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Commentary

Molecular Testing for Respiratory Tract Infections May Have Favorable Impact on Real-world Healthcare Costs

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Abstract: Molecular testing by Polymerase Chain Reaction (PCR) has improved diagnostic performance to inform appropriate treatment. However, its impact on healthcare utilization and costs related to respiratory tract infections are yet to be studied in detail. The aim of this study is to evaluate the costs of healthcare utilization following traditional culture and molecular PCR diagnostic testing for respiratory tract infections. Real-world healthcare costs were evaluated over 4-weeks in patients (n = 1,362,226) with an upper respiratory tract infection who received a PCR test, compared to patients who received no test or who received a culture test in the Marketscan® Commercial Database by Merative™. Compared to culture ($586.32±$600.04 PMPM), the PCR test ($353.42±$291.95 PMPM) and no test cohorts ($377.19±$279.35 PMPM) were associated with lower total costs over a 4-week period. A significant component of this was attributed to lower pharmacy costs in the PCR cohort ($35.90±5.87) compared to the culture cohort ($61.10±9.11 PMPM) (p = 0.005). Given the dual global threats of respiratory infections and antibiotic resistance, this real-world observational analysis shows the potential for molecular testing to favorably impact subsequent healthcare utilization and costs.

Keywords: Polymerase Chain Reaction, Syndromic Multiplex Panels, Influenza Viruses, Respiratory Virus, Respiratory Tract Infection

Introduction

Acute respiratory tract infections (including non-specific upper respiratory infections, otitis media, sinusitis, pharyngitis, acute bronchitis, influenza, and pneumonia) are the most common reason patients seek ambulatory care in the United States, accounting for approximately 120 million visits per year or about 10% of all outpatient visits (Renati and Linder, 2016). While acute respiratory infections are often attributed to viral causes, antibiotics are prescribed in 10% of adult visits and 22% of pediatric outpatient visits (Steinman *et al*., 2003). Together, this accounts for the majority of antibiotics prescribed in both adult (47-56% of prescriptions) and pediatric (75-80% of prescriptions) populations, at 221 antibiotic prescriptions per 1000 population annually (Steinman *et al*., 2003; Fleming-Dutra *et al*., 2016). However, only 50% of these antibiotic prescriptions are considered to be appropriate for these conditions (Fleming-Dutra *et al*., 2016).

The inappropriate use of antibiotics to treat respiratory infections caused by viral pathogens leads to antibiotic resistance. Each year in the United States, antibiotic resistance causes 2.8 million infections and 35,000 deaths (CDC, 2024). As the clinical signs and symptoms of acute respiratory tract infections with viral and bacterial causes are similar, differentiation between causal pathogens is essential for enabling accurate diagnosis and appropriate pathogen-directed therapy (Hanson *et al*., 2020). Nucleic Acid Amplification Tests (NAATs), including Polymerase Chain Reaction (PCR), have improved the ability to detect and distinguish respiratory viral and bacterial pathogens, facilitate pathogen-directed treatment, reduce unnecessary use of antibiotics, and shorten hospital length of stay (Murdoch, 2016; Torres *et al*., 2016; Bibby *et al*., 2022). As a result, 2024 guidelines from the Infectious Disease Society of America (IDSA) have identified several important applications for PCR testing over rapid antigen and culture diagnostics for respiratory pathogen detection (Miller *et al*., 2024). Despite substantial evidence demonstrating improved test performance, the evidence surrounding the impact of PCR diagnostics on healthcare outcomes and costs for respiratory tract infections is inconclusive. Thus, the purpose of this real-world study

was to evaluate the impact of PCR testing across all test providers for acute respiratory infections on short-term healthcare costs through a retrospective analysis of large population-level healthcare claims.

Materials and Methods

Cohort Selection

Healthcare claims from the 2021 *Marketscan® Database by Merative™* were used to assess the real-world utilization and impact of PCR testing for respiratory tract infections. This database represents more than 20 million commercially insured individuals and this analysis encompassed data from the entire 2021 calendar year. Patients aged 18-65 with a healthcare claim (index claim) occurring at an outpatient site of service and an ICD-10-CM code indicating an acute respiratory infection diagnosis or associated symptoms (ICD-10-CM J00, J01.90, J06.9, J18.9, J20.9, R05.1, R09.81, and R50.9) were included in this study. Patients were further stratified by the diagnostic test associated with the index claim into the PCR cohort (CPT codes 87631, 87632, 87633, 87486, 87581, 87635, 87498, 87502, 87634 and 87798), the Culture cohort (CPT codes 87070, 87077, 87140, 87143, 87147, 87149, 87181, 87184, 87185 and 87186), or the No Test cohort (determined by the ICD-10-CM diagnosis with the absence of indicated CPT codes). It is important to note that the use of point-of-care rapid antigen testing was not explicitly assessed in this analysis and as such, patients in each cohort may have had rapid antigen diagnostic testing performed in addition to the cohort descriptors.

