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Challenges in treating ophthalmia neonatorum

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Abstract

Introduction: Ophthalmia neonatorum is a severe, sight-threatening condition that occurs in neonates worldwide. Etiological factors include chemical agents, viruses, and bacteria, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* acquired from infected mothers at birth. Prevalence varies geographically, depending upon socioeconomic conditions, maternal health care, and prophylactic treatments available. Antibiotic resistance, particularly in *N. gonorrhoeae*, is a major challenge in treating ophthalmia neonatorum.

Areas covered: This review explores the epidemiology and diagnosis of ophthalmia neonatorum and analyses the history and practices of prophylaxis and treatment. In this context, the challenges in treating ophthalmia neonatorum today are discussed and innovations that may overcome these challenges in the future are presented. Advantages and challenges of strategies to prevent ophthalmia neonatorum involving prophylaxis of infants and those using screening and treatment of mothers are explored.

Expert commentary: Despite the potential to rapidly cause blindness, there are no universal guidelines for the prevention and treatment of ophthalmia neonatorum. Due to the increasing number of treatment failures, particularly those of extensively drug-resistant *N. gonorrhoeae*, a pragmatic approach is needed. Enhanced availability of screening and treatment of pregnant mothers, coupled with development of new antimicrobial ocular prophylaxis and treatments, provide options for a variety of settings.

Key words: Antibiotic resistance, neonatal conjunctivitis, *Chlamydia trachomatis*, gonococcal blindness, *Neisseria gonorrhoeae*, prophylaxis, bacterial eye infections, novel antimicrobials

1.0 Introduction

Ophthalmia neonatorum, also called neonatal conjunctivitis, is a term for all forms of conjunctival inflammation that occurs in neonates within the first month of birth [1-2]. The conjunctiva lines both the sclera (the white outer surface of the eye) and the inside of the eyelids, as the bulbar conjunctiva and the palpebral conjunctiva, respectively [3-4]. Both of these conjunctival surfaces that touch one another, are involved in ophthalmia neonatorum. The etiological agents of ophthalmia neonatorum include sexually transmitted bacteria, non-sexually transmitted bacteria, viruses, and chemical toxicity from substances such as silver nitrate [5-6]. Clinical manifestations of ophthalmia neonatorum include purulent discharge and redness and swelling of the eyelid and conjunctiva [7-9]. In severe cases, the cornea may become affected, resulting in inflammation, thinning, ulceration, perforation, and ultimately blindness [10]. Chemical conjunctivitis usually resolves within 2 days [10-11] and may not usually require treatment [11], while those of infectious origin often require treatment [12-13].

Ophthalmia neonatorum is described as an ocular emergency [14] because of the potential to not only cause blindness but, depending on the infectious organism, its sequelae can also extend to other parts of the body causing infections that can be potentially fatal, depending on the infecting organism [10,15].

1.1 Sexually transmitted infections that cause ophthalmia neonatorum

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the main sexually transmitted bacteria that cause 2% to 40% and under 1% of ophthalmia neonatorum cases, respectively, whilst sexually transmitted viruses like herpes simplex virus cause under 1% of cases [5]. Sexually transmitted infections of the mother are transferred to the eyes of the infant during passage through the birth canal. In addition, there have been reports of intrauterine as well as transplacental or transmembrane infection in cases of caesarean section [16].

1.2 Non-sexually transmitted infections that cause ophthalmia neonatorum

Non-sexually transmitted infections that cause ophthalmia neonatorum include those caused by *Streptococcus pneumoniae, Streptococcus viridans*, *Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenza*e, *Escherichia coli*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*, being responsible together for about 30% - 50% of cases, with adenovirus implicated in about 1% of cases [5,15,17-19]. Some of these species linked with ophthalmia neonatorum, such as *S. aureus* and *P. aeruginosa*, may be acquired within hospital neonatal wards or intensive care units [20]. Whilst several studies have identified *S. aureus* or *Staphylococcus epidermidis* as causative agents of ophthalmia neonatorum [8,19-23], the occurrence of the bacteria on the conjunctiva and as a skin flora surrounding the areas of the eyes have raised questions regarding their involvement as etiologic agents of ophthalmia neonatorum [6,19,23].

1.3 History, epidemiology, and burden of disease

1.3.1 Ophthalmia neonatorum before antibiotics

In the pre-antibiotic era, the burden of ophthalmia neonatorum disease was readily apparent, with large numbers of infants losing their eyesight at birth. For example, in 1880, ophthalmia neonatorum was responsible for 79% of the cases of blindness in children in institutions for the blind [24]. In the United States between 1906 and 1911, 24% of new admissions to schools for the blind were due to ophthalmia neonatorum [25]. A new hospital was opened in 1918, in London, to specifically treat infants with ophthalmia neonatorum, due to the high number of cases and the need for prompt treatment in an attempt to prevent ocular perforation and blindness [26-27]. This was one of two hospitals arranged to be provided in London at the time and followed examples set in Liverpool, Glasgow, and Manchester [26-27]. A major breakthrough in the prevention of ophthalmia neonatorum came with the introduction of Credé's silver nitrate prophylaxis, first introduced in 1881 [28], which reduced the cases of ophthalmia neonatorum due to infection, although it was not without some chemical conjunctivitis and toxicity [6,29-30]. This will be discussed in detail in section 1.5.1.

1.3.2 Ophthalmia neonatorum prevalence today

Ophthalmia neonatorum remains a global issue, threatening the sight of children worldwide [31-32]. The prevalence of ophthalmia neonatorum varies for different regions of the world and due to underreporting, decades of relatively low rates of ophthalmia neonatorum associated blindness in developed regions, and lack of resources for either diagnostics or treatment in low resource areas, there are few recent figures available and those that are available are specific to a particular etiological agent [5-6,8-9,18-24].

Ophthalmia neonatorum is listed amongst the World Health Organization (WHO) priority eye diseases as a major cause of childhood blindness in low-income countries [33]. The burden of childhood blindness affects the quality of life, productivity of the child, and impacts socioeconomically on the family as well as the wider society [34-35]. Ophthalmia neonatorum remains one of the major reasons for blindness in low-income countries [33,36]. The rate of visual impairment or blindness attributable to ophthalmia neonatorum have been reported to be between 0.4% and 5.9% in parts of Asia [34,37-41] and Africa [37,42-46] as shown in Figure 1.

