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Ocular Prophylaxis for Gonococcal Ophthalmia Neonatorum: A Reaffirmation Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: To systematically review evidence regarding the benefits and harms of ocular prophylaxis for the prevention of gonococcal ophthalmia neonatorum to support the update of the USPSTF's 2011 A recommendation for this topic.

Data Sources: We conducted a literature search of PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2008, to January 16, 2018.

Study Selection: We screened 282 abstracts and 6 full-text articles against *a priori* inclusion criteria. We included studies conducted in countries categorized as "high" or "very high" on the Human Development Index.

Data Analysis: Two investigators independently critically appraised each article that met inclusion criteria using design-specific criteria.

Results: No new eligible studies were identified.

Limitations: Our review was designed to identify evidence that could result in a change in the 2011 USPSTF recommendation; therefore, it targeted only those studies in countries categorized as high or very high on the Human Development Index.

Conclusions: Ocular prophylaxis for the prevention of gonococcal ophthalmia neonatorum is the standard of care in the United States. Foundational evidence in support of this practice included largely observational studies from developing countries over 2 decades ago demonstrating substantial reductions in GON incidence associated with prophylaxis. Our brief evidence update found no new evidence of the benefits or harms of ocular prophylaxis for gonococcal ophthalmia neonatorum.

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Chapter 1. Introduction

Condition Background

Condition Definition

Ophthalmia neonatorum is conjunctivitis in infants during the first month of life. Ophthalmia neonatorum can be caused by infection with *Neisseria gonorrhoeae (N. gonorrhoeae), Chlamydia trachomatis (C. trachomatis),* or other bacteria or viruses.[1] This report specifically evaluates ocular prophylaxis for gonococcal ophthalmia neonatorum (GON), which occurs when gonococcal infection is transmitted to newborns during delivery by mothers infected with *N. gonorrhoeae*.[2] Ophthalmia neonatorum is caused far less often by *N. gonorrhoeae* than by other bacteria or viruses and is rare in the United States; however, prevention is important because GON is associated with a high risk of corneal perforation and blindness which can occur within 24 hours.[3]

Disease Incidence and Burden of Disease

The rates of gonococcal conjunctivitis in infants are determined by the rates of gonorrhea among women of reproductive age (**Table 1**). Robust estimates of gonorrhea in pregnant women in the United States primary care setting are not available, but older data from the World Health Organization (WHO) suggest that rates of gonorrhea in pregnant women in most industrialized countries is less than 1 percent;[4] self-reported data from the United States Pregnancy Risk Assessment Monitoring System from 5 states from 2009–2011 suggests a similar rate of 0.5 percent.[5, 6] The rate of GON has remained low in the United States in recent years. When defined as gonorrhea in infants less than 1 year with a specimen source of "eye" or "conjunctiva," there were an estimated 0.4 cases or fewer per 100,000 live births per year during 2013-2017.[7] However, limitations in reporting suggest this is an underestimate;[8-10] nearly 85 percent of combined chlamydial and gonococcal cases in infants less than 1 year do not report the specimen source so are not counted among cases.[10] With a broader definition including cases with unknown, other, or missing specimen sources, the prevalence of GON was possibly as high as 1.1 to 1.6 cases per 100,000 live births from 2010–2015. Additionally, while GON is defined as gonococcal conjunctivitis in infants age 1 month or less, national reporting of cases is for age 1 or less, meaning that precise estimates of GON rates are not available. Of the combined chlamydial and gonococcal conjunctivitis cases reported from 2010–2015 with age 1 year or less, 36.2 percent were among Non-Hispanic black infants, followed by those reporting "other" or "unknown" race (32.0%), non-Hispanic whites (20.1%), and Hispanics (11.7%).[10]

The incidence of gonorrhea varies widely by age, race and ethnicity, geography, and sex. Adolescents and young adult women have the highest rates of gonorrhea, with incidence peaking at age 19 (872.2 cases per 100,000 women); among women 20-24 years of age, there were 684.8 reported cases per 100,000 women in 2017.[11] The racial and ethnic distribution of neonatal conjunctivitis cases in infants generally corresponds with that of incident gonorrhea in women of childbearing age. In 2017, the rate of gonorrhea in black women was 7.6 times the rate in white

women (444.3 vs. 58.5 cases per 100,000 women) (**Table 1**).[11] Rates of gonorrhea in women are highest in the South (194.0 cases per 100,000 women vs. 129.6 in the Northeast, 169.0 in the West, and 170.6in the Midwest) (**Table 2**). Rates of reported gonorrhea are higher in men than in women (202.5vs. 141.8 cases per 100,000 population).[11]Although rates of reported gonococcal infections have declined since national screening programs for women were implemented in the 1970s, there has been a recent increase in rates of reported gonorrhea cases, from 105.3 cases per 100,000 population in 2013 to 171.9 cases per 100,000 population in 2017.[11]

Infants of mothers at increased risk for sexually transmitted infections are more likely to develop gonococcal conjunctivitis. Risk factors for gonorrhea among women of childbearing age include living in a high-morbidity area, previous or coexisting sexually transmitted infection(s), new or multiple sexual partners, inconsistent condom use among persons not in mutually monogamous relationships, and exchanging sex for money or drugs. A high proportion of pregnant women with gonococcal infections are asymptomatic; it is estimated that 80 percent of gonococcal infections in women are asymptomatic.[12]

