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RESEARCH
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COST-EFFECTIVENESS ANALYSIS OF LEUKOCYTE COUNTERS FOR DIAGNOSIS IN SUS

Análise de custo-efetividade de contadores de leucócitos para diagnóstico no SUS
Análisis de coste-efectividad de contadores de leucocitos para diagnóstico en SUS

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ABSTRACT

Objective: to evaluate the cost-effectiveness of point-of-care leukocyte analyzers to aid in the diagnosis of airway infections in the SUS. **Method:** this is a cost-effectiveness study using a deterministic model developed from a decision tree. **Results:** the use of devices to perform diagnostic tests at the point of treatment has become increasingly popular and accepted around the world in view of the increased demand for care and the need to reduce the time it takes to return exam results to optimization of outcomes. After the Roll Back of the decision tree, the most cost-effective strategy was a white blood cell count-driven clinical investigation using the point-of-care analyzer to guide antibiotic prescribing. **Conclusion:** Evidence suggests that the use of POC analyzers for WBC counts and differentials at the point of care is a cost-effective alternative as part of a strategy to aid in the diagnosis and therapeutic management of cases of non-specific acute respiratory infections.

DESCRIPTORS: Cost-effectiveness; Leukogram; Acute respiratory diseases; Laboratory diagnosis, Health technology assessment.

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RESUMO

Objetivo: avaliar o custo-efetividade de analisadores de leucócitos do tipo ponto de atendimento para o auxílio diagnóstico de infecções de vias aéreas no SUS. **Método:** trata de um estudo de custo-efetividade usando modelo determinístico desenvolvido a partir de uma árvore de decisão. **Resultados:** o uso de dispositivos para a realização de testes diagnósticos em ponto de tratamento tem se tornado cada vez mais popular e aceito em todo o mundo diante do aumento da demanda de atendimentos e da necessidade de redução do tempo de retorno dos resultados dos exames para otimização dos desfechos. Após o *Roll Back* da árvore de decisão, a estratégia mais custo-efetiva foi a de investigação clínica orientada por contagem de leucócitos utilizando o analisador de ponto de atendimento para orientar a prescrição de antibióticos. **Conclusão:** as evidências sugerem que o uso de analisadores POC para contagem de leucócitos e diferenciais no local de atendimento é uma alternativa custo-efetivo como parte de uma estratégia para auxiliar no diagnóstico e no manejo terapêutico dos casos de infeções respiratórias agudas inespecíficas.

DESCRITORES: Custo-efetividade; Leucograma; Doenças respiratórias agudas; Diagnóstico laboratorial, Avaliação de tecnologias em saúde.

RESUMEN

Objetivo: evaluar la rentabilidad de los analizadores de leucocitos en el lugar de atención para ayudar en el diagnóstico de infecciones de las vías respiratorias en el SUS. **Método:** se trata de un estudio de rentabilidad utilizando un modelo determinista desarrollado a partir de un árbol de decisiones. Resultados: el uso de dispositivos para realizar pruebas de diagnóstico en el punto de tratamiento se ha vuelto cada vez más popular y aceptado en todo el mundo en vista de la mayor demanda de atención y la necesidad de reducir el tiempo que lleva devolver los resultados del examen a la optimización de los resultados. Después de la reversión del árbol de decisiones, la estrategia más rentable fue una investigación clínica basada en el recuento de glóbulos blancos utilizando el analizador en el punto de atención para guiar la prescripción de antibióticos. **Conclusión:** La evidencia sugiere que el uso de analizadores POC para recuentos y diferenciales de GB en el punto de atención es una alternativa rentable como parte de una estrategia para ayudar en el diagnóstico y manejo terapéutico de casos de infecciones respiratorias agudas inespecíficas.

DESCRIPTORES: Rentabilidad; Leucograma; Enfermedades respiratorias agudas; Diagnóstico de laboratorio, Evaluación de tecnologías sanitarias.

INTRODUÇÃO

Respiratory diseases are an important public health problem and currently represent the leading cause of mortality in children under five years of age. While upper respiratory tract infections (URIs) are very frequent but rarely life-threatening, lower respiratory tract infections (LRTIs) are responsible for more serious illnesses such as influenza, pneumonia, tuberculosis, and bronchiolitis, which are major contributors to mortality from acute respiratory infections (ARIs).[1–4]

The lymphocyte count as well as the neutrophil count (WBC) can serve as a simple marker to discriminate between severe bacterial and viral infections, and are better predictors of bacteremia than routine parameters such as the C-reactive protein (CRP) level.[1,2]

At best, test times can range from 4 to 48 hours, although the recommended turnaround time is less than 60 minutes, allowing, in the shortest amount of time, the healthcare professional to have access to critical laboratory information to inform rapid treatment decisions and monitor the patient's therapeutic response.[7–8]

In the Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS (SIGTAP) the WBC test is registered in the group of procedures with diagnostic purpose, and is considered a medium complexity test and financed by the medium and high complexity.

