ABSTRACT

Influenza and respiratory syncytial virus (RSV) infection are common causes of lower airway diseases. Rapid tests (antigen-based by immunochromatographic and molecular technique - RIT and RMT, respectively) with good diagnostic accuracy directly impacts the quality of patient care and hospitalization costs. This study aims to evaluate the implementation of point of care PCR (RMT) compared to rapid antigen-based tests (RIT) for influenza and RSV in the emergency department. Prospective cross section study in an Emergency Room (ER) from August to September 2019, where all patients with influenza like illness went through RIT and RMT. The patients were divided in a model of four clinical scenarios to evaluate cost and isolation time in the ER. Four hundred and twenty four patients were included in the study. RIT showed sensitivity of only 40% compared with RMT (100% specificity; PPV 100%; NPV 68.7%), causing 103 patients to mistakenly leave respiratory isolation, raising biological risk in the ER. Fast results from RMT led negative patients to leave isolation early (262:10 less hours of isolation), allowing cost reduction of USD 1.921,20. Nonetheless, RMT had higher cost than RIT in all clinical scenarios with an increase of USD 12.788,90 (69.9% of cost related to tests and isolation precautions). RIT had a lower direct cost, and due to the variation in sensitivity, it should not be indicated to exclude viral respiratory diseases, which may result in biological risk for the hospital environment. RMT had better diagnostic performance with faster results, allowing for less isolation time per patient tested.
KEYWORDS


RESUMO

Influenza e infecção pelo vírus sincicial respiratório (VSR) são causas comuns de doenças das vias aéreas inferiores. Testes rápidos (baseados em antígenos pela técnica imunocromatográfica e molecular - RIT e RMT, respectivamente) com boa precisão diagnóstica impactam diretamente na qualidade do atendimento ao paciente e nos custos de hospitalização. Este estudo visa avaliar a implementação RMT para influenza e VSR realizado no local de atendimento em comparação com testes rápidos baseados em antígenos (RIT) no departamento de emergência. Estudo prospectivo de corte transversal realizado em uma sala de emergência (SE), no período de agosto a setembro de 2019, onde todos os pacientes com diagnóstico de influenza passaram pelos testes RIT e RMT. Os pacientes foram divididos em um modelo de quatro cenários clínicos para avaliar o custo e o tempo de isolamento na SE. Quatrocentos e vinte e quatro pacientes foram incluídos no estudo. O RIT mostrou sensibilidade de apenas 40% comparado ao RMT (100% de especificidade; VPP 100%; VPN 68,7%), fazendo com que 103 pacientes saíssem erroneamente do isolamento respiratório, aumentando o risco biológico na ER. Resultados rápidos do RMT levaram os pacientes negativos a deixar o isolamento mais cedo (262:10 horas a menos de isolamento), permitindo uma redução de custos de USD 1.921,20. No entanto, o RMT teve um custo maior do que o RIT em todos os cenários clínicos com um aumento de USD 12.788,90 (69,9% do custo relacionado a testes e precauções de isolamento). RIT apresentou um custo direto menor, e devido a variação de sensibilidade não deve ser indicado para para excluir doenças respiratórias virais, podendo resultar em risco biológico para o ambiente hospitalar. RMT teve melhor desempenho no diagnóstico com resultados mais rápidos, permitindo menos tempo de isolamento por paciente testado.

PALAVRAS-CHAVE


RESUMEN

La influenza y la infección por el virus respiratorio sincitial (VRS) son causas comunes de enfermedad de las vías respiratorias inferiores. Las pruebas rápidas (basadas en antígenos por técnica inmu-
nocratica y molecular - RIT y RMT, respectivamente) con una buena precisión diagnóstica rec- percuten directamente en la calidad de la atención al paciente y en los costes de hospitalización. Este estudio tiene como objetivo evaluar la implementación de RMT para la gripe y el VRS en el punto de atención en comparación con las pruebas rápidas basadas en antígenos (RIT) en el servicio de emergencias. Estudio transversal prospectivo en una sala de emergencias (SE) de agosto a septiembre de 2019, donde todos los pacientes con enfermedad similar a la gripe fueron sometidos a RIT y RMT. Los pacientes se dividieron en un modelo de cuatro escenarios clínicos para evaluar el coste y el tiempo de aislamiento en la SE. Se incluyeron 424 pacientes en el estudio. La RIT mostró una sensibilidad de solo el 40% en comparación con la RMT (especificidad del 100%; VPP del 100%; VPN del 68,7%), lo que provocó que 103 pacientes salieran erróneamente del aislamiento respiratorio, aumentando el riesgo biológico en la SE. Los resultados rápidos de la RMT hicieron que los pacientes negativos abandonaran antes el aislamiento (262:10 horas menos de aislamiento), lo que permitió una reduci- ón de costes de 1.921,20 USD. La RMT tuvo un coste mayor que la RIT en todos los entornos clínicos, con un aumento de 12.788,90 USD (69,9% del coste relacionado con las pruebas y las precauciones de aislamiento). RIT tuvo un costo directo menor, y debido a la variación en la sensibilidad, no debe indicarse para excluir enfermedades respiratorias virales, lo que puede resultar en un riesgo bioló- gico para el ambiente hospitalario. RMT tuvo un mejor rendimiento diagnóstico con resultados más rápidos, permitiendo menos tiempo de aislamiento por paciente sometido a prueba.

