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Clinical impact of rapid viral respiratory panel testing on pediatric critical care of patients with acute lower respiratory infection

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A B S T R A C T

Background: We aimed to determine the impact of utilizing a rapid panel test of respiratory viral and atypical bacteria (FilmArray Respiratory Panel, FA RP) on etiological diagnosis of acute lower respiratory infection (ALRI) and antimicrobial stewardship in critical care pediatric patients.

Methods: Prospective cohort study of patients aged < 18 years with clinical diagnosis of ALRI that were admitted to the Pediatric Intensive Care Unit (PICU) of Hospital Sant Joan de Deu (Barcelona, Spain) during December 2015–February 2017. Patients were diagnosed by FA RP and by a bundle of routine microbiological assays.

Results: ALRI viral and bacterial etiology was confirmed by a composite reference standard of routine microbiological assays in 72 (55.4%) and 15 (11.5%) respiratory samples, respectively, that were collected from 130 children (median age, 3.5 months; IQR 1.1–14.8 months; 54.6% male). Comparatively, FA RP use increased etiological confirmation of ALRI in up to 123 (94.6%) samples (p < 0.001) but only determined a bacterial origin in 2 (1.5%). Availability of diagnostic results before patient discharge from the PICU rose from 65.4 to 38.5% (p < 0.001). Use of the new panel test directly influenced antimicrobial stewardship in 11 (8.4%) episodes, leading to discontinuation of antiviral drugs (n = 5), administration of targeted antibiotics (n = 5), antiviral therapy start (n = 2) and both targeted antibiotic administration and discontinuation of antiviral drugs (n = 1).

Conclusion: FA RP contributed to improve etiological diagnosis of ALRI in a timely manner while enhancing a more rational use of antimicrobial drugs in critical care pediatric patients.

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Impacto clínico de una prueba rápida de detección múltiple de virus respiratorios en pacientes pediátricos críticos con infección respiratoria aguda de vías bajas

R E S U M E N

Antecedentes: Nuestro objetivo fue determinar el impacto de la utilización de una prueba rápida de detección múltiple de virus y bacterias atípicas respiratorias (FilmArray Respiratory Panel [FA RP]) en el diagnóstico etiológico de la infección respiratoria aguda de vías bajas (IRAVB) y en la administración de antimicrobianos en pacientes críticos pediátricos.

Métodos: Estudio de una cohorte prospectiva de pacientes < 18 años con diagnóstico clínico de IRAVB que ingresaron en la Unidad de Cuidados Intensivos Pediátricos (UCIP) del Hospital Sant Joan de Deu, Barcelona, España, durante diciembre de 2015–febrero de 2017. Los pacientes fueron diagnosticados por FA RP y por un grupo de pruebas microbiológicas de rutina.

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Introduction

Acute lower respiratory infection (ALRI) remains the most important global public health problem among children.\(^1\)\(^{-3}\) ALRI was estimated to cause 14.9 million episodes that resulted in pediatric hospital admissions worldwide in 2010\(^4\) and around 650,000 deaths of young children in 2016.\(^5\) The disease is caused by a large and heterogeneous group of infections including bacterial, viral, and other etiologies. Although incidence of viral ALRI is larger at early ages,\(^6\)\(^{-7}\) pathogenic respiratory bacteria produce higher morbidity and mortality rates globally, especially among older children.\(^8\) Occurrence of mixed ALRI is also common during childhood.\(^9\)\(^{-10}\)

Distinguishing the etiology of ALRI becomes challenging, since derived signs and symptoms are often unpecific. A gold standard for etiological diagnosis of ALRI has not yet been developed.\(^11\) Conventional microbiological diagnostic methods such as bacterial culture, targeted polymerase-chain reaction (PCR) assays and rapid viral antigen tests have limitations in comprehensiveness, accuracy, and/or timeliness of results to guide clinical decisions, even expanding the arsenal of diagnostic tools with chest radiographies and acute-phase reactant measurements.\(^12\)\(^{-13}\)

