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Vitamin A supplementation for the prevention of chronic lung disease in premature infants: A cost-utility analysis

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Abstract

Introduction: Despite the growing evidence on efficacy, little is known regarding the efficiency of Vitamin A supplementation to decrease the probability of chronic lung disease (CLD) in preterm infants. This study aims to determine the cost-utility of Vitamin A to prevent CLD in preterm infants in Colombia.

Methods: A decision tree model was used to estimate the cost and quality-adjusted life-years (QALYs) of Vitamin A supplementation in preterm infants. Multiple sensitivity analyses were conducted to evaluate the robustness of the model. Cost-effectiveness was evaluated at a willingness-to-pay value of US$5180.

Results: Vitamin A was associated with lower costs and higher QALYs. The expected annual cost per patient with Vitamin A was US$1579 (95% CI US$1555–US$1585) and without Vitamin A was US$1913 (95% CI US$1891–US$1934). The QALYs per person estimated with Vitamin A was 0.66 (95% CI 0.66–0.67) and without Vitamin A was 0.61 (95% CI 0.60–0.61). This position of absolute dominance (Vitamin A has lower costs and higher QALYs than without Vitamin A) is unnecessary to estimate the incremental cost-effectiveness ratio.

Conclusion: Our economic evaluation shows that Vitamin A is cost-effective to reduce the incidence rate of CLD in premature infants in Colombia. Our study provides evidence that should be used by decision-makers to improve clinical practice guidelines.

KEYWORDS

Colombia, corticosteroids, healthcare, health economics, public health

1 | INTRODUCTION

Vitamin A deficiency is frequent in infants with low birth weight, with a prevalence in preterm infants with birth weights of less than 1000, 1000, or 1500 g of 42%, 25%, and 5%, respectively.[1,2] The lack of Vitamin A has been associated with a decrease in expression of SP-A, SP-B, and SP-C mRNAs, and a reduction of fatty acid synthase genes, affecting the synthesis of lung surfactant, which is necessary to regulate surface tension at the air-liquid interface in the lungs.[3] Retinoic acid, a Vitamin A derivative, promotes alveolar septation to increase gas exchange area and mitigate the altered lung development and functional deficits resulting from preterm birth and abnormal gaseous and mechanical exposures.[4]

Abbreviations: CAP, community-acquired pneumonia; ICER, incremental cost effectiveness ratio; OR, odds ratio; QALY, quality adjusted life years; RR, relative risk; RTC, a randomized controlled trial; WTP, willingness-to-pay.

WHO and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommend a daily intake of 700–1500 μg/kg/day of Vitamin A for preterm infants.[5] Recent meta-analyses evaluate the effectiveness and safety of supplemental Vitamin A in preterm infants (doses between 2000 and 5000 IU intramuscularly three times a week for 2–4 weeks) and showed that the incidence of chronic pulmonary disease in the Vitamin A group was significantly less than that of the control group (OR = 0.67, CI 95% [0.52–0.88]).[6] Despite this evidence, there is still much variability in clinical practices in this regard. These doubts can be explained by concerns regarding the economic impact of adopting this supplementation. However, to date, no economic evaluations have been published in developing countries. 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 results that are inputs for estimating the impact of such an intervention on public health, such as the cost-savings per patient treated with Vitamin A. This study aims to determine the cost-utility of Vitamin A to prevent chronic lung disease (CLD) in preterm infants in Colombia.

2 | MATERIALS AND METHODS

2.1 | Base case

A decision tree model was used to estimate the cost and quality-adjusted life-years (QALYs) of Vitamin A as a preventive treatment of CLD. It was decided to use a decision tree model because we are going to model interventions (Vitamin A vs. placebo) with an outcome (the incidence of CLD 1 year after the onset of this supplementation) that can be measured at a specific time point. Although the majority of clinical trials that have evaluated the effectiveness of this supplement in the incidence of CLD have had a follow-up of fewer than 6 months, in this economic evaluation it was assumed that effectiveness extends up to a year after starting this intervention.[6]