PALABRAS-CLAVE

Influenza A, Influenza B, Virus Respiratorio Sincitial, Técnicas de Diagnóstico Molecular, Inmuno- ensayo, Farmacoeconomía.

1 INTRODUCTION

Lower airway infections caused 2.6 million deaths in 2019, being the fourth leading cause of death in the world (WHO, 2022). The percentage of deaths attributed to these infections remained above the epidemic threshold, particularly for influenza at the end of 2021 (WHO, 2021). The impact is even greater in children under 5 years of age, being the second leading cause of mortality in this age group and causing significant morbidity (BIONDO et al., 2018; WHO, 2020).

Influenza and respiratory syncytial virus (RSV) are common causes of these infections since they have respiratory tropism. Clinical manifestations of respiratory viral infections range from mild symp- toms, such as sore throat and coryza, to severe clinical conditions, including pneumonia and acute respiratory distress syndrome (ARDS), being difficult to distinguish the causative agent. Performing early etiological diagnosis through laboratory tests provides more specific clinical management deci- sions (BASILE et al., 2018; CLEMENTI et al., 2021).
Among the diagnostic tests most used today are direct and indirect immunofluorescence (IF), rapid diagnostic tests based on the detection of antigens such as the rapid immunochromatographic test (RIT), polymerase chain reaction - reverse transcriptase (RT-PCR) and the point-of-care rapid molecular tests (RMT) (BIANCHINI et al., 2020; SBP, 2020). Rapid tests are widely used to guide early treatment decisions and disease prevention, especially in pandemic contexts. RMT are more sensitive compared to antigen-based tests and their use is recommended in hospital settings over RIT (94% and 53.9% of sensitivity in adults, respectively) (AAP, 2021; VAN DER KRAAN et al., 2021).

The main objective of this study was to evaluate the implementation of rapid molecular tests compared to rapid antigen-based tests, and costs related to respiratory isolation in the ER.

2 METHODS

This is a prospective cross-sectional study comparing RMT diagnostic test for RSV and influenza A/B with the currently used immunochromatography methodology (RIT) for the routine diagnosis of respiratory viruses. The study was ethically approved by the Research Ethics Committee – University of Caxias do Sul, Rio Grande do Sul, Brazil (16476619.1.0000.5341).

The period of diagnostic tests application took place during the influenza season in southern Brazil from August to September 2019 at the Emergency Department at Unimed Nordeste Hospital (Caxias do Sul, Rio Grande do Sul, Brazil).

The study included all patients treated at the hospital’s emergency department, older than 30 days of life (no upper age limit), with influenza-like illness respiratory symptoms. Influenza-like illness was defined in children over 2 years old, adolescents, adults and elderly patients as cough or sore throat, with sudden onset fever - even if referred, associated with myalgia, headache, or arthralgia (BRASIL, 2017).

In children up to 2 years of age, the criteria for defining a flu syndrome were cough, runny nose and nasal obstruction associated with sudden onset fever - even if referred (BRASIL, 2017). None of the patients were excluded from the study because there was no incorrect completion or lack of data in the assessment of medical records. To reduce the possibility of bias, data collection and tabulation was performed by the principal investigator.

Two swabs were obtained from each patient, one for influenza A and B through nasal collection and the other for RSV, through nasopharyngeal collection. The sample size was defined through the number of ID NOW™ kits (RMT) made available by the Abbott® company. The collection was performed for convenience by the laboratory shift. The emergency protocol for respiratory infections management was turned into a flowchart, including pathways for both tests (RIT and RMT) and was used to measure time of each step and estimate cost. The flowchart can be observed in Figure 1.

