ORIGINAL ARTICLE

Analysis of the Budget Impact of Fractional Exhaled Nitric Oxide Monitoring in the Management of Childhood Asthma: The Colombian National Health System Perspective

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) testing is a simple, noninvasive approach to assessing airway inflammation with minimal discomfort that provides results within a few minutes. For policy makers, the economic impact of this technology is the main concern, especially in developing countries. We evaluated the budget impact of asthma management using FeNO monitoring in patients aged between 4 and 18 years in Colombia.
Methods: A budget impact analysis was performed to evaluate the potential cost of FeNO monitoring. The analysis was based on a 5-year time horizon and performed from the perspective of the Colombian National Health System. The incremental budget impact was calculated by subtracting the cost of the new treatment, in which FeNO is reimbursed, from the cost of conventional treatment without FeNO (management based on clinical symptoms [with or without spirometry/peak flow] or asthma guidelines [or both] for asthma-related cases). Univariate 1-way sensitivity analyses were performed.
Results: In the base case analysis the 5-year costs associated with FeNO and non-FeNO were estimated to be €469 904 130 and €480 485 149, respectively, indicating savings for the Colombian National Health System of €10 581 019 if FeNO is adopted for the routine management of patients with persistent asthma. This result proved to be robust in the univariate 1-way sensitivity analysis.
Conclusion: FeNO monitoring generated cost savings in emergency settings for infants with persistent asthma. This evidence can be used by decision makers in Colombia to improve clinical practice guidelines and should be replicated to validate the results in other middle-income countries.

Key words: Fractional exhaled nitric oxide. Colombia. Persistent asthma.

Resumen

Antecedentes: El óxido nítrico en aire exhalado es una medición simple y no invasiva de la inflamación de las vías respiratorias cuyos resultados están disponibles en pocos minutos. Para los responsables de la formulación de políticas sanitarias, la principal preocupación es el impacto económico que implica la adaptación de esta tecnología, muy especialmente en los países en desarrollo. Este estudio tiene como objetivo evaluar el impacto presupuestario, en el sistema Nacional de Salud de Colombia, del manejo del asma mediante la monitorización de óxido nítrico exhalado en pacientes entre 4 y 18 años.
Métodos: Se realizó un análisis de impacto presupuestario para evaluar el posible impacto financiero derivado de la implementación de la monitorización óxido nítrico exhalado fraccionado en el asma. El análisis consideró un horizonte temporal de 5 años y la perspectiva del Sistema Nacional de Salud de Colombia. El impacto presupuestario incremental se calculó restando el costo del nuevo tratamiento, en el que se reembolsa el FeNO, del costo del tratamiento convencional sin FeNO (manejo basado en síntomas clínicos (con o sin espirometría / flujo máximo) o guías de asma (o ambos), para los relacionados con el asma). Se realizaron análisis de sensibilidad univariantes de una vía.
Resultados: En el análisis del caso base, los costos a 5 años asociados a FeNO y no FeNO se estimaron en 469.904.130 € y 480.485.149 € respectivamente, lo que indica un ahorro para la Salud Nacional de Colombia igual a 10.581.019 € si se adopta la monitorización de FeNO, en el manejo rutinario de pacientes con asma persistente. La solidez de este resultado fue confirmada en el análisis de sensibilidad univariante, unidireccional.
Conclusión: El óxido nítrico exhalado fraccionado ahorró costos en los entornos de emergencia en población pediátrica con asma persistente. Esta evidencia puede ser utilizada por los tomadores de decisiones en nuestro país para mejorar las guías de práctica clínica y debe ser replicada para validar sus resultados en otros países de ingresos medios.

Palabras clave: Óxido nítrico exhalado. Colombia. Asma persistente.

Introduction

Periodic assessment and early management of airway inflammation in patients with asthma are the principal strategies for preventing hospitalizations, as recommended by international and local clinical guidelines (1). Frequent measurement of airway inflammation during monitoring plays an important role in anticipating exacerbations and optimizing the use of biological drugs and corticosteroids [2,3].

Fractional exhaled nitric oxide (FeNO) may be a surrogate marker for type 2 airway inflammation (2). FeNO testing is a simple, noninvasive approach to measuring airway inflammation that entails minimal discomfort for the patient and yields results within a few minutes. FeNO correlates with airway eosinophilia in biopsy and bronchoalveolar lavage fluid specimens (3). In fact, a meta-analysis of 8 clinical trials in children found that FeNO-guided treatment reduced asthma exacerbations (4). However, the routine use of FeNO monitoring in asthma and in children has not been uniformly adopted by all countries, especially developing countries.

