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GROUP B STREPTOCOCCUS IN PREGNANCY, EPIDEMIOLOGICAL PECULIARITIES OF EARLY AND LATE ONSET STREPTOCOCCAL INFECTIONS IN NEWBORNS

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Abstract

Introduction*: Group B streptococci, also known as Streptococcus agalactiae, commonly inhabit the female genital tract without causing symptoms. However, during labor, it can transmit to the newborn, causing neonatal sepsis and meningitis. Group B Streptococcus is a leading cause of early-onset neonatal sepsis, contributing significantly to perinatal morbidity and mortality globally.*

Material and methods*: This study aims to investigate the role of Group B Streptococcus in neonatal diseases and assess prevention approaches on a global scale while considering the local situation in Armenia. The research entails a comprehensive review of existing literature, focusing on Group B Streptococcus colonization, perinatal transmission, prevention strategies, and associated neonatal outcomes. Data from various studies and epidemiological reports are analyzed to derive insights.*

Results*: Intrapartum antibiotic prophylaxis has been a crucial approach in preventing early-onset Group B Streptococcus disease. However, the targeting strategy, whether based on clinical risk factors or prenatal Group B Streptococcus screening, remains uncertain. Universal bacteriological screening of pregnant women during late pregnancy is widely adopted, yet questions persist regarding its benefits and potential drawbacks. Notably, current preventive strategies do not sufficiently guard against late-onset disease and its related sequelae.*

Conclusion: *To effectively reduce neonatal morbidity and mortality associated with Group B Streptococcus, it is imperative to enhance prevention and treatment strategies. Maternal vaccination against Group B Streptococcus emerges as a promising avenue to alleviate the global burden of this invasive disease, particularly in preventing late-onset disease and its long-term effects. Future efforts should prioritize optimizing vaccination strategies to protect both mothers and their infants, ultimately advancing the goal of reducing neonatal Group B Streptococcus-related diseases and their devastating consequences.*

Keywords: *Group B Streptococcus, perinatal infection, vaginal colonization, rectal colonization, pregnancy, early-onset disease, late-onset disease, antibiotic prophylaxis.*

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INTRODUCTION

Group B Streptococcus or Streptococcus agalactiae is a gram-positive bacterium which colonizes the gastrointestinal and genitourinary tract. It is recognized as a leading cause of illness and mortality in newborns. It is responsible for both early-onset and late-onset infections in neonates, but current interventions are only effective in the prevention of early-onset disease.

The objective of this study was to explore the involvement of Group B Streptococcus in the development of both early and late-onset neonatal diseases. Additionally, we aimed to compare the preventive strategies employed in various countries with the local situation in Armenia.

Pathophysiology: Group B Streptococci typically appear in pairs or short chains and share a common antigen known as the Lancefield group B polysaccharide antigen. They are distinguished by their type-specific capsular polysaccharides, expressed prominently on their surfaces, with 10 structurally and antigenically distinct types (Ia, Ib, II, III, IV, V, VI, VII, VIII, IX) [*Kong F et al., 2007*]. The capsule serves as the primary virulence factor, enabling Group B Streptococcus to evade host immune defenses by impeding phagocytic clearance [*Chen V et al., 2013*]. While all Group B Streptococcus serotypes can cause invasive infections, the majority of cases in neonates and adults are attributed to five serotypes (Ia, Ib, II, III, and V).

Invasive Group B Streptococci disease: Group B Streptococcus, or Streptococcus agalactiae, primarily causes invasive disease in infants, pregnant or postpartum women [*Pass M et al., 1982; Phares C et al., 2008*], and elderly individuals, with the highest incidence among newborns [*Phares C et al., 2008*]. Infections occurring within the first week of an infant's life are termed early-onset diseases, while late-onset infections manifest in infants older than one week, with most cases appearing within the first three months of life. Given the substantial disease burden among infants and the availability of effective preventive measures for early-onset Group B Streptococcus disease, this guidance focuses exclusively on early-onset disease. While the interventions used to prevent early-onset Group B Streptococcus disease may offer some protection against perinatal maternal infections [*Locksmith G et al., 1999; Schrag S et al., 2000*], they do not address late-onset infant disease [*Jordan H et al., 2008*].