The incidence of ophthalmia neonatorum has been closely linked to the burden of sexually transmitted infections (STIs) in a population, particularly the maternal population [47-48]. Of the STIs causing ophthalmia neonatorum, *C. trachomatis* is the most common etiology, however *N. gonorrhoeae* causes more severe complications that can progress to blindness within 24 hours [49-50]. Although chlamydial ophthalmia neonatorum does not rapidly progress and directly compromise the integrity of the eye via perforation like gonococcal infection, chlamydial sequelae may result in conjunctival scarring and infiltration of the cornea by abnormal vessels and fibrous tissue also known as micropannus [51-52]. A conservative estimation reveals that over 50% of women with *N. gonorrhoeae* and *C. trachomatis* infection are asymptomatic and so are unaware of the infection [53-55].

In developed countries, *C. trachomatis* is the most common infectious agent causing ophthalmia neonatorum, accounting for 2-40% of cases, compared to less than 1% caused by *N. gonorrhoeae* [5,56-57]. The prevalence rate of gonococcal and chlamydial ophthalmia

neonatorum is reported as 3.7 per 100,000 and 6.9 per 100,000 live births, respectively, in the United Kingdom [58]. However, a study of hospital data in England from 2000-2011 showed marked fluctuations in annual figures and underestimations, suggesting that the rate may be much higher [59]. In the United States, prevalence rates of chlamydial and gonococcal conjunctivitis in 2015 were 2.1 and 0.2 cases per 100,000 live births, however this is also predicted to be an underestimate [60]. In a surveillance study by Kreisel et al. [60] using isolates sent to the Centers for Disease Control and Prevention (CDC), it was noted that 85% of potential ophthalmia neonatorum cases were excluded because the specimen source for the gonococcal or chlamydial isolates in patients less than one year-old was not indicated as "eye" or "conjunctiva", with 52% having an "unknown", "other-not specified", or "missing" specimen source. In New Zealand, the prevalence rate for chlamydial ophthalmia neonatorum from 2013-2016 was 145.9 per 100,000 live births and for gonococcal ophthalmia neonatorum 3.79 per 100,000 live births [61].

It is estimated that 20-75% and 15-35% of ophthalmia neonatorum cases in developing countries that present to the hospital are attributable to *N. gonorrhoeae* and *C. trachomatis*, respectively [31]. *C. trachomatis* accounts for 1.8% to 33% of ophthalmia neonatorum cases in hospitals in Africa [7,62-66] and 12.5% - 60% in hospitals in Asia [67-69]. It should be noted that in some investigations no *C. trachomatis* are identified. This is due to regional differences in practice, influenced by the availability of diagnostic facilities and resources in different healthcare settings. Even where possible and best practice, it is sometimes not routine; 85% of surveyed global members of the American Association of Paediatric Ophthalmology and Strabismus stated that they treat ophthalmia neonatorum empirically within the first 10 days of life and 75% do so thereafter [87]. Culture for diagnostic growth of *C. trachomatis* is often not used, due to the requirement to culture on eukaryotic cell monolayers, however identification of the bacteria by this method is possible when facilities are available [19, 70]. Nucleic acid amplification tests (NAATs) are often considered superior for identification of urogenital infections of *C. trachomatis* [70]; for ocular infections, NAATs are recommended by the WHO [92], but not by the US Food and

Drug Administration (FDA), which instead recommends direct fluorescence antibody (DFA) assays for chlamydial ophthalmia neonatorum diagnostics [93]. Testing for *C. trachomatis* can also be achieved via cytological examination from smears taken from the infant's eyes [58,70]. This Giemsa staining method can have up to 90% sensitivity in diagnosing acute inclusion conjunctivitis in newborns, however molecular detection methods using PCR have greater sensitivity [58,70].

Cases of gonococcal ophthalmia neonatorum vary by region; a hospital in Singapore, for example reported 68% of cases between 1983 and 1986 were caused by *N. gonorrhoeae* [71]. Infection of the same patient with both *N. gonorrhoeae* and *C. trachomatis*, a coinfection causing ophthalmia neonatorum, has been reported with a rate estimated at 3% [63,69].

With the decline in gonorrhoea sexually transmitted infections in industrialized countries in the 1970's and early 1980's, there was a decline in ophthalmia neonatorum caused by *N. gonorrhoeae* [24,47], however the same was not observed for *C. trachomatis* [47]. Also, some developed countries instituted prenatal screening of pregnant women for sexually transmitted infections [24]. These circumstances reduced the incidence of ophthalmia neonatorum in many developed countries. However, this dynamic changed due to changes in STI prevalence and antimicrobial resistance. There was a substantial rise in the diagnoses of *N. gonorrhoeae* infections in England from 14,985 in 2008 to 56,259 in 2018 [72]. Gonorrhoea diagnoses in the United States have also risen, climbing from a historic low in 2009 up 75.2% to 555,608 in 2017 [73]. There were 87 million cases of gonorrhoea STI estimated by the WHO in 2016 and increasingly fewer options for effective antibiotic treatment of many isolates [74-78]. Also, factors such as demographic, social, and legal barriers may restrict access to needed infection control measures [74]. The case reported of a multi-drug resistant strain of *N. gonorrhoeae* in the UK of a heterosexual man who had sexual contact with a female partner in South East Asia explains the role of migration and sex tourism in increasing the risk of sexually transmitted infection in the general population, having been acquired from a high-risk population [74-75].

The Western Pacific region, where this extensively resistant strain originated, has been reporting widespread high level resistance to penicillin and ciprofloxacin and increased minimum inhibitory concentration (MIC) values for ceftriaxone, as well as ceftriaxone resistance, for several years from its 37 countries including developed countries like Japan, Australia, and developing countries such as Vietnam, Malaysia, and the Philippines [79].

On the other hand, non-sexually transmitted bacteria have been reported to cause ophthalmia neonatorum, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Haemophilus influenzae*, *Escherichia coli*, *Streptococcus viridans*, *Streptococcus pneumoniae*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* [8,19,22-23,80-81]. Although there is concern about whether *S. aureus* is the cause of ophthalmia neonatorum, given its presence as normal flora and presence from swab in healthy infants, it has a reported prevalence of 51.5% in Norway [22], 27.6% in Argentina [80], 31% in Iran [23], 36% in Hong Kong [81], 17.8% in southern China [19], and 65% in Pakistan [8].