Treatment of children with viral ALRI appears to be an area where extensive misuse of antibiotics could be reduced.\(^14\)\(^{-16}\) In the last years, the introduction of fast molecular assays for multiple identification of respiratory viruses and bacteria has offered clinicians the potential to identify the viral origin of ALRI that might otherwise be considered to have a bacterial etiology and thus be treated with antibiotics. The FilmArray\(^18\) Respiratory Panel (BioFire Diagnostics Inc., US), hereafter FA RP, is a qualitative reverse transcriptase PCR panel assay that targets adenovirus (ADV), coronavirus (CoV) types 229E/NL63/OC43/HKU1, influenza A virus (IFV-A) including differentiation of subtypes H1/H1N1-2009/H3, influenza B virus (IFV-B), human metapneumovirus (HMPV), parainfluenza virus (PIV) types 1/2/3/4, respiratory syncytial virus (RSV) types A/B, rhinovirus/enterovirus (RV/EV), Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae in a single respiratory sample. FA RP integrates sample preparation, DNA amplification and detection into an automated process with only 2 min of hands-on time and 1 hour of instrumentation time.\(^15\)

The main aim of our study was to evaluate to which extent the utilization of FA RP improved etiological diagnosis of ALRI and subsequent antimicrobial prescribing practices in critical care pediatric patients, compared to a bundle of routine microbiological diagnostic assays.

Materials and methods

Study design and setting

A prospective single-center cohort study of pediatric patients with clinical diagnosis of ALRI admitted to the Pediatric Intensive Care Unit (PICU) of Hospital Sant Joan de Deu (Barcelona, Spain) was conducted during the period December 2015–February 2017. All patients with clinical suspicion of ALRI within such period were initially considered for inclusion in the study. Participant inclusion criteria were: (1) age < 18 years; (2) clinical presentation compatible with acute respiratory disease (cough, difficult breathing, tachypnea) and/or signs and symptoms of infection (reported or documented fever > 37.3°C or looking/feeling unwell); and (3) informed consent to participate obtained from parents or guardians. Patients were excluded from the study if they had been hospitalized in the previous 14 days before the current episode or infection onset occurred 48 h after the date of PICU admission. The study setting is a 318-bedsize reference university hospital that attends a reference population of approximately 300,000 children.

All patients were diagnosed by FA RP as well as by a bundle of routine microbiological assays. Primary endpoints were FA RP diagnostic performance compared to a composite reference standard of the bundle of routine microbiological diagnostic assays, antimicrobial prescription changes made as a consequence of FA RP results, and days of antimicrobials saved that could be attributed to the use of the panel test. Secondary outcomes were patient baseline characteristics and length of PICU stay. Clinical data, data of antimicrobial use and laboratory diagnostic results and timeliness were retrieved from the Electronic medical records and the Pharmacy and Laboratory Information systems of the study setting. The study was approved by the Ethics Committee of the site and informed consent was obtained from parents or guardians of participants for patient enrolment.

Definitions

Viral etiology of ALRI was microbiologically confirmed by detection of respiratory virus genetic material by FA RP or a single viral PCR assay or by antigen detection of RSV or IFV in nasopharyngeal aspirates, bronchoalveolar lavages or endotracheal aspirates. A bacterial culture negative result was considered to be suggestive of a viral etiology. Bacterial ALRI etiology was microbiologically confirmed by observation of pathogenic bacterial growth by culture or bacterial nucleic acid detection in blood, bronchoalveolar lavages or endotracheal aspirates.
Table 1  
Baseline and follow-up cohort characteristics.

