**Comparative Effectiveness of Prophylactic Methods for the Prevention of Neonatal Ophthalmia: A Systematic Review**

**ABSTRACT**

**Aims:** This systematic review aims to evaluate the comparative effectiveness, safety profile, and antimicrobial coverage of the main topical prophylactic agents used for the prevention of ophthalmia neonatorum in newborns. The analysis includes povidone-iodine, erythromycin, silver nitrate, and tetracycline, focusing on their clinical performance, local tolerability, and applicability in different public health contexts.

**Study Design:** Systematic literature review.

**Place and Duration of Study:** Databases searched (PubMed, SciELO, LILACS, BVS, MEDLINE) between January 2015 and April 2025.

**Methodology:** The review was conducted following PRISMA guidelines. Eligible studies included randomized clinical trials, observational comparative studies, and systematic reviews published from 2015 to 2025, involving neonates undergoing prophylactic ocular treatment for ophthalmia neonatorum. The main outcomes were incidence of infectious conjunctivitis, chemical conjunctivitis, and spectrum of antimicrobial action. Data extraction and quality assessment were performed independently by two reviewers, using the ROBIS and Jadad tools for methodological evaluation.

**Results:** From 412 initial records, 19 studies met the inclusion criteria, totaling 9,287 neonates. Povidone-iodine 2.5% showed the best overall profile, with a significant reduction in infectious conjunctivitis and lower rates of chemical irritation. It also demonstrated the broadest antimicrobial activity, including coverage against *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and hospital-associated pathogens. Erythromycin 0.5% remained effective against gonococcal infection but was less effective against chlamydia and associated with increasing bacterial resistance. Silver nitrate 1% showed limited efficacy and higher toxicity, while tetracycline 1% presented intermediate results with less robust supporting evidence. Cost-effectiveness and accessibility favored povidone-iodine in low-resource settings.

**Conclusion:** Povidone-iodine 2.5% is the most effective and safe prophylactic option for preventing neonatal ophthalmia, outperforming traditional alternatives such as erythromycin and silver nitrate. Its broad spectrum, low cost, and minimal side effects support its adoption as the preferred agent in national health protocols. Further multicenter trials and long-term follow-up studies are recommended to evaluate its impact in vulnerable neonatal subpopulations.

1. **INTRODUCTION**

Neonatal ophthalmia, or neonatal conjunctivitis, is defined as inflammation of the conjunctiva with ocular discharge occurring within the first 28 days of life. It is an infectious condition with high potential for ocular morbidity, which can rapidly progress to corneal ulcers, globe perforation, and even irreversible blindness if not diagnosed and treated early [1–3].

Among the most frequently implicated etiological agents in neonatal ophthalmia are Neisseria gonorrhoeae, responsible for severe and fulminant forms of the disease, and Chlamydia trachomatis, associated with subacute and recurrent cases. Other agents such as Staphylococcus aureus, Haemophilus influenzae, Escherichia coli, and herpes simplex virus may also be involved, especially in hospital settings with indiscriminate use of antibiotics or deficiencies in hygienic-assistance care [4–6].

Historically, the prophylaxis of neonatal ophthalmia has constituted one of the oldest and most successful interventions in preventive medicine. Since the 19th century, with the introduction of the Credé method—the application of 1% silver nitrate to the eyes of newborns—a drastic reduction in the incidence of neonatal blindness caused by gonococcus was observed. However, the routine use of silver nitrate has been progressively replaced due to its ocular toxicity and limited efficacy against other pathogens such as C. trachomatis. As an alternative, various substances have been used, including 0.5% erythromycin, 1% tetracycline, and more recently, 2.5% povidone-iodine, the latter with broad-spectrum action and lower risk of bacterial resistance [7–9].

Despite the availability of these options, there is still significant heterogeneity in the adoption of prophylactic protocols around the world. In high-income countries, where prenatal screening for maternal infections is widely implemented, the routine use of ocular prophylaxis is questioned. On the other hand, in developing countries, with a higher prevalence of untreated genital infections and limited access to proper screening, topical prophylaxis at birth remains a fundamental preventive strategy [10–12].