1.4 Investigation of ophthalmia neonatorum

Presented with an infant with a suspected case of ophthalmia neonatorum, ocular specimens are obtained and investigated to identify the etiological agent, using various culture and non-culture tests, depending upon the facilities available and current practice in the healthcare setting. In some cases paediatricians and eyecare specialists treat without microbial identification; if the symptoms clear, no further investigation is undertaken [87]. Investigations in some clinical settings may involve laboratory cultures and microscopy, including Gram staining from conjunctival swabs and Giemsa staining of epithelial cells scraped from conjunctivae in cases of suspected chlamydial ophthalmia neonatorum to determine the etiologic agent [7-8,17,23,5870,82-83,92-93]. Gram stain results revealing Gram-negative diplococci in conjunctival exudate can rapidly give a strongly presumptive diagnosis of gonococcal ophthalmia neonatorum [7-8,17,82-83,91-92]. In healthcare settings with facilities and resources to do so, the standard may be to conduct non-culture tests such as NAATs, which amplify sequences specific to *N.*

gonorrhoeae and *C. trachomatis* [70,91-92]. Despite the greater sensitivity and specificity of NAATs compared to culture, the FDA does not recommend it for identification of gonococcal or chlamydia conjunctival infections [92-93]. Less commonly used enzyme immunoassays (EIA) can also identify gonococcal or chlamydial antigens [70,82-83,91-93]. Molecular tests, including NAATs, exhibit greater sensitivity, can detect non-viable organisms improving specimen collection and storage, offer the option of clinician or self-collected swabs, and can be non-invasive, however when culture-based testing is available, it is particularly useful because it can be applied to a variety of specimen sources, including ocular, and culture-based methods are able to detect antimicrobial resistance, which is an important consideration in gonococcal ophthalmia neonatorum [6,12,58,70,82,91-92].

The greater sensitivity of NAATs may lead to false positive results such as was observed in studies where NAAT positive cases of gonococcal infection exhibited a corresponding culture negative result for the same cases [84]. For ophthalmia neonatorum, the opposite may also be the case, where NAATs results are negative when *N. gonorrhoeae* are present. A comparison of three commercial NAATs kits showed variability in results dependent upon sample site location, with eye swabs giving the worst results, confirming known positive cases from only 54.5% of samples [85]. Although the CDC and Public Health England (PHE) do not recommend using less sensitive non-NAAT tests (including culture test) to confirm positive results of highly sensitive tests like NAAT, the additional use of culture tests for isolation of microbial strains and antimicrobial resistance testing [70,82] and perhaps as follow-up testing [84-85], including proof of cure testing in cases of STI, may be beneficial.

Laboratory test results are often available within 24 to 72 hours, depending on the type of test used and diagnostic facilities available [70,82]. This is a concern when managing potential gonococcal ophthalmia neonatorum, which can cause severe damage to the cornea and rapidly cause permanent visual impairment, including blindness within 24 hours [24,49-50]. Hence, there may be the need to start treatment while laboratory test results are being awaited.

1.5 Management of ophthalmia neonatorum

The management of ophthalmia neonatorum involves the implementation of various strategies aimed at prevention and at treatment following development of symptoms. Preventative approaches involve administration of eye prophylaxis at birth [6,24-25,28-30,32,57,60,66,86-87] screening and treatment of pregnant women for sexually transmitted infection during the antenatal period [6,18,24,56,72-74,82-83], and preventive measures against the spread of sexually transmitted infection [18,72-74,82]. Treatment of ophthalmia neonatorum involves the use of anti-infective agents to eliminate the condition in the neonate [6,12-13,18,57-58,87-88].

1.5.1 Use of prophylaxis to prevent ophthalmia neonatorum

The practice of eye prophylaxis at birth involves cleaning the eyes of the neonate before administering a safe anti-infective agent into the eye, which should reduce growth of ophthalmia neonatorum causing organisms. Historically, prophylaxis for ophthalmia neonatorum began with Carl Siegmund Franz Credé, a German obstetrician who reduced the high incidence of ophthalmia neonatorum in babies born to mothers in his hospital from 13.6% to 0.05% in 1881 through instillation of silver nitrate into the eyes of the newborns at birth [28]. A similar reduction in the incidence of ophthalmia neonatorum also occurred in Europe and other parts of the world following the use of Credé's prophylaxis [26-27,30]. However, chemical conjunctivitis, inflammation of the eyes, and redness were observed in up to 91% of cases, although this resolved within 24-48 hours [6,30,65,89]. With the arrival of the antibiotic era and discovery that silver nitrate was ineffective against chlamydial ophthalmia neonatorum [18,57,88], its use has been largely abandoned [30].

Alternative prophylactic agents that have been used include penicillin, erythromycin, tetracycline, povidone iodine, gentamicin, neomycin, and chloramphenicol [87,89-90]. The World Health Organisation (WHO) [91], CDC [92], American College of Obstetricians and Gynecologists (ACOG), and American Academy of Pediatrics (AAP) [57], strongly favour the practice of ocular

prophylaxis for preventing gonococcal conjunctivitis in all neonates. Additionally, the WHO supports ocular prophylaxis for chlamydial conjunctivitis in newborns and conditionally recommends using prophylactic agents like 0.5% erythromycin eye ointment, 1% tetracycline hydrochloride eye ointment, 2.5% povidone iodine, 1% silver nitrate solution, and 1% chloramphenicol eye ointment, depending on cost and local resistance to the prophylactic agents [88,91,93]. The CDC, however, does not recommend silver nitrate, tetracycline, gentamicin, bacitracin, or povidone iodine, but favours 0.5% erythromycin as ocular prophylaxis for ophthalmia neonatorum [57,92].

Different studies have suggested that the effectiveness of these prophylactic agents against ophthalmia neonatorum varies when they are compared together. In a 1947 study, benzylpenicillin (2,500 units/ml) was administered topically once a day for three days, demonstrating good results with less irritation compared to silver nitrate [94]. However, it is not effective against *C. trachomatis* and may instead contribute to persistence of chlamydial infection [95]. This limitation, the prevalence of penicillin resistance in *N. gonorrhoeae* currently [96], and the need for dose administration over several days, makes it suboptimal as a prophylaxis for ophthalmia neonatorum.