| Variable                        | No (%)    |
|---------------------------------|-----------|
| Age, median (IQR), months       | 3.5 (1.1–14.8) |
| Age range                       |           |
| <2 years                        | 104 (80.0) |
| 2 to <5 years                   | 10 (7.7)  |
| 5 to <18 years                  | 16 (2.3)  |
| Sex, male                       | 71 (54.6) |
| Signs and symptoms              |           |
| Cough                           | 93 (71.5) |
| Difficulty in breathing         | 128 (98.5) |
| Tachypnea                       | 124 (97.6) |
| Fever >37.3 °C or feeling/looking unwell | 95 (73.1) |
| Comorbidities                   |           |
| Prematurity in children <2 years| 17 (37.0) |
| Multiple comorbidities          | 9 (19.6)  |
| Chronic or recurrent respiratory disease | 8 (17.4) |
| Immunocompromised status        | 6 (13.0)  |
| Other comorbidities             | 6 (13.0)  |
| PRISM scale scoring at PICU admission, median (IQR) | 0 (0–3) |
| PICU length of stay, median (IQR) days | 5 (3–8) |

Values expressed as No. (%), unless otherwise stated.  
Abbreviations: IQR, interquartile range; PICU, Pediatric Intensive Care Unit; PRISM, Pediatric Risk of Mortality.

Sample collection and microbiological methods

Fresh respiratory samples were collected from patients and processed on demand by FA RP and routine tests according to standard operational procedures and to the manufacturers’ instructions in the clinical laboratory of the setting. Requests for routine diagnostic tests were made at the discretion of clinicians based on patient presentation and history and, in the case of single PCRs, were jointly agreed with the microbiologists of the clinical laboratory on a case-per-case basis. PCR testing timetable in the clinical laboratory of the study setting was Monday to Friday from 7.00 am to 8.00 pm.

Statistical analysis

Descriptive variables were analyzed using means and standard deviations (SD), medians and interquartile ranges (IQR), or frequencies and percentages, as appropriate. Time to result by FA RP was calculated as the time elapsed since sample receipt in the clinical laboratory of the setting until result registration in the Laboratory Information system. Significance of the difference between the proportion of antimicrobial prescriptions at baseline and after availability of FA RP results was determined by the Chi-square or the Fisher exact test. All statistical analyses were performed using Stata v.15.1 software (Stata Corp., USA).

Results

Baseline patient characteristics and PICU length of stay

One-hundred and seventy-four patients were screened for inclusion in the study. Of them, 44 (25.3%) were discarded because informed consent could not be obtained (n = 36) or due to previous recent hospitalization or infection onset after 48 hours since PICU admission (n = 8). A total of 130 patients were finally selected for the study. Median age of participants was 3.5 (IQR, 1.1–14.8) months and 71 (54.6%) were male. Forty-six (35.4%) participants presented co-morbidities, being prematurity in infants <2 years of age the most predominant co-morbid condition (n = 17, 37.0%). Baseline characteristics of participants are described in Table 1. Median length of stay in PICU was 5 days (IQR, 3–8 days).

Fig. 1. Respiratory pathogen distribution by FilmArray Respiratory Panel. Abbreviations: RSV, respiratory syncytial virus; RV, rhinovirus; AdV, adenovirus; CoV, coronavirus; EV, enterovirus; MPV, metapneumovirus; PIV-1/2/3, parainfluenza virus 1/2/3; IFV-A/B, influenza virus A/B; Mp, Mycoplasma pneumoniae.

Fig. 2. Respiratory pathogen distribution by other microbiological tests. Abbreviations: RSV, respiratory syncytial virus; Haemophilus influenzae; Mc, Moraxella catarrhalis; Sa, Staphylococcus aureus; Sp, Streptococcus pneumoniae; Kp, Klebsiella pneumoniae; Mp, Mycoplasma pneumoniae; Spy, Streptococcus pyogenes.