In the absence of ocular prophylaxis, studies have estimated transmission rates of 30 to 50 percent from mother to newborn.[4] Untreated gonococcal ophthalmia neonatorum can result in corneal scarring, ocular perforation, and blindness as early as 24 hours after birth.[13-15] There are no published contemporary estimates of GON-related blindness in the US; it is considered rare in industrialized countries.[16] Even historical information about GON-related blindness is limited. In the late 19th century, prior to Crede's prophylaxis with silver nitrate, ophthalmia neonatorum, primarily caused by gonorrhea, was considered a major cause of childhood blindness; in Europe at that time, the prevalence of ophthalmia neonatorum among live births in maternity hospitals was greater than 10 percent, resulting in corneal damage in 20 percent and blindness in approximately 3 percent of these infected infants.[16, 17] An observational study from Nairobi, Kenya in the 1980s reported that 16 percent of a series of 64 infants with GON had corneal involvement.[18]

Prevention

Gonococcal ophthalmia neonatorum may be most effectively prevented by screening and treating gonococcal infections in pregnant women, as well as by administering ocular prophylaxis. Risk-based prenatal gonorrhea screening is widely recommended in the US as screening tests are highly accurate and effective treatments are available.[2, 19, 20] Neonatal ocular prophylaxis is mandated in most states and is considered most effective when administered up to 1 hour after birth. Erythromycin ophthalmic ointment is currently the only FDA-approved prophylactic agent available in the United States.[21] There are reports of failures of ocular prophylaxis to prevent GON and it has been postulated that reasons for these failures can include poor compliance with protocols, reinfection from other portals of entry such as the oropharynx, or contact spread.[22] It is unknown whether antimicrobial resistance may also reduce the efficacy of prophylaxis. Other preparations, such as tetracycline ophthalmic ointment and silver nitrate, have been evaluated but are no longer available in the United States. There are reports that gentamicin was used during a period where there was an erythromycin shortage but resulted in ocular reactions.[21]

The growing threat of antimicrobial resistance may constrain successful treatment of gonorrhea. The bacterium responsible for gonorrhea, *N. gonorrhoeae,* has developed resistance to the majority of antibiotics used to treat gonorrhea in adults, including sulfonamides, penicillin, tetracycline, and fluoroquinolones, such as ciprofloxacin.[23] There are reports from other countries of high *N. gonorrhoeae* resistance to erythromycin (32.4%), but these data are not for an ophthalmic ointment formulation.[24] Resistance of *N. gonorrhoeae* to erythromycin is not surveilled in the United States because it is not a recommended treatment; erythromycin has not been a recommended treatment since the 1980s because of treatment failures in the United States that were reported at that time.[2] It is unclear whether the high concentration of erythromycin in the eye during prophylaxis would overcome resistance.[1] Gonococcal resistance to other macrolides, namely azithromycin, has increased over time and raises concerns about ongoing treatment using this agent.[25]

In addition to prevention, treatment of diagnosed GON can prevent the sequelae of infection. The CDC recommends GON treatment with a single dose of systemic ceftriaxone in those neonates diagnosed with GON as well as presumptive treatment in those neonates born to mothers with untreated gonorrhea.[2]

Previous USPSTF Recommendation and Current Clinical Practice in the United States

The 1996 A recommendation for prophylactic ocular topical medication for all newborns for the prevention of GON was based on good evidence that blindness due to GON has become rare in the United States since the implementation of universal preventive medication of infants in addition to screening programs for women; this procedure is required by law in most states.[26] In 2005, as part of a broad review of gonococcal screening in adults, the USPSTF reviewed an updated literature search on the harms of ocular prophylaxis and reaffirmed its A recommendation. Again in 2011, the USPSTF reaffirmed its previous recommendation, using a brief evidence update that found no substantial new evidence regarding the benefits or harms of prophylaxis for the prevention of GON.[13]

The Centers for Disease Control and Prevention, American Academy of Pediatrics, and WHO also recommend universal topical ocular prophylaxis for the prevention of gonococcal ophthalmia neonatorum (**Table 3**). These organizations explicitly recommend administering prophylaxis to all infants at birth. Conversely, recent recommendations from the Canadian Pediatric Society suggest that neonatal ocular prophylaxis may no longer be useful and should not be routinely recommended. Its recommendation to rescind regulations that mandate ocular prophylaxis is in line with that of several European countries, including Denmark, Norway, Sweden, and the United Kingdom, which abandoned universal prophylaxis decades ago.[1] Estimates of GON incidence since this practice stopped are not robust,[16] due in part to its rarity. Canada discontinued national surveillance of neonatal ophthalmia in 2000 due to low incidence.[1]

The prevention of GON can also be achieved by gonorrhea screening and treatment of pregnant women prior to delivery. In 2014, the USPSTF issued a B recommendation to screen pregnant women age 24 years and younger and in older women at increased risk of infection (**Table 4**).[19]

The 2017 joint recommendation from the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) is similar, calling for screening of all pregnant women at risk for gonorrhea or living in an area with high prevalence at the first prenatal visit, where those with gonococcal infection are retested in 3 to 6 months, preferably in the third trimester.[20] In addition, if the first test is negative, but the woman is at high risk for gonorrhea, a retest at the beginning of the third trimester is recommended. While Canadian recommendations no longer recommend ocular prophylaxis for GON, they call for increased gonorrhea screening, to include screening all pregnant women at the first prenatal visit.[1]