The following were evaluated for each pathway: a) times and costs (including the cost per molecular test so that there is cost neutrality in both flows); b) number of positive patients; c) qualitative evaluation of the molecular test in the emergency room and d) reduction of patient isolation time with flow using the RMT, if any.
Costs in United States Dollar (USD/2019) and economic assumptions were established for the preparation of the calculations to be performed: RIT 12,40 USD, RMT 49,61 USD, Radiography 12,40 USD, Laboratory exams 8,68 USD, Isolation Room per Hour 7,31 USD. Oseltamivir is provided free of charge by the Ministry of Health; therefore, it is not included in treatment cost for the hospital.

The fact that the patient has a positive test is not decisive for the hospitalization, as it depends on clinical stability. Thus, this variable was not included in the comparative cost analysis. The cleaning/disinfection of the diagnostic imaging room and isolation unit is independent of the test results. After establishing the diagnostic process flowchart, patients were classified in four categories/clinical scenarios (CS):

- **CS 1 (Y/Y)** - Patients who underwent chest radiography and blood tests in addition to the diagnostic test for respiratory disease.
- **CS 2 (N/Y)** - Patients who only underwent blood tests in addition to the diagnostic test for respiratory disease.
- **CS 3 (Y/N)** - Patients who only underwent chest radiography in addition to the diagnostic test for respiratory disease.
- **CS 4 (N/N)** - Patients who underwent the diagnostic test for respiratory disease.

RMT tests were not allowed to be performed in the ER, so the samples went to the laboratory to be processed and were performed with some delay according to the available professional at the time. The time considered for RMT was the sample collection time plus fifteen minutes, according to the manufacturer’s guidelines. The processing time in ideal conditions for the RMT as recommended by the manufacturer (to be performed in the ER) was considered for analysis as the ideal RMT time (RMTi) (Figure 1).

The time of the test results, as well as the time of isolation ending in case of a negative test was considered. In the CS4, since the patients did not go through blood tests or chest X-ray, both positive and negative tests would end the isolation period due to medical discharge. The following were recorded for each patient for determination of patient release time with RIT and RMT:

a) Emergency isolation time using the immunochromatographic method in hours.
b) Time from sample collection plus fifteen minutes and the ideal RMT time in hours was used for RMT results.
c) Time in hospital: Time of arrival to administrative discharge in hours.
Figure 1 – Flowchart of the diagnostic process by immunochromatographic test (RIT) and molecular technique (RMT). Rio Grande do Sul, Brazil, 2019

Source: Elaborated by the authors.

3 RESULTS

A total of 424 patients were evaluated, from which 24 were hospitalized for different reasons (two patients had RMT positive for RSV and the other two patients for influenza) and were excluded from
all analysis. Also, RIT and RMT had the same results on all these 24 patients.

When considering only patients who did not require hospitalization, the RMT detected 174 cases of influenza and 4 cases of RSV, while the RIT identified 71 and 2 cases, respectively. The RIT demonstrated a sensitivity of 40.8%, specificity of 100%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 68.7% and diagnostic accuracy of 74%, when compared to the RMT.

The number of patients in each scenario and cost comparison can be observed on Table 1. The request for additional tests, such as chest x-ray and blood count, was defined by the attending physician, considering the patient’s clinical manifestations and the waiting time for diagnostic tests. The comparison of the values shown in the table was performed on the absolute number of patients who fit the clinical scenarios.