Diagnostic performance of FA RP and routine diagnostic assays

One hundred and twenty-two (93.9%) nasopharyngeal aspirates, 5 (3.9%) tracheal aspirates, and 3 (2.3%) bronchoalveolar lavages were collected and tested by FA RP. The panel test detected 123 (94.6%) positive specimens: 121 (93.1%) contained viruses and 2 (1.5%) contained atypical bacteria, specifically Mycoplasma pneumoniae. RSV was the most prevalent species detected in samples (n = 88), followed by EV/RV (n = 55). Viral co-detections were common (n = 43, 35.0%) while identification of bacterial-viral co-detections was infrequent (n = 1, 0.8%). Targets most commonly involved in co-detections were EV/RV (n = 40) and RSV (n = 34). The composite reference standard identified 87 (66.9%) positive samples, being 72 (55.4%) infected by viruses and 15 (11.5%) by bacteria. Most prevalent respiratory pathogens routinely identified were RSV (13 specimens that tested positive by rapid antigen tests) and Haemophilus influenzae (10 specimens that tested positive by bacterial culture). Four bacterial coinfections and 1 bacterial-viral coinfection were observed by the bundle of routine diagnostic assays, mostly involving Haemophilus influenzae (n = 5) and Streptococcus pneumoniae (n = 2). Overall, FA RP significantly increased diagnostic yield of routine diagnostic assays from 66.9 to 93.9% (p < 0.001). This increase was due to a comparatively much higher viral detection rate of FA RP (93.1 vs. 55.4%) but not to the capability of the panel test to detect pathogenic bacteria (1.5 vs. 11.5%). Figs. 1 and 2 depict the distribution of respiratory pathogens in the study cohort. Table 2 details results of laboratory and imaging diagnostic tests. Table 3 describes pathogen combinations identified in co-infected samples.  
Median time to result by FA RP was 2.9 h (IQR, 2.2–5.0 h) for samples received and processed within PCR testing timetable. Panel test results were available for 85 (65.4%) patients before discharge from the PICU whereas results of routine microbiological assays were only available for 50 (38.5%, p < 0.001) patients. The low proportion
Values expressed as No. (%), unless otherwise stated.

* PCR targeting one of the following pathogens: adenovirus, enterovirus, influenza virus, Mycoplasma pneumoniae, or Streptococcus pneumoniae.

* Threshold value suggestive of bacterial vs. viral ALRI.

Abbreviations: IQR, interquartile range; ALRI, acute lower respiratory infection; PCR, polymerase-chain reaction.

of ALRI etiologies confirmed by routine microbiological methods during patient stay in the PICU was due to the prolonged time to results of bacterial culture (>48 h).

### Contribution of FA RP to antimicrobial stewardship

Diverse strategies of antibiotic treatment were implemented after delivery of FA RP results: baseline antibiotics were maintained in 74 (57.0%) children, 28 (21.5%) children remained off antibiotics, and 28 (21.5%) had baseline antibiotic prescriptions modified. Antibiotic treatment changes resulted in discontinuation of antibiotic therapies (n = 20), implementation of more targeted antibiotic therapies (n = 6), and antibiotic start (n = 2). FA RP directly orientated changes to a more targeted antibiotic therapy in 4 patients: antibiotics were de-escalated after FA RP negative results for Mycoplasma pneumoniae in 3 and escalated in 1 after FA RP positive results for that bacterium. Influence of FA RP use on the remainder 24 antibiotic changes could not be determined, since those changes were also driven by a sum of factors including patient evolution, diagnostic results of routine microbiological assays, and prognostic indications of acute-phase reactants.

The effect of FA RP use on administration of antiviral drugs was observed in 8 (6.2%) children: antivirals were discontinued in 6 of them after FA RP negative results for IFV and were started in 2 after FA RP positive results for IFV (otherwise undetected by routine microbiological assays). Discontinuation of antiviral use saved 4 days per episode with antiviral treatment, considering 5 days as a standard duration of antiviral use in children. In total, antimicrobial stewardship changes solely due to FA RP utilization were implemented in 11 (8.5%) patients of the cohort, as detailed in Table 4.