Alternatively, there are technologies available in the national market, known as point-of-care (POC) technologies, which enable WBC counting at the point of care. These technologies are also known as point-of-care technologies and are increasingly being used for screening or diagnostic purposes, although they are still not widespread in Brazil.[8–10]

They are suitable for use in clinical laboratories and for point-of-care testing, operated directly by the healthcare professional during the care of pediatric (≥ 3 months) and adult patients.[9–10] The analytical accuracy and feasibility for WBC counts and differentials is comparable to that of central laboratory analyzers. The mean difference (bias) between the POC and the reference test result was 1.1 109/L (95% limits of agreement of -6.5 to 8.8 109/L) for WBC count. The single measurement correlation coefficient between the POC and the reference method was 0.988 (95% CI 0.980 - 0.992).[11–12]

In terms of accuracy, compared to central analyzers, the average coefficient of variation is quite small, around 2.22% (95% CI 1.23 - 3.82%) for white blood cells, 2.44% (range 1.37-4.17%) for neutrophils, 8.56% (range 2.46 -10.14%) for lymphocytes and 15, 2% (range 0.00-16.1%) for monocytes, demonstrating good comparability between the methods, suggesting that POC is a viable and relatively accurate method for WBCs among children, although less accurate for differential counts of lymphocytes, monocytes, and eosinophils.[12]

The use of POC has been shown to change the flow of care and assist in triaging patients seen in emergency departments by providing additional information that helped confirm the patient's clinical condition, aiding and positively impacting clinical decisions.[13–14]

Although studies may suggest that this is a safe and reliable technology, especially in terms of diagnostic accuracy, its costs are still relatively higher than the tests performed in central laboratories. In this sense, the question of this research is whether the effectiveness of POC analyzers for leukocyte count at the point of care and reduction of antibiotic prescriptions in SUS, justifies their cost.

METHODS

This is a cost-effectiveness analysis study, with a static model based on a decision tree to estimate the incremental cost-effectiveness of using a care strategy in primary health care units. Effectiveness was assessed as a reduction in antibiotic prescribing rates and was estimated from a systematic review of the literature.

The study design followed the premises of the Methodological Guidelines of the Ministry of Health.15 In order to increase the transparency of the proposed study, the main aspects of the studies were summarized according to the CHEERS Task Force Report checklist.[16]

The objective of this economic analysis is to estimate the incremental cost-effectiveness of using a strategy of care in primary health care units or in emergency care units, of patients with symptoms suggestive of acute non-specific respiratory infection, with WBC and differential counts to five cells at the point of care, using a POC device, compared to a strategy of care in the same settings, but without the prior WBC count and with antibiotic prescription for all patients at the first visit according to the institutional protocol.

Target population: pediatric patients (≥ 3 months) and adults presenting symptoms suggestive of acute nonspecific respiratory infection, seen in primary care units and sus emergency care units.

Perspective of analysis: Unified Health System (SUS). Buyers: care strategies without prior WBC count, with antibiotic prescription for all patients at the first visit according to institutional protocols. Time horizon: 6 (six) months. Discount rate: not applicable. Effectiveness measures: rate (%) of antibiotic prescription. Cost estimate: direct costs associated with the POC exam, antibiotic use, outpatient follow-up and hospitalizations. Currency: local currency (Real). Model chosen: decision tree. Sensitivity analysis: deterministic (Tornado Diagram) and probabilistic (Monte Carlo Simulation).

Concerning the costs of the strategies, considering that the POC can be used more than once for diagnostic support in many cases,

and not only once and for a single patient, the estimated costs for its acquisition were not considered in the model, but only the costs of a microcuvette needed to perform an exam. The other costs considered in the model were the costs with antibiotic therapy, the costs with outpatient care, and the costs with hospitalization. It should be noted that the performance of WBC counts and differentials using POC is not yet incorporated in the SUS' list of procedures.

To estimate the costs of antibiotic therapy, we considered the Protocol of the Hospital das Clinicas, Botucatu Medical School, for the treatment of lower respiratory tract infection, specifically pneumonia. The recommended duration of treatment can vary from 5 to 7 days by oral or gastric route, and may be the use of tablets, capsules, or oral suspension, depending on the presentation available on the national market.[17]

The protocol for the treatment of community-acquired pneumonia, developed by the Hospital das Clinicas of the Botucatu School of Medicine, is described below.

Previously healthy patients without previous antibiotic therapy: first option with the use of macrolides: azithromycin 500mg on the first day and 250mg/day for another 4 days or clarithromycin 500mg 12/12 hours. As a second option - betalactams: amoxicillin + clavulanate 625mg 8/8h or amoxicillin 500mg 8/8h or cefuroxime 500mg 12/12h.

Patient with associated diseases or recent treatment with antibiotics (< 3 months): first choice - betalactam + macrolide: amoxicillin 500mg 8/8h + azithromycin 500mg on day 1 and 250mg/day for another 4 days or cefuroxime 500mg 12/12h + azithromycin on day 1 and 250mg/day for another 4 days or amoxicillin + clavulanate 625mg 8/8h + azithromycin on day 1 and 250mg/day for another 4 days. Clarithromycin 500mg 12/12h as an option to azithromycin in either option. The second option - quinolone: levofloxacin 750mg/day or moxifloxacin 400mg/day.