There are limitations for each of the prophylaxis agents 1% (w/v) silver nitrate, 1% (w/v) tetracycline ointment, and 0.5% (w/v) erythromycin ointment (Table 1). Silver nitrate is inexpensive, but due to issues with toxicity and chemical conjunctivitis has fallen out of favour and has been discontinued in many parts of the world [30]. Additionally, prophylaxis failures with silver nitrate still require treatment. By comparison, tetracycline is non-toxic, readily available in many developing countries, and the ointment is effective against *N. gonorrhoeae*, provided it is not resistant to tetracycline [24,30] However, routine tetracycline ocular prophylaxis is ineffective against chlamydial infection, which could subsequently result in respiratory infection in the infant. Erythromycin is considered ineffective for treatment of gonococcal STIs, thus the WHO recommended use of azithromycin in dual therapy [91]. Azithromycin is not, however,

available for ocular application. Erythromycin prophylaxis for ophthalmia neonatorum is recommended in many countries and is effective against *C. trachomatis* and possibly some sensitive isolates of *N. gonorrhoeae* and other infectious agents. Unfortunately, it is often not available in many lower income countries, due to the cost of erythromycin ointment [24,88,91]. Although prophylactic use of erythromycin has been linked with the occurrence of infantile hypertrophic pyloric stenosis, a condition that causes chronic vomiting in infants [98], the United States Preventative Serves Task Force (USPTF) recommends 0.5% erythromycin ophthalmic ointment prophylaxis in neonates [57].

Povidone iodine has been reported to possess antibacterial and antiviral properties, better efficacy, less toxicity, and less antimicrobial resistance than silver nitrate, tetracycline, and erythromycin [24,32,99]. The effectiveness of povidone iodine was also shown in some cases to be comparable with chloramphenicol for prophylaxis against ophthalmia neonatorum [101-102] and to have antiviral activity against herpes simplex virus and human immunodeficiency virus [30,95]. The minimal toxicity exhibited by 2.5% (w/v) povidone iodine is within neonatal tolerable limits [29,95], however this becomes a cause for concern with higher 5% (w/v) povidone iodine concentrations or more [29,103]. A study that observed a higher toxicity rate for povidone iodine 2.5% when compared to tetracycline, also noted that the rates were still lower than was previously reported [86]. According to the CDC, povidone iodine use has not been sufficiently studied [92] and a risk of harm may result because of the likely confusion with the well-known detergent formulation [56,87,91-92].

Gentamicin was previously recommended as an alternative ocular prophylaxis, due to shortages in availability of erythromycin ointment. Gentamicin is no longer recommended for neonatal application because of severe reactions, such as lid swelling and dermatitis associated with its use [18,92].

1.5.2 Treatment of ophthalmia neonatorum with anti-infective agents

After the establishment of infection, anti-infective agents must be used to treat ophthalmia neonatorum to eliminate the bacteria and potential damage to the eye resulting from untreated infection. Systemic treatment, in addition to topical treatment, is helpful in stopping the spread of the infectious agent causing ophthalmia neonatorum to other parts of the body [6,87-88,91-93]. The sole use of topical ocular agents may not be sufficient and in some cases may not be used in favour of systemic treatment [92]. Treatment should be guided by the causative agent that is involved. After diagnosis, treatment for chlamydial conjunctivitis involves administration of a daily dose of 50 mg/kg of oral erythromycin in four divided doses for two weeks [92,104]. As an alternative, the CDC recommends a daily dose of 20 mg/kg azithromycin suspension administered orally for three days [92]. Azithromycin, at this dosage, is the standard recommendation from the WHO, over erythromycin because of the potential risk of infantile hypertrophic pyloric stenosis with erythromycin [98]. There is consensus, however, that the infant should be monitored for side effects with either medication [91-92].

Treatment for neonatal gonococcal conjunctivitis recommended by the CDC involves a single dose of 25-50 mg/kg (125 mg maximum) ceftriaxone given intravenously or intramuscularly [92]. This regimen is also advocated for neonates without signs of infection that are born to mothers infected with untreated *N. gonorrhoeae* [92]. The WHO recommends treatment of gonococcal ophthalmia neonatorum with a single dose of ceftriaxone 50 mg/kg (maximum 150 mg) given intramuscularly, or a single dose of kanamycin 25 mg/kg (maximum 75 mg) given intramuscularly, or a single dose of spectinomycin 25 mg/kg (maximum 75 mg) administered intramuscularly [91].

1.5.3 Screening and treatment of pregnant women

Since ophthalmia neonatorum is associated with sexually transmitted infections in the mother, screening of pregnant women for STIs during the antenatal stage of pregnancy has been advocated in some developed countries such as Canada [18], the USA [92], and Australia [105]. Following screening, mothers positive for STIs receive treatment for the infection rather than

subjecting the neonate to prophylaxis at birth. Screening of pregnant women may also help identify their sexual partners, diminish transmission, and decrease adverse pregnancy outcomes such as low birth weight [106], premature birth, premature rupture of the membranes surrounding the baby, pre-term labour, and miscarriage [107-108]. Screening and treatment of pregnant mothers has been found to be equally as effective in reducing the incidence of ophthalmia neonatorum in neonates [83] as prophylaxis of the infants at birth. Cost analysis has shown that as the prevalence of infections such as *C. trachomatis* increase in a population, there is an increase in the cost-effectiveness of screening all women compared to not screening or selectively screening, particularly in settings where resources for laboratory testing is already in place [56,105]. Modelling from The Netherlands of screening for *C. trachomatis* has demonstrated cost-effectiveness in screening all women. This model took a broad, yet conservative, view of whole health costs for treatment of infants and mothers if they were not identified in screening, rather than just comparing the cost of screening versus cost of prophylaxis [109].

Implementation of a screening and treatment strategy in resource limited areas would require a point of care solution. One potential is the Cepheid GeneXpert *C. trachomatis* / *N. gonorrhoeae* (CT/NG) assay, which has been successfully used in indigenous communities in Australia [110-111] and Papua New Guinea [112]. Such successes for this fully automated molecular test in high burden, low resource settings demonstrate the feasibility of application of point of care testing to a screening and treatment strategy, provided appropriate treatments are available locally. The GeneXpert assay has similar accuracy as NAATs, however in this assay the reagents come in disposable cartridges and results are available in 90 minutes, facilitating prompt management of infection treatment [111-112]. In comparison, NAATs results are available after 24 to 72 hours, necessitating a second visit to the clinic for patients to obtain treatment once a positive test result is obtained [82]. In remote communities, where greater commuting may be required for patients to reach test sites, there may be longer delays [113]. For this reason, point of care and rapid tests that are easy to use and provide a diagnosis while

patients wait may provide the needed solution to increasing the strategy of screening and treatment as a means to reduce ophthalmia neonatorum worldwide [110,114].

Test of cure in the mothers has also been recommended to detect treatment failure if STI symptoms persist, if re-infection from the partner is suspected, or if therapeutic adherence is in doubt [92].