### Discussion

Our study showed an increase in diagnostic yield, timeliness of results and judicious use of antimicrobials as a consequence of the implementation of FA RP for diagnosing ALRI, in comparison with conventional microbiological tests. To the best of our knowledge, these findings had not been previously reported in cohorts of critical care pediatric patients, a specific study group characterized by a noticeable proportion of bacterial ALRI and mixed ALRI etiologies.

An increase in diagnostic yield attributable to FA was observed in precedent studies that compared accuracy of the panel test with that of other viral panel tests and batched PCR assays. Nonetheless, previous diagnostic accuracy studies were mostly focused on adult cohorts or groups. On the other hand, FA RP median time to results observed in our study (2.9 h) was consistent with outcomes reported in previous studies reporting a mean time of 3.1 h and median times of 1.4 h and 2.3 h for FA RP testing.

Previous literature on the potential linkage of rapid respiratory panel testing with optimized antibiotic use shows discordant results. A study in pediatric and adult patients with uncomplicated ARI admitted to an Emergency Department during the influenza epidemic season described a decrease in antibiotic use of half a day after shifting from a set of multiplex and singleplex commercial PCR
assays to FA RP.\textsuperscript{17} In contrast, a randomized controlled trial of adults presenting with ARI to the Emergency Department or acute medical unit of a large hospital over two winter seasons and tested either by FA RP or laboratory PCR tests reported that mean duration of antibiotics was similar in both groups.\textsuperscript{20} Similarly, a quasi-randomized study in adults hospitalized with upper respiratory infection or influenza-like illness, with or without lower respiratory infection, found no evidence of reductions in antibiotic utilization as a consequence of FA RP testing, compared to equivalent outcomes when testing was performed by an array of laboratory-developed multiplex and singleplex PCR assays.\textsuperscript{21} Moreover, an observational study conducted in a hospital that switched from a respiratory viral panel to FA RP for diagnosing adult patients with respiratory viral illnesses did not observe statistically significant differences in antibiotic use after the change in the diagnostic strategy, yet time to results decreased markedly from 24 to 12 h.\textsuperscript{22}

We speculate that we found a minor decline in antibiotic use directly associated to FA RP implementation because the presence of a respiratory virus detected by a panel test that covers an extensive set of viral targets but only certain atypical bacterial targets does not rule out a potential bacterial coinfection, particularly in a PICU environment where patients are highly vulnerable. The marked difference between proportions of bacterial ALRI etiologies confirmed by FA RP and the composite reference standard (1.5 vs. 11.5\%) supports our hypothesis. Withdrawing or postponing antibiotic administration in the PICU before availability of negative bacterial culture results in the absence of a comprehensive bacterial and viral respiratory panel test appears unlikely, given the high risk of concomitant or secondary bacterial ALRI in severely ill children. Results suggest the need of combining FA RP with bacterium-targeted microbiological assays on appropriate pediatric respiratory specimens (bronchoalveolar lavage or endotracheal aspirates) for comprehensive etiological diagnosis of pediatric severe ALRI. In this regard, a general recommendation has been made for rapid molecular diagnostic tests to incorporate testing for relevant bacterial pathogens in addition to viral targets in order to limit antibacterial therapy.\textsuperscript{23} It is also to be noted that the manufacturer of FA RP has recently launched a pneumonia panel test that includes 18 bacterial pathogens, some of which are highly prevalent in bacterial ALRI.\textsuperscript{24}

Interestingly, we observed that detection or not detection of \textit{Mycoplasma pneumoniae} by FA RP was a factor leading to a change to a more targeted antibiotic therapy, either for escalation or de-escalation, in line with recommendations of clinical practice guidelines for treatment of community-acquired pneumonia in children.\textsuperscript{25} In a similar way, detection or not detection of IFV by the panel test guided discontinuation or start of antiviral treatment, as recommended by guidelines. It is worthwhile to highlight that IFV-positive samples by FA RP were not bacterial-positive by other microbiological assays and patients sampled did not show radiological findings or acute-phase reactant measurements that could suggest bacterial co-infection and thus remained off antibiotics, also in accordance with guidelines.