This decision tree model was constructed according to the natural history of CLD in preterm infants, Figure 1. The base case corresponds to a patient with a gestational age between 24 and 33 weeks, with a birth weight between 500 and 1500 g. The decision tree begins with a decision node in which there are two options: placebo or Vitamin A. The Vitamin A regimen used in this base case was 5000 IU IM every 3 days for 4 weeks for 60 days.[6] Then, in both decision nodes, there are two possibilities about whether the patient develops CLD or not. Then in both branches, there are two possibilities that the patient is hospitalized or not and then that the patient died or not. The only difference between the two decision branches is the probability CLD. This probability in the branch Vitamin A is lower than in the branch placebo because it was multiplied by the relative risk of this intervention as detailed later. CLD was defined as the need for oxygen at 36 weeks' postmenstrual age following the definition of CLD in a randomized clinical trial published by Ding et al.[6] We choose this paper because this was the randomized clinical trial with more weight (77%) in the results of the metanalysis published by Ding from which it extracted the relative risk used in this economic evaluation.[6]

The time horizon defined was 1 year. 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.[7] Data on mortality from CLD and recurrent pneumonia were obtained from local data reported by national surveillance of acute respiratory infections and national vital statistics.[8–10] The relative risk and probability of CLD were extracted from a recent systematic review and meta-analysis of nine randomized clinical trials with 1409 patients.[6] This study showed that the incidence of BPD in the Vitamin A group was significantly less than that of the control group (OR = 0.67, 95% CI [0.52–0.88] $I^2 = 0$), without a difference in the incidence of adverse events between groups. All transition probabilities were extracted from local studies conducted on

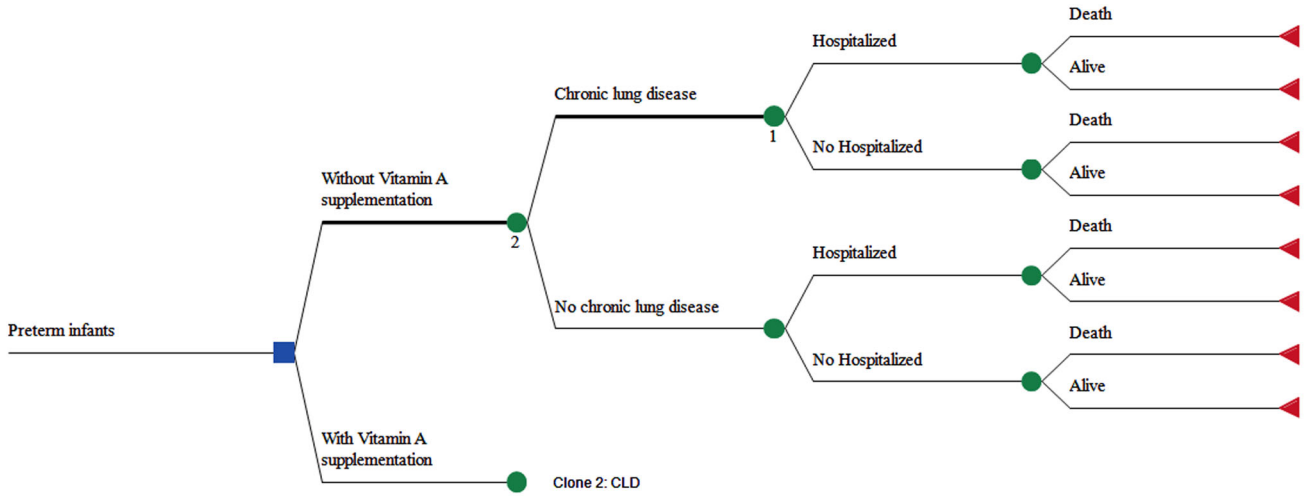

FIGURE 1 Decision tree model [Color figure can be viewed at wileyonlinelibrary.com]

premature infants in Colombia.[11–14] Utilities were extracted from EPICure study that estimate the health utilities (using Health Utilities Index Mark III) associated with 190 extremely preterm birth in the United Kingdom and Ireland[15]; utilities that have also been used in other economic evaluations carried out in extremely premature infants in other countries,[16] Table 1. Since utilities and relative risks do 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.[17] We did this analysis from a payer perspective (including direct costs). All direct costs were extracted from a previously cost-utility study in premature infants in Colombia.[18] Drug costs were taken from the National Drug Price Information System (SISMED).[19] All cost costs were transformed to 2021 costs using official inflation data in Colombia. We used US dollars (Currency rate: US$ 1.00 = COP$ 3900) to express all costs in the study.[9] The incremental cost-effectiveness ratio (ICER) was calculated using the following formula:

$$\text{ICER} = \frac{\text{Expected annual cost per patient with Vitamin A} - \text{Expected annual cost per patient without Vitamin A}}{\text{QALY per patient with Vitamin A} - \text{QALY per patient without Vitamin A}}$$

Also, we estimated the net monetary benefit (NMB). NMB represents the value of an intervention in monetary terms.[20] NMB is calculated as (incremental benefit × threshold) − incremental cost. Incremental NMB measures the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given WTP threshold.

