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Cost Effectiveness and Resource Allocation

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Cost-effectiveness of high-dose vitamin D supplementation to reduce the occurrence of repeat episodes of pneumonia in children

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Abstract

Introduction Despite the growing evidence on efficacy, little is known regarding the efficiency of Vitamin D supplementation (VDS) to reduce the incidence of repeat episodes of pneumonia in children. This study aimed to determine the cost-utility of VDS to reduce the incidence rate of repeat episodes of pneumonia in children.

Methods A decision tree model was used to estimate the cost and quality-adjusted life-years (QALYs) of VDS in a patient aged 2 to 60 months with a clinical diagnosis of community-acquired pneumonia requiring in-hospital management. Multiple sensitivity analyses were conducted to evaluate the robustness of the model. Cost-effectiveness was evaluated at a willingness-to-pay (WTP) value of US$5180.

Results The QALYs per person were 0,93 with VDS and 0,92 without VDS. The total costs per person were US$ 1148 for VDS and US$ 1284 without VDS. This position of absolute dominance of VDS makes it unnecessary to estimate the incremental cost-effectiveness ratio. The ICER was sensitive to changes in the relative risk of Vitamin D supplementation.

Conclusion In conclusion, our study shows that VDS is a cost-effective to reduce the incidence rate of repeat episodes of pneumonia in children, from a societal perspective. However, the sensitivity of ICER to relative risk makes it necessary to take the results of this economic evaluation with caution.

Keywords Health economics, Public health, Healthcare, Colombia, Corticosteroids

Introduction

Although the number of community-acquired pneumonia (CAP) episodes in children has decreased by 22% in recent decades, this disease remains among the top ten most common causes of death in children worldwide [1]. Improvements in rates of exclusive breastfeeding, nutrition, complete immunization, and reduction of indoor air pollution and pediatric HIV across all regions between 2000 and 2015 explain the reduction in pneumonia [1, 2]. Also, increases in access to health services have been reflected in an 187% increase in hospital admissions for pneumonia [1]. This increasing economic burden affects especially in countries or settings with low economic resources.

1,25(OH)2D3 is a key component of response in immune cells in response to pathogens. In macrophages infected, the expression of several cytokines, including interleukin 1β (IL-1β), a core component of innate immune responses, and the neutrophil chemokine IL-8/CXCL8 are induced in presence of 1,25(OH)2D3 [3].

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Also, 1,25(OH)2D3 contributes to the suppression of peripheral inflammatory T cell responses and enhanced development of T-regulatory (Treg) cells [4, 5].

A systematic review and meta-analysis of 7434 pediatric patients found high levels (64% of frequency) of 25OHD deficiency (47% < 50 nM) in children with sepsis ($p<0.0001$), also associated with increased mortality (OR 1.81; 95% CI 1.24 to 2.64; $p=0.002$, I2=25.7%) [6]. Also, other systematic review and meta-analysis of 13 randomized controlled trial, with 4786 patients, found that Vitamin D supplementation (VDS) reduced the risks of repeat episodes of pneumonia (RR=0.66; 95% CI, 0.48–0.90), duration<3 months (RR=0.55; 95% CI,0.33–0.91), or dose of VD<300,000 IU (RR=0.51; 95% CI, 0.29–0.89) [7]. The vitamin D deficiency is frequently in Colombian children. For example, a cross-sectional study in 52 healthy prepubertal girls found almost 40% of them have 25OHD deficiency [8].

There is no consensus among clinical practice guidelines in recommending Vitamin D supplementation to reduce the recurrence of pneumonia in children. Unfortunately, only the effectiveness and safety of this treatment have been evaluated in most clinical practice guidelines, ignoring the need for a third element such as efficiency. To our knowledge, no economic evaluation of VDS to prevent recurrence of pneumonia episodes has been published. The contribution of an economic evaluation to the current evidence lies not only in estimating whether it is cost-effective, but also in determining other outcomes that are inputs for estimating the impact of such an intervention at the public health, such as the cost-savings per patient treated with this supplementation. Also, to evaluate if there is any effect-modifying that can estimate under what conditions if supplementation is efficient. In synthesis, more economic evaluations incorporating the new evidence and in the pediatric population are needed to know the efficiency of this treatment. The objective of the present study was to estimate the cost-utility of VDS to reduce the incidence rate of repeat episodes of pneumonia in children.