Early-Onset Group B Streptococcus Disease: Early-onset Group B Streptococcus disease is frequently linked to maternal complications. Infants with this condition typically exhibit symptoms such as respiratory distress, apnea, or signs of sepsis within the initial 24-48 hours of life [*Franciosi R et al., 1973; Baker C, 1978*]. The primary clinical manifestations of early-onset disease include sepsis and pneumonia, with occasional instances leading to meningitis.

Transmission of early-onset infections occurs vertically, as infants are exposed to Group B Streptococcus from the colonized mother's vagina. Neonatal infection typically takes place when the bacteria ascends from the vagina into the amniotic fluid following the onset of labor or membrane rupture. In some cases, the bacteria can breach intact membranes [*Desa D, Trevenen C, 1984; Katz V, Bowes W, 1988*]. The fetal lungs can aspirate Group B Streptococcus, leading to bacteremia. Alternatively, infants may contract the infection during birth canal passage. The primary risk factor for early-onset disease is maternal intrapartum Group B Streptococcus colonization, with additional risk factors including gestational age <37 weeks, prolonged membrane rupture, and intra-amniotic infection [*Adair C et al., 2003*]. A previous history of delivering an infant with this invasive disease also increases the risk of early-onset disease in subsequent deliveries [*Carstensen H et al., 1988*].

Mortality rates are higher among preterm infants, with case-fatality rates reaching approximately 20% and potentially rising to 30% for infants born at ≤33 weeks' gestation, in contrast to 2-3% among full-term infants [*Schrag S et al., 2000; Phares C et al., 2008*]. The majority of early-onset Group B Streptococcus cases are attributed to its serotypes Ia and III, followed by Ib, II, and V [*Edmond K et al., 2012*].

Late-onset Group B Streptococcus disease: Late-onset Group B Streptococcus disease manifests after the first week of life but within the first 90 days. It frequently involves meningitis in up to 50% of cases. Unlike the early-onset form, this disease can be acquired prenatally through breast milk or from nosocomial and community sources. Prematurity is a key risk factor for late-onset disease, with the risk increasing proportionally with

each additional week of prematurity. Serotype III is the primary causative agent of late-onset disease. While the mortality rate is lower than that of early-onset disease, morbidity remains substantial, with approximately 50% of neonates surviving Group B Streptococcus infection experiencing complications, including cognitive impairment, hearing loss, and delays in speech and language development [*Heath P, Schuchat A, 2007*].

In the United States, the introduction of national consensus guidelines for aspirate Group B Streptococcus disease prevention by the Centers for Disease Control and Prevention in 1996, with updates in 2002, recommended universal screening of pregnant women for rectovaginal Group B Streptococcus colonization at 35-37 weeks of gestation and intrapartum antimicrobial prophylaxis for carriers. This led to a decline in early-onset Group B Streptococcus incidence from 0.47 per 1000 live births in 1999-2001 to 0.34 per 1000 live births in 2003-2005. However, the incidence of late-onset disease in infants aged 7-89 days remained stable despite these preventive measures, occurring at an average rate of 0.34 per 1000 live births in the USA from 1999 to 2005 [*Phares C et al., 2008*].

Late-late-onset Group B Streptococcus infection: Cases of infection occurring 90 days after birth are rare but have been documented, accounting for 0.37-0.73 cases per 100,000 in the USA. These cases often involve premature infants, with risk factors including prolonged hospitalization, likely linked to prematurity, an immature immune system, and persistent mucosal colonization.

Although early-onset disease has become less common in recent years, the rates of maternal Group B Streptococcus colonization (and consequently the risk of early-onset disease in the absence of intrapartum antibiotic prophylaxis) have remained unchanged since the 1970s [*Laura F et al., 2021*].