Despite recent health care reforms in the United States, approximately 11.8 percent of women ages 18-24 and 14.6 percent of women ages 25-34 years were still without health insurance in 2016.[27] Likewise, in 2016, an estimated 6.2 percent of births in the United States occurred in women who received little to no prenatal care.[28] The percent of women receiving late or no prenatal care varies widely by race and ethnicity; it is lowest among White women (4.3%) and highest among Native Hawaiian or Pacific Islanders (19.2%). Thus, while prenatal screening and treatment of maternal gonorrhea are considered the most effective preventive strategy for neonatal gonococcal ophthalmia neonatorum, universal neonatal ocular prophylaxis remains the standard of care in the United States.

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence update to update its 2011 A recommendation on ocular prophylaxis for gonococcal ophthalmia neonatorum.[29] Topics that represent well-established, evidence-based standards of practice within the scope of the USPSTF and remain a USPSTF priority undergo an updating process known as "reaffirmation."[30] Systematic review methods for reaffirmation evidence updates are described in detail elsewhere.[31] The aim for evidence updates supporting the reaffirmation process is to identify "new and substantial evidence sufficient enough to change the prior recommendation."[30, 31] As such, only targeted key questions for benefits and harms of prophylaxis are updated. In consultation with members of the USPSTF, we developed an analytic framework (**Figure 1**) and two Key Questions (KQs) to guide our evidence update.

1. What is the effectiveness of ocular prophylaxis for the prevention of gonococcal ophthalmia neonatorum and associated blindness?
2. What are the harms of ocular prophylaxis for the prevention of gonococcal ophthalmia neonatorum?

Data Sources and Searches

We conducted a literature search of PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2008, to January 16, 2018. We worked with a research librarian to develop our search strategy, which was peer-reviewed by a second research librarian (**Appendix A**). We limited our searches to articles published in English. We managed literature search results using EndNote® version X7 (Thomson Reuters, New York, NY).

Study Selection

We developed specific inclusion criteria to guide study selection (**Appendix A Table 1**). Two reviewers independently reviewed the title and abstracts of all identified articles using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers then independently evaluated the full text of all potentially relevant articles. We resolved differences in abstract or full-text review by discussion. For all KQs, studies conducted in any birth setting in countries categorized as "high" or "very high" on the Human Development Index (HDI) were eligible. Consistent with the methods of the USPSTF,[30] restrictions based on "high" or "very high" HDI were made to ensure applicability to the United States. Editorials, narrative reviews, and case reports were excluded.

For evidence on the effectiveness of ocular prophylaxis for the prevention of gonococcal ophthalmia neonatorum (KQ1), we included randomized controlled trials, systematic reviews, and meta-analyses. For evidence on the harms of ocular prophylaxis for the prevention of

gonococcal ophthalmia neonatorum (KQ2), we additionally allowed cohort studies, case-control studies and large case series of 100 or greater. Ocular prophylaxis needed to be conducted in newborns, but no restrictions were made for timing of administration or agents used.

Quality Assessment and Data Abstraction and Synthesis

Two reviewers independently assessed the methodological quality of each included study using predefined criteria (**Appendix A Table 2**); disagreements were resolved by discussion. There were no studies eligible for inclusion, thus, no data abstraction or synthesis were performed.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from December 7, 2017, to January 10, 2018. The draft Research Plan was additionally reviewed by USPSTF Federal Partners from the CDC and clarifications were made as appropriate. The draft version of this report was reviewed by four invited experts and three USPSTF Federal Partners. Experts were selected based on their expertise in pediatric infectious disease. All expert comments were considered. Additional historical and epidemiological background information was added to the Introduction and themes in the Discussion were extended based on expert feedback. Additionally, a draft of the full report was posted on the USPSTF Web site from September 11, 2018 to October 9, 2018. Updated epidemiologic data that were published by the CDC during the public comment period were incorporated into the Final Report and minor clarifying revisions were made in the Introduction.

USPSTF Involvement

This reaffirmation evidence update was funded by an AHRQ contract to support the USPSTF. We consulted with USPSTF members during the development of the research plan, including the analytic framework, KQs, and inclusion criteria. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the evidence update, and assisted with public comment on the research plan and draft report. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the evidence update.

Chapter 3. Results

Literature Search

Our literature search yielded 282 unique citations. From these citations, we accepted six articles for full-text review based on titles and abstracts (**Appendix B Figure 1**). Our review and critical appraisal of the full-text articles resulted in no new publications for either key question. **Appendix D** contains a list of the six articles reviewed at full-text and their reasons for exclusion.

Results of Included Studies

Key Question 1. What Is the Effectiveness of Ocular Prophylaxis for the Prevention of Gonococcal Ophthalmia Neonatorum and Associated Blindness?

Our literature search and appraisal revealed no studies.

Key Question 2. What Are the Harms of Ocular Prophylaxis for the Prevention of Gonococcal Ophthalmia Neonatorum?

Our literature search and appraisal revealed no studies.