Materials and methods

Baseline finding

A decision tree model was used to estimate the cost and quality-adjusted life-years (QALYs) of VDS as an adjuvant treatment of pneumonia. It was decided to use a decision tree model because we are going to model interventions that have distinct outcomes that can be measured at a specific time point, such in this case cost and QALY associated with the incidence of new episodes of pneumonia at six months after hospitalization by CAP. This decision tree model was constructed according to the natural history of CAP, Fig. 1. The base case is a patient aged 2 to 60 months with a clinical diagnosis of community-acquired pneumonia requiring in-hospital management. The decision tree begins with a decision node in which there are two options: management with antibiotics or management with antibiotics and VDS (100,000 IU single dose). Then, in both decision nodes, there are two possibilities that the patient dies or survives this first episode of pneumonia. In turn, patients who survive have two options at 6 months, to have or not to have suffered other episode of pneumonia again, and to have survived or died during this recurrence. The only difference between the two decision branches is the probability of new episode of pneumonia by six months. This probability in the on the branch with VDS is lower than in the branch without this supplementation because it was multiplied by the relative risk of this intervention as detailed later.

The time horizon defined was six months. Given the short time horizon, no discount rates were applied to costs or QALYs. Cost-effectiveness was evaluated at a willingness-to-pay (WTP) value of US$5180 [9]. Data on mortality from CAP and recurrent pneumonia were obtained from local data reported by national surveillance of acute respiratory infections and national vital statistics [10–12]. The probability of recurrent pneumonia at 6 months in patients with VSD was extracted from systematic review and meta-analysis of 13 randomized controlled trials with 4786 patients that found that VDS had more reducing effects on repeat episodes of pneumonia in children (RR=0.66; 95% CI, 0.48–0.90) [7]. QALYs

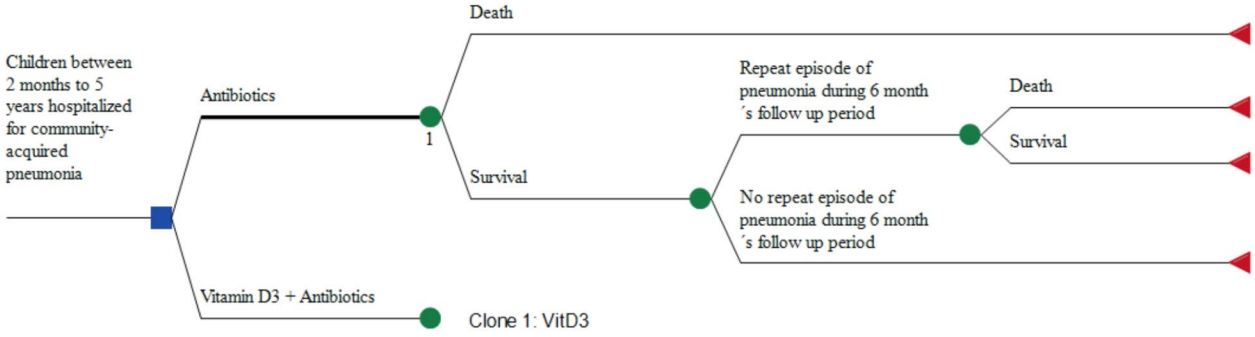

Fig. 1 Decision tree model

Table 1 Model inputs

Model input	Base case value	Distribution
Probabilities		
Repeat episode of CAP	**0.20**	β(SD: 0.05)
Mortality CAP	**0,0001**	β(SD: 0.00002)
Mortality Repeat episode of CAP	**0,008**	β(SD: 0.001)
Utility		
CAP	**0.94**	β(SD: 0.01)
Repeat episode of CAP	**0.87**	β(SD: 0.2)
Cost		
CAP (US$)	**880**	Γ (SD: 222)
Repeat episode of CAP (US$)	**2022**	Γ (SD: 505)
Vitamin D 400 IU/Day (US$)	**20,650**	Γ (SD: 5,16)
Vitamin D effectiveness		
Relative risk (RR)	**0,55**	LogN(SD: 0.25)

are calculated by multiplying the time spent in a particular health state by the corresponding health-related quality of life (HRQL) score. HRQL were extracted from a study of parent preferences for pediatric health outcomes conducted in 4016 participants [13], Table 1.