Epidemiology: The global incidence of Group B Streptococcus infections varies across regions. The highest incidence is observed in Africa, with a rate of 1.21 per 1000, followed by the Americas at 0.67 per 1000, and Europe at 0.57 per 1000. Southeast Asia reports the lowest incidence at 0.02 per 1000. It's worth noting that limited data is available from Southeast Asia, and this low incidence could be influenced by various factors, including widespread antibiotic usage before proper culturing, high case fatality rates before sample collection, or a lack of adequate laboratory facilities and culture methods. Similar challenges are faced in Armenia, where unregulated antibiotic use and inadequate microbiological culture data are significant public health concerns.

The guidelines for this disease prevention, initially issued by the Centers for Disease Control and Prevention in 1996 and updated in 2002, recommend universal screening of pregnant women for rectovaginal Group B Streptococcus colonization at 35-37 weeks of gestation and administering intrapartum antimicrobial prophylaxis to carriers. These guidelines were associated with a reduction in the incidence of early-onset disease from 0.47 per 1000 live births in 1999-2001 to 0.34 per 1000 live births in 2003-2005 in the United States.

However, in the Netherlands, the rate of early-onset infections increased from 0.11 per 1000 live births in 1987 to 0.19 per 1000 live births in 2011, despite implementing similar prevention guidelines for vertical transmission. Japan also saw no change in the rates of early-onset infections before and after implementing prevention guidelines at delivery in 2008, with rates of 0.08 per 1000 live births in 2004-2008 and 0.10 per 1000 live births in 2009-2010, respectively. These countries had lower initial incidences of Group B Streptococcus diseases than the US, suggesting that countries with lower disease incidence may not experience the same benefits from prevention strategies. In the case of Japan, the incidence of late-onset diseases also remained stable at 0.10 per 1000 live births from 2004 to 2010, mirroring the trend observed in early-onset diseases. Despite the implementation of prophylactic measures, the incidence of late-onset infections among infants aged 7-89 days remained consistent, averaging 0.34 per 1000 live births in the USA from 1999 to 2005. These guidelines were subsequently updated and republished in 2021, with key changes related to specimen and methods, which will be detailed in the relevant section [*Laura F et al., 2021*].

Prevention of early-onset Group B Streptococcus disease: The primary risk factor for early-onset disease is the presence of Group B Streptococcus in the maternal genital tract during labor. Group B Streptococcus is typically a part of the normal gastrointestinal tract flora, and maternal colonization is often linked to this source. It is advisable to perform Group B Streptococcus cultures

during each pregnancy because colonization can be temporary. A positive urinary tract infection due to Group B Streptococcus at any point during pregnancy is indicative of heavy colonization, and such patients should receive prophylaxis, even if Group B Streptococcus culture results are negative between 35 to 37 weeks of pregnancy. Additional risk factors for early-onset disease include young maternal age, Black race, preterm labor (delivery before 37 weeks), maternal fever during labor (temperature greater than 100.4°F or 38°C), and prolonged rupture of membranes (lasting more than 18 hours). The incidence of its colonization during pregnancy ranges from 10% to 30%. Without preventive measures, early-onset disease affects 1% to 2% of neonates born to mothers with Group B Streptococcus colonization [*Verani J et al. 2010*].

The American College of Obstetricians and Gynecologists issued guidelines in 2019 outlining Group B Streptococcus prophylaxis [*Baker C, 1978*]. According to these guidelines, intrapartum prophylaxis is not required for women who go into labor with an unknown colonization status if they have negative intrapartum Group B Streptococcus nucleic acid amplification testing results and no clinical risk factors.

Intrapartum nucleic acid amplification testing without enrichment is associated with an unacceptably high false negative rate, ranging from 6.3% to 22% [*Carstensen H et al., 1988; Schrag S et al. 2002; Adair C et al., 2003*]. As a result, the American College of Obstetricians and Gynecologists does not endorse the use of intrapartum nucleic acid amplification testing without enrichment to determine the need for prophylaxis.

For women undergoing cesarean delivery, routine vaginal and rectal screening for Group B Streptococcus at 35 to 37 weeks of gestation is recommended, as labor or membrane rupture can occur before planned delivery. In cases where Group B Streptococcus colonization is confirmed, intrapartum antibiotic prophylaxis should be administered. However, if the results are negative or if there are no risk factors present, prophylactic antibiotics are not recommended.