2.0 Challenges in preventing ophthalmia neonatorum

2.1 The question of prophylaxis

Despite the merits of the various strategies employed in managing ophthalmia neonatorum, there are certain inherent limitations. There are differences of opinion regarding the advantages of prophylactic treatment over non-use of prophylaxis [86,97,99,115-116]. Some studies show that ocular prophylaxis is clearly advantageous. However, in some areas, including Taiwan and Iran, current prophylaxis regimens (erythromycin, tetracycline, silver nitrate) are becoming ineffective, such that similar incidences of ophthalmia neonatorum occur with and without prophylaxis [116-117]. This may be due to the etiological agents. For example, a 2007 study of the causative bacteria of cases in Iran identified, from most to least commonly isolated, coagulase-negative staphylococci, Gram-negative bacilli, Gram-positive bacilli, *Escherichia coli*, enterobacter, and coagulase-positive staphylococci [117]. Despite this evidence that current prophylaxis is not able to completely prevent ophthalmia neonatorum in some regions, there are numerous examples in the literature of hospitals returning to prophylaxis after a brief hiatus, making it clear that the prophylaxis has had a positive, real-world impact [118-119] and with the right new prophylaxis, which is effective against the disease causing agents, could do so again.

As an historic example of the benefits of prophylaxis, silver nitrate use was discontinued for six months in 1957, at a hospital in New York (USA), during which time there were four cases of gonococcal ophthalmia neonatorum compared to a total of ten cases in the previous 25 years.

Silver nitrate prophylaxis was re-instated in the hospital [119]. In 1977, a similar reservation about chemical conjunctivitis led to a brief suspension of prophylactic use of silver nitrate solution in a maternity ward of a hospital in the United Republic of Cameroun. During an eight-week period, 14% of women included in the study were culture positive for *N. gonorrhoeae*. These mothers gave birth to 12 infants with eyes that were culture positive for *N. gonorrhoeae* at delivery. Of these, four received silver nitrate prophylaxis and did not develop ophthalmia neonatorum. Of the remaining eight, seven returned in three days with purulent conjunctivitis and received treatment; the eighth did not return for follow-up [118]. As reported in 1984, a hospital in Nairobi, Kenya had discontinued ocular prophylaxis for six months and observed that 23% of infants developed ophthalmia neonatorum, with 31% caused by *C. trachomatis*, 12% by *N. gonorrhoeae*, and 3% by both [120]. These cases led to a call to reintroduce ocular prophylaxis [12]. Prophylaxis to prevent ophthalmia neonatorum continues in countries including Spain [121], Brazil [122], the United States of America [57], Slovenia [123], Croatia [9], Canada [18], France [124], and Tanzania [125] (Table 2). However, prophylaxis has been discontinued in other countries, where the incidence of STIs is believed to be lower and where ophthalmia neonatorum risk is believed to therefore be lower, such as in Australia [126], United Kingdom [72], The Netherlands [109], Sweden [30], Denmark [30], and Belgium [127] (Table 2). In such countries, mothers may be screened or assessed for risk of STI prior to giving birth.

2.2 Multi-drug resistant *N. gonorrhoeae*

Despite over 100 years of medical intervention to prevent ophthalmia neonatorum from causing permanent ocular damage and blindness, it is still a concern today. Blindness can still result from treatment failures due to delayed or incorrect treatments, particularly in the face of extensively antibiotic resistant *N. gonorrhoeae* [75-77], or in regions of the world where treatment is not available. *N. gonorrhoeae* was designated as a high priority pathogen in the antibiotic-resistant bacteria global priority list of the World Health Organization in 2017 [128].

N. gonorrhoeae has shown resistance to all known antibiotic agents used for its treatment, making this etiological agent the single biggest challenge in treating ophthalmia neonatorum.

In some regions, due to availability, cost, or shortages, the only available drug for either prophylaxis or treatment may be penicillin [129-130]. It was the first antibiotic to treat gonococcal eye infections. In 1930, a crude extract of *Penicillium notatum* cured gonococcal ophthalmia neonatorum [131]. However, many gonococci today are resistant to penicillin [96].

Tetracycline ointments and ophthalmic solutions have also been used worldwide to prevent ophthalmia neonatorum [86,116,132-133]. According to the CDC advice in 1966, 1% (w/v) tetracycline ointment provided effective prophylaxis against both gonococcal and chlamydial conjunctivitis when given once soon after birth [133]. However, in 1985, tetracycline resistant strains of *N. gonorrhoeae* emerged, and tetracycline was thereafter no longer recommended as a first line treatment [134-135]. Today, many *N. gonorrhoeae* are also resistant to tetracycline [135].

Erythromycin ointment (0.5% w/v) is recommended in the US for prophylaxis of gonococcal eye infections [57], despite the emergence of resistance to erythromycin in the late 1970's [135-136]. The ineffectiveness of erythromycin against gonorrhoea STIs [136-137] and subsequent recommendations by the WHO and CDC to use azithromycin means that resistance data for erythromycin is not generally collected, but what has been assessed historically was high, necessitating the cessation of use of erythromycin against gonococcal STIs [91-92].

The current internationally recommended treatment for gonorrhoea in the reproductive tract is a dual therapy with azithromycin (1-2 g) and ceftriaxone (250-500 mg). *N. gonorrhoeae* resistance to ceftriaxone has been observed in several countries including Austria, England, France, Japan, Norway, Slovenia, Spain, and Sweden, [138-141] with rising resistance figures world-wide [149-141]. The rise in gonorrhoea cases that are nearly impossible to treat due to high level resistance to both azithromycin and ceftriaxone [75-76], will inevitably lead to difficult and potentially impossible to treat cases of ophthalmia neonatorum. From a global public health

point of view, a new therapeutic compound or antimicrobial agent is essential for effective control of infectious ophthalmia neonatorum.

Apart from antimicrobial resistance, cost and access to current antibiotics remain a challenge in treating ophthalmia neonatorum [30]. There is therefore the need to identify cost effective, potent, and accessible therapeutic agents for prophylaxis and treatment of ophthalmia neonatorum, to which the bacteria are unlikely to develop resistance.

2.3 Challenges of screening during pregnancy

Screening of pregnant women for sexually transmitted infection based on sexual history, behaviour, and screening tests, even though beneficial in managing ophthalmia neonatorum [6,18,24,56,72-74,82-83,92,105] may result in missed cases because of the asymptomatic nature of these infections. The high cost of screening and treating pregnant women, the possibility of reinfection, and inadequacy of health care in certain regions may make this option not viable [30,87-88,142]. Socially vulnerable women may not be able to access prenatal screening; it is believed that they are less apt to utilise prenatal care [143]. Apprehension about potentially testing positive for sexually transmitted diseases, including the possibility of false positive test results, may create panic and cause women not to attend clinics for prenatal care [143-145]. Alternative strategies involving antimicrobial treatment of all expectant mothers for infections may expose uninfected mothers to unwanted side effects of the medications [143].