Healthcare utilization was evaluated by week for each cohort over a 4-week follow-up period to determine the short-term impact of laboratory test use. Catastrophic claims (>$100,000) and claims attributed to non-infectious complications (i.e., ER visits with ICD-10-CM documentation of broken leg) were excluded from the follow-up cost analysis.

Statistical Analysis

Table (1) summarizes the 4-week average of healthcare-related costs calculated per member per month (Cost of service/total number of members) for each cohort. One-way Analysis of Variance (ANOVA) was used to compare the three cohorts. A p-value of less than 0.05 was set to indicate statistically significant differences.

The study involved a retrospective analysis using secondary data and no interventions were made to patients during this study. All patient data included in the analyses were de-identified. Thus, this study was exempt from Institutional Review Board (IRB) review and in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Table 1: Monthly healthcare costs (per member) over 4-week follow-up for patients with no test compared to PCR and culture tests

	Per Member Per Month ($)			
	No test (n = 1,525,127)	PCR (n = 277,071)	Culture (n = 20,095)	p-value
Outpatient facility	$ 92.86 (±62.60)	$ 82.93 (±77.31)	$ 192.36 (±226.47)	0.513
Professional	$ 99.35 (±75.56)	$ 75.36 (±63.36)	$ 137.33 (±128.81)	0.654
Inpatient facility	$ 178.19 (±110.38)	$ 99.68 (±48.38)	$ 233.53 (±187.55)	0.376
Pharmacy	$ 50.15 (±8.73)	$ 35.90 (±5.87)	$ 61.10 (±9.11)*	0.005
Lab	$ 22.19 (±25.62)	$ 31.01 (±47.17)	$ 37.28 (50.56)	0.882
Other	$ 6.88 (±3.05)	$ 4.48 (±2.54)	$ 11.45 (±7.81)	0.196
Total PMPM	$377.19 (±279.35)	$353.42 (±291.95)	$586.32 (±600.04)	0.696

* Represents a statistically significant difference in the One-way ANOVA test ($p<0.05$). Values shown as (±) represent standard deviation

Results

In our study, 1,822,293 patients had a diagnosis or symptoms of an acute respiratory infection. A total of 83% of those patients (n = 1,525,127) received no diagnostic test beyond rapid antigen point-of-care testing. The use of PCR at the index visit was 13 times more common than the use of culture (n = 20,095 with culture; n = 277,071 with PCR). Both PCR ($353.42±$291.95 PMPM) and no test ($377.19±$279.35 PMPM) cohorts had lower total healthcare costs over the 4-week follow-up period compared to patients in the culture cohort ($586.32±$600.04 PMPM). Compared to culture, patients in the PCR cohort had lower pharmacy costs ($61.10±9.11 vs. $35.90±5.87). Within the follow-up period, the PCR cohort had no observed cost savings during the first week, however weeks two through four had reductions of 88.5, 29.5 and 11.8% respectively.

Discussion

This real-world observational analysis of healthcare claims across more than 1.8 million patients with respiratory tract infections demonstrated that only 14% of patients received diagnostic testing beyond the use of point-of-care antigen testing. In the outpatient setting, the use of PCR testing was 13 times more common than the use of culture, highlighting that most outpatient healthcare providers only test for bacterial respiratory pathogens in limited circumstances. While laboratory testing may not be considered necessary when the respiratory infection is considered mild and self-limiting, observed reductions in pharmacy spend in the group that

received molecular PCR testing in the month following diagnosis, provide preliminary insight suggesting that testing may result in more targeted and less empiric therapy (Stellrecht, 2017). Consequently, the findings of our analysis provide supporting evidence that the use of PCR testing for respiratory infections can aid in antibiotic stewardship efforts.