Since HRQL and probability of recurrent pneumonia at 6 months in patients with VSD does not come from the Colombian population, they were subjected to probabilistic sensitivity analysis as detailed below as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement [14]. We did this analysis from a societal perspective (including direct and indirect costs). All direct and indirect costs were extracted from a previously published cost-illness study in children with pneumonia in Colombia [15]. This study estimates the direct medical costs and indirect non-medical costs of pneumonia in children under 5 years, based on information obtained from 275 patients hospitalized using the databases of the Individual Registry of Services Provision and Sufficiency and a survey constructed, validated, and applied to parents, mothers, and caregivers of children hospitalized by these events [15]. Drug costs were taken from the National Drug Price Information System (SISMED, 2020) [16]. All cost costs were transformed to 2021 costs using official inflation data in Colombia. We used US dollars (Currency rate: US$ 1.00=COP$ 3,500) to express all costs in the study [11]. Cost-effectiveness was evaluated at a willingness-to-pay (WTP) value of US$5180 [9].

Sensitivity analysis

We conduct a one-way sensitivity presenting these results in the tornado diagram. Probabilistic sensitivity analysis was also performed. For this purpose, random sampling was performed from each of the variable distributions. We used the beta distribution for relative risk and utilities and the gamma distribution for costs, see Table 1. For each treatment, we calculated the expected costs and QALYs using the combination of all parameter values in the model. To do this calculation, a second-order Monte Carlo simulation with 10,000 replications of each parameter was made: resulting in the expected cost-utility for each treatment. To represent decision uncertainty, we plot the cost-effectiveness and acceptability frontiers. TreeAge Pro Healthcare 2022 software® was used in all analyses.

Results

The base-case analysis showed that VDS was associated with lower costs and higher QALYs than treatment without this supplementation. The QALYs per person estimated by the Monte Carlo simulation for those treatments were 0,93 (CI 95% 0,930-0,931) with VDS and 0,92 (CI 95% 0,924-0,926) without VDS. The total costs per person were US$ 1148 (CI 95% US$1142- US$1153) for VDS and US$ 1284 (CI 95% US$1278- US$1290) without VDS. Since VSD generates more QALYs than non-VSD treatment, and the expected cost per patient with VSD is lower than without VSD (i.e., the incremental cost of VSD relative to non-VSD treatment is negative), there is an absolute dominance position of VSD relative to non-VSD treatment., Table 2.

Sensitivity analysis

In the deterministic sensitivity analyses, our base-case results were robust to variations in utilities, transition probabilities, and cost; Fig. 2. The ICER was sensitive to changes in relative risk. If the relative risk of VDS is equal or higher than 0.9; the ICER will be higher than WTP and VDS is not cost-effective. The results of the probabilistic sensitivity analysis are graphically represented in the cost-effectiveness plane, Fig. 3. This scatter plot shows that 96% of simulations were graphed below WTP in quadrants 2 or 3. Vitamin D supplementation is cost-effective in more than 90% of cases with respect to treatment without this supplementation, independent of WTP, as can be seen in the acceptability curve. Figure 4.

Discussion

Our economic evaluation shows that VDS is cost-effective in reducing the incidence of repeat episodes of pneumonia in children in Colombia. Evaluating treatments to

Table 2 Cost effectiveness analysis

Strategy	Cost (US$)	Diff ($)	QUALYs	Diff (QALYs)	NMB (IC 95%)
Vit D3 + Antibiotics	1148		0,93		3672 (3666–3678)
Antibiotics	1284	136	0,92	0,01	3505 (3497–3513)