The estimate of the cost of antibiotic therapy considered only the costs with the acquisition of antibiotics. The weighted average prices of these drugs were extracted from the Health Price Bank (BPS).[17] For the maximum and minimum values, a variation of ± 50% was considered, as well as the average costs with the use of the following antibiotics for 7 days of treatment relative to the first and second treatment options provided in the protocol: 1- Scheme A. Recommended for patients with no previous treatment: azithromycin 250mg oral suspension 12/12h (1st option) or amoxicillin + clavulanate 625mg 8/8h (2nd option). Total of 1 bottle of azithromycin and 21 tablets of amoxicillin + clavulanate. 2 - Scheme B. Recommended for patients with associated diseases or recent treatment with antibiotics: cefuroxime 500mg12/12h + azithromycin 500mg capsule 8/8h (1st option) and levofloxacin 750mg (2nd option). Total of 14 cefuroxime tablets, 21 azithromycin tablets and 7 levofloxacin tablets.

These regimens were chosen because they represent the maximum and minimum values of the treatment regimen options considered in the protocol.[17] The cost of antibiotic therapy was estimated from the arithmetic mean of the sum of the two treatment options in each regimen. Table 1 describes the total cost of antibiotic therapy for 7 days of treatment according to the regimens assumed in the model, considering a ±50% variation.

The cost with the WBC count and differential tests using the POC considered the need to perform 01 or 02 tests on average per patient. For all costs except hospitalization, an average variation of ± 50% was considered. For hospital costs, the mean costs and the maximum and minimum values (variation by region of the country) were considered, related to procedure 0303140151 - treatment of pneumonias or influenza (GRIPE), Subgroup 0303 - Clinical treatment (other specialties), elective and urgent care, for a mean length of stay of 6.6 days (6 to 7.2).

The costs with outpatient care (Table 2) considered procedure 03.01.06.009-6 - medical care in emergency unit, Group 03 - Clinical procedures and Subgroup 01 - Consultations / Attendances / Follow-up, Form of Organization 06 - Consultation / Emergency care (in general). For the patient›s follow-up, we considered 03 consultations until healing / discharge and a range of 1 to 5 consultations.

The measure of effectiveness was the rate of reduction in antibiotic prescriptions in the strategies evaluated. The estimates were taken from a randomized clinical trial developed in Italy that estimated the effectiveness of the diagnostic investigation strategy with the use of POC at 77% and of the strategy without use of POC at 23%.[14]

All patients presented with some sign or symptom suggestive of acute nonspecific upper respiratory tract infection, such as cough, sneezing, muscle pain, nasal discharge, or purulent mucus, with an evolution time of no more than 10 days), associated with at least one finding of hyperemia of the pharynx and/or tympani, and normal breath sounds.

The model did not consider patients with a history of congenital or acquired immunodeficiency, chronic lung diseases (cystic fibrosis, ciliary dyskinesia, bronchodysplasia, chronic bronchiectasis, congenital or acquired), and leukemia, as well as patients with an unequivocal and already defined diagnosis of acute otitis media, acute sinusitis, and lower respiratory tract infections, which are usually easier to diagnose from the findings of fever and/or otalgia, bulging and hyperemia of the eardrum, prevalent in cases of otitis media; fever, purulent rhinorrhea, postnasal drip, and cough lasting for more than 10 days with improvement after treatment, often seen in cases of acute sinusitis; and cough, abnormal breath sounds, wheezing, and crackles, findings often seen in cases of pneumonias, the most common lower respiratory tract disease in pediatric patients.

A WBC count >15,000/mm^3 was considered as the cut-off point for the recommendation of empiric antibiotic therapy, according to the scheme established in the institutional protocol. For patients with WBC counts <15,000/mm^3, the recommendation was to treat symptomatically, without the use of antibiotics, with the possibility of admitting their use if the patient remains febrile 48 hours after the first visit. In the alternative scenario, only patients with leukocytosis (Total Leukocytes >15,000 mm^3) revealed by the exam with the use of POC at the point of care receive antibiotic therapy at medical discretion.[17]

All patients are followed up as outpatients with up to three visits and for up to six months of follow-up, depending on the evolution of the condition, and whether or not symptoms disappear or are cured. Hospital admission could be indicated for patients diagnosed with pneumonia, or who remained febrile after seven days of outpatient follow-up and antibiotic therapy, or who presented some complication during follow-up.

For outpatient follow-up, it was considered that all patients who do not have complications, regardless of diagnosis, need only a single visit. For those who remained febrile after the seventh day of treatment, even after antibiotic prescription, but who did not require hospital admission, the model assumed three outpatient visits.

Cure was defined as absence of fever, absence of pharyngeal hyperemia, absence of rhinorrhea and sneezing, diminished cough, and normal breath sounds. The currency is the Real. In the decision tree model (Figure 1), each of the alternatives in the decision node has its own costs and consequences. For the

Table 1 – Total cost of antibiotic therapy for 7 days of treatment according to the schemes assumed in the model, considering a variation of ±50%.