Chapter 4. Discussion

Summary of Evidence

Our systematic review yielded no relevant new studies since the 2010 review addressing the effectiveness or harms of GON prophylaxis (**Table 5**).[32] A systematic review by Darling et al[22] confirmed the scarcity of new evidence, concluding that there were insufficient data to estimate the clinical or comparative effectiveness of GON prophylaxis. Given the relatively low reported rates of maternal gonorrhea, these studies are underpowered. The foundational evidence for prior USPSTF recommendations largely consisted of observational studies from sub-Saharan Africa conducted 30 years ago (1987–1995) showing statistically significant and substantial reductions in GON after implementation of GON prophylaxis.[29, 33, 34] While the USPSTF, Centers for Disease Control, American Academy of Pediatrics, and World Health Organization recommend universal GON prophylaxis based on this evidence (**Table 3**), others have questioned the current applicability of such evidence because the universal prenatal screening and treatment of STIs—including gonorrhea and chlamydia—introduced in the 1970s is considered the most effective preventive strategy and the standard of care.[35-37] Historically, there has been some US and international observational evidence from over 30-50 years ago indicating that cessation of prophylaxis led to increases in GON incidence;[38, 39] however, there is no contemporary observational evidence to examine this trend in the era of prenatal screening and treatment. In the United States where risk-based prenatal gonorrhea screening is recommended, and ocular prophylaxis is the standard of care, the individual contribution of each method for preventing GON is unknown. A trial to evaluate the comparative effectiveness of each strategy is not feasible because of the extremely low incidence of GON.

In 2015, the Canadian Pediatric Society recommended against universal GON prophylaxis and instead supported enhanced prenatal screening and treatment, and proposed a more customized prevention program based on local epidemiology.[1] It is possible that state-mandated ocular prophylaxis may be less warranted in some settings due to health care systems' provision of more comprehensive access to prenatal care, presenting more opportunities to screen pregnant women for gonorrhea and address the infection prior to birth; such a strategy also considers maternal health directly. These guidelines have been met with controversy raising issues around the effectiveness of prenatal screening and treatment strategies, emergence of antimicrobial resistance, and effects on socially vulnerable populations.[40] There is scant information available to estimate current adherence to prenatal gonorrhea screening recommendations in U.S. clinical practice. One laboratory study from a decade ago (2005-2008) including nearly 1.3 million pregnant women reported that less than 60 percent had been tested for gonorrhea.[41] Furthermore, there remain pregnant women in the United States who lack adequate prenatal care. In 2016, 6.2 percent of births were to women with late or no prenatal care, with a greater proportion of these women belonging to racial and ethnic minority groups.[28] Removal of universal prophylaxis could disproportionately affect these populations and consequences of missed cases have substantial clinical sequelae. One potential alternative for women solely presenting to care in labor could be rapid screening at hospital entry followed by intrapartum maternal treatment or immediate postpartum maternal and infant treatment; the timing of such a strategy may present logistic challenges. Alternatively, providing neonatal ocular prophylaxis in those whose mothers are at

high risk for gonorrhea (e.g., no prenatal gonorrhea screening or no prenatal care, younger maternal age) could be considered.

Topical silver nitrate, erythromycin and tetracycline ointment appear to be effective for GON prophylaxis, although again conclusions about comparative effectiveness are limited by lack of power. The systematic review by Darling et al[22] included three comparative effectiveness studies[42-44] (N=18,280) showing no statistically significant differences in comparative effectiveness of GON prophylactic agents. These studies compared erythromycin 0.5% solution, povidone-iodine 2.5% solution, and silver nitrate 1% solution; tetracycline 1% ointment, erythromycin 0.5% ointment, and silver nitrate 1% solution; and tetracycline 1% ointment and silver nitrate 1% solution. Additionally, we identified two newer comparative effectiveness studies.[45, 46] One was an Indonesian RCT (N=60) comparing chloramphenicol 1% ointment to povidone-iodine 2.5% solution; however, no GON cases were found in either treatment group. The other was an Israeli RCT (n=410) comparing 2.5% povidone-iodine solution to tetracycline 1% ointment; no cases of GON were found. For comparative harms, one trial demonstrated a higher risk of noninfective (sterile) conjunctivitis with povidone-iodine solution compared with tetracycline ointment.[45] Additionally, during a manufacturing shortage of erythromycin, the CDC listed gentamicin and azithromycin as alternative agents;[21] there are published reports that gentamicin ophthalmic ointment is associated with severe ocular reactions.[47-49] Silver nitrate is associated with chemical conjunctivitis. In a 1975 U.S. study of 1,000 newborns, 90 percent given silver nitrate had conjunctivitis 3 to 6 hours after birth, however the conjunctivitis resolved after 24 hours in all but 7 percent.[50] In terms of selection of agents for GON prophylaxis, erythromycin is the only topical ophthalmic antibiotic currently available in the United States;[2] silver nitrate 1% ophthalmic solution was discontinued due to rates of chemical conjunctivitis associated with its use and tetracycline ophthalmic ointment is no longer available. Povidone-iodine is not approved for this indication in the United States.