Intravenous intrapartum antibiotic prophylaxis: In the 1980s, studies revealed that intrapartum antibiotic prophylaxis was effective in reducing the vertical transmission of Group B Streptococcus and thereby preventing early-onset disease in infants [*Chen V et al., 2010*]. Observational studies have shown the effectiveness to be in the range of 86% to 89% among infants born to women who received intrapartum Group B Streptococcus prophylaxis [*Lin F et al., 2001; Schrag S et al., 2002*].

Several other strategies were considered for preventing early-onset disease, including intramuscular intrapartum antibiotic prophylaxis [*Easmon C et al., 1983*], antenatal (oral or intramuscular) antibiotics [*Weeks J et al., 1997*], and the use of chlorhexidine vaginal wipes or douches [*Stade B et al., 2004; Bakr A, Karkour T, 2005; Cutland C et al., 2009*]. However, these approaches have not demonstrated effectiveness in preventing early-onset disease.

Clinical trials have demonstrated the efficacy of both penicillin [*Garland S, Fliegner J, 1991*] and Ampicillin [*Kong F et al., 2007*] when administered intravenously as intrapartum agents for preventing early-onset neonatal disease. In one clinical trial, the use of penicillin and ampicillin intravenously during labor resulted in a similar presence of ampicillin-resistant gram-negative organisms in postpartum vaginal-perineal cultures [*Edwards R et al., 2002*]. The dosages of penicillin and ampicillin used for intrapartum Group B Streptococcus prophylaxis are carefully calibrated to achieve adequate levels in fetal circulation and amniotic fluid rapidly while avoiding potentially neurotoxic serum levels in both the mother and the fetus [*Colombo D et al., 2006*]. Administration of beta-lactam antibiotics for Group B Streptococcus prophylaxis for at least four hours before delivery has been found highly effective in preventing vertical transmission of the bacteria [*de Cueto M et al., 1998*] and early-onset disease [*Lin F et al., 2001*]. Additionally, colonization data suggest that durations of at least two hours before delivery may provide some protection [*de Cueto M et al., 1998*].

The efficacy of alternatives to penicillin or ampicillin used to prevent early-onset disease in infants born to penicillin-allergic mothers (such as cefazolin, clindamycin, erythromycin, and vancomycin) has not been measured in controlled trials. Cefazolin, however, exhibits a relatively narrow spectrum of activity, similar pharmacokinetics and dynamics to penicillin and ampicillin, and can achieve high intra-amniotic concentrations [*Fiore Mitchell T et al., 2001*]. In contrast, data on the ability of clindamycin, erythromycin, and vanco-

mycin to attain bactericidal levels in fetal circulation and amniotic fluid are limited. Available data suggest that erythromycin and clindamycin, when provided to pregnant women, may not reliably reach fetal tissue [*Philipson A et al., 1973*].

Secondary prevention of early-onset Group B Streptococcus among infants: Current Group B Streptococcus prevention strategies do not guarantee the prevention of all cases of early-onset disease. To minimize morbidity and mortality among the cases that still occur, it is crucial to rapidly detect neonatal infections and initiate appropriate treatment. Detecting early-onset disease presents clinical challenges for neonatal healthcare providers as they must consider the infant's clinical appearance, the presence of maternal risk factors for the disease, and the infant's exposure to intrapartum antibiotics.

There were concerns that the use of intrapartum antibiotics to prevent early-onset disease might delay or mask signs of sepsis in newborns, making it difficult for clinicians to identify cases [*Mercer B et al., 1995*]. However, several studies conducted since 1996 have not found any significant difference in the clinical presentation of early-onset disease between infants exposed to intrapartum antibiotics and those who were not exposed [*Bromberger P et al., 2000*].