Proposed Scheme	Total Cost	Average Cost	littlelest	Larger
Scheme A	R$ 20,37	R$ 10,18	R$ 5,09	R$ 15,27
Scheme B	R$ 195,65	R$ 97,82	R$ 48,91	R$ 146,73
Custo from antibiotic therapy (scheme A + scheme B)	R$ 216,02	R$ 108,01	R$ 54,00	R$ 162,01

Source: Healthcare Price Bank (HPCB). The records shown specify purchases made in the last 18 months, which corresponds to the following period: 01-09-2019 to 01/03/2021.3

Table 2 – Inpatient and outpatient costs for the treatment of community-acquired pneumonia

Procedures	Average Cost	Littlelest	Larger
Outpatient follow-up (03.01.06.009-6)	R$ 11,00	R$ 5,09	R$ 15,27
Hospital admissions (0303140151)	R$ 1.292,88	R$ 1.013,99	R$ 1.552,08
Microcuvettes	R$ 23,32	R$ 15,55	R$ 31,10

Source: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/qiuf.def e NOTA TÉCNICA N° 1/2021-DAHU/SAES/MS.

parameters imputed in the model, an arbitrary variation of ± 50% was allowed for the cost estimates, 20% for the effectiveness and probability estimates. Only parameters of the pneumonia death variable were extracted from official SUS data. All other estimates, both for effectiveness and probability, were extrapolated from a randomized clinical trial.[14]

For all patients who had no complications, although they were not cured and regardless of whether or not they received antibiotic therapy, and regardless of the WBC count, the model assumed that after 6 months, because of loss to follow-up, the patients were considered alive as those who did not die from pneumonia after hospital admission. For those patients with pneumonia but who did not require hospital care, the model assumed that they remained in outpatient follow-up and had three visits at follow-up. For all these possibilities (death from pneumonia, outpatient follow-up), the model considered absorbing states.

As for the sensitivity analysis, only parametric and second-order uncertainties were explored in the model. To this end, multivariate sensitivity analysis was performed by plotting Tornado plot of the Net Monetary Benefit (BLM). For the probabilistic sensitivity analysis,1,000 Monte Carlo simulations were performed. The imputed variables in the model were converted to probabilistic distributions, assuming Beta distribution for the effectiveness and probability variables and Gamma distribution for the cost variables.