The ideal candidate agent for prophylaxis would: 1) be effective against GON with low risk for antibiotic resistance; 2) not cause chemical conjunctivitis; 3) be inexpensive in single-dose vials;[51] 4) and be FDA approved and available in the United States. Currently, erythromycin fulfills most of these criteria, but there remain some concerns about potential antibiotic resistance.[24] Some have postulated that because current prophylaxes for gonococcal ophthalmia neonatorum rely on antibiotic ointments, alternative treatments should be developed for continued successful prevention of the condition.[52] Data on the incidence of chemical conjunctivitis with erythromycin agent are scarce; limited evidence suggests that the risk of chemical conjunctivitis is between 10 and 13 percent.[43, 51] While it would be ideal if this agent also was effective against the more common ophthalmia neonatorum due to *Chlamydia trachomatis*, none of the aforementioned agents is considered effective for the prevention of chlamydial ophthalmia.[2, 42] Furthermore, other commonly infected sites such as the lungs would not be covered with ocular prophylaxis.

Limitations

Our review was intended to support the USPSTF reaffirmation process and thus includes only the interval evidence accrued since the last recommendation in 2011. Our review was scoped to

identify evidence that could result in a change in this recommendation and therefore has some notable exclusions listed here. Studies were excluded if they were not conducted in countries listed as "high" or "very high" on the Human Development Index. One study from Angola was excluded on this basis, however, had less than 10 percent followup.[53] Another study conducted in Iran, a "high" Human Development Index country, was excluded because the full-text article was not available in English.[54] There are no clinical effectiveness trials in the United States, and such trials would be unethical given that erythromycin prophylaxis is considered the standard of care; additionally, the incidence of GON is too low for any such trial to be feasible.

Conclusion

There is no new evidence since the 2011 USPSTF recommendation endorsing the clinical effectiveness of GON prophylaxis. Foundational evidence supporting the effectiveness of current practice of erythromycin is derived from observational studies performed over 20 years ago outside of the United States without prenatal gonorrhea screening practices. Nonetheless, substantial historical declines in GON incidence in the U.S. are likely the result of a combination of preventive strategies including prenatal gonorrhea screening and treatment and neonatal prophylaxis.

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Figure 1. Analytic Framework

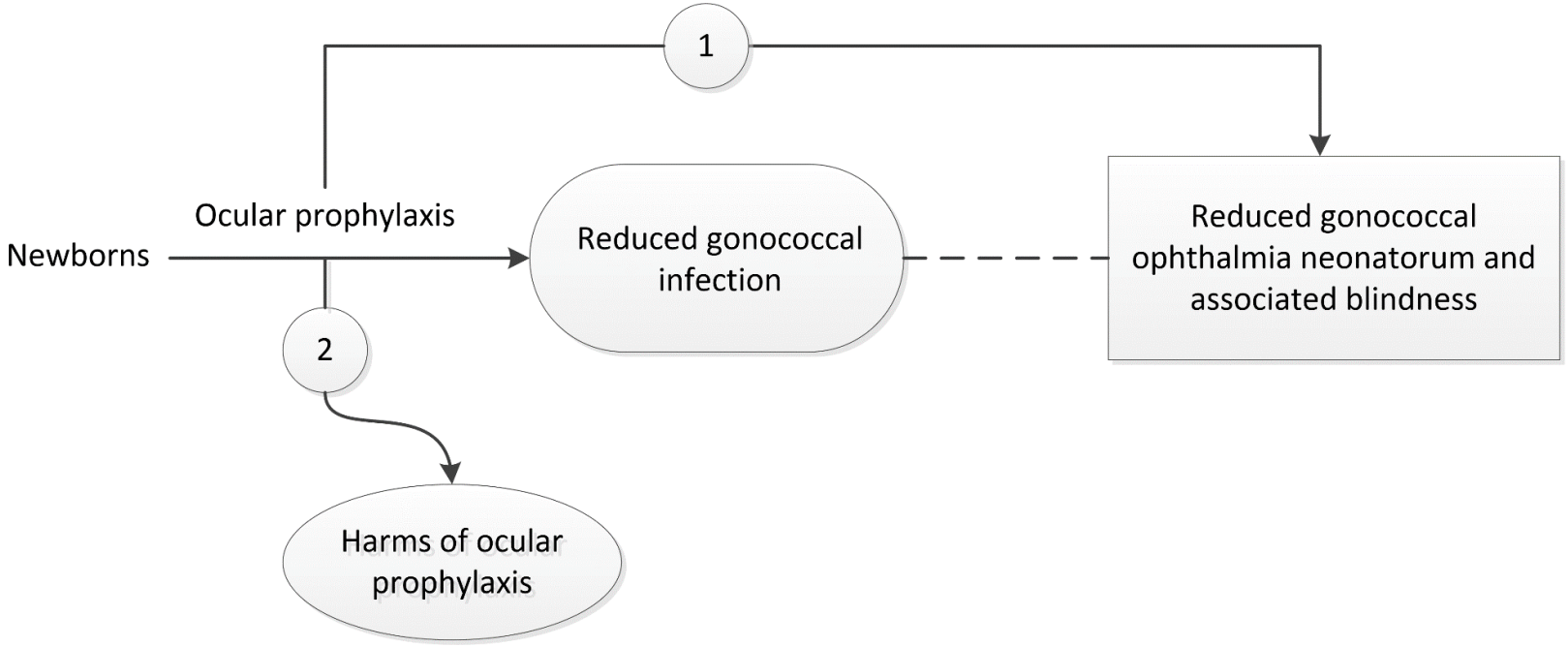


Table 1. Rates of Reported Gonorrhea Cases per 100,000 Women of Childbearing Age by Race/Ethnicity and Age Group, United States, 2017[11]