2.2 | Sensitivity analysis

We conduct a one-way sensitivity presenting these results in the tornado diagram of incremental NMB. Probabilistic sensitivity analysis was also performed. For this purpose, random sampling was performed from each of the parameter distributions. We used the beta distribution for relative risk and utilities and the gamma distribution for costs, see Table 1. For each treatment strategy, 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 strategy. To represent decision uncertainty, we plot the cost-effectiveness and acceptability frontiers. We combined a

TABLE 1 Model inputs

Model input	Base case value	Distribution
Probabilities		
CLD	0.55	β (SD: 0.13)
Hospitalization with CLD	0.473	β (SD: 0.013)
Hospitalization without CLD	0.186	β (SD: 0.005)
Mortality in preterm hospitalizated infant with CLD	0.0600000	β (SD: 0.0092)
Mortality in preterm hospitalizated infant without CLD	0.0150000	β (SD: 0.003)
Utility		
Preterm infant hospitalizated with CLD	0.5	β (SD: 0.1)
Preterm infant hospitalizated without CLD	0.8	β (SD: 0.2)
Cost, US$		
Preterm infant hospitalizated with CLD (episode/patient)	3154	Γ (SD: 788)
Preterm infant hospitalizated without CLD (episode/patient)	681	Γ (SD: 170)
Outpatient clinic costs (annual/per patient)	775	Γ (SD: 193)
Vitamin A 5000 IU	2	Γ (SD: 0.5)
Annual exacerbation rate		
Preterm infant hospitalizated with CLD (episode/patient)	1.51	Γ (SD: 0.37)
Preterm infant hospitalizated without CLD (episode/patient)	0.21	Γ (SD: 0.05)
Vitamin A effectiveness		
Relative risk on CLD	0.67	LogN (SD: 0.13)

Abbreviation: CLD, chronic lung disease.

nonparametric bootstrap-based estimation of uncertainty intervals (UI 95%) and probabilistic sensitivity analysis, by drawing a vector of values from normal distributions representing the parameter uncertainties of the cost parameters, alongside 1000 bootstrap replications. TreeAge Pro Healthcare 2022 software® was used in all analyses.

3 | RESULTS

The main results are presented in Table 2. The base-case analysis showed that compared with placebo, Vitamin A was associated with lower costs and higher QALYs. The expected annual cost per patient with Vitamin A was US$1579 (UI 95% US$1555–US$1585) and without Vitamin A was US$1913 (UI 95% US$1891–US$1934). The QALYs per person estimated with Vitamin A was 0.66 (UI 95% 0.66–0.67) and without Vitamin A was 0.61 (95% CI 0.60–0.61). The NMB with Vitamin A was US $ 11,121 (UI 95% 11 068–11,174) and without Vitamin A was US$ 9703 (UI 95% 9653–9752). This position of absolute dominance (Vitamin A has lower costs and higher QALYs than without Vitamin A) is unnecessary to estimate the incremental cost-effectiveness ratio.

3.1 | Sensitivity analysis

In the deterministic sensitivity analyses, our base-case results were robust to variations in utilities, transition probabilities, relative risk, and cost; Figure 2. That is, changing each of the parameters, within the ranges mentioned in the methods section, of cost, utilities, transition probabilities, and relative risk did not change the ICER and the result (Vitamin A is dominant over placebo). The results of the probabilistic sensitivity analysis are graphically represented in the cost-effectiveness plane, Figure 3. This scatters plot shows that 88% of simulations of the ICER were below WTP in quadrants 2 (70%) or 1 (18%). The incremental net monetary benefit (INMB) calculated in the second-order Monte Carlo simulation was US $635 (UI 95% US$626–US$644). This positive value of INMB means that the incremental benefits in monetary terms for the WTP are higher than the incremental costs of this drug in Colombia; thus, this medication can

TABLE 2 Cost effectiveness analysis

Strategy	Cost, US$ (905% CI)	Diff ($)	QUALYs (95% CI)	Diff (QALYs)	NMB US$ (95% CI)
Supplementation with Vitamin A	1579 (1555–1585)		0.66 (0.66–0.67)		11,121 (11,068–11,174)
No supplementation with Vitamin A	1913 (1891–1934)	342	0.61 (0.60–0.61)	0.05	9703 (9653–9752)

Abbreviations: NMB, net monetary benefit; QALYs, quality-adjusted life-years.