Table 1 – Costs in clinical scenarios 1, 2, 3 and 4 with RIT and RMT

<table>
<thead>
<tr>
<th>Variables</th>
<th>CS 1</th>
<th>CS 2</th>
<th>CS 3</th>
<th>CS 4</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=111)</td>
<td>(n=25)</td>
<td>(n=113)</td>
<td>(n=151)</td>
<td>(n=400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood tests</td>
<td>RIT</td>
<td>RMT</td>
<td>RIT</td>
<td>RMT</td>
<td>RIT</td>
<td>RMT</td>
</tr>
<tr>
<td>cost (USD)</td>
<td>903.85</td>
<td>903.85</td>
<td>217.08</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diagnostic test</td>
<td>1,376.93</td>
<td>5,507.72</td>
<td>310.11</td>
<td>1,401.74</td>
<td>5,606.96</td>
<td>1,873.12</td>
</tr>
<tr>
<td>Negative test isolation cost</td>
<td>1,485.72</td>
<td>995.36</td>
<td>175.65</td>
<td>91.48</td>
<td>1,606.48</td>
<td>925.83</td>
</tr>
<tr>
<td>Positive test isolation cost</td>
<td>1,410.55</td>
<td>1,738.22</td>
<td>274.45</td>
<td>343.08</td>
<td>1,083.18</td>
<td>1,251.51</td>
</tr>
<tr>
<td>Cleaning</td>
<td>55.07</td>
<td>55.07</td>
<td>12.40</td>
<td>12.40</td>
<td>56.96</td>
<td>56.06</td>
</tr>
<tr>
<td>Total (USD)</td>
<td>5,283.12</td>
<td>9,260.22</td>
<td>989.69</td>
<td>1,005.41</td>
<td>4,147.46</td>
<td>7,840.36</td>
</tr>
<tr>
<td>Total per patient (USD)</td>
<td>47.59</td>
<td>83.42</td>
<td>39.58</td>
<td>76.21</td>
<td>36.70</td>
<td>69.38</td>
</tr>
</tbody>
</table>

Source: Research data
All costs in United States Dollar (USD) – 2019.
Direct conversion value to United States dollar in 2019 - US$ 1 = R$ 4.0307.5
CS: Clinical Scenario; RIT: Rapid Immunochromatographic Test; RMTi: Rapid Molecular Test in ideal conditions.

As observed on Table 1, patients with negative tests had a significant decrease in isolation time when using RMTi in all scenarios. In CS1 we had less 67h of isolation, 11.5h in CS2, 93h in CS3, 90.5h in CS4, and less 262h in all scenarios, which resulted in savings of USD 1,921.19 in total patients. Patients with positive tests, on the other hand, had a cost increase of USD 574.59 (a total of 78.5 hours) when using RMTi in almost all scenarios, except for CS4 (additional tests were not necessary and the patient could be discharged after the test results even when positive). The cost increase comes from the greater number of patients diagnosed assertively and kept in isolation until they leave the hospital. Comparison of isolation time in negative patients can be seen in the box plot (Figure 2)

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5 Data from the Central Bank of Brazil - Quotation date used: 12/31/2019.
Figure 2 – Comparison of isolation time between RMTi and RIT in negative patients. CS: Clinical Scenario; RIT: Rapid Immunochromatographic Test; RMTi: Rapid Molecular Test in ideal conditions

4 DISCUSSION

In this study, a sensitivity of only 40.8%, specificity of 100% and a diagnostic accuracy of 74% for RIT was found. A meta-analysis of 308 articles evaluated the diagnostic accuracy of point-of-care tests in lower airway infections. When evaluating RIT for influenza, a sensitivity of 69% (95% CI 64% - 74%) and specificity of 97% (95% CI 96% - 98%) were observed. For RSV, RIT sensitivity and specificity were 83% (95% CI 77% - 87%) and 97% (95% CI 95% - 98%), respectively (GENTILOTTI et al., 2022).

The same study showed that RMT performed better with 92% (95% CI 88% - 94%) sensitivity for influenza and 94% (95% CI 71% - 99%) for RSV, and specificity of 98% (95% CI 95% - 99%) and 97% (95% CI 64% - 100%), respectively (GENTILOTTI et al., 2022). These results, while showing a significant difference between RIT and RMT performances, report RIT sensitivity much higher than the observed in our study.

Kanwar and collaborators (2020) also demonstrated that among different rapid molecular tests, all of them had high sensitivity for influenza A and B diagnosis, in addition to a specificity
> 97%. In that same study, the sensitivities found for RMT ID NOW were 93.2% and 97.2% for influenza A and B, respectively.

Due to the large amount of evidence available on the accuracy of RMTs, the Infectious Diseases Society of America (IDSA) recommended in 2018 the use of RMTs over RITs. When not available, RIT could be used but with the guidance of performing molecular tests to confirm negative results (UYEKI et al., 2019). Thus, negative results from a RIT should be evaluated with caution as they do not exclude the disease.

Despite the clear advantages of using this molecular diagnostic methods, RMT remains a technology that is not widely available in hospitals in Brazil due to its higher unit cost. Mac and collaborators (2020) evaluated the cost-effectiveness of implementing point-of-care RMT in different therapeutic decision-making scenarios (based on different types of diagnostic tests, clinical assessment only, treatment of all patients regardless of exams or not to treat) and used as a measure of cost-effectiveness the Net Health benefit (NHB), a calculation that takes into account the total cost of the strategy, the total amount of health resulting from the strategy (quality-adjusted life years - QALYs) and cost-benefit limit (unit: $/QALY).