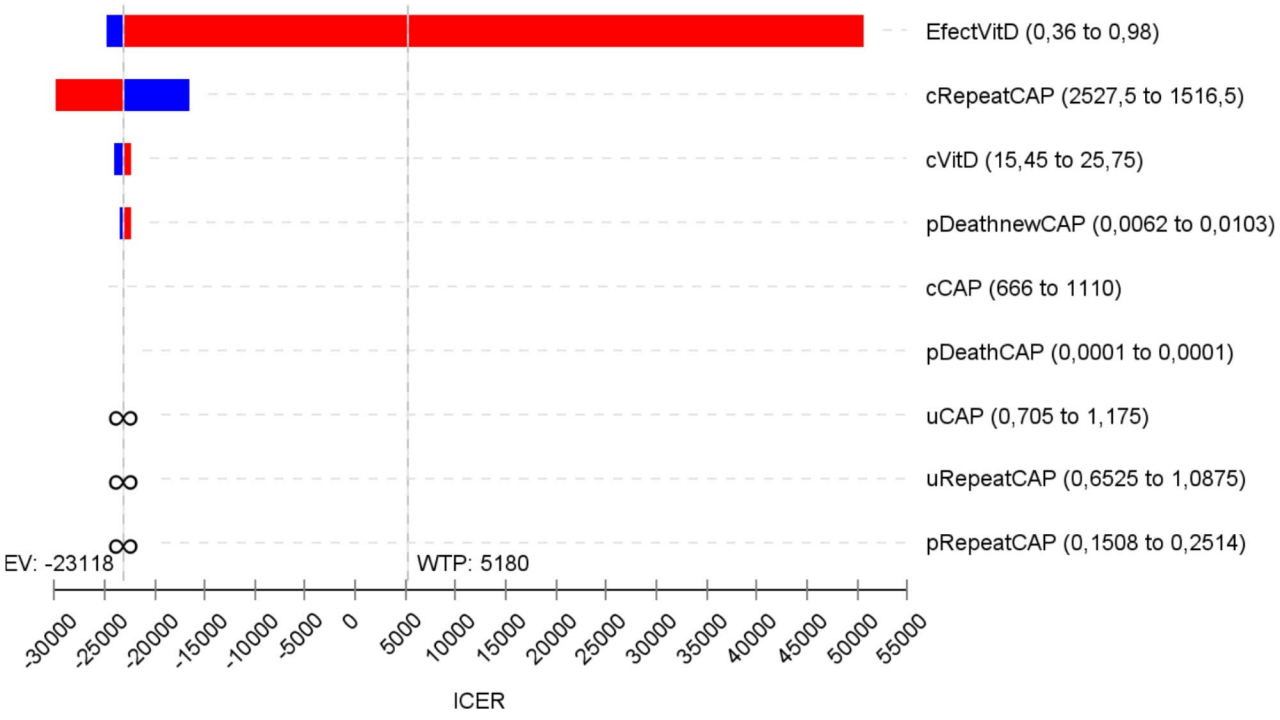

Fig. 2 Tornado diagram
EfectVitD: Relative risk of Vitamin D supplementation
CRepeatCAP: Cost of new episode of community acquired pneumonia (CAP)
CVitD : Cost of vitamin D supplementation per patient
PDeathnewCAP : Mortality of new episode of CAP
CCAP: Cost of community acquired pneumonia (CAP)
PDeathCAP: Mortality of CAP
UCAP: Utility of CAP
URepeatCAP: Utility of new episode of CAP
PRepeatCAP: Probability of new episode of CAP

reduce costs and optimize health resources is a priority for all health systems, especially in pneumonia, which, due to their frequency, generate a high economic burden in developing countries. In our study, VDS was a treatment that generated savings of US$ 136 per patient, which is not insignificant given the frequency of CAP in most developing and developed countries.

To our knowledge, this is the first economic evaluation of vitamin D to reduce the incidence of repeat episodes of pneumonia in children. Another economic evaluation has evaluated other treatments. Sakai et al., evaluate the cost-effectiveness of gargling to prevent upper respiratory tract infection during an RCT in 252 healthy adults volunteers [17]. Gargling (Gargle with approximately 20 ml of water or povidone-iodine for about 15 s, 3 times/day) was cost-effective, after 60 days, with an increase in QALY of 0.43 and ICER of $31,800 per QALY; model that was sensible to HRQL scores. From Japan's societal perspective, this ICER was within the range of other preventive methods such as influenza vaccination. Barber et al. evaluated the cost-effectiveness of OM-85 to prevent acute respiratory infections (ARI) in children 2–6 years in Mexico from a third payer perspective. OM-85 was cost-effective in preventing ARI and also showed cost savings in over 70% of cases for direct costs with a reduction of 2.61 episodes of ARI during a follow-up of six months [18]. These results with OM-85 have been similar to those obtained in other countries such as France and Italy [19–21]. There is no consensus concerning interventions to prevent ARI or recurrent acute respiratory infections. Reducing exposure to damp and mold, for example, is the intervention for which a good-quality systematic review supports the elimination of this risk factor for recurrent respiratory acute infections [22]. Other environmental interventions with low or very low-quality studies are also recommended, such as discouraging exposure to second and third-hand smoke and pollutants in general, in addition, to improving handwashing as one of the best methods to reduce respiratory infections [22, 23].