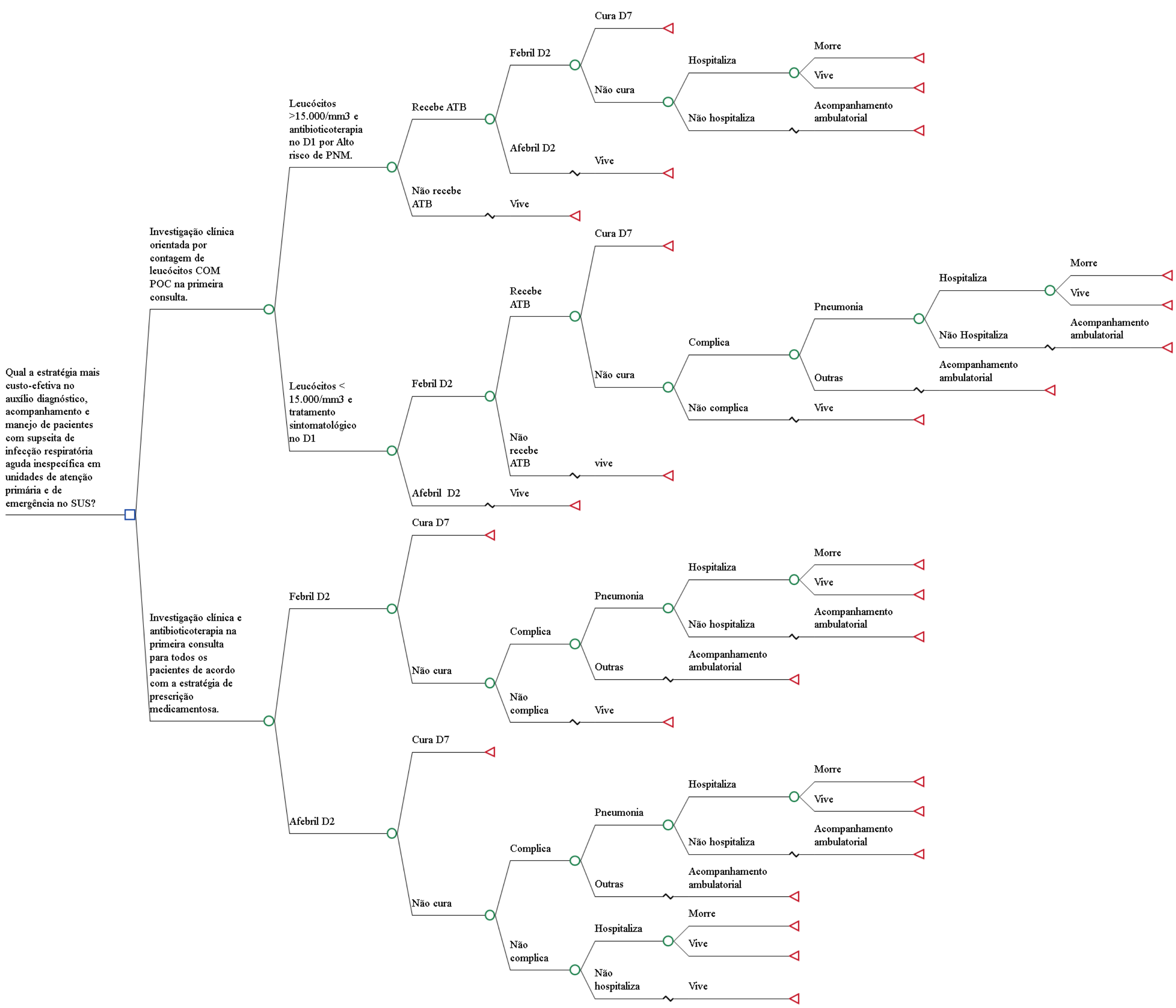

Figure 1 – Decision tree model.
Prepared with the aid of TreeAge Pro Healthcare Software®.

RESULTS

The results of the model show that using the HemoCue® WBC DIFF POC as part of a strategy to aid in the diagnosis and therapeutic management of pediatric patients to reduce antibiotic prescription rates in primary care and urgent care units is the most cost-effective alternative.

After rolling back the decision tree model, the result revealed that the most cost-effective strategy is the WBC count-guided clinical investigation using the HemoCue® WBC DIFF POC at the point of care, at the first visit. As can be seen in the graph of the cost-effectiveness analysis presented in Figure 2, there was absolute dominance of the alternative scenario strategy using the POC over the strategy used in the reference scenario.

According to the cost-effectiveness analysis report (Table 1) the alternative strategy using POC resulted in an incremental effectiveness of 53% reduction in antibiotic prescriptions and a savings of R$70.80 when compared to the strategy used in the alternative scenario, with an incremental cost-effectiveness ratio (ICER) of -R$132.02 per patient per 6 months, confirming absolute dominance.

Deterministic sensitivity analysis, performed using a Tornado Diagram, demonstrated that for an expected value of R$27,031.97, considering a hypothetical willingness-to-pay threshold of R$35. 172.00 (1 GDP per capita of 2020), the variable that most impacted the model was the effectiveness of the HemoCue® WBC DIFF POC as part of the strategy used in the alternative scenario, and could in the worst BLM scenario reach R$ 21,000.00 and, in the best scenario, R$ 32,000.00, but in both cases, assumed positive values.

The results of the Monte Carlo simulations (1,000 iterations) were plotted on incremental cost-effectiveness and acceptability curve graphs to evaluate the robustness of the model, based on the random variability of the imputed parameters. The results of the 1,000 Monte Carlo simulations are plotted in Figure 3, in the CEI Scatter Plot. The alternative scenario is in the comparator and the reference scenario is in the baseline. Therefore, the alternative scenario was compared to the reference scenario. For this analysis, the willingness to pay was only $1,000.