For policy makers, the economic impact of adapting FeNO monitoring is the main concern, especially in developing countries. Economic evaluations of this approach to asthma management in developed countries have shown FeNO monitoring to be cost-effective (5-8). However, cost-effectiveness analyses alone do not provide information on the drug's impact on the total health care budget, because this is dependent on the number of treated patients. In this paper, we aimed to evaluate the budget impact of asthma management based on FeNO monitoring in patients aged between 4 and 18 years in Colombia.

Methods

Analytical Framework

A budget impact analysis was performed to evaluate the potential cost of FeNO monitoring. The analysis was performed from the perspective of the Colombian National Health System over a 5-year period. A budget impact model was developed as a Microsoft Excel macro-enabled workbook to evaluate the incremental budget impact of asthma management based on FeNO monitoring. The incremental budget impact was calculated by subtracting the cost of the new treatment, in which FeNO monitoring is reimbursed, from the cost of the conventional treatment without FeNO monitoring (management based on clinical symptoms with or without spirometry/peak flow or asthma guidelines [or both], for asthma-related cases). During the construction of the economic model, 100% adherence to the FeNO strategy was assumed, as were the absence of differences in market share between the brands and a stable incidence of asthma during the study period. Details of these assumptions are provided in Table 1.

Base Case and Estimation of Target Population

The base case was a child aged 5 to 18 years with no cardiac, neurological, respiratory, or other chronic disease

Table 1. Assumption Used to Develop the Base Case Analysis

Assumption	References
Adherence is considered to be 100%	Assumption based on the opinion of clinical experts
All trademarks during the study period have the same market share, with no price differences between them	Assumption based on the opinion of clinical experts, since this technology is not yet approved in local clinical practice guidelines and no trademark has entered the local market
The incidence of persistent asthma is stable over the study period	Assumption based on the opinion of clinical experts

Table 2. Parameters Used in the Base Case

Type of parameter	Base case value	Range for 1-way sensitivity analyses	Reference
Demographics			
Population between 5-18 years	9 541 341		[9]
Annual population growth	1.5%		[9]
Epidemiology			
Prevalence of asthma	9.2%	5%-12%	[10]
Persistent asthma, %	53%	20%-60%	[11]
Infants with controller treatment, %	20%	10%-30%	[12]
Effectiveness of FeNO			
Relative risk of reduction of exacerbations	0.76	0.49-0.80	[4]
Market share			
1 y	20%		
2 y	40%		
3 y	60%		
4 y	80%		
5 y	100%		

Abbreviation: FeNO, fractional exhaled nitric oxide.

and a diagnosis of persistent asthma managed with controller treatment and FeNO monitoring (1). To estimate the size of the target population, we estimated the size of the population for the first year by applying data for the total population aged 4-18 years in Colombia (9), the prevalence of asthma in children aged 4-18 years in Colombia (10), the frequency of persistent asthma in Colombia (11), and the proportion of patients with persistent asthma with controller treatment in Colombia (12). An annual population growth of 1.5% was assumed based on the average national growth rate for the period 2015-2019 (9) (Table 2).

Intervention

Information regarding the effect of FeNO monitoring was extracted from a recent systematic review and meta-analysis of 8 randomized clinical trials that evaluate the efficacy of tailoring asthma interventions based on FeNO compared with not using FeNO (management based on clinical symptoms [with or without spirometry/peak flow] or asthma guidelines or both for asthma-related cases). In this study, asthma exacerbations were significantly less frequent in the FeNO group than in the control group (OR, 0.62; 95%CI, 0.49-0.80; 1279 participants; 8 studies) (4). We assumed that commercially available FeNO monitoring would become more frequent. In the base case scenario, the uptake rate of FeNO was assumed to be 20%, increasing by 20% each year based on the estimates of the marketing authorization holder.

This study was approved by the Institutional Review Board of University of Antioquia (2015-4690).

Study Period

The study period was 5 years. The maximum follow-up time was set to be 4 years. A longer perspective was not considered relevant for the budget holder. All results are depicted cumulatively from 1 to 5 years.