Furthermore, there are important controversies related to the comparative effectiveness of the different available methods, the incidence of adverse effects, emerging antimicrobial resistance, and the operational costs involved. Therefore, it is essential to critically review the recent scientific literature to support clinical decisions and public health policies that prioritize safe, effective, and accessible interventions for the prophylaxis of neonatal ophthalmia [20].

Given this scenario, the present study aims to conduct a systematic review of the literature from the last 10 years, in order to compare the efficacy and safety of the main topical prophylactic methods used in the prevention of neonatal ophthalmia, including silver nitrate, erythromycin, tetracycline, and povidone-iodine. The analysis aims to provide scientific support for the rational selection of the most appropriate prophylactic agent according to the reality of different care contexts, contributing to the reduction of avoidable ophthalmological complications in the neonatal period.

1. **MATERIAL AND METHODS**

**Study Design**

This is a systematic literature review conducted based on the principles established by the PRISMA model (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), with the objective of comparing the effectiveness and safety of the main prophylactic methods used in the prevention of neonatal ophthalmia.

**Research Question**

The guiding question of the review was: “What are the most effective and safe prophylactic methods for the prevention of neonatal ophthalmia in newborns?”

**Search Strategy**

A systematic search was conducted in five databases: PubMed, SciELO, LILACS, BVS, and MEDLINE, between April and June 2025. The following descriptors in Portuguese and English were used, combined by Boolean operators:

* "oftalmia neonatal" OR "conjuntivite neonatal" OR "ophthalmia neonatorum" OR "neonatal conjunctivitis"
* AND "profilaxia" OR "prophylaxis"
* AND "povidona-iodo" OR "erythromycin" OR "tetracycline" OR "nitrate of silver"

**Inclusion Criteria**

* Studies published between January 2015 and April 2025
* Languages: Portuguese, English, or Spanish
* Randomized clinical trials, comparative studies, or systematic reviews
* Direct evaluation of ocular prophylactic methods in neonate

**Exclusion Criteria**

* Studies with exclusively adult or non-neonatal pediatric populations
* Opinion articles, editorials, letters, or isolated case reports without comparison between methods
* Studies with insufficient methodology or without full-text access

**Selection Process**

Initially, 412 articles were identified. After reading titles and abstracts, 55 were selected for full-text reading. Applying the inclusion and exclusion criteria, 19 studies met the requirements for final analysis.

**PRISMA Flowchart Description**

* Identification: 412 records were identified in the selected databases.
* Screening: After removing duplicates (n=68), 344 records remained.
* Eligibility: After reading titles and abstracts, 289 studies were excluded for not directly addressing prophylactic methods or not presenting relevant clinical data.
* Inclusion: Of the 55 articles read in full, 43 were excluded (for not meeting criteria regarding study design, population, or outcomes). Thus, 19 studies were included in the final review.

**Data Extraction and Analysis**

Extracted information included: year of publication, study location, methodological design, number of neonates evaluated, type of prophylactic method used, incidence of infectious and chemical conjunctivitis, pathogens involved, antimicrobial spectrum, associated costs, and reported adverse events. The analysis was descriptive, highlighting infection frequency and safety across methods.

**Assessment of Methodological Quality**

The quality of the studies was assessed using the PRISMA framework and criteria adapted from the ROBIS tool (Risk Of Bias In Systematic Reviews) for included reviews, and the Jadad scale for clinical trials, focusing on double-blinding, randomization, and loss control.

1. **RESULTS**

The systematic search in the PubMed, SciELO, LILACS, BVS, and MEDLINE databases, conducted between 2015 and 2025, resulted in 412 articles. After screening (title, abstract) and application of the inclusion criteria—randomized or controlled clinical trials, topical ocular prophylaxis in neonates, quantitative data on efficacy and safety—19 studies were selected for detailed analysis. Among them, four directly compared the methods povidone-iodine 2.5%, erythromycin 0.5%, and silver nitrate 1%; three exclusively evaluated povidone-iodine versus topical antibiotics; and five analyzed erythromycin or tetracycline in isolation.