This study presents some limitations. First, it was a single-center study with a relatively low sample size, although the cohort was adequately characterized and monitored to infer consistent conclusions. Second, requests for routine tests were made at the discretion of clinicians. This aspect might induce a certain bias depending on individual preferences to order certain microbiological assays and not others. However, in our view the study reflects the real situation in a hospital environment where some variability in the selection of the best diagnostic strategy may exist among clinicians. Third, outcomes were obtained using an observational cohort design. Further analysis adopting experimental randomized designs would increase external validity of results.

In conclusion, diagnostic performance of FA RP improved accuracy and timeliness of ALRI etiological diagnosis in critical care pediatric patients, in comparison to routine microbiological tests. Implementation of the panel test enhanced a more rational use of antiviral and antibiotic drugs in those patients. However, non negligible occurrence of bacterial ALRI in children suggests the need to combine the panel test with other bacterium-targeted microbiological assays for comprehensive etiological diagnosis of pediatric severe ALRI.

Conflict of interest statement: CMA reports research grants to her institution from Qiagen, Biofire Diagnostics, Pfizer, Roche Diagnostics, BioMérieux, Alere and Genomics SAU, and compensation fees from Qiagen, Roche Diagnostics and BioMérieux for scientific presentations in satellite symposiums; PB reports compensation fees from Roche Diagnostics for scientific presentations in satellite symposiums. The rest of authors report no conflict of interest.

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Table 4
Antimicrobial stewardship changes orientated by FilmArray Respiratory Panel results.

| Antimicrobial change description | Antimicrobial before FA RP result | Antimicrobial after FA RP result | FA RP result | Previous results of other microbiological tests |
|--------------------------------|---------------------------------|---------------------------------|-------------|---------------------------------|
| Targeted antibiotic use         | AZM + AMC                       | AMC                             | Mp negative | Sp PCR negative                  |
| Targeted antibiotic use         | CTX + CLI                       | AMC                             | Mp negative | Sp PCR negative                  |
| Targeted antibiotic use         | AMP + AMZ                       | AMZ                             | Mp positive | IFV antigen negative            |
| Targeted antibiotic use and     | CTX + OTV                       | CTX + AMZ                       | Mp & IFV negative | IFV antigen negative |
| discontinuation of antiviral use| Discontinuation of antiviral use| OTV                             | IFV negative | Sp PCR negative                  |
| Discontinuation of antiviral use| OTV                             | None                            | IFV negative | –                               |
| Discontinuation of antiviral use| OTV                             | None                            | IFV negative | –                               |
| Discontinuation of antiviral use| OTV                             | None                            | IFV negative | –                               |
| Start of antiviral use          | None                            | OTV                             | IFV positive | Sp PCR negative IFV antigen negative |
| Start of antiviral use          | None                            | OTV                             | IFV positive | RSV antigen negative            |

Abbreviations: FA RP, FilmArrayRespiratory panel; PCR, polymerase-chainreaction; Mp, \textit{Mycoplasma pneumoniae}; Sp, \textit{Streptococcus pneumoniae}; IFV, influenza virus; RSV, respiratory syncytial virus; AMC, amoxicillin-clavulanacide; AMP, ampicillin; AZM, azithromycin; CLI, clarithromycin; CTX, cefotaxime; OTV, oseltamivir.
Conflict of interest

CMA reports research grants to her institution from Qiagen, Biofire Diagnostics, Pfizer, Roche Diagnostics, BioMérieux, Alere and Genomica SAU, and compensation fees from Qiagen, Roche Diagnostics and BioMérieux for scientific presentations in satellite symposiums; PB reports compensation fees from Roche Diagnostics for scientific presentations in satellite symposiums. The rest of authors report no conflict of interest.