Resource Use and Cost

A Markov simulation model with 3 mutually exclusive nonabsorbent states was used to compare the estimated cost associated with asthma management based on FeNO monitoring compared with asthma management without FeNO monitoring (standard therapy). According to the natural history, 3 health states were defined, as follows: no symptoms or asthma controlled, suboptimal control without exacerbation, and asthma exacerbation with a cycle length of 1 week. All patients entering the model were symptom-free

Table 3. Costs (in Euros) Used in the Base Case and Sensitivity Analyses

Model input	Base case value	SA range for 1-way sensitivity analyses	Distribution
Intervention cost			
FeNO per patient	39.6	4.2-45	γ(SD:1.08)
Cost of hospitalization			
Daily cost in pediatric ward	84.5	71.4-90.7	γ(SD:8.53)
Hospital length of stay, d	5.50	4.00-8.00	γ(SD:1.04)
PICU-related cost			
Daily cost in PICU	361	382-311	γ(SD:18.89)
PICU length of stay, d	10.9	7.75-15.05	γ(SD:3.26)
Emergency visit prior hospitalization cost			
Daily cost of emergency ward	59	45.5-63.5	γ(SD:19.27)
Direct medical cost per patient-day			
Specialist referrals	9.5	9.2-9.8	γ(SD:1.72)
Chest physiotherapy	4.6	4.4-4.8	γ(SD:1.23)
Chest radiography	2.5	2.4-2.7	γ(SD:0.73)
Other diagnostic imaging	0.01	0-0.2	γ(SD:0.08)
Complete blood cell counts	1.0	0.96-1.0	γ(SD:0.28)
Other laboratory tests	3.9	3.7-3.9	γ(SD:0.37)
Oxygen	1.2	1.1-1.3	γ(SD:0.41)
Nebulization	14.4	1.1-1.3	γ(SD:4.52)
Levalbuterol	1.0	0.9-1.1	γ(SD:0.16)
Systemic antibiotics	1.1	0.9-1.1	γ(SD:0.49)
Systemic or inhaled corticosteroids	0.1	0-0.8	γ(SD:4.18)
Bronchodilators	0.03	0.03-0.04	γ(SD:0.02)
Other drugs	0.6	0.6-0.7	γ(SD:0.04)
Medical devices	9.1	8.6-10	γ(SD:2.66)
Indirect cost patient-day	15.3	14-17	γ(SD:4.30)

Abbreviations: FeNO, fractional exhaled nitric oxide; PICU, pediatric intensive care unit.

children diagnosed with mild-to-moderate allergic asthma and receiving inhaled corticosteroids as maintenance therapy. The probabilities of the model and the cost of each health state were extracted from a previously published study of asthma in Colombia (13). In brief, all data on costs and use of resources were collected directly from medical invoices and electronic medical records. The direct costs considered in the analysis included visits to the emergency department, specialist referrals, chest physiotherapy, diagnostic support (eg, laboratory, electrocardiogram, x-ray), medication (eg, oxygen, nebulization, antibiotics, corticosteroids, bronchodilators), medical devices, stay in intensive care units, and stay in general medical wards (Table 3). All costs were expressed in US dollars (currency rate: €1.00 = COP$ 4.238) (14),(15). The human capital method was used for the evaluation of the indirect costs associated with parents' loss of productivity, assuming that everyone receives an income of at least the legal minimum wage for formal or informal work. The opportunity cost of the productivity loss at the workplace and that of the caregiver were assessed based on the minimum wage (Colombian minimum wage per month for 2019: €204). The government-approved legal minimum wage was taken as a reference instead of an average or median wage, as over 75% of the Colombian population earns the minimum wage (9). Given that all the patients with asthma included in this study were children, we assumed that at least 1 family member accompanied the patient permanently during hospitalization, since pediatric hospitals in Colombia usually allow only 1 companion per patient in the hospital. The cost associated with transportation and food (not including an overnight stay) was assumed to correspond to 50% of the minimum wage per day.

Sensitivity Analyses

The robustness of the base case was evaluated using 1-way sensitivity analyses. The parameters used and their range in the 1-way sensitivity analyses are detailed in Table 3. Expert opinion and literature data were consulted to determine ranges of parameters to be tested in the sensitivity analysis. The results of the sensitivity analysis are presented in a tornado diagram showing the impact on the base case of uncertainty in the parameters used in the model. A threshold analysis of the cost of FeNO was used to determine its threshold value. Microsoft Excel was used in all analyses.