Performing RMT was the second most cost-effective strategy, with the highest NHB (15.0277 QALYs), and the lowest number of deaths (1,571 per 100,000). Although the strategy of treating all patients without testing was more cost-effective, it resulted in a greater number of adverse events, inappropriate treatment, and lack of diagnostic confirmation (UYEKI et al., 2019).

Van der Kraan and collaborators (2021) compared the cost-effectiveness of RMT with RT-PCR in the emergency department and observed a saving of €93.26 per patient, in addition to a negative predictive value of 99% for patient withdrawal of isolation. Another unexpected benefit observed was the use of the RMT as an additional tool for the clinical decision of patient release.

Schmidt and collaborators (2019), reported the importance of rapid and sensitive detection of viruses causing airway infection to define therapeutic and isolation approaches for the hospital infection control service. Faster results of diagnostic tests allow for better management of hospital beds, reduction of infectious diseases’ transmission and early antiviral administration. Brachmann and collaborators (2019) comments that by having fast and safe diagnostic methodologies performed in emergency departments, there is a significant reduction in the laboratory workflow and optimization in case management, with better results in medical care.

In this study, the RMT cost was higher in all clinical scenarios (average of USD 33.24 per patient). The impact of RMT reducing unnecessary isolation time due to fast results was taken into consideration, while also considering the increased cost in patients with positive tests due to greater diagnostic assertiveness. The increase in the isolation time of these patients is essential for the safety of others in the hospital. The difference on the price of the test was very significant (USD 14.885,74) and even if the RMT were performed in the emergency department, the resulting extra savings of USD 1.393,86 would not make RMT cost less than RIT.

Previous studies show that RMT is a strategy that can be cost-effective when analyzing direct and indirect costs. You and collaborators (2017) had a unit cost of USD 48 per RMT, being a cost-effective strategy only in the period of high influenza circulation with an influenza prevalence threshold of...
14.3% or higher, showing the cost of RMT almost halved compared to RT-PCR (43.73 euros vs. 80.44 euros). The RMT was four times more expensive than the RIT in our study, even considering the indirect gains in a period of high influenza circulation in southern Brazil. Molecular tests still have high direct costs, overlapping agility in results and indirect gains, and even in a period of high prevalence of the disease, direct costs impact on their indication.

In the study carried out by O’Connell and collaborators (2020), an important decrease in antibiotic prescribing (33% less) and length of hospital stay (from 5.26 days to 3.73 days) was also observed when implementing point-of-care RMT. Considering the great worldwide problem of the indiscriminate use of antibiotics causing bacterial resistance, reliable diagnostic tests that help to reduce their prescription are of great value (MURRAY et al., 2022).

Analysing the flowchart of the diagnostic process, the use of RMT has the potential to reduce the request for additional tests (chest radiography and blood tests), since these would be left to the physician’s discretion in case of a positive result. Since 400 patients did not require hospitalization due to clinical stability, the positive result of the RMT could reassure the physician on duty to guide and treat most patients at home with less complementary exams. Diagnostic tests with faster results would also bring the indirect benefit of patient satisfaction for having defined their diagnosis (BRACHMANN et al., 2019).

Among the relevant aspects of this study, the impact of positive and negative results was measured separately. This allowed part of the cost increase to be classified as a gain in infection control due to the use of a better test. This increase would mask the decrease in respiratory isolation viewed in negative tests as unnecessary isolation time. The fact that the tests were performed on the same patients, results in differences that are entirely due to each test performed.

Limitations must be observed. As patients took both tests we could not compare two different groups for a more complete analysis. Also, some variables were estimated (like the RMT result time) and mixed with real world variables. The use of antibiotics in the ER and the time of onset of symptoms cannot be evaluated due to lack of uniformity in medical records. Finally, it is not possible to know whether the additional exams were performed before or after the release of the results so we couldn’t measure the RMT impact in those requests.

5 CONCLUSION

The use of the RMT ID NOW has demonstrated greater diagnostic effectiveness, improving the management of patients with positive tests. Despite the direct cost per patient being higher in all scenarios evaluated, our study showed total savings of USD 2.096,85 in the isolation of patients, diminishing the cost difference between RIT and RMT from USD 14.885,74 to USD 12.788,90. The greatest benefit of RMT implementation was the increase in diagnostic assertiveness, decrease in the risk of nosocomial transmission and unnecessary respiratory isolation, and faster flow of patients through the ER.
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