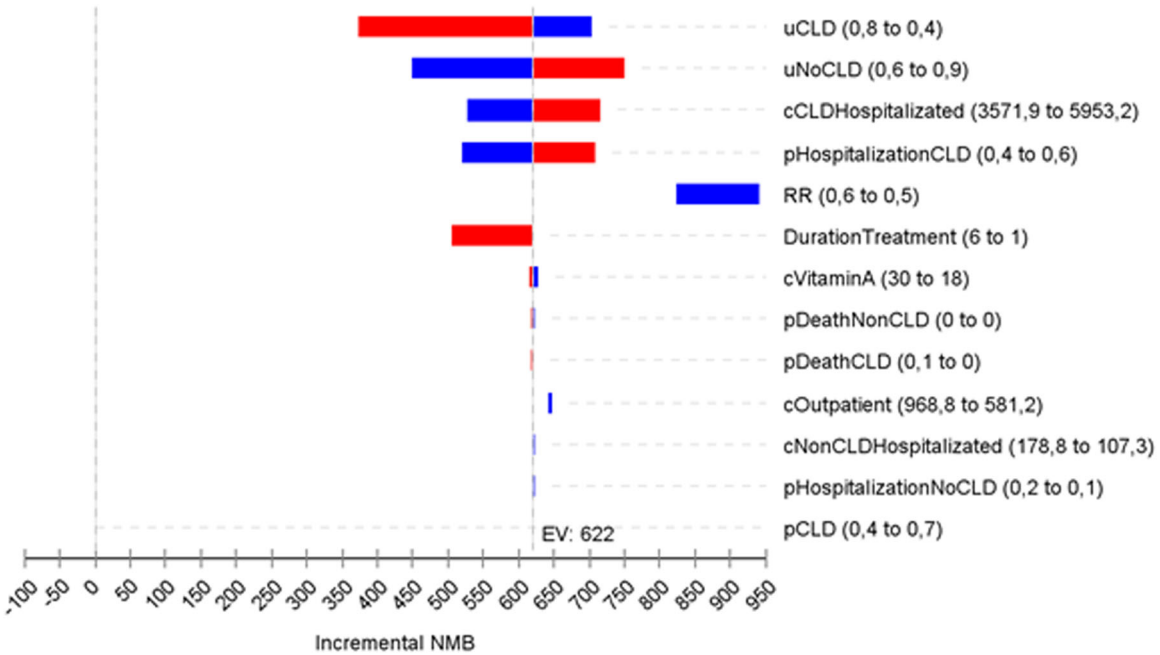

FIGURE 2 Tornado diagram. Causes RR, relative risk; CCLDHospitalizated, cost hospitalization; CLD, chronic lung disease; CLD PhospitalizationCLD, probability of hospitalization by CLD; cNonCLDHospitalizated, cost hospitalization nonCLD; COutopatient, cost of outpatient care; CVitaminA, cost of Vitamin D; PCLD, probability of CLD; PdeathCLD, mortality by CLD; PDeathnonCLD, mortality by non-CLD; pHospitalizationCLD, probability of hospitalization by CLD; Ucld, utility CLD state; UNoCLD, utility CLD nonstate. [Color figure can be viewed at wileyonlinelibrary.com]