The one-way sensitivity analysis, as can be seen in the tornado graph, showed a different result according to the

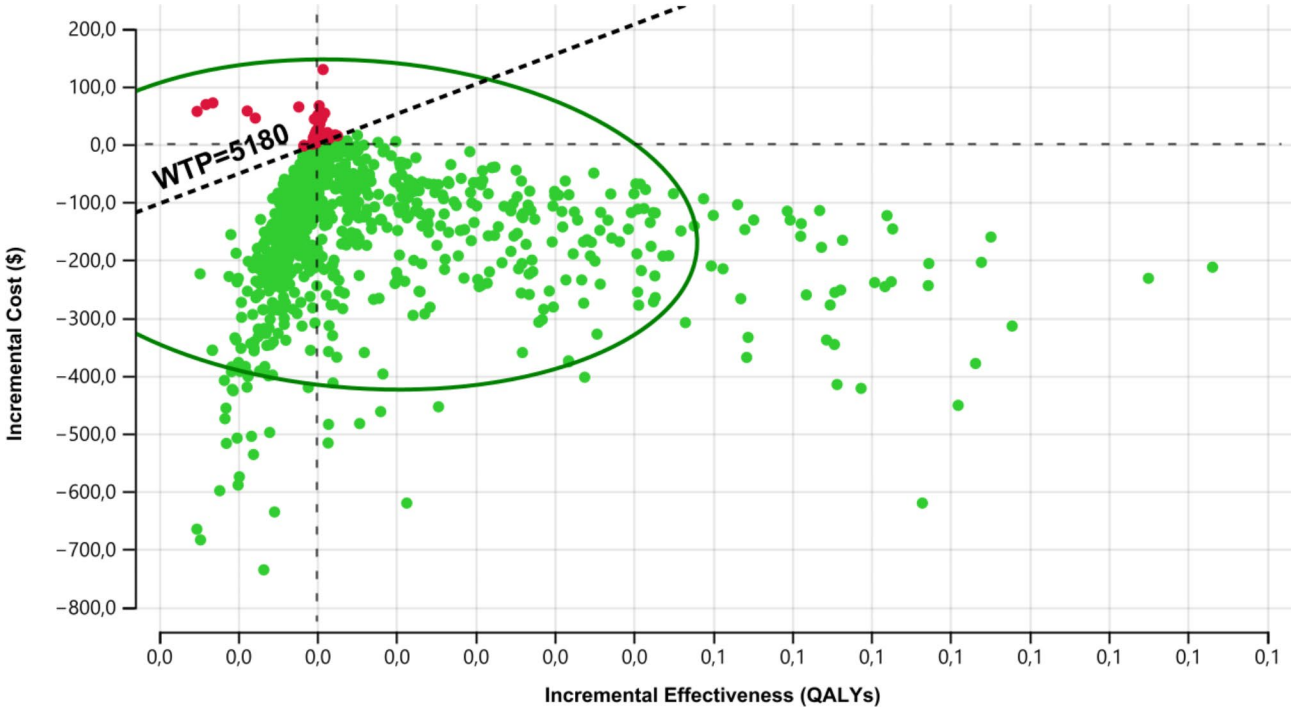

Fig. 3 Cost-effectiveness plane

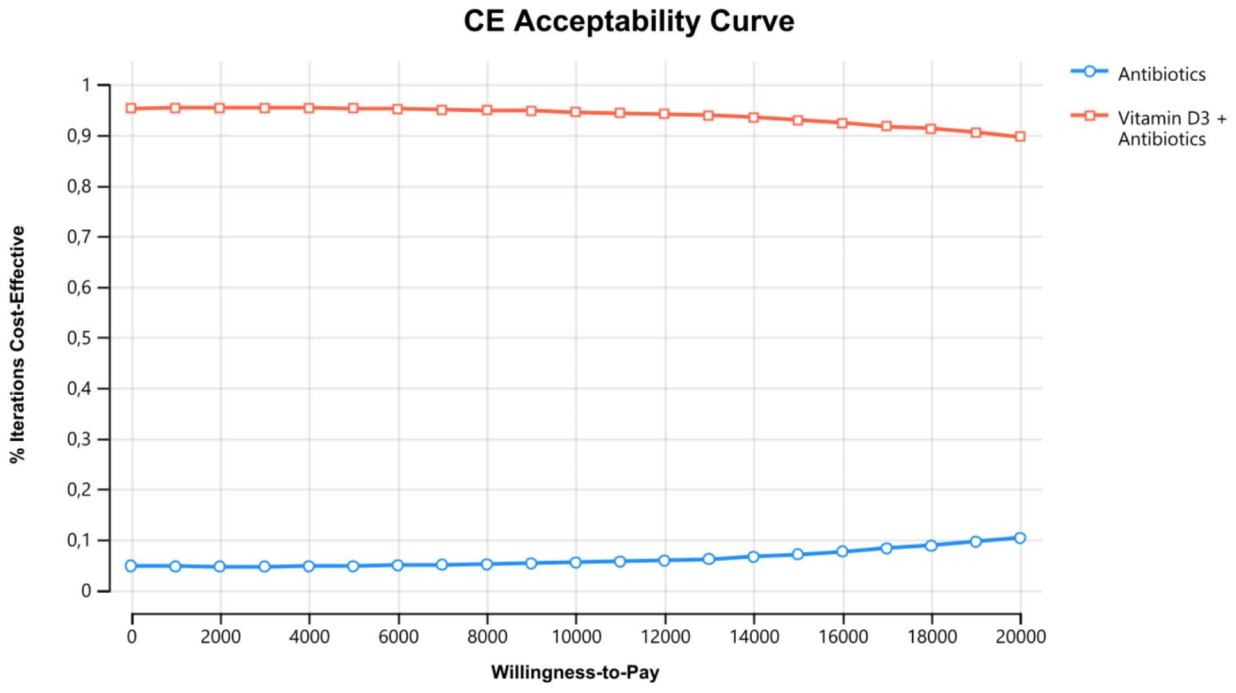

Fig. 4 Acceptability curve

RR of vitamin D in preventing pneumonia recurrences. If the RR is less than 0.9, vitamin D is cost-effective; if it is greater than 0.9, it is not cost-effective, being outdone by antibiotic treatment without this supplement. This is not a minor aspect, considering the heterogeneity in the estimations of RR in the different clinical trials published. This heterogeneity is also expressed in the results of the probabilistic sensitivity analysis. About 95% of the

simulations are in planes II and III, in which the vitamin D is always less costly but with differences in benefit. In other words, the effectiveness is the variable that most explains the variability in the results of the simulated ICERs. The sensitivity of ICER to relative risk values make it necessary to take the results of this economic evaluation with caution. The contribution of our economic evaluation to the current discussion on whether vitamin D should be recommended to prevent recurrence of pneumonia is to have estimated this threshold and thus to encourage the generation of information on local effectiveness with real-life studies. If in these studies the RR is lower than this threshold, the use of vitamin D as a supplement is efficient; otherwise, it would not justify its use.

Our study has some limitations. We use relative risk extracted from the literature and not estimated directly from our population. As was mentioned previously, the reliability and robustness of the results were evaluated by sensitivity analysis. The results of this economic evaluation given the base case are only applicable to children. Given the time horizon of this economic evaluation, these results cannot be extrapolated beyond 6 months nor can we conclude about effects after this time period. The direct medical cost was obtained from a retrospective study published previously from Colombia and cannot exclude selection or information bias in these values. However, the ICER estimate was robust to any variation in the cost in the study.

Conclusion

In conclusion, our study shows that VDS is a cost-effective to reduce the incidence rate of repeat episodes of pneumonia in children, from a societal perspective. However, the sensitivity of ICER to relative risk makes it necessary to take the results of this economic evaluation with caution.

Abbreviations

CAP	Community-acquired pneumonia
ICER	Incremental cost effectiveness ratio
OR	Odds ratio
QALY	Quality adjusted life years
RR	Relative risk
RTC	Randomized controlled trial
WTP	Willingness-to-pay

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Author contributions

JAB and DG participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Data availability