While select previous studies have shown similar impacts to antibiotic prescribing, the existing body of literature surrounding the impact of PCR diagnostics on healthcare resource utilization shows conflicting results; highlighting differences in provider practice dependent on the site of care (Brittain-Long *et al*., 2011; McCulloh *et al*., 2014; Noël *et al*., 2019; Beal *et al*., 2020; Clark *et al*., 2023). This study focused on the use of diagnostic testing exclusively in outpatient healthcare and contributed to a preliminary assessment of PCR diagnostics specific to ambulatory medicine. Noteworthy differences in mean total costs, outpatient facility costs, inpatient facility costs, and total costs were observed (though not statistically significant) between the culture and PCR cohorts. Nevertheless, large variability in costs by group and category was also noticed. While a difference in mean total costs per patient of $232.90 can have meaningful implications for efficiently managing a large patient population, new statistical methods need to be developed to analyze and interpret claims data with high variability and skewness in the real-world interpretation of such results (Mihaylova *et al*., 2011; Malehi *et al*., 2015).

Conclusion

Our report here demonstrated that PCR testing for respiratory infections was associated with lower subsequent healthcare costs compared to culture testing. This finding supports both the higher observed use of PCR testing compared to culture for respiratory tract infections and recent guidelines from the IDSA on molecular testing for respiratory infections supporting more accurate diagnoses and favorable healthcare outcomes. While this analysis shows a potentially meaningful impact, there are several limitations that must be considered when interpreting the results. The cohorts included in this analysis were not propensity-matched or adjusted based on risk assessment and as such the data presented here include real-world differences in provider test selection. In addition, this study assessed pharmacy spending as a whole and did not restrict the data assessed to antibiotic prescriptions alone. Thus, the interpretation of the pharmacy spending results in regard to reduced antibiotic prescriptions must be considered accordingly. Besides, this study is observational alone and in the absence of a matched cohort design precludes us from drawing direct conclusions that the cost reduction observed in the PCR and No Test cohorts equate to potential cost savings. Further research addressing these limitations and applying a propensity-matched design may help attribute cost-saving to the diagnostic testing administered. Finally, future research is needed to evaluate the impact of PCR testing on appropriate antibiotic prescribing. As PCR tests are becoming more widely adopted to identify respiratory pathogens, evaluation of current datasets will help demonstrate evidence of clinical utility and avoid underrepresentation of the test.

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Author's Contributions

Jairus Reddy: Conceptualization and design of the study. Contributed to writing of the manuscript.

Azia Evans: Methodology design. Contributed to conceptualization and research design of the study. Contributed to writing of the manuscript.

Vijay Singh: Formal data analysis and interpretation Contributed to data acquisition. Contributed to writing of the manuscript.

Maren S. Fragala: Original manuscript preparation. Contributed to data collection analysis. Project administration.

Pallavi Upadhyay: Contributed to data analysis and writing of the manuscript. Final editing and review of the manuscript.

Andrea French: Contributed to study methodology, data review and manuscript writing.

Steven E. Goldberg: Contributed to data acquisition and collection. Contributed to reviewing the article critically for intellectual content.

Ethics

The author does not see any ethical issues that may arise after the publication of this manuscript.

References

Beal, S. G., Posa, M., Gaffar, M., Reppucci, J., Mack, J. A., Gurka, M. J., Rand, K., Houck, H., & Kelly, M. N. (2020). Performance and Impact of a CLIA-waived, Point-of-care Respiratory PCR Panel in a Pediatric Clinic. *Pediatric Infectious Disease Journal*, *39*(3), 188–191. https://doi.org/10.1097/inf.0000000000002544

Bibby, H. L., de Koning, L., Seiden-Long, I., Zelyas, N., Church, D. L., & Berenger, B. M. (2022). A pragmatic randomized controlled trial of rapid on-site influenza and respiratory syncytial virus PCR testing in pediatric and adult populations. *BMC Infectious Diseases*, *22*(1), 854. https://doi.org/10.1186/s12879-022-07796-3

Brittain-Long, R., Westin, J., Olofsson, S., Lindh, M., & Andersson, L.-M. (2011). Access to a polymerase chain reaction assay method targeting 13 respiratory viruses can reduce antibiotics: a randomised, controlled trial. *BMC Medicine*, *9*(1), 44. https://doi.org/10.1186/1741-7015-9-44

CDC. (2024). *Antimicrobial Resistance Facts and Stats*. Antimicrobial Resistance. https://www.cdc.gov/antimicrobial-resistance/data-research/facts-stats/index.html