Age	White	Black	Asian	Native Hawaiian/Other Pacific Islander	American Indian/ Alaska Native	Hispanic	Overall
15-19*	197.5	1,843.8	52.3	498.0	806.0	247.6	557.4
20-24	280.0	2,066.8	71.9	769.7	1,232.2	339.6	648.8
25-29	205.8	1,104.4	37.8	392.7	1,164.9	229.0	413.7
30-34	134.6	489.9	26.7	230.0	819.1	131.5	223.3
35-39	81.4	245.2	18.0	225.7	446.3	81.5	129.3
40-44	40.6	106.0	10.4	86.4	298.7	37.6	63.8
All Ages	58.5	444.3	16.7	177.3	363.6	87.5	141.8

* Reported cases of gonorrhea in women are largest at age 19, with 872.2 cases per 100,000.

Table 2. Rates of Reported Gonorrhea per 100,000 Women by Region, United States, 2017[11]

Northeast	Midwest	South	West	Overall
84.5	157.9	172.7	120.1	141.8

Table 3. Recommendations for Ocular Prophylaxis for Gonococcal Ophthalmia Neonatorum

Organization Year	Recommendation
American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG)[20] 2017	Antimicrobial ophthalmic prophylaxis soon after delivery is recommended for all newborn infants but should be delayed until after the initial breastfeeding in the delivery room. A variety of topical agents appear to be equally efficacious, but only erythromycin ophthalmic ointment is currently commercially available in the US. Application of a 1-cm ribbon of sterile ophthalmic ointment containing erythromycin (0.5%) in each lower conjunctival sac is recommended. Care should be taken to ensure that the agent reaches all parts of the conjunctival sac. The eyes should not be irrigated with saline or distilled water after application of any of these agents; however, after 1 minute, excess ointment can be wiped away with sterile cotton.
World Health Organization[55] 2016	For all neonates, the WHO STI guideline recommends topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum. Strong recommendation, low quality evidence.
American Academy of Pediatrics[56] 2015	For prevention of gonococcal ophthalmia in newborn infants, 0.5% erythromycin ophthalmic ointment should be instilled in each eye in a single application.
Centers for Disease Control and Prevention[2] 2015	To prevent gonococcal ophthalmia neonatorum, a prophylactic agent should be instilled into both eyes of all newborn infants. Recommended regimen: Erythromycin (0.5%) ophthalmic ointment in each eye in a single application at birth
Canadian Pediatric Society[1] 2015	Neonatal ocular prophylaxis with erythromycin, the only agent currently available in Canada for this purpose, may no longer be useful and, therefore, should not be routinely recommended. Pediatricians and other physicians caring for newborns should advocate to rescind ocular prophylaxis regulations in jurisdictions in which this is still legally mandated. Jurisdictions in which ocular prophylaxis is still mandated should assess their current rates of neonatal ophthalmia and consider other, more effective preventive strategies.
U.S. Preventive Services Task Force[29] 2011	Provide prophylactic ocular topical medication for the prevention of gonococcal ophthalmia neonatorum. (A recommendation)

Table 4. Recommendations for Prenatal Gonorrhea Screening and Treatment

Organization Year	Recommendation
U.S. Preventive Services Task Force[29] 2011	Screen pregnant women age 24 years and younger and in older women at increased risk of infection (B recommendation)
American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG)[20] 2017	Screen all pregnant women at increased risk for gonorrhea or living in an area with high prevalence at the first prenatal visit • If negative but high risk, retest at 3rd trimester • If positive, retest in 3 to 6 months, preferably in the 3rd trimester
Canadian Pediatric Society[1] 2015	Screen all pregnant women at the first prenatal visit • If negative but high risk, retest at 3rd trimester • If positive, treat and retest to ensure therapeutic success; retest in 3rd trimester, failing that, retest at delivery Pregnant women not screened during pregnancy should be screened at delivery

Table 5. Snapshot of the Evidence

	Rationale for previous GON prophylaxis USPSTF recommendations[13, 33, 34] and foundational evidence	Limitations of foundational evidence	New evidence findings
Benefits	Consistent evidence that topical ocular prophylactic preparations including erythromycin 0.5% ophthalmic ointment, tetracycline 1% ophthalmic ointment, or 1% silver nitrate solution are effective in preventing gonococcal ophthalmia neonatorum Strong evidence that universal administration of ocular prophylaxis has reduced incidence of gonococcal ophthalmia neonatorum in the United States	Primarily based on observational evidence from studies conducted in countries with limited applicability to the US over 20 years ago Limited evidence evaluating comparative effectiveness of prophylactic preparations that do not rely on antibiotics (i.e., povidone-iodine)	No new studies identified for clinical effectiveness Few new studies identified evaluating comparative effectiveness of prophylactic agents from countries with limited applicability to the United States. One study from Israel using 2003-2004 data found no difference in GON cases between iodine and tetracycline.
Harms	Harms not discussed	Reporting of harms is sparse and nonspecific, generally indicating the occurrence of chemical conjunctivitis, particularly with the use of silver nitrate	No new harms studies identified