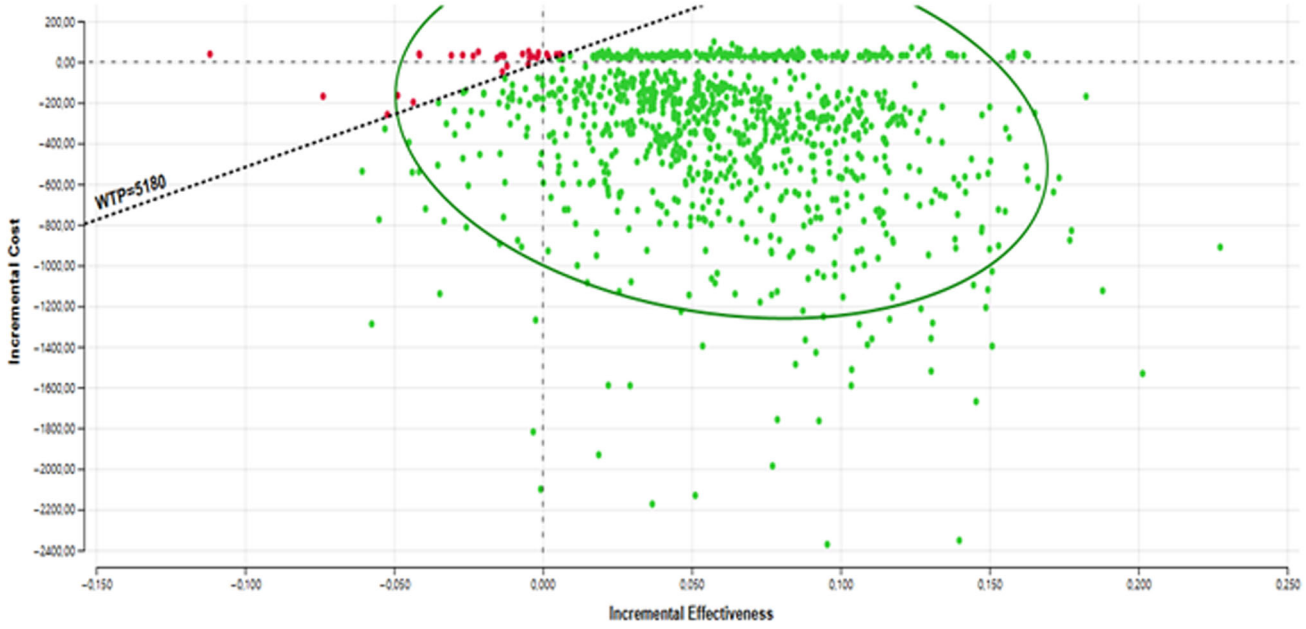

FIGURE 3 Cost effectiveness plane [Color figure can be viewed at wileyonlinelibrary.com]

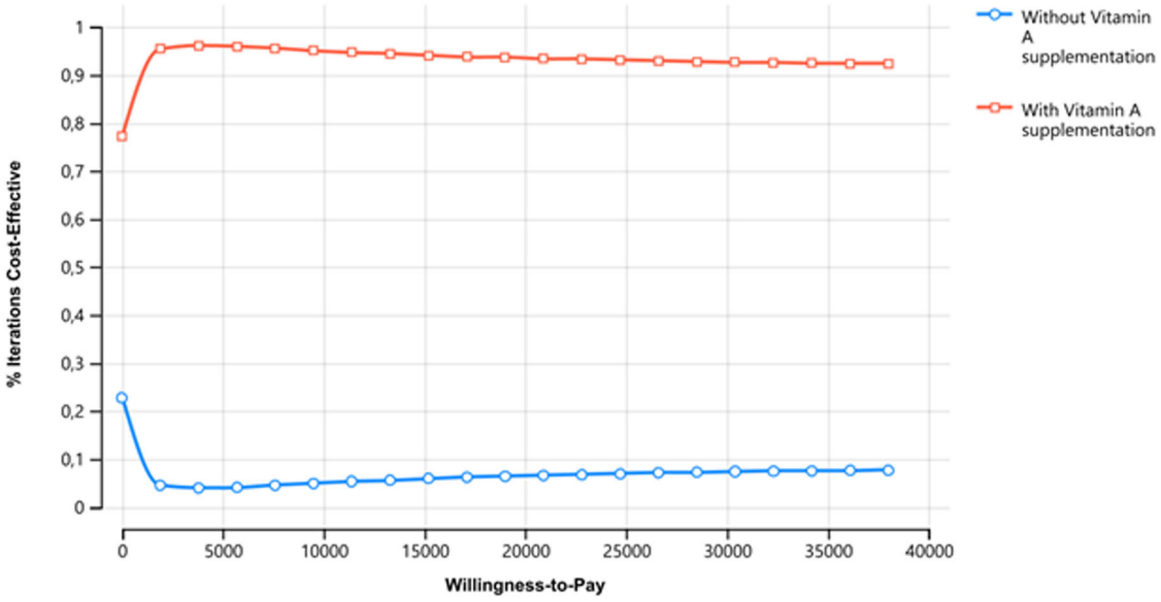

FIGURE 4 Acceptability curve [Color figure can be viewed at wileyonlinelibrary.com]

be declared cost-effective. For WTP in Colombia (US$5180 per QALY), Vitamin A is cost-effective in 98% of cases versus placebo as can be seen in the acceptability curve, Figure 4.