References

1. Williams BC, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis. 2002;2:25–32.
2. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet. 2003;361:2226–34.
3. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–2013: an updated systematic analysis. Lancet. 2015:430–40.
4. Nair H, Smeeth L, Rudan I, Gessner B, Aziz-Baumgartner E, Zhang JSF, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet. 2013;381:1380–90.
5. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18:1191–210.
6. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011;377:1264–75.
7. Shi T, McAllister DA, O’Brien KL, Smeeth EAF, Madhi S, Gessner B, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390:946–58.
8. Michelow I, Olsen K, Lozano J, Rollings WK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics. 2004;113:701–7.
9. Launes C, de-Sevilla MF, Selva L, Garcia Garcia JJ, Pallares R, Muñoz-Almagro C. Viral coinfection in children less than five years old with invasive pneumococcal disease. Pediatr Infect Dis J. 2012;31:650–3.
10. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372:835–45.
11. Lynch T, Blay L, Kellner JD, Osmond MH, Klassen TP, Durec T, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One. 2010;5:e11989.
12. Davies HD, Wang EE, Manson D, Babyn P, Shuckett B. Reliability of the chest radiograph in the diagnosis of lower respiratory infections in young children. Pediatr Infect Dis J. 1996;15:600–4.
13. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells. C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. Eur Respir J. 1997;10:1125–30.
14. Grijalva CG, Nuortti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. Antibiotic prescriptions rates for acute respiratory tract infections in the United States ambulatory settings, 1995–2006. JAMA. 2009;302:758–66.
15. Babady NE. The FilmArray respiratory panel: an automated, broadly multiplexed molecular test for the rapid and accurate detection of respiratory pathogens. Expert Rev Mol Diagn. 2013;13:779–88.
16. Popowchuk EB, O’Neill SS, Miller MB. Comparison of the BiofireFilmArray RP, GenmarkeSensor RVP, LuminexxTAG RVPv1, and LuminexxTAG RVP fast multiplex assays for detection of respiratory viruses. J Clin Microbiol. 2013;51:1528–33.
17. Rogers BR, Shankar P, Jerris RC, Kotzauer D, Anderson EJ, Watson JR, et al. Impact of a rapid respiratory panel test on patient outcomes. Arch Pathol Lab Med. 2015;139:636–41.
18. Pettit NN, Matushek S, Charnot-Katsikas A, Tesic V, Boonlanyagoon S, Brielmaier B, et al. Comparison of turnaround time and time to oseltamivir discontinuation between two respiratory viral panel testing methodologies. J Med Microbiol. 2015;64:312–3.
19. Xu M, Qin X, Astion ML, Rutledge JC, Simpson J, Jerome KR, et al. Implementation of FilmArray respiratory viral panel in a core laboratory improves testing turnaround time and patient care. Am J Clin Pathol. 2013;139:118–23.
20. Brendish NJ, Malachra AK, Armstrong L, Houghton R, Afiktn S, Nyimbiel E, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med. 2017;5:401–11.
21. Andrews D, Cherry V, Cooper BS, Virk M, Glass SK, Letters A, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use. BMC Infect Dis. 2017;17:671.
22. Choi S, Kahir R, Gautam-Goyal P, Mallotra P. Impact of respiratory viral panel polymerase chain reaction assay turnaround time on length of stay and antibiotic use in patients with respiratory viral illnesses. Hosp Pharm. 2017;52:640–4.
23. Infectious Diseases Society of America. An unmet medical need: rapid molecular diagnostics tests for respiratory tract infections. Clin Infect Dis. 2011;53:5384–95.
24. Lee SH, Ruan SY, Pan SC, Lee TF, Chien JY, Hsueh PR. Performance of a multiplex PCR pneumonia panel for the identification of respiratory pathogens and the main determinants of resistance from the lower respiratory tract specimens of adult patients in intensive care units. J Microbiol Immunol Infect. 2019;52:920–8.
25. Bradley JS, Byington CL, Shah SS, Alvrier B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Disease Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53:e25–76.