Literature Search Strategies

CENTRAL

#1 (gonorr* or chlamyd*):ti,ab,kw
#2 conjunctiv*:ti,ab,kw
#3 (eye or ocular):ti,ab,kw near/3 infect*:ti,ab,kw
#4 #1 and (#2 or #3)
#5 inclusion:ti,ab,kw near/1 (blennorrhea* or conjunctiv*):ti,ab,kw
#6 trachoma*:ti,ab,kw
#7 #4 or #5 or #6 968
#8 (infan* or newborn* or (new* next born*) or neonat* or (neo next nat*)):ti,ab,kw
#9 #7 and #8
#10 ophthalmia:ti,ab,kw near/5 (infan* newborn* or (new* next born*) or neonat* or (neo next nat*)):ti,ab,kw
#11 #9 or #10 Publication Year from 2008 to 2018, in Trials

PUBMED

#29 Search #28 AND English[Language] AND ("2008/01/01"[Date - Publication] : "3000"[Date - Publication])

#28 Search #26 NOT #27

#27 Search animals[MeSH Terms] NOT (animals[MeSH Terms] AND Humans[MeSH Terms])

#26 Search #23 OR #24 OR #25

#25 Search ophthalmia[tiab] AND (newborn*[tiab] OR new-born*[tiab] OR "newly born"[tiab] OR neonat*[tiab] OR neo nat*[tiab])

#24 Search Ophthalmia Neonatorum[MeSH:NoExp]

#23 Search #21 AND #22

#22 Search "Infant, Newborn"[Mesh] OR infan*[tiab] OR newborn*[tiab] OR new-born*[tiab] OR "newly born"[tiab] OR neonat*[tiab] OR neo nat*[tiab]

#21 Search #16 OR #17 OR #18 OR #19 OR #20

#20 Search trachoma*[tiab

#19 Search inclusion[tiab] AND (blennorrhea*[tiab] OR conjunctiv*[tiab])

#18 Search trachoma[MeSH:NoExp]

#17 Search "conjunctivitis, inclusion"[MeSH:NoExp]

#16 Search #9 AND #15

#15 Search #10 OR #11 OR #12 OR #13 OR #14

#14 Search (eye*[tiab] OR ocular[tiab]) AND infect*[tiab]

#13 Search conjunctiv*[tiab]

#12 Search eye infections[Mesh:NoExp]

#11 Search "conjunctivitis, bacterial"[MeSH:NoExp]

#10 Search conjunctivitis[Mesh:NoExp]

#9 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#8 Search chlamyd*[tiab]

Appendix A. Detailed Methods

#7 Search Chlamydia Infections[Mesh:NoExp]

#6 Search chlamydia trachomatis[Mesh:NoExp]

#5 Search chlamydia muridarum[MeSH:NoExp]

#4 Search chlamydia[MeSH:NoExp]

#3 Search gonorr*[tiab]

#2 Search neisseria gonorrhoeae[MeSH:NoExp]

#1 Search "Gonorrhea"[Mesh:NoExp]

Appendix A Table 1. Inclusion and Exclusion Criteria

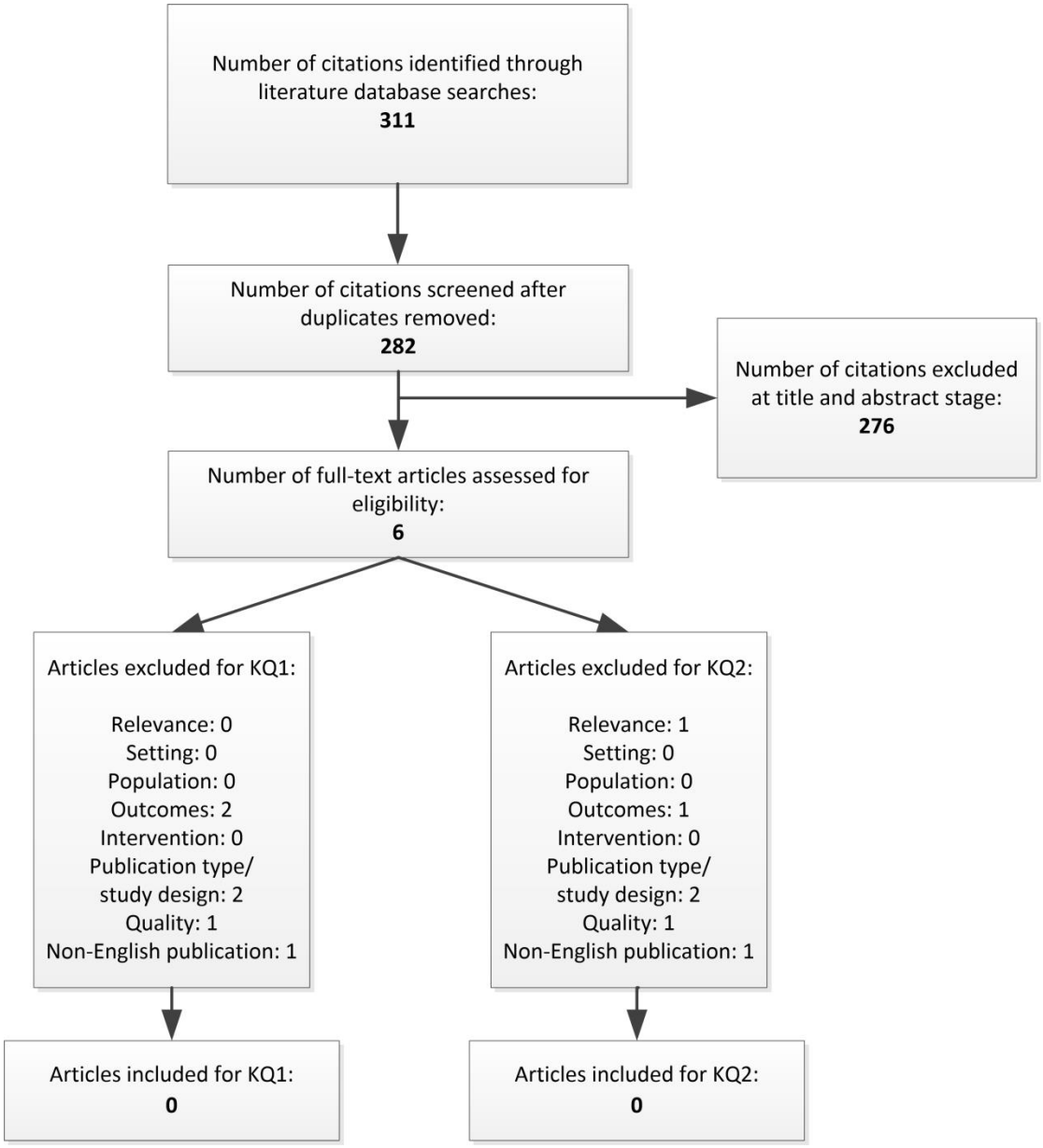
Category	Included	Excluded
Populations	Newborns	Populations other than newborns
Interventions	Ocular prophylaxis for gonococcal ophthalmia neonatorum	Treatments other than ocular prophylaxis
Comparisons	**KQ1:** No treatment, placebo (randomized, controlled trials) **KQ2:** No treatment (randomized, controlled trials) or no comparator (observational studies)	Comparative effectiveness
Outcomes	**KQ1:** Incidence of gonococcal ophthalmia neonatorum, visual impairment, blindness **KQ2:** Harms of ocular prophylaxis	Cost-effectiveness or cost-related outcomes
Setting	Any birth setting	No exclusions
Country	Studies conducted in countries categorized as "high" or "very high" on the Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries categorized as less than "high" or "very high"
Study design	**KQ1**: Randomized, controlled trials; systematic reviews and meta-analyses **KQ2:** Randomized, controlled trials; systematic reviews and meta-analyses; cohort studies, case-control studies, and large case series (≥100)	Narrative reviews, editorials, and case reports
Publication language	English-language only	Languages other than English
Study quality	Fair- or good-quality studies	Poor-quality studies