Clark, T. W., Lindsley, K., Wigmosta, T. B., Bhagat, A., Hemmert, R. B., Uyei, J., & Timbrook, T. T. (2023). Rapid multiplex PCR for respiratory viruses reduces time to result and improves clinical care: Results of a systematic review and meta-analysis. *Journal of Infection*, *86*(5), 462–475. https://doi.org/10.1016/j.jinf.2023.03.005

Fleming-Dutra, K. E., Hersh, A. L., Shapiro, D. J., Bartoces, M., Enns, E. A., File, T. M., Finkelstein, J. A., Gerber, J. S., Hyun, D. Y., Linder, J. A., Lynfield, R., Margolis, D. J., May, L. S., Merenstein, D., Metlay, J. P., Newland, J. G., Piccirillo, J. F., Roberts, R. M., Sanchez, G. V., … Hicks, L. A. (2016). Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *JAMA*, *315*(17), 1864. https://doi.org/10.1001/jama.2016.4151

Hanson, K. E., Azar, M. M., Banerjee, R., Chou, A., Colgrove, R. C., Ginocchio, C. C., Hayden, M. K., Holodiny, M., Jain, S., Koo, S., Levy, J., Timbrook, T. T., & Caliendo, A. M. (2020). Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations From the IDSA's Diagnostics Committee. *Clinical Infectious Diseases*, *71*(10), 2744–2751. https://doi.org/10.1093/cid/ciaa508

Malehi, A. S., Pourmotahari, F., & Angali, K. A. (2015). Statistical models for the analysis of skewed healthcare cost data: a simulation study. *Health Economics Review*, *5*(1), 11. https://doi.org/10.1186/s13561-015-0045-7

McCulloh, R. J., Andrea, S., Reinert, S., & Chapin, K. (2014). Potential Utility of Multiplex Amplification Respiratory Viral Panel Testing in the Management of Acute Respiratory Infection in Children: A Retrospective Analysis. *Journal of the Pediatric Infectious Diseases Society*, *3*(2), 146–153. https://doi.org/10.1093/jpids/pit073

Mihaylova, B., Briggs, A., O'Hagan, A., & Thompson, S. G. (2011). Review of statistical methods for analysing healthcare resources and costs. *Health Economics*, *20*(8), 897–916. https://doi.org/10.1002/hec.1653

Miller, J. M., Binnicker, M. J., Campbell, S., Carroll, K. C., Chapin, K. C., Gonzalez, M. D., Harrington, A., Jerris, R. C., Kehl, S. C., Leal, S. M., Patel, R., Pritt, B. S., Richter, S. S., Robinson-Dunn, B., Snyder, J. W., Telford, S., Theel, E. S., Thomson, R. B., Weinstein, M. P., & Yao, J. D. (2024). Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2024 Update by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). In *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciae104

Murdoch, D. R. (2016). How recent advances in molecular tests could impact the diagnosis of pneumonia. *Expert Review of Molecular Diagnostics*, *16*(5), 533–540. https://doi.org/10.1586/14737159.2016.1156536

Noël, K. C., Fontela, P. S., Winters, N., Quach, C., Gore, G., Robinson, J., Dendukuri, N., & Papenburg, J. (2019). The Clinical Utility of Respiratory Viral Testing in Hospitalized Children: A Meta-analysis. *Hospital Pediatrics*, *9*(7), 483–494. https://doi.org/10.1542/hpeds.2018-0233

Renati, S., & Linder, J. A. (2016). Necessity of office visits for acute respiratory infections in primary care. *Family Practice*, *33*(3), 312–317. https://doi.org/10.1093/fampra/cmw019

Steinman, M. A., Gonzales, R., Linder, J. A., & Landefeld, C. S. (2003). Changing Use of Antibiotics in Community-Based Outpatient Practice, 19911999. *Annals of Internal Medicine*, *138*(7), 525. https://doi.org/10.7326/0003-4819-138-7-200304010-00008

Stellrecht, K. A. (2017). *Molecular Testing for Respiratory Viruses* (W. B. Coleman & G. J. Tsongalis, Eds.; pp. 123–137). Academic Press. https://doi.org/10.1016/b978-0-12-800886-7.00011-x

Torres, A., Lee, N., Cilloniz, C., Vila, J., & Van der Eerden, M. (2016). Laboratory diagnosis of pneumonia in the molecular age. *European Respiratory Journal*, *48*(6), 1764–1778. https://doi.org/10.1183/13993003.01144-2016