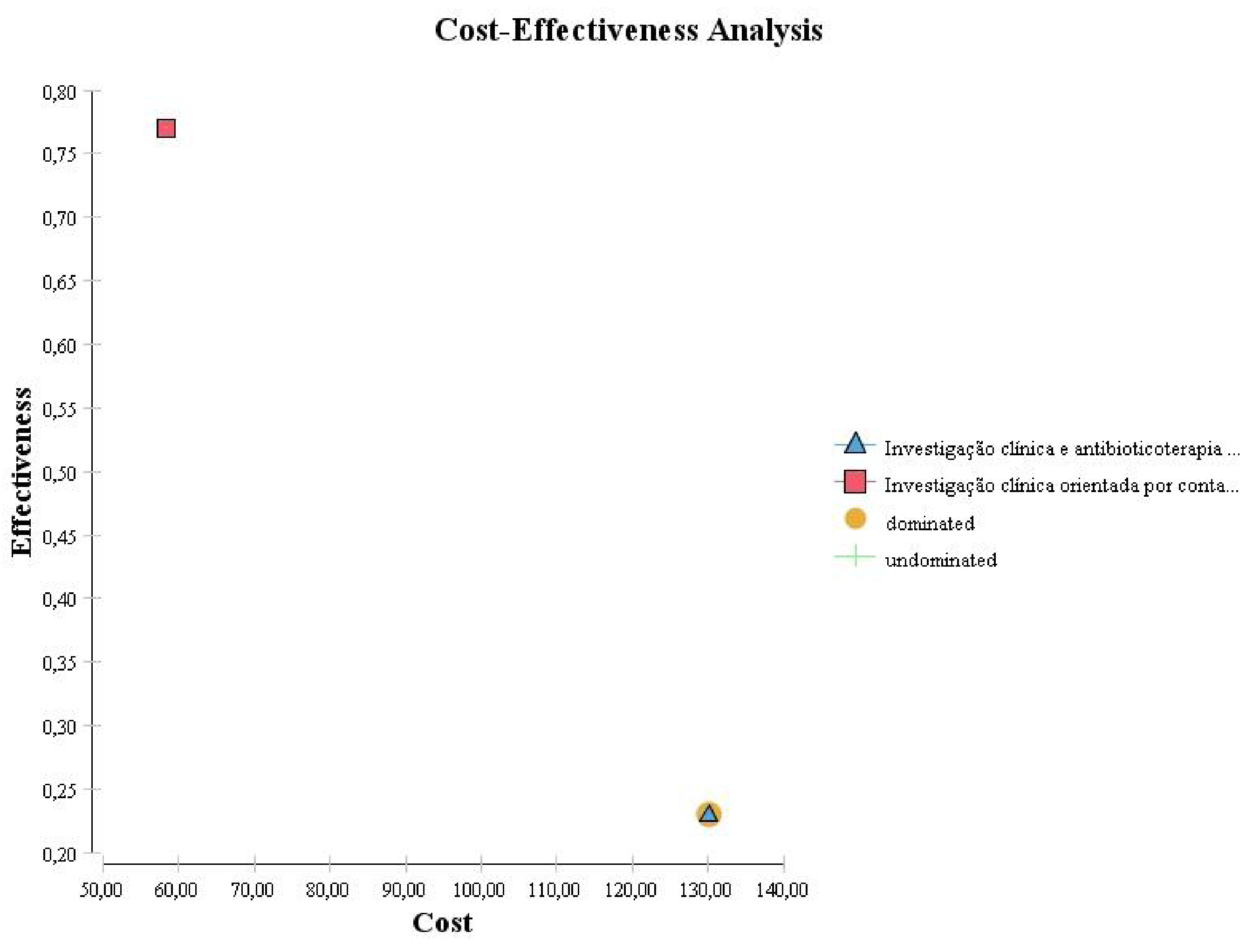

Figure 2 – Graph of the cost-effectiveness analysis.