Zenodo. https://doi.org/10.5281/zenodo.5895163.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. McAllister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. Lancet Glob Health. 2019;7(1):e47–57.
2. Howie SRC, Murdoch DR. Global childhood pneumonia: the good news, the bad news, and the way ahead. Lancet Glob Health. 2019;7(1):e4–5.
3. Verway M, Bouttier M, Wang TT, Carrier M, Calderon M, An BS, et al. Vitamin D induces interleukin-1beta expression: paracrine macrophage epithelial signaling controls M. tuberculosis infection. PLoS Pathog. 2013;9(6):e1003407.
4. Urry Z, Chambers ES, Xystrakis E, Dimeloe S, Richards DF, Gabrysova L, et al. The role of 1alpha,25-dihydroxyvitamin D3 and cytokines in the promotion of distinct Foxp3 + and IL-10 + CD4 + T cells. Eur J Immunol. 2012;42(10):2697–708.
5. Vargas Buonfiglio LG, Cano M, Pezzulo AA, Vanegas Calderon OG, Zabner J, Gerke AK, et al. Effect of vitamin D3 on the antimicrobial activity of human airway surface liquid: preliminary results of a randomised placebo-controlled double-blind trial. BMJ Open Respir Res. 2017;4(1):e000211.
6. Cariolou M, Cupp MA, Evangelou E, Tzoulaki I, Berlanga-Taylor AJ. Importance of vitamin D in acute and critically ill children with subgroup analyses of sepsis and respiratory tract infections: a systematic review and meta-analysis. BMJ Open. 2019;9(5):e027666.
7. Yang C, Lu Y, Wan M, Xu D, Yang X, Yang L, et al. Efficacy of high-dose vitamin D supplementation as an adjuvant treatment on pneumonia: systematic review and a meta-analysis of randomized controlled studies. Nutr Clin Pract. 2021;36(2):368–84.
8. Dianna Mayrene Ramírez-Prada BC. Ana Catherine Arévalo, María Alejandra Granja, Pilar Zafrilla. Deficiencia de vitamina D en preadolescentes sanas que viven en Colombia 2021.
9. Espinosa O, Rodriguez-Lesmes P, Orozco E, Avila D, Enriquez H, Romano G et al. Estimating cost-effectiveness thresholds under a managed healthcare system: experiences from Colombia. Health Policy Plan. 2021;37(3):359–68.
10. Salud INd. Informe de evento. Infeccion Respiratoria Aguda Bogota, Colombia: INS. 2017 [https://www.ins.gov.co/buscador-eventos/Informesdeevento/Informe IRA Final 2017.pdf
11. (DANE) DNdE. Archivo nacional de datos 2019 [https://sitios.dane.gov.co/anda-index/.
12. (IHME) IfHMaE. Colombia Seattle. WA: University of Washington; 2021. www.healthdata.org.
13. Carroll AE, Downs SM. Improving decision analyses: parent preferences (utility values) for pediatric health outcomes. J Pediatr. 2009;155(1):21–5.
14. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Value Health. 2013;16(2):e1–5.
15. Moyano Ariza L. Estimación de costo-enfermedad por neumonía y bronquiolitis en niños menores de 5 años en Colombia. 2019.
16. Ministerio de salud C. Sistema de Informacion de Precios de Medicamentos (SISMED) 2021 [03/07/2121]. www.sispro.gov.co/central-prestadores-de-servicios/Pages/SISMED-Sistema-de-Informacion-de-Precios-de-Medicamentos.aspx
17. Sakai M, Shimbo T, Omata K, Takahashi Y, Satomura K, Kitamura T, et al. Cost-effectiveness of gargling for the prevention of upper respiratory tract infections. BMC Health Serv Res. 2008;8:258.
18. Berber A, Del-Rio-Navarro BE. Cost-effectiveness analysis of OM-85 vs placebo in the prevention of acute respiratory tract infections (ARTIs) in children that attend day-care centers. Health Econ Rev. 2019;9(1):12.

19. Zagar S, Lofler-Badzek D. Broncho-Vaxom in children with rhinosinusitis: a double-blind clinical trial. ORL J Otorhinolaryngol Relat Spec. 1988;50(6):397–404.
20. Pessey JJ, Megas F, Arnould B, Baron-Papillon F. Prevention of recurrent rhinopharyngitis in at-risk children in France: a cost-effectiveness model for a nonspecific immunostimulating bacterial extract (OM-85 BV). PharmacoEconomics. 2003;21(14):1053–68.
21. Ravasio R. Economic analysis of the immunostimulant OM-85 for the prevention of paediatric recurrent upper respiratory tract infections. Global Reg Health Technol Assess. 2015;2(3):GRHTA5000200.
22. Chiappini E, Santamaria F, Marseglia GL, Marchisio P, Galli L, Cutrera R, et al. Prevention of recurrent respiratory infections: inter-society consensus. Ital J Pediatr. 2021;47(1):211.
23. Esposito S, Jones MH, Feleszko W, Martell JAO, Falup-Pecurariu O, Geppe N et al. Prevention of new respiratory episodes in children with recurrent respiratory infections: an expert consensus statement. Microorganisms. 2020;8(11).

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