With a prenatal screening strategy alone, cases will be missed, and infants will develop ophthalmia neonatorum requiring treatment. If the infecting organism is a multi-drug resistant *N. gonorrhoeae*, where the disease progresses rapidly, and the treatment options are limited or may not exist locally, infants may be left with permanent loss of visual acuity or blindness. As circulating strains acquire more resistance markers, the limited treatment options may disappear.

3.0. Innovative potential prophylaxis and treatment options for ophthalmia neonatorum

Fatty acids and their derivatives have been demonstrated to possess antimicrobial properties [146] that show promise as alternative prophylaxis and treatment regimens for ophthalmia neonatorum [146-149]. These antimicrobial agents occur abundantly in the natural environment making the potential for development of them into inexpensive therapies attractive, particularly in developing countries [146-151]. Monocaprin, myristoleic acid, palmitoleic acid, and linolenic acid have been demonstrated to rapidly kill *N. gonorrhoeae* in artificial tear fluid, eliminating all bacteria within 2 minutes [146]. *N. gonorrhoeae* did not develop resistance to monocaprin even when repeatedly passaged on media containing sublethal concentrations of this antimicrobial monoglyceride, nor did mutations accumulate in the genome indicative of the evolution of resistance [152]. In addition, monocaprin exhibits broad spectrum bactericidal activity against *C. trachomatis* [150-151], *N. meningitidis*, *S. aureus*, and *P. aeruginosa* [148]. This is especially important in cases where it may not be possible to readily differentiate the causative organism because of similarities in clinical manifestation and potential complications that may arise from instances of co-infection. Most importantly, these fatty acids and their derivatives have been demonstrated to be non-irritating in three separate ocular irritation assays [146]. Monocaprin has been shown to be effective at killing *N. gonorrhoeae* infecting primary human corneal cells in co-culture and to be able to clear bacteria infecting the surface of an explanted bovine eye [146]. With rapid antimicrobial activity, lack of irritation, and absence of resistance, fatty acids and their derivatives are promising as either a prophylaxis to prevent infection or a treatment to eliminate established bacterial infections caused by a range of species.

There have also been investigations into antimicrobial natural products, which may address the challenges of prophylaxis and treatment of ophthalmia neonatorum, including those from traditional medicine and antimicrobial natural products. Antimicrobial activity has been demonstrated for mixed preparations based on a medieval treatment called 'Bald's Eye Salve',

This contains allium species, garlic and leek or onions, mixed with wine and oxgall, left to react in a dark brass vessel for nine days [153-154]. Laboratory-generated mixtures, based on the medieval recipe demonstrated bactericidal activity against *S. aureus*, even in biofilms, [153-154], with the highest antimicrobial activity observed from the combination of ingredients specified in *Bald's Leechbook* [153]. Although modern irritation studies have not yet been conducted, the historic document indicates that this preparation should be administered to the eyes of the patient [153]. Datamining of medieval texts is yielding information about additional recipes with promising antimicrobial properties, including those cited in these texts as being treatments for diseases of the eyes [155].

Essential oils extracted from plants like the *Syzygium aromaticum* flower (clove) have potent antibacterial activity and are therefore attractive as potential therapeutic agent to treat *S. aureus* bacterial infections of the eye [156]. The antimicrobial activity of eyebright, *Euphrasia rostkoviana* Hayne (Scrophylariaceae), has been demonstrated against *S. aureus*, *S. epidermidis*, *Enterococcus faecalis*, *Escherichia coli*, and *Klebsiella pneumoniae* [157] and some small-scale studies have investigated their use for conjunctivitis [158]. Bactericidal activity has been demonstrated for *Melaleuca alternifolia* essential oil against *S. aureus*, suggesting its potential use as a topical agent [159]. Due to the potential for essential oils to cause irritation, additional research and safety testing is needed before these could be considered as viable options.

4.0 Conclusions

Ophthalmia neonatorum remains a global concern and there is need for global action to revise the recommendations for prophylaxis and treatment options in the face of evolving resistance in *N. gonorrhoeae*. There are many challenges involved with ophthalmia neonatorum prophylaxis and treatment including chemical conjunctivitis, resistance to both topical and systemic antibiotics, inadequate access to medications due to cost, absence of screening during pregnancy, and lack of treatment for sexually transmitted infections in pregnant women in

developing countries. Despite these challenges, interventions such as fatty acids, natural products, and essential oils may be formidable treatment and prophylaxis regimens suitable for development into future clinical applications to protect infant sight.

5.0. Expert commentary

There are currently no universal guidelines regarding prophylaxis or treatment for ophthalmia neonatorum, largely due to vast differences in the prevalence of infectious agents within the population and availability of healthcare for pregnancy risk assessment, screening, treatment, infant prophylaxis, and infant treatment. Compounding these issues are rising rates of sexually transmitted infections worldwide, including in developed countries and the increasing reports of *N. gonorrhoeae* that are resistant to last-line antibiotics [74-79].

Whilst the treatment recommendations for reproductive tract *N. gonorrhoeae* infections have changed several times over the last few years to address the growing threat of extensively drug resistant gonorrhoea, there has been little change in treatment recommendations for ophthalmia neonatorum. The shortcomings of guidance in the light of *N. gonorrhoeae* resistance, the clinical consequences of corneal perforation, and the need for prompt treatment and follow-up has been highlighted by clinicians [160]. The CDC recommendation for adult cases of gonococcal conjunctivitis is both a single 1 g dose of ceftriaxone given intramuscularly and a single 1 g oral dose of azithromycin [92], however this is theoretical and consultation with an infectious-disease specialist is recommended. When these antibiotics are ineffective, as in a case of gonococcal STI in 2018 [75], it is unclear what treatment options remain. Silver nitrate was highly effective in the past at preventing ophthalmia neonatorum, but it is clear that even if we are willing to accept the risk of chemical conjunctivitis and toxicity as have clinicians of the past [161], it was never effective in treatment of established infections. In 10-17% of infants receiving silver nitrate prophylaxis, ophthalmia neonatorum still developed [162] requiring treatment, which may not be possible if the bacteria are fully resistant to antibiotics.