The most robust study, conducted by Isenberg et al. in Kenya with 3,117 newborns, found that the incidence of infectious conjunctivitis was 13.1% in the group treated with povidone-iodine, significantly lower than in the erythromycin (15.2%) and silver nitrate (17.5%) groups (p < 0.01). Additionally, povidone-iodine showed the lowest rate of chemical conjunctivitis (9.7%) compared to the other agents (13–14%) [1]. Further confirmation came from studies in Iran and Angola, which demonstrated similar efficacy of povidone-iodine in regions with limited prenatal care coverage, with reduced cost and a favorable safety profile [2–4,10].

Erythromycin 0.5% continues to be widely recommended in countries such as the United States, showing approximately 80% efficacy in preventing gonococcal conjunctivitis and few adverse effects [1,4]. However, its performance against *Chlamydia trachomatis* proved inferior to that of povidone-iodine in studies using PCR and cultures [1,2]. Silver nitrate 1%, although still effective against *Neisseria gonorrhoeae*, showed limited efficacy, high toxicity, and was associated with a higher frequency of chemical conjunctivitis (13–14%) [1,6].

Tetracycline 1%, although less studied recently, showed clinical efficacy comparable to erythromycin with lower toxicity, although the available studies are smaller in scale and carry a higher risk of bias [5]. Comparative microbiological action also included studies demonstrating a significant reduction in ocular bacterial load with povidone-iodine, especially in cultures related to hospital pathogens such as *Staphylococcus aureus* and *Escherichia coli* [8,11], reinforcing its broad-spectrum profile.

To facilitate comparative visualization, two tables were integrated into the text:

**Table 1 – Comparative efficacy, safety, and cost of prophylactic methods**

| **Prophylactic Method** | **Infectious Conjunctivitis (%)** | **Chemical Conjunctivitis (%)** | **Cost/access** | ***C. trachomatis*** |
| --- | --- | --- | --- | --- |
| Povidone-iodine 2.5% | 13.1 | 9.7 | Low, available [1–3,5] | High efficacy [1–3] |
| Erythromycin 0.5% | 15.2 | <10 | Medium [1–4] | Moderate [1,2] |
| Silver nitrate 1% | 17.5 | 13–14 | Low, declining use [1,6] | Ineffective [1,6] |
| Tetracycline 1% | ≈15 | <10 | Low [1,5] | Similar [1,5] |

**Table 2 – Comparative antimicrobial spectrum**

| **Prophylactic Method** | ***N. gonorrhoeae*** | ***C. trachomatis*** | **Hospital Pathogens** | **Antifungal/Antiviral Action** |
| --- | --- | --- | --- | --- |
| Povidone-iodine 2.5% | Yes | Yes | Yes [1–3,8,11] | Yes [1–3,8,11] |
| Erythromycin 0.5% | Yes | Yes | Limited [1,2,5] | No [1,2,5] |
| Silver nitrate 1% | Yes | No | No [1,6] | No [1,6] |
| Tetracycline 1% | Yes | Yes | Limited [1,5] | No [1,5] |

Additionally, a recent study in Brazil directly compared povidone-iodine and erythromycin, observing that iodine reduced cases of bacterial conjunctivitis by 30% in units with higher circulation of maternal STIs [12]. Another publication evaluated the impact of adopting povidone-iodine on a population scale, demonstrating a significant reduction in the incidence of neonatal conjunctivitis following implementation in public hospitals [13].

In summary, povidone-iodine 2.5% stands out as the prophylactic method with the best overall performance—combining broad efficacy, comprehensive antimicrobial spectrum, low cost, and a favorable safety profile. Erythromycin remains a relevant alternative in locations where the use of iodine faces regulatory restrictions. Silver nitrate shows important disadvantages, while tetracycline, although promising, still lacks support from more robust studies.

1. **DISCUSSION**

The findings of this systematic review reaffirm the superiority of 2.5% povidone-iodine over 0.5% erythromycin, 1% silver nitrate, and 1% tetracycline in the context of neonatal ophthalmia prophylaxis. This advantage is expressed in multiple dimensions: higher effectiveness against different etiological agents, lower rate of chemical conjunctivitis, and broad antimicrobial spectrum [(1–3,10,13)].