Any newborn displaying signs of sepsis, regardless of maternal colonization status, should be evaluated for early-onset disease. Such evaluations should include a blood culture, a complete blood count with a white blood cell differential and platelet count, and a chest radiograph if there are any abnormal respiratory symptoms. It's worth noting that blood cultures can yield sterile results in as many as 15% to 33% of newborns with meningitis [*Visser V, Hall R, 1980*], and the clinical management of an infant with abnormal cerebrospinal fluid findings differs from that of an infant with normal cerebrospinal fluid [*Ansong A et al., 2009*].

If sepsis is suspected and the newborn is stable enough to undergo the procedure, a lumbar puncture should be performed. Treatment for the infant should include antimicrobial agents effective against Group B Streptococcus, such as intravenous ampicillin.

Well-appearing newborns born to mothers with suspected chorioamnionitis should be evaluated and administered antibiotic therapy while awaiting culture results.

For well-appearing infants of any gestational age whose mothers received adequate intrapartum Group B Streptococcus prophylaxis (more than four hours of penicillin, ampicillin, or cefazolin before delivery), observation for over 48 hours is recommended, and routine diagnostic testing is not necessary [*Laura F et al., 2021*].

Resistance: Group B Streptococcus remains susceptible to antibiotics such as Penicillin, Ampicillin, and first-generation Cephalosporins [*Chen K et al., 2005; Phares C et al., 2008*]. However, there have been reports of Group B Streptococcus isolates with increasing minimum inhibitory concentrations to Penicillin or Ampicillin [*Robertson J, Iwamoto K, 2019*].

Notably, relatively higher minimum inhibitory concentrations to Cefazolin (1 *μg/ml*) were reported among a small fraction (0.05%) of 5,631 invasive Group B Streptococcus isolates collected during the Centers for Disease Control and Prevention's active surveillance from 1999 to 2005. Two of these isolates also exhibited elevated minimum inhibitory concentrations to Penicillin (0.12 *μg/ml*) [*Robertson J, Iwamoto K, 2019*]. Although the Clinical and Laboratory Standards Institute guidelines do not specify susceptibility breakpoints for Cefazolin, they recommend considering all isolates susceptible to Penicillin as also susceptible to Cefazolin [*Baker C et al., 1988*].

Over the past two decades, there has been an increase in the proportion of Group B Streptococcus isolates showing in vitro resistance to Clindamycin or Erythromycin. Resistance to Erythromycin is often associated with but not always linked to resistance to Clindamycin. A longitudinal study of early-onset Group B Streptococcus sepsis found that although the overall rate of early-onset disease decreased over time, Erythromycin-resistant Group B Streptococcus accounted for a growing proportion of cases during this period. However, the incidence of antibiotic-resistant early-onset sepsis remained stable [*Chen K et al., 2005*].

Today, the development of antimicrobial drug resistance is a significant global health concern. According to international analysis based on the Anatomical Therapeutic Chemicals classification, drugs containing Azithromycin are the most commonly used (26.6%), followed by combinations of Amoxicillin and Clavulanic acid (17.2%), and Ceftriaxone (12.7%). Amoxicillin (9.3%),

Levofloxacin (6.1%), and Ciprofloxacin (5.5%) also feature prominently. Azithromycin is primarily used in oral formulations, while Ceftriaxone is prevalent in injectable formulations. Based on the World Health Organization's Access Watch and Reserve classification, most monitored antimicrobial drugs (63.9%) possess a high potential for drug resistance and should only be prescribed in limited circumstances.

Regarding drug consumption in Armenia, the use of third-generation cephalosporins, macrolides, and quinolones remains high. However, according to the new World Health Organization classification, these antibiotics are subject to monitoring due to their high potential for drug resistance and should be used sparingly when no alternative drugs are available. The highest consumption of antimicrobial drugs was recorded in 2020.

In Armenia, there is a concerning practice of freely selling intravenous antibiotics, which contributes to the proliferation of drug resistance within the community.