Even in the United States and Canada there is inequality in access to prenatal care, which impacts the success of screening and treatment strategies for prevention of ophthalmia neonatorum [18,57]. For this reason, prophylaxis is still recommended in the US [57]. In addition, the average cost per infant for neonatal ocular prophylaxis with erythromycin is US$1.94 [163], while the cost of prenatal screening is US$13-US$20 [56,109]. There is therefore a cost advantage to prophylaxis compared to screening.

Increases in antibiotic resistant gonococci and other non-STI ophthalmia neonatorum species mean that it is imperative that alternative ocular therapies are investigated, such as the fatty acid containing eye drops [146,148,150], the Medieval manuscript inspired remedies [153], and other antimicrobials such as essential oils [156-159] that may be able to be used as readily accessible and inexpensive prophylaxis and as treatments for when prophylaxis fails or has not been administered. Options for treatment will also be important in cases of adult infections [2,50,160,164].

In addition to novel medical interventions, to meet the challenge of ophthalmia neonatorum, the issues surrounding stigma and shame associated with STIs must not be ignored. Even in regions with good access to healthcare and resources, patients avoid screening because of the stigma and shame implied by having an STI in many cultures [144,165-166]. Addressing the stigma of sexually transmitted diseases will require a partnership between stakeholders such as the WHO, governmental, and non-governmental organisations as well as multi-disciplinary collaborations with doctors, nurses, scientists, paediatricians, gynaecologists, optometrists, ophthalmologists, and primary health care workers. Working with local communities and being sensitive to cultures, it may be possible to reduce the stigma around STIs, increase the availability of testing for women, make treatment more accessible, and therefore reduce the risk of mothers transmitting sight-threatening infections to infants at birth.

6.0. Five-year view

The identification of novel antimicrobial agents for prophylaxis and treatment of ophthalmia neonatorum that are inexpensive, have broad spectrum activity, cause less toxicity, do not generate ocular irritation, to which there is no resistance, and which are readily available for use in local communities, looks promising in meeting the challenge of ophthalmia neonatorum. If adequate funding is made available to research into fatty acids, natural products, historical remedies, and essential oils as options for ophthalmia neonatorum it may be possible to significantly reduce preventable blindness from infectious diseases, a major cause of infant blindness world-wide. This would make an important impact upon the quality of life for these individuals and their families, as well as their communities as a whole. Within five years it may be possible, given the current state of research in the area, to advance this work to the stage where these novel agents have been assessed in clinical trials and perhaps be in use as a standard therapy for universal prophylaxis and treatment of ophthalmia neonatorum.

7.0. Key issues

- Sexually transmitted infections are on the increase around the world, which will contribute to an increase in cases of ophthalmia neonatorum.
- The most common causes of ophthalmia neonatorum are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, passed to the infant at birth from a mother who may be asymptomatic and unaware of her infection.
- Ophthalmia neonatorum can lead to loss of visual acuity and even blindness within days of birth, particularly when caused by *N. gonorrhoeae*, where the disease progresses rapidly.
- Prevention of ophthalmia neonatorum induced visual impairment can be achieved by preventing transmission of the bacteria to the infant or through prophylaxis shortly after birth.

- To prevent transmission of ocular infection causing bacteria to the infant, pregnant women must receive adequate health care, including screening and risk assessment for sexually transmitted infections, treatment for infection, and test of cure.
- Prophylaxis with an antimicrobial agent applied to the ocular surface shortly after birth is intended to prevent the growth of bacteria that may have been transferred from mother to child during passage through the birth canal.
- Not all mothers receive pre-delivery assessments and not all infants receive prophylaxis and even amongst those that do, some infants develop ophthalmia neonatorum requiring treatment.
- Treatment for ophthalmia neonatorum has become more challenging due to increasing resistance to antibiotics, particularly in the case of *N. gonorrhoeae*.
- Research and investment into innovative non-antibiotic agents for prophylaxis and treatment of ophthalmia neonatorum should be encouraged to replace or augment current antimicrobial agents.

Additional information

Figures and tables

The figures are confirmed to be original works of the authors and have not been previously published.

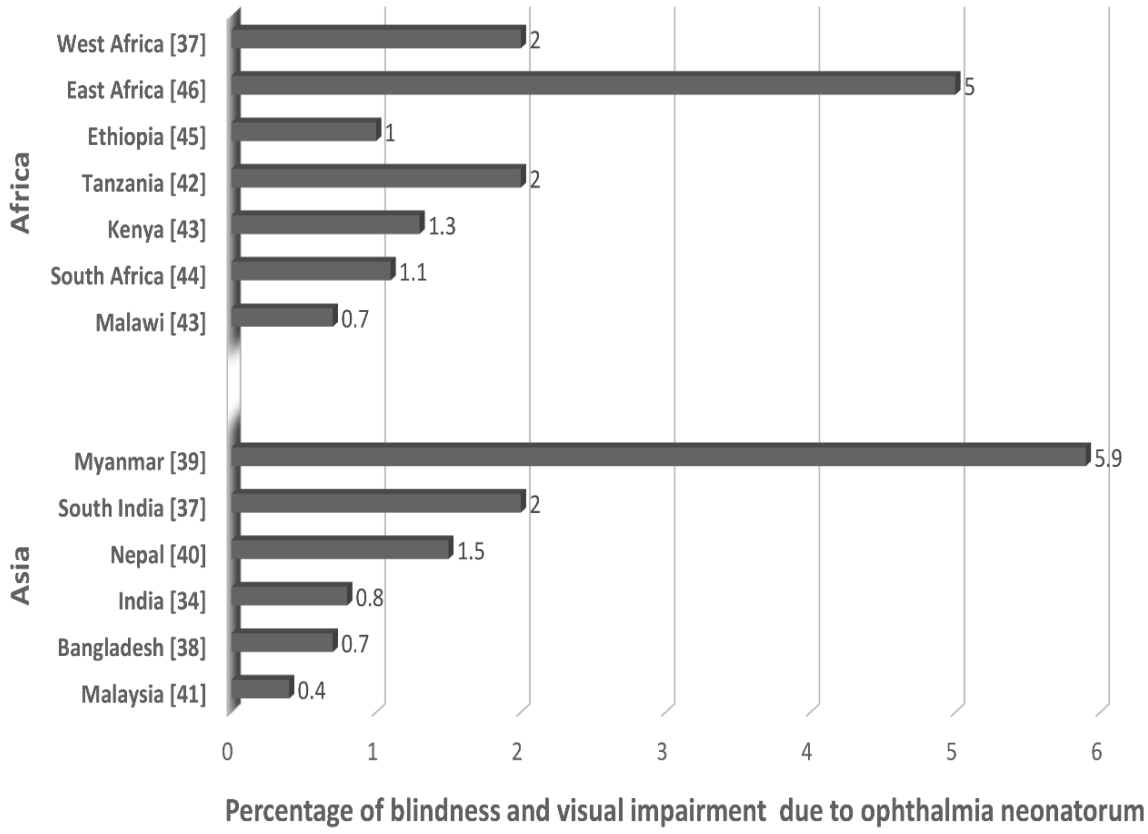

Figure 1. Percentage of blindness and visual impairment due to ophthalmia neonatorum in parts of Asia and Africa. Countries and regions in Africa (top) and Asia (bottom) reporting cases of ophthalmia neonatorum as one of the causes of vision loss in populations of visually impaired or blind children. References are provided in square brackets beside each country / region [34,37-46].