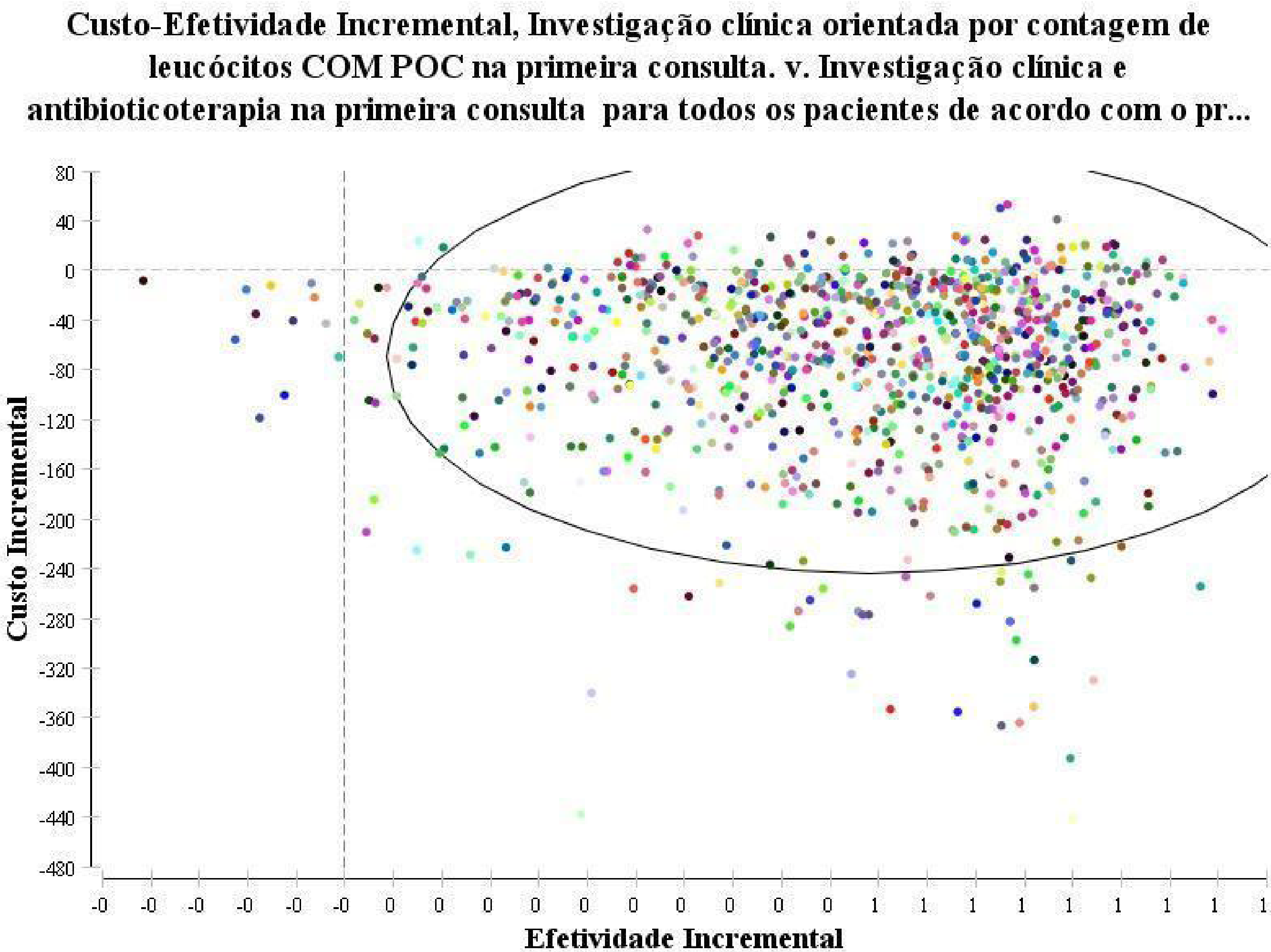

Figure 3 – Scatter Plot of Incremental Cost-Effectiveness. Clinical investigation guided by WBC count with POC at first visit vs Clinical investigation and antibiotic therapy at first visit for all patients according to the protocol.

In the report of the results of the 1,000 iterations of the Monte Carlo simulations, it is observed that the proportion of iterations concentrated in quadrant IV (upper) was 0.904 and zero in the C6 component of quadrant II (lower), thus demonstrating the absolute dominance of the strategy proposed in the alternative scenario (HemoCue® WBC DIFF POC) in more than 90% of the simulations, in the probabilistic sensitivity analysis.

The acceptability curve was plotted, in order to evaluate the variation of the probability that the strategy used in the reference scenario is cost-effective, as a function of the variation of the willingness-to-pay threshold. Considering that the CERI was negative and in the order of approximately -R$132.02, a willingness-to-pay variation of 0 to R$100.00 was considered. The result of the analysis shows a small variation in the probability of the strategy used in the alternative scenario being cost-effective (90 - 100%), with no possibility of being outperformed by the reference scenario strategy, even if the willingness-to-pay threshold was close to zero, reaffirming once again the absolute dominance.

DISCUSSION

In most cases of suspected non-specific acute respiratory infection, the choice of antibiotic takes into consideration the most likely pathogen at the site of disease acquisition; individual risk factors; presence of associated diseases; and epidemiologic and cost-effectiveness factors. Although still controversial, the use of antibiotics to treat atypical pathogens in cases of community-acquired pneumonia (CAP) of lesser severity has often been used because of the inability to obtain WBC and microbiological profile results soon after CAP diagnosis, which would allow choosing antibiotics targeted to specific agents and avoiding unnecessary prescribing of these drugs.

Portable equipment for point-of-care blood tests, although already available in the national market, are still little used. In general, POC analyzers tend to measure lower WBC counts than the laboratory method, which could be considered something undesirable, but which does not compromise the correlation between the two methods especially when it comes to total WBC, neutrophil and lymphocyte counts, whose correlation coefficient was reported in the studies as higher than 0.95 between the two methods, and therefore demonstrating their clinical utility in the diagnostic aid and clinical management of patients seen in primary care units and emergency units with suspected acute non-specific respiratory infections.[7]

The possibility of reducing turnaround time and increasing the chance of more timely medical decisions in remote emergency departments or outpatient clinics appears to be possible with the safe and effective use of point-of-care technologies.[7]

POC analyzers for WBC and differential count seem to provide a safe, precise test with satisfactory accuracy for point-of-care use by non-laboratory health professionals, such as physicians and nurses, with prior training, and effective for diagnostic support and reducing antibiotic prescription rates at the first visit, thus avoiding unnecessary prescription and use of these drugs.

The results of the model show that the use of POC as part of a strategy to aid in diagnosis and therapeutic management in order to reduce antibiotic prescription rates in primary care and emergency care units is the most cost-effective alternative.

The use of POC showed in the model incremental effectiveness of 53% for reducing antibiotic prescriptions and a savings of R$70.80 and incremental cost-effectiveness ratio (ICER) of -R$132.02 per patient per 6 months, confirming its absolute dominance.

CONCLUSION

Evidence suggests that the use of POC analyzers for WBC and differential counts at the point of care is a cost-effective alternative as part of a strategy to aid diagnosis and therapeutic management of cases of non-specific acute respiratory infections.

Considering the high incidence of acute non-specific respiratory infections seen in the SUS, the incorporation of this technology may, in the medium and long term, enable an interesting saving of financial resources with the avoided prescription and use of antibiotics.

REFERENCES

1. Fioravanti C. Progress and challenges for respiratory health in Brazil. Lancet Respir Med. [Internet]. 2015 [cited 2021 oct 07]; 3(5). Available from: http://dx.doi.org/10.1016/S2213-2600(15)00152-6.

2. Chalupa P, Beran O, Herwald H, Kaspříková N, Holub M. Evaluation of potential biomarkers for the discrimination of bacterial and viral infections. Infection. [Internet]. 2011 [cited 2021 oct 07]; 39(5). Available from: http://dx.doi.org/10.1007/s15010-011-0126-4.