Appendix A Table 2. Study Design–Specific Quality Rating Criteria

Study Design	Adapted Quality Criteria
RCT[30]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias in classifying interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported
Cohort[57]	• Was selection of exposed and non-exposed cohorts drawn from the same population? • Can we be confident in the assessment of exposure? • Can we be confident that the outcome of interest was not present at start of study? • Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? • Can we be confident in the assessment of the presence or absence of prognostic factors? • Can we be confident in the assessment of outcome? • Was the follow up of cohorts adequate? • Were co-Interventions similar between groups?

Abbreviations: CCT = controlled clinical trial; RCT = randomized, controlled trial

Appendix B Figure 1. Literature Flow Diagram



Appendix C. List of Included Studies

No studies were included for KQ1 or KQ2.

Appendix D. List of Excluded Studies

Reason for Exclusion	
E1	**Study relevance**
E2	**Setting:** Not in “high” or “very high” Human Development Index country
E3	**Population:** Not newborns
E4	**Outcome**: No relevant outcomes
E5	**Intervention:** Not ocular prophylaxis for gonococcal ophthalmia neonatorum
E6	**Publication type/study design**
E7	**Study quality**
E8	**Publication not available in English**

1. Ghaemi S, Navaei P, Rahimirad S, et al. Evaluation of preventive effects of colostrum against neonatal conjunctivitis: A randomized clinical trial. J Educ Health Promot. 2014;3:63. PMID: 25077156. **KQ1E4, KQ2E4.**
2. Nathawad R, Mendez H, Ahmad A, et al. Severe ocular reactions after neonatal ocular prophylaxis with gentamicin ophthalmic ointment. Pediatr Infect Dis J. 2011;30(2):175-6. PMID: 20885334. **KQ1E4, KQ2E7.**
3. Scott WJ, Eck CD. Povidone-iodine and ophthalmia neonatorum. Ophthalmology. 2012;119(3):653-4; author reply 4. PMID: 22385492. **KQ1E6, KQ2E6.**
4. Wexelblatt SL, Greenberg JM, Nathan AT. Regional care model enables rapid response to adverse drug events. J Perinatol. 2010;30(4):300. PMID: 20351711. **KQ1E6, KQ2E6.**
5. Silva LR, Gurgel RQ, Lima DR, et al. Current usefulness of Crede's method of preventing neonatal ophthalmia. Ann Trop Paediatr. 2008;28(1):45-8. PMID: 18318948. **KQ1E7, KQ2E1.**
6. Ghotbi N, Mansori M, Kalantar M, et al. Comparison of the effect of tetracycline 1% and erythromycin 0.5% ophthalmic ointments for prophylaxis of ophthalmia neonatorum. Scientific Journal of Kurdistan University of Medical Sciences. 2012;17(3):20-5. PMID: None. **KQ1E8, KQ2E8**