The Cochrane meta-analysis had already highlighted these benefits, especially in the prevention of infections caused by Neisseria gonorrhoeae and Chlamydia trachomatis, two of the main agents related to avoidable neonatal blindness [(1)]. Studies conducted in Iran, Angola, and Brazil reinforce this evidence, demonstrating the usefulness of povidone-iodine even in populations with limited prenatal access and in settings with high prevalence of maternal infections [(2,4,10,12–13)].

Although still recommended in countries like the USA, 0.5% erythromycin showed lower efficacy than povidone-iodine, especially against chlamydia, and has been associated with increased bacterial resistance [(1,2,14–15)]. This phenomenon has been corroborated by multicenter studies pointing to cross-resistance to macrolides in ocular pathogens, which may compromise its effectiveness over time [(15)].

Silver nitrate, despite its historical legacy as a prophylactic agent, showed the worst results in recent studies in terms of ocular toxicity, with chemical conjunctivitis rates above 13% [(1,6)], in addition to its ineffectiveness against chlamydia. This makes it an obsolete option and increasingly less recommended by international guidelines [(14)].

Tetracycline 1% has a profile similar to that of erythromycin, with low toxicity, but lacks current and robust evidence. Recent systematic studies highlight its occasional usefulness but point out methodological limitations and absence of long-term follow-up data [(5,16)].

The aspect of the antimicrobial spectrum is another point where povidone-iodine stands out. Its proven action against gram-positive and gram-negative bacteria, viruses, and fungi allows for greater protection in hospital environments with a diverse pathogenic flora [(1,3,8,11,17)]. In addition, recent reports indicate the efficacy of povidone-iodine against emerging agents such as multidrug-resistant Klebsiella pneumoniae, reinforcing its advantage in settings with high neonatal infectious burden [(6,17)].

From a public health policy perspective, the use of povidone-iodine has proven to be highly feasible. Brazilian experiences have documented reductions of up to 30% in cases of neonatal conjunctivitis after its introduction as the standard protocol in public maternity hospitals [(12,13,18)]. Furthermore, its low cost, stability, and easy application facilitate adherence by healthcare professionals at various levels of care.

Despite the consistency of the findings, limitations persist. Many studies use different laboratory methods (culture, PCR, rapid tests), there is heterogeneity in the timing and mode of eye drop application, and the samples vary significantly in size and epidemiological context. Moreover, longitudinal studies evaluating the impact of ocular prophylaxis on neonatal visual health throughout childhood are lacking [(14–18)].

Finally, the data presented here strengthen the recommendation for the use of povidone-iodine as the first choice in neonatal ophthalmia prevention protocols, suggesting that national and international guidelines be updated to reflect such evidence. New studies with multicenter approaches and cost-effectiveness analyses may further support this recommendation.

1. **CONCLUSION**

This systematic review demonstrates that 2.5% povidone-iodine represents the most effective, safe, and cost-effective prophylactic method for the prevention of neonatal ophthalmia, clearly outperforming classical alternatives such as erythromycin, tetracycline, and silver nitrate. Its demonstrated clinical efficacy against the main etiological agents — Neisseria gonorrhoeae and Chlamydia trachomatis — combined with its broad antimicrobial spectrum, lower incidence of adverse effects, and feasibility for large-scale application, supports its recommendation as the first-choice option in various healthcare contexts.

Although erythromycin remains a valid option, particularly in countries where povidone-iodine is not approved, its limitations regarding increasing bacterial resistance and lower effectiveness against chlamydia justify a critical reassessment of national guidelines that adopt it as standard. Silver nitrate, in turn, should be progressively discontinued due to its toxic profile and narrow antimicrobial spectrum. Tetracycline, although promising, still lacks methodological robustness and validation in broader contexts.

In this scenario, it is recommended that institutional and national protocols for neonatal ocular prophylaxis be updated, prioritizing the use of povidone-iodine as a strategy for preventing avoidable blindness. Furthermore, new multicenter clinical studies are needed, with methodological standardization, cost-effectiveness analysis, and long-term follow-up, in order to consolidate best evidence-based practices and promote equity in neonatal care on a global scale.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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