3. World Health Organization (WHO). Respiratory tract diseases. [Internet]. 2015 [cited 2021 oct 07]. Available from: http://www.emro.who.int/health-topics/respiratory-tract-diseases/index.html.

4. World Health Organization (WHO). WHO Guidelines. Pandemic and epidemic diseases. Infection prevention and control of epidemic and pandemic-prone acute respiratory infections. 2014 [cited 2021 oct 07]. Available from: http://apps.who.int/iris/bitstream/10665/112656/1/9789241507134_eng.pdf?ua=1.

5. European Respiratory Society - ERS. Forum of International Respiratory Societies. The Global Impact of Respiratory Disease – Second Edition. European Respiratory Society. [Internet]. 2017 [cited 2021 oct 07]. Available from: https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf.

6. ECRI Institute. Building Quality into Point-of-Care Testing Programs: Recommendations for POCT Coordinators and New Service Providers. [Internet]. 2021 [cited 2021 oct 07]. Available from: https://www.ecri.org/search-results/member-preview/hdjournal/pages/building-quality-into-point-of-care-testing-programs.

7. Hawkins RC. Laboratory turnaround time. The Clinical biochemist. [Internet]. 2007 [cited 2021 oct 07]; 28(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2282400/pdf/cbr28_4p179.pdf.

8. Sonego M, Pellegrin MC, Becker G, Lazzerini M. Risk factors for mortality from acute lower respiratory infections (ALRI) in children under five years of age in low and middle-income countries: a systematic review and meta-analysis of observational studies. PLoS One. [Internet]. 2015 [cited 2021 oct 07];10(1):e0116380. Available from: http://dx.doi.org/10.1371/journal.pone.0116380.

9. Lindberg S, Jönsson I, Nilsson M, Johnsson E, Jonasson-Bjäräng T. A novel technology for 5-part differentiation of leukocytes point-ofcare. Point Care. [Internet]. 2014 [cited 2021 oct 07]; 13. Available from: http://dx.doi.org/10.1097/POC.0000000000000015.

10. Lohman AC, VAN Rijn I, Lindhardt CL, Vonthein R, Rades D, & Holländer, NH. Preliminary Results from a Prospective Study Comparing White Blood Cell and Neutrophil Counts from a Laboratory to Those Measured with a New Device in Patients with Breast Cancer. In vivo. [Internet]. 2018 [cited 2021 oct 07]; 32(5). Available from: http://dx.doi.org/10.21873/invivo.11378.

11. Ivaska L, Niemelä J, Leino P, Mertsola J, Peltola V. Accuracy and Feasibility of Point-Of- Care White Blood Cell Count and C-Reactive Protein Measurements at the Pediatric Emergency Department. PLoS ONE. [Internet]. 2015 [cited 2021 oct 07]; 10(6): e0129920. Available from: https://doi.org/10.1371/journal.pone.0129920.

12. Spaeth B, Shephard M, Kokcinar R, Duckworth L, Omond R. Impact of point-of-care testing for white blood cell count on triage of patients with infection in the remote Northern Territory of Australia. Pathology. [Internet]. 2019 [cited 2021 oct 07]; 51(5). Available from: https://doi.org/10.1016/j.pathol.2019.04.003.

13. Cioffi L, Limauro R, Sassi R, Boccazzi A, Del Gaizo D. Decreased Antibiotic Prescription in an Italian Pediatric Population With Nonspecific and Persistent Upper Respiratory Tract Infections by Use of a Point-of-Care White Blood Cell Count, in Addition to Antibiotic Delayed Prescription Strategy. Glob Pediatr Health. [Internet]. 2016 [cited 2021 oct 07]; 8(3):2333794X15615771. Available from: https://doi.org/10.1177/2333794X15615771.

14. Ministério da Saúde (BR). Secretaria de Atenção à Saúde. Diretrizes Metodológicas: Diretriz de Avaliação Econômica. 2a edição. Brasilia: Ministério da Saúde; 2014 [acesso em 07 de outubro 2021. Disponível em: http://bvsms.saude.gov.br/bvs/ct/PDF/dirtrizes_de_avaliacao_economica.pdf.

15. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al*. ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. [Internet]. 2013 [cited 2021 oct 07]; (2). Available from: https://doi.org/10.1016/j.jval.2013.02.002.

16. Gaiolla, PSA, Coelho LS, Cavalcante RS. Recomendações para o atendimento aos pacientes com infecção do trato respiratório inferior: pneumonia adquirida na comunidade, pneumonia associada aos cuidados de saúde, pneumonia hospitalar, exacerbação de doença pulmonar obstrutiva crônica, exacerbação de bronquiectasia / Paula Schmidt Azevedo Gaiolla; Liana Sousa Coelho, Ricardo De Sousa Cavalcante. – Botucatu – SP. Hospital das Clínicas da Faculdade de Medicina de Botucatu. Botucatu – SP, 2015.

17. Ministério da Saúde (BR). Banco de Preços em Saúde. 2018. Brasília: Ministério da Saúde; 2018 [acesso em 07 de outubro 2021]. Disponível em: http://bps.saude.gov.br/visao/consultaPublica/relatorios/geral/index.jsf.