Results

Base Case

In the base-case analysis, the 5-year costs associated with FeNO and no-FeNO were estimated to be €469 904 130 and €480 485 149, respectively, indicating savings for Colombian National Health System of €10 581 019 if FeNO monitoring is adopted for the routine management of patients with persistent asthma (Table 4). Savings increased over the years as more and more patients received FeNO. The final saving was 4.34%.

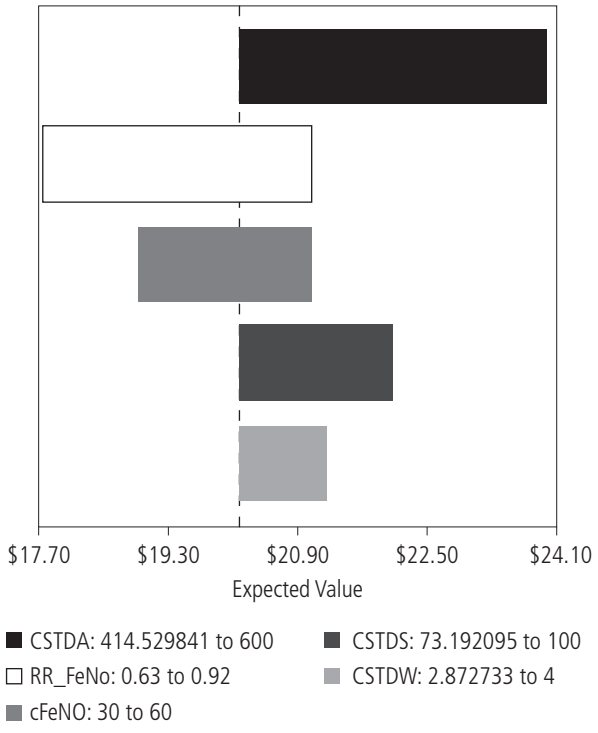

Figure 1. Tornado diagram. CSTDA indicates cost per well-controlled patient; FeNO, fractional exhaled nitric oxide; RR_FeNO, relative risk of reduction of exacerbations of FeNO; cFeNO, cost of FeNO; CSTDS, cost per patient in suboptimal control; CSTDW, cost per patient in asthma exacerbation.

Table 4. Base Case

	No. of patients	No. of patients treated with FeNO	Cost FeNO, €	Cost No FeNO, €	Savings, €	Savings, %
Year 1	86 979	9220	111 455 654	112 430 562	974 909	0.87%
Year 2	93 502	19 822	118 766 801	120 862 855	2 096 054	1.73%
Year 3	94 905	30 180	119 484 556	122 675 797	3 191 242	2.60%
Year 4	96 328	40 843	120 197 120	124 515 934	4 318 814	3.47%
Year 5	97 773	51 820	120 904 178	126 383 673	5 479 495	4.34%
Total	371 714	100 065	469 904 130	480 485 149	10 581 018	2.20%

Abbreviation: FeNO, fractional exhaled nitric oxide.

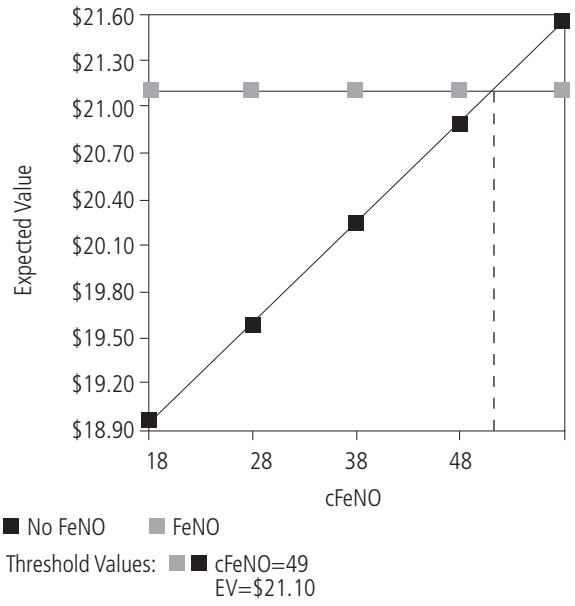

Figure 2. Threshold analysis of the cost of FeNO. cFeNO indicates cost of FeNO; FeNO, fractional exhaled nitric oxide; EV, expected value.

