeking additional medical visits. In the intervention group, 21 of 314 families (7%) stated that the test results influenced how they sought medical care.

Most clinicians were trained in pediatric emergency medicine (144 [33%]) and had completed training within the past 0 to 5 years (84 [58%]). Clinical decisions were changed 17% (72 of 435) of the time based on RRP results. Attending physicians (including emergency medicine–trained physicians and pediatrics) made the most changes in clinical decision-making (26 [36%]) followed by nurse practitioners (21 [29%]) and those who had completed training within the past 0 to 5 years (25 [35%]) (eTable 3 in Supplement 2). When changes in clinical decision-making were observed, it was most commonly antiviral prescribing (prescribing oseltamivir, n = 11; not prescribing oseltamivir, n = 15) (Figure 3).

Discussion

To our knowledge, this is the largest randomized clinical trial evaluating the clinical utility of rapid molecular testing in a pediatric ED setting. A meta-analysis20 highlighted the need for a large randomized clinical trial to evaluate rapid molecular diagnostics in the acute care setting using antibiotic prescribing as the primary outcome, given the limited existing data and small numbers of participants preventing meaningful conclusions from being reached, which formed the rationale for our study design. We found that children in the intervention group whose clinicians were aware of RRP results were more likely to receive antibiotics, with no significant difference in antiviral prescribing, ED length of stay, subsequent ED visits, and rates of hospitalization in ITT analyses. The increase in antibiotic prescribing was no longer significant after adjustment for relevant confounders. In our adjusted modified ITT analyses (RRP results known vs not known to clinicians), children whose clinicians knew the RRP results were more likely to receive antivirals, be hospitalized, and have a longer ED length of stay. Antibiotic prescribing was also more common in this modified intervention group but was no longer significant.

The reason for increased antibiotic use among clinicians who knew the RRP results is unknown. Although we effectively randomized children between the intervention and control groups, there was an increase in diagnoses whereby antibiotic use was justified in the intervention group.

Figure 3. Clinician Clinical Decision-Making in the Emergency Department Based on Results of Rapid Respiratory Pathogen Testing

Clinician survey responses (intervention group only) to determine whether knowledge of the test results influenced their decision-making in the emergency department with respect to prescribing oseltamivir, making decisions about hospital admission vs discharge, ordering additional tests, and prescribing antibiotics.
Antibiotic prescribing was also higher in children testing negative for a respiratory pathogen or positive for a bacterial pathogen. In these situations, RRP testing may inadvertently increase antibiotic prescribing when not clinically indicated. Notably, a similar outcome was observed in a randomized clinical trial conducted in a pediatric hospital setting demonstrating significantly higher antibiotic therapy in the intervention group (41.6%) compared with the control group (27.4%). In both studies, antibiotic prescribing decisions were likely made immediately following clinical evaluation, before results were available.

Other pediatric studies have demonstrated that knowledge of respiratory testing did not lead to a significant change in antibiotic prescribing or other outcomes. A meta-analysis of rapid viral diagnostic testing for acute respiratory infections in the pediatric ED setting included 4 randomized clinical trials before the rapid molecular testing era (3 for influenza-only testing and 1 including a respiratory pathogen panel) reported a nonsignificant decrease in antibiotic use in the ED. A study evaluating a multiplex rapid respiratory panel demonstrated no significant difference in antibiotic prescribing in the ED, but noted a reduction in antibiotic prescription after ED discharge. One potential strategy to decrease unnecessary antibiotic prescribing that warrants further study is RRP testing in conjunction with antimicrobial and diagnostic stewardship efforts, which have been associated with improved outcomes for other rapid molecular platforms, such as blood culture identification panels.

We surveyed clinicians and parents to better understand the effect of RRP test results on antimicrobial prescribing, testing, and disposition, as well as family acceptance of testing. We found acceptance of RRP testing among families, especially if test results were available in 20 minutes. We also found that the most common reason for a change in clinical decision-making was either prescribing an antiviral if influenza was detected or withholding antivirals if test results were negative for influenza. Similar findings have been reported highlighting the benefits of rapid testing for influenza in the ED setting, with a meta-analysis suggesting an increase in appropriate antiviral prescribing and decreased antibiotic use. We had relatively low rates of influenza in our study, so the effect of an influenza diagnosis on antibiotic prescribing was difficult to assess. Nevertheless, our results and other findings in the literature suggest the higher value of rapid molecular influenza testing rather than respiratory pathogen panel testing in an ED setting. Despite the increase in antibiotic prescribing in the intervention group, only 7 clinicians stated that RRP test results affected their decision to prescribe antibiotics; therefore, these survey data do not completely capture the rationale of this observed finding.

Limitations
There are several limitations of this trial. Our trial was conducted at a single academic center, so the generalizability of the findings to other settings is not known. We attempted to better mimic an urgent care setting with similar illness severity by limiting our population to children with conditions of lower acuity, but 16% of the children in the cohort were hospitalized, and we were unable to enroll patients with conditions of very low acuity evaluated in the fast-track area (20-minute evaluations). The study was underpowered to detect a difference in per protocol analyses, but we observed similar findings to the modified ITT analyses. We adjusted for illness severity by diagnosis categories in our modified ITT analyses, but this adjustment may not have completely accounted for illness acuity. Therefore, we conducted a sensitivity analysis excluding hospitalized children and noted similar findings. In addition, more than one-third of the children were discharged before clinicians knew the RRP test results. This timing likely took place among children with lower illness acuity who were rapidly evaluated and discharged from the ED. To account for this factor, we conducted modified ITT analyses, comparing children whose clinicians knew the test results with those who did not know the results, using inverse probability weighting, but these findings could have occurred due to other factors for which we were not able to adjust. We planned to conduct this study in a real-life setting without interrupting clinicians’ workflow and postulate that the 45-minute turnaround time is likely too long to affect clinical decision-making in the ED, particularly in patients with lower-acuity condition.
conditions who are rapidly discharged. It is possible that testing with even shorter turnaround time may have a greater influence in the ED and urgent care settings, which should be the subject of further study.

Conclusions

The results of this randomized clinical trial show that RRP testing for children with acute respiratory illnesses in an ED setting did not lead to a decrease in antibiotic prescribing. The greatest effect on clinicians' clinical decision-making was appropriate antiviral use for children based on influenza test results, supporting the potential benefit for rapid molecular influenza testing in this setting.

ARTICLE INFORMATION

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REFERENCES


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Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
eTable 1. Clinical Outcomes of Study Participants by Study Group, Per Protocol Analyses
eTable 2. Risk Ratio or Geometric Ratio of Clinical Outcomes of Interest of Intervention Group Compared With Control Group, Excluding Hospitalized Patients (Intention-to-Treat and Modified Intentions-to-Treat Analyses)
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SUPPLEMENT 3.
Data Sharing Statement