An analysis of drug sales in Armenian pharmacies reveals that systemic antibacterial drugs are primarily comprised of drugs from the (Anatomical Therapeutic Chemicals, code: J01) Macrolides, Lincosamides, and Streptogramins (J01F) group, accounting for 23.3% of sales. This is followed by Beta-lactam antibacterial drugs (penicillins) (Anatomical Therapeutic Chemicals, code: J01C) at 19.7% and other Beta-lactam antibacterial drugs (Anatomical Therapeutic Chemicals, code: J01D) at 13.7%. Quinolones (Anatomical Therapeutic Chemicals, code: J01M) closely trail behind, making up 12.3% of sales. The remaining subgroups collectively constitute less than 5% of antibiotic sales [*Robertson J, Iwamoto K, 2019*].

It's noteworthy that Armenia lacks regulations for prescribing and ensuring the proper use of antimicrobial drugs in healthcare organizations. This, coupled with the limited availability of first-line antibiotics for Group B Streptococcus treatment in Armenia, contributes to the situation described above.

Vaccines to prevent Group B Streptococcus disease: Maternal immunization using capsular polysaccharide-based vaccines holds promise for preventing both early-onset and late-onset neonatal infections. Studies involving female mice and rats have shown that immunization with a type III glycoconjugate vaccine can reduce vaginal colonization, infection of the chorioamniotic/placental membranes, and bacterial transmission to fetuses and pups. These vaccines trigger the production of type III-specific antibodies in vaccinated mothers and their offspring. These findings suggest that Group B Streptococcus glycoconjugate vaccines may have a preventive effect during various stages of pregnancy. Additionally, it has been demonstrated that sufficient levels of type-specific serum IgG antibodies against Group B Streptococcus capsular polysaccharides in mothers can protect their infants from invasive disease [*Baker C et al., 1988*].

Despite the potential benefits, it's important to note that there is currently no licensed vaccine available. Further research is necessary to assess the effectiveness and safety of these vaccines for use in humans. Development and approval of a Group B Streptococcus vaccine would represent a significant advancement in preventing neonatal infections caused by this specific pathogen.

Current situation in Armenia: In Armenia we have a very poor statistic data regarding this topic but we found some data from National Institute of Health in Armenia. The number of sick newborn and diseased infants per 1000 full-term births in 2021 for all the diseases was 104.8 from which septicemia 0.7 and neonatal pneumonia 10.1 all the numbers were increased comparing to 2010. The numbers for all diseases were 71.8, septicemia was 0.4 and neonatal pneumonia 3.2. Summarizing the data of full-term births for about 10 years, there was a 1.75-fold increase in sepsis, a 3.1-fold increase in neonatal pneumonia, and a 1.5-fold increase in overall morbidity in Armenia.

The number of sick newborn and diseased infants per 1000 of immature new born in 2021 for

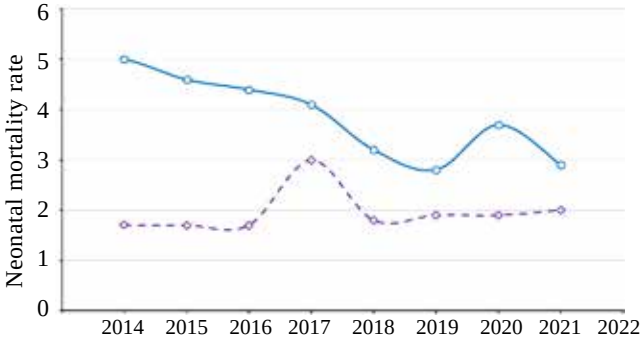

FIGURE 1. *Mortality rate per 100 for neonates aged 0-27 days in Armenia over a 10-year period (2012-2022). Solid line- early neonatal 0-7days, dotted line- late neonatal 7-27 days.*