Univariate 1-way sensitivity analysis was performed to assess the robustness of the results from the base case. The major parameters used in the analysis were varied once, as detailed in Tables 2 and 3. The results of the sensitivity analysis are presented in a Tornado diagram showing the potential impact on the base case results of uncertainty about the main parameters used in the model (Figure 1). In this figure, the 3 variables with the greatest influence on the expected cost of FeNO monitoring were the cost per well-controlled patient, the relative risk of reduction of exacerbations of FeNO monitoring, and the cost of FeNO monitoring per patient. In the threshold analysis of FeNO cost, the threshold value was €49. An increase in the total cost of FeNO monitoring per patient higher than this value resulted in a higher expected cost per patient in the FeNO scenario than in the non-FeNO scenario. It also resulted in a loss of the savings expected in the population (Figure 2).

Discussion

Our study suggests that FeNO monitoring generates cost-savings for treatment of infants with persistent asthma. Compared with the current therapy (non-FeNO) over a 5-year period, the alternative with FeNO monitoring provided total cost savings of €10 581 019. This study is the first economic analysis in Colombia to show the real impact of this approach if adopted for the treatment of patients with persistent asthma. We consider this cost-saving as relevant if we compare it with the national budget allocated for communicable diseases. The magnitude of the savings for the health system is not negligible. Total public health spending for chronic diseases in Colombia ranges from €432 to €441 million annually (16). The savings generated by FeNO monitoring at 4 years would correspond to almost 1.2% of this budget, which could be achieved with a single intervention. This is not a negligible value in our setting.

Our findings are in line with those of previous studies (8). Adding FeNO monitoring to standard asthma care saved €62.53 per patient-year and improved quality-adjusted life years by 0.026 per patient-year. The budget impact analysis revealed a potential net yearly saving of €129 million if FeNO monitoring had been used in primary care settings in Spain. Similarly, Harnan et al [8] assessed the cost-effectiveness of the hand-held electrochemical devices NIOX MINO (Aerocrine), NIOX VERO (Aerocrine), and NO breath (Bedfont Scientific) for the diagnosis and management of asthma. The de novo management model indicated that the incremental cost-effectiveness ratio of guidelines plus FeNO monitoring using NO breath compared with guidelines alone in children is expected to be approximately £45 200 per quality-adjusted life year gained, concluding that FeNO-guided management has the potential to be cost-effective, although this is largely dependent on the duration of the effect.

The latest version of the Global Initiative for Asthma refers to children, as follows: "FeNO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatment (Evidence A) [1]. However, further studies are needed to identify the populations most likely to benefit from FeNO-guided treatment and to determine the optimal frequency of FeNO monitoring" [1]. References that support this statement only include randomized controlled trials, with no corroborating economic evaluations. The dynamic between clinical research on effectiveness and research into efficiency must be coordinated and synchronous in order to generate recommendations from the individual to the public health level. While we realize that the transferability of economic evaluations is highly complex, our findings highlight the need to assess health technologies based on an approach that not only evaluates effectiveness and safety, but that also reviews cost-related topics, thus making it possible to increase the level of recommendations in clinical guidelines.

A very important aspect of our model is that it was robust with respect to changes in the values of its utilities, probabilities, and costs using 1-way sensitivity analysis. FeNO monitoring was always the most cost-effective strategy. A relevant result was to find a drug cost of FeNO per patient at which this therapy does not generate cost savings. This threshold (€49) can be used as a reference for the control and regulation of prices in Colombia. Showing evidence for the economic impact of this drug is essential for policy makers and physicians (17), especially in developing countries, where it is increasingly common to evaluate the costs of drugs and medical devices in pediatric patients (18-22).

Our study is subject to a series of limitations. We used retrospective data reported in a previous cost-effectiveness study; consequently, medical invoices may have been incomplete or data missing. We did not include costs associated with school absenteeism, which are considered indirect costs in chronic diseases. Nevertheless, our study used several measures to ensure data accuracy, including software with automatic calculation functions and error alerts and a review of outliers by the research team. Another limitation in the design

was the assumption of complete adherence to therapy, which can reduce the budget impact of FeNO.