4 | DISCUSSION

Our economic evaluation shows that Vitamin A is cost-effective to reduce the incidence rate of CLD in premature infants in Colombia. In our analysis, Vitamin A had a position of absolute dominance in treatment without Vitamin A supplementation. Evaluating treatments to reduce costs and optimize health resources is a priority for all health systems, especially in CLD, which, generates a high economic burden in all countries. In our study, Vitamin A was a strategy that generated savings of US$342 (95% CI US$334–US$349) per patient, which is not insignificant given the frequency of premature infants in most developing and developed countries. Very low birth weight (<1500 g) represents 1.4% of the total births, but with a mortality rate of 23%. The incremental costs associated with morbidities, such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis, and

late-onset sepsis are high, justifying studies evaluating interventions aimed at preventing or reducing these costly morbidities.[21] For example in the United States, the marginal impact on direct costs ranged from US$10,055 for late-onset sepsis to US$31,565 for BPD.[21] In this sense, all interventions that reduce the risk of complications are useful both in developed and developing countries.

To the best of our knowledge, there are no previously published economic evaluations of Vitamin A for CLD in premature infants. Regarding other interventions to prevent respiratory complications or CLD, Vitamin A supplementation would accompany other interventions that are cost-effective for this purpose, such as the administration of palivizumab,[22] surfactant replacement therapy,[23] recombinant human superoxide dismutase,[24] and human milk feedings to reduce the risk of prematurity-related morbidities in very-low-birth-weight infants.[25] Vitamin A deficiency is a major health risk for infants and children in low- and middle-income countries. oral Vitamin A supplementation (using doses of 50,000–200,000 IU) in children aged 6 months to 5 years reduced all-cause mortality (RR 0.88, 95% CI 0.83–0.93).[26] A recent systematic review of four randomized controlled trials with 800 patients found that oral Vitamin A supplementation in preterm infants had slightly shorter noninvasive ventilation duration (MD −0.96 days; 95% CI −1.59 to −0.33 days) without adverse drug-related events.[27] Another systematic review of 12 randomized controlled trials with 2111 very low birth weight infants found that oral Vitamin A supplementation seems to reduce the incidence of periventricular leukomalacia (RR 0.68; 95% CI 0.47–0.97 and retinopathy of prematurity of any grade (RR 0.61, 95% CI 0.48–0.76).[28] Although there has been an improvement in the outcomes mentioned with oral supplementation with Vitamin A, with this route of administration there has been no reduction in the incidence of BPD. In the recent metanalysis of Yanxiu et al, the subgroup analysis showed that Vitamin A supplementation by intramuscular injection reduced the incidence of oxygen dependence at 36 weeks' PMA (RR 0.85, 95% CI 0.74–0.98), but the oral counterparts did not (RR 0.78, 95% CI 0.51–1.19)[28]; results are similar to those previously published by Ding et al.[6] This difference can be explained by heterogeneity and small sample sizes of studies evaluating the oral administration route of Vitamin A. The consistency in the results of these two meta-analyses regarding the protective role of Vitamin A supplementation in preterm infants lends robustness to the results of the present economic evaluation where the intramuscular route of Vitamin A supplementation was evaluated.

Our study has some limitations. We use relative risk and utilities extracted from the literature and not estimated directly from our population. The reliability and robustness of the results were evaluated by sensitivity analysis. Changing each of these parameters, within their ranges did not alter the incremental cost-effectiveness ratio significantly or change its interpretation. The direct medical cost was obtained from a retrospective study published previously in 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.

5 | CONCLUSION

In conclusion, our economic evaluation shows that Vitamin A is cost-effective to reduce the incidence rate of CLD in premature infants in Colombia. Our study provides evidence that should be used by decision-makers to improve clinical practice guidelines.

AUTHOR CONTRIBUTIONS

Jefferson Antonio Buendía and Diana Guerrero Patiño and Erika Fernanda Lindarte participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in zenodo at doi:10.5281/zenodo.6528215. Zenodo. OM-BV (Data set). Zenodo. doi:10.5281/zenodo.6528215

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