Table 1: Comparison of different prophylactic agents for ophthalmia neonatorum[a]

Intervention/comparator	Results	Location of study	Study design[b]	Study Size[c]	Reference
Erythromycin vs Silver nitrate	Erythromycin ointment was found to be more effective against chlamydial ophthalmia neonatorum than 1% silver nitrate	Seattle, USA	RCT	60	[97]
Tetracycline vs Silver nitrate	Silver nitrate (1%) was as effective as 1% (w/v) tetracycline ointment against ophthalmia neonatorum	Zaire, DR Congo	Quasi RCT	450	[167]
Tetracycline vs Silver nitrate	The effectiveness of 1% tetracycline is comparable with 1% silver nitrate in preventing gonococcal ophthalmia neonatorum	Nairobi, Kenya	Quasi RCT	2732	[162]
Erythromycin vs Silver nitrate Tetracycline vs Silver nitrate	There was no significant difference in the effectiveness of 0.5% erythromycin or 1% tetracycline compared to silver nitrate in reducing incidence of chlamydial ophthalmia neonatorum.	Brooklyn, NY, USA	Quasi RCT	230 for CT[d] 12431 for GC[e]	[168]
Tetracycline vs Silver nitrate	Tetracycline drops performed better against chlamydial ophthalmia neonatorum than silver nitrate solution up to the 14th day. Comparable results after day 15 onwards.	Saint-Germaine-en-Laye, France	Quasi RCT	900	[132]
Silver nitrate vs No prophylaxis Tetracycline vs No prophylaxis Erythromycin vs No prophylaxis	Erythromycin (0.5%; 1 or 2 doses) or 1% tetracycline or 1% silver nitrate did not greatly lower the incidence of chlamydial ophthalmia neonatorum when compared to no prophylaxis	Taiwan, China	Quasi RCT	4544	[116]

Povidone iodine vs Silver nitrate Erythromycin vs Silver nitrate	Povidone iodine solution (2.5%) had greater efficacy against chlamydial ophthalmia neonatorum than 1% silver nitrate or 0.5% erythromycin ointment. Erythromycin performed better than silver nitrate.	Kikuyu, kenya	Quasi RCT	3117	[99]
Chloramphenicol vs povidone iodine	Povidone iodine (2.5%) was less effective than chloramphenicol for ophthalmia neonatorum due to chlamydia. Povidone iodine was associated with more conjunctival reactions than chloramphenicol	Southern Mexico	Quasi RCT	2004[f]	[101]
Povidone iodine vs Erythromycin	Povidone iodine (2.5%) significantly reduced incidence of ophthalmia neonatorum more than 0.5% (w/v) erythromycin ointment	Tehran, Iran	RCT	310	[115]
Povidone iodine vs Erythromycin	Povidone iodine (2.5%) reduced incidence of ophthalmia neonatorum more than 0.5% (w/v) erythromycin ointment	Tehran, Iran	RCT	360	[100]
Povidone iodine vs Tetracycline	Tetracycline (1%) was slightly better than 2.5% povidone iodine against infective ophthalmia neonatorum and significantly better than povidone iodine against non-infective ophthalmia neonatorum. Povidone was linked with more conjunctival reactions or sterile conjunctivitis.	Nahariya, Israel	RCT	410	[86]
Chloramphenicol vs Povidone iodine	The effectiveness of 2.5% povidone iodine was comparable to 1% chloramphenicol in reducing the bacteria colony forming units in ophthalmia neonatorum	Jakarta, Indonesia	RCT	60	[102]

[a]Studies differed in diagnostic tests for detection of chlamydia. Pregnant women were only screened in two studies [97,168]. Efficacy against chlamydial ophthalmia neonatorum could not

be determined in three studies because no *C. trachomatis* were detected [86,102,167]. Efficacy against gonococcal ophthalmia neonatorum could not be determined in eight studies because no *N. gonorrhoeae* were detected [86,97,100-102,115-116,132].

[b]The study design was RCT, a randomized control trial, or Quasi RCT, a quasi-randomized control trial.

[c]The study size indicates the number of subjects involved in the study.

[d]*C. trachomatis* ophthalmia neonatorum

[e]*N. gonorrhoeae* ophthalmia neonatorum

[f]There were a lot of babies lost to follow up in the study, which may have affected the sample size [101].

Table 2: Examples of countries that do and do not use prophylaxis for ophthalmia neonatorum

Countries	Practice of prophylaxis[a]	Routine screening of pregnant women[a,b]	References
Australia	No	Yes[c]	[126]
Belgium	No	Yes	[127]
Brazil	Yes	No	[122]
Canada	Yes[d]	Yes	[18]
Croatia	Yes	No	[9]
Denmark	No	Yes	[30]
France	Yes	No	[124]
The Netherlands	No	Yes	[109]
Slovenia	Yes	No	[123]
Spain	Yes	No[e]	[121]
Sweden	No	Yes	[30]
Tanzania	Yes	No	[125]
United Kingdom	No	Yes	[72]
United States	Yes	Yes[b]	[57]

[a]Prenatal screening may require access to healthcare and compliance by pregnant women whereas prophylaxis may be more accessible, if available.

[b]In some countries screening is only conducted on women deemed to be at risk of STI.

[c]Chlamydia (not gonorrhoeae testing) is part of routine prenatal screening.

[d]Although routine prenatal screening is practised in Canada, ocular prophylaxis is still used and even mandatory in some provinces.

[e]Chlamydia screening is not recommended for all pregnant women but is recommended for asymptomatic pregnant women at risk of STIs.

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