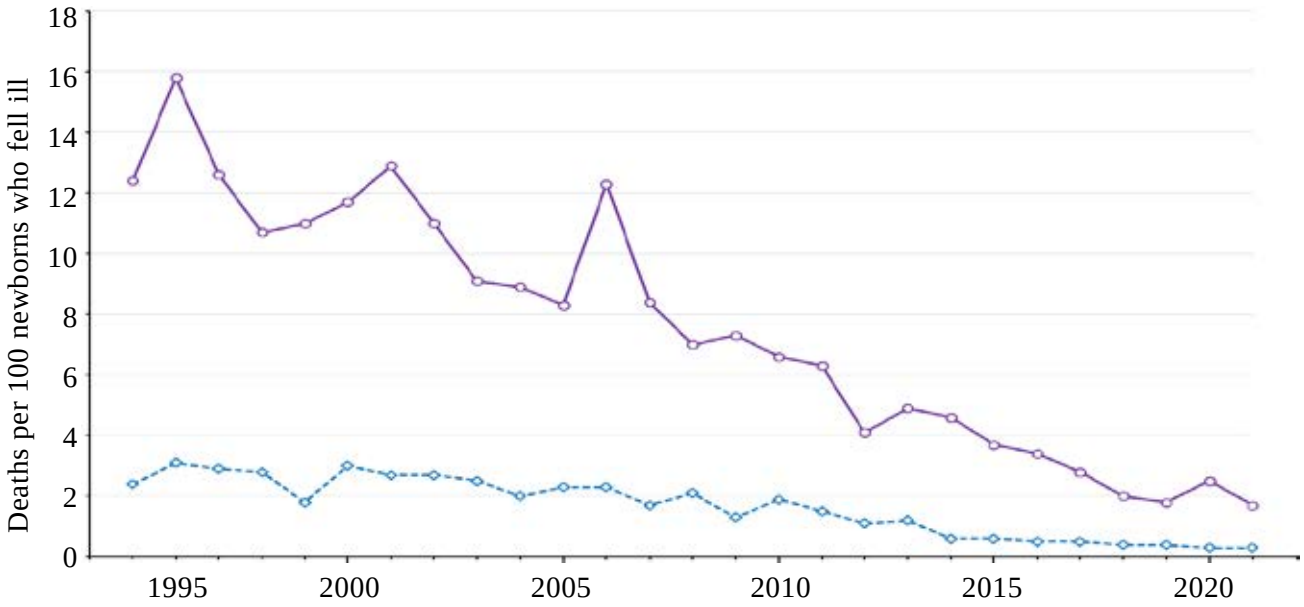

Figure 2. *Mature newborn (solid line) and immature newborns (dotted line) mortality dynamics 1990-2020*

all the diseases was 646.0 from which septicemia 23.9 and neonatal pneumonia 113.3 all the numbers were also increased comparing to 2010 the numbers were of all diseases 570.0 septicemia was 12.8 and neonatal pneumonia 46.7. Summarizing the data of immature births for about 10 years, there was a 1.85-fold increase in sepsis, a 2.4-fold increase in neonatal pneumonia in Armenia.

We associate such results with incomplete data collection in 2010, as well as with the increase in the number of general pneumonia and sepsis caused by Covid-19 in 2021. In the collected data, there is no data on the etiological factor not in statistics, and even nor in the individual medical records of the patients;

The number of dead infants per 100 infected in 2021 for full term new born 0.3 and for immature 1.7 from which early onset 2.9 (absolute value 106) and late onset 2.0 (absolute 73).

Although early-onset mortality dominates late onset mortality based on the last 10 years of data early-onset mortality tends to decrease, in contrast late onset tends to increase (Fig. 1).

Comparing to 2010 where the full term new born recorded 1.9 and the immature 6.6 times. Calculated significant test shows the $p>0.05$. This means that the results are reliable.

Children face the highest risk of dying in their first month of life at an average global rate decreased 51 per cent from 1990 to 2021.In Armenia at the same time period the mortality rate of newborns decreased 88 per cent for mature and 86.6 for immature (Fig. 2).

Because the data were so general so we are going to do pilot study to understand the main causes of early-onset and late-onset diseases, expediency of screening programs for all pregnant or only for the risk groups for Armenia. As well as to evaluate sensitivity to antibiotics of all causative agents of neonatal infectious pathologies to offer local protocols of antibiotic prophylaxis and treatment. It will help to improve quality of Health Care, make it more target, save resources, decrease level of neonatal morbidity and mortality.

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