In conclusion, FeNO generated cost savings in emergency settings for infants with persistent asthma. Our findings can be used by decision makers in Colombia to improve clinical practice guidelines and should be replicated to validate the results in other middle-income countries.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Global Iniciative for Asthma Management and Prevention 2020 [Available from: www.ginaasthma.org].
2. Silvestri M, Sabatini F, Spallarossa D, Fregonese L, Battistini E, Biraghi MG, et al. Exhaled nitric oxide levels in non-allergic and allergic mono- or polysensitised children with asthma. Thorax. 2001;56(11):857-62.
3. Kennedy WA, Girard F, Chaboillez S, Cartier A, Cote J, Hargreave F, et al. Cost-effectiveness of various diagnostic approaches for occupational asthma. Can Respir J. 2007;14(5):276-80.
4. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database Syst Rev. 2016;11:CD011439.
5. Berg J, Lindgren P. Economic evaluation of FE(NO) measurement in diagnosis and 1-year management of asthma in Germany. Respir Med. 2008;102(2):219-31.
6. Sabatelli L, Seppala U, Sastre J, Crater G. Cost-effectiveness and Budget Impact of Routine Use of Fractional Exhaled Nitric Oxide Monitoring for the Management of Adult Asthma Patients in Spain. J Investig Allergol Clin Immunol. 2017;27(2):89-97.
7. Brooks EA, Massanari M. Cost-Effectiveness Analysis of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in the Management of Asthma. Manag Care. 2018;27(7):42-8.
8. Harnan SE, Tappenden P, Essat M, Gomersall T, Minton J, Wong R, et al. Measurement of exhaled nitric oxide concentration in asthma: a systematic review and economic evaluation of NIOX MINO, NIOX VERO and NObreath. Health Technol Assess. 2015;19(82):1-330.
9. Departamento, Nacional, (DANE) DE. Archivo Nacional de Datos 2019 [Available from: https://sitios.dane.gov.co/anda-index/].
10. Dennis RJ, Caraballo L, Garcia E, Rojas MX, Rondon MA, Perez A, et al. Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study. BMC Pulm Med. 2012;12:17.
11. Miranda MPA., SBD. H. Prevalencia de asma infantil en la ciudad de Cartagena. Alerg Asma Inmunol Pediatr. 2014;23(2):39-42.
12. Romano G, Agudelo Y, López-Delgado N. Análisis de impacto presupuestal del tratamiento farmacológico de asma en pacientes menores de edad (0-18 años) en Colombia. Bogotá D.C.2017 [Available from: http://www.iets.org.co/Archivos/30/158_Asma_20-11-17.pdf].
13. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Metered-dose inhalers vs nebulization for the delivery of albuterol in pediatric asthma exacerbations: A cost-effectiveness analysis in a middle-income country. Pediatr Pulmonol. 2020;55(4):866-73.
14. Estadisticas DAN. Índice de Precios al Consumidor - IPC 2020 [Available from: https://www.dane.gov.co/index.php/estadisticas-por-tema/precios-y-costos/indice-de-precios-al-consumidor-ipc]
15. la Bd, Republica. Tasa Representativa del Mercado (TRM - Peso por dólar) 2019 [cited 2020. Available from: https://www.banrep.gov.co/es/estadisticas/trm].
16. MinSalud. Estructura del gasto en Salud Pública en Colombia 2018 [Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/PES/estructura-gasto-salud-publica-colombia.pdf].
17. Buendia JA, Zuluaga AF. [Physicians insight about adverse drug reaction to frequently used medication groups in Bogota (Colombia)]. Biomedica. 2014;34(3):403-8.
18. Buendia JA, Sanchez-Villamil JP, Urman G. [Cost-effectiveness of diagnostic strategies of severe bacterial infection in infants with fever without a source]. Biomedica. 2016;36(3):406-14.
19. Antonio Buendia J, Colantonio L. Costo-Efectividad de la Proteina C Reactiva, Procalcitonina y Escala de Rochester: Tres Estrategias Diagnosticas para la Identificacion de Infeccion Bacteriana Severa en Lactantes Febriles sin Foco. Value Health Reg Issues. 2013;2(3):375-80.
20. Buendia JA, Acuna-Cordero R, Rodriguez-Martinez CE. The cost-utility of intravenous magnesium sulfate for treating asthma exacerbations in children. Pediatr Pulmonol. 2020;55(10):2610-6.
21. Buendia JA, Talamoni HL. Cost-utility of use of sputum eosinophil counts to guide management in children with asthma. J Asthma. 2022:59(1):31-7.
22. Buendia JA, Acuna-Cordero R. The cost-effectiveness of hypertonic saline inhalations for infant bronchiolitis. BMC Health Serv Res. 2020;20(1):1001.

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