Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

# Background Paper 6.23
# Neonatal Conditions

**By Clara Setiawan, MPH, BSc**

# Table of Contents

## Glossary

| Terms and acronyms | Definitions |
|---|---|
| CI | Confidence interval |
| COX | Cyclo-oxygenase |
| DALYs | Disability-adjusted life years |
| EU | European Union |
| IgG | Immunoglobulin |
| LOC | Lab-on-a-chip |
| MDG | Millennium Development Goal |
| MNCH | Maternal, newborn, and child health |
| NMR | Neonatal mortality rate (per 1 000 livebirths) |
| PA | Progestational agents |
| PCR | Polymerase chain reaction |
| pPROM | Premature rupture of membranes |
| RDS | Respiratory distress syndrome |
| RR | Relative risk |
| STI | Sexually transmitted infection |
| Tx | Treatment |
| WHO | World Health Organization |
| YLD | Years lived with disability |
| YLL | Years of life lost |

## Executive Summary

The neonatal period is only the first 28 days of life and yet accounts for 40% of all deaths in children under-five. Globally, neonatal conditions accounted for 3 072 000 deaths in 2010 alone. Although the number of neonatal deaths has decreased since 1990, all regions have seen slower reductions in neonatal mortality compared to under-five mortality resulting in an increased share of neonatal deaths among total under-five deaths. In order to achieve the Millennium Development Goal 4 in reducing the under-five mortality rate by two-thirds by 2015, neonatal conditions need to be addressed immediately.

Among many neonatal conditions; 1) premature birth, 2) neonatal infections, and 3) birth asphyxia, were identified as major contributors to the global burden of disease. Due to the complex etiology of these conditions, preventive methods, diagnostic tools, and treatments remain limited. Many of the current preventive approaches focus on maternal health prior to the newborn's arrival such as maternal immunization and ensuring a healthy pregnancy. Several treatments exist for neonatal conditions that may reduce the risk of maternal and neonatal mortality. However, these treatments are still not ideal in formulation, packaging, and/or accessibility. For example, several tocolytics are available to inhibit preterm labor, but are often accompanied by adverse side effects to both the mother and newborn. The current formulation and packaging for the recommended antibiotics to treat neonatal sepsis are not readily available and require properly trained care providers to administer them. Surfactant preparations are effective in treatment of newborns with respiratory distress syndrome, but are expensive to produce and are limited. Furthermore, lack of rapid diagnostics often leads to non-judicial use of antibiotics that may contribute to the rising concern for antimicrobial resistance. These are only several challenges that currently exist in addressing neonatal conditions.

Despite the large global burden from neonatal conditions, investment in research funding for neonatal survival is extremely low. It is estimated that only around US$ 20 million per year is invested into research for neonatal survival. A recent global analysis suggests that newborn survival will remain vulnerable on the global agenda without adequate funding and without high-level engagement of policy-makers. For this reason it becomes imperative that more funding and long-term support from the European Commission be allocated towards research and development addressing neonatal conditions.

# 1. Introduction

In 2004, a report, *Priority Medicines for Europe and the World*, was written by Warren Kaplan and Richard Laing and published by the World Health Organization (WHO). The topic and background paper on neonatal conditions was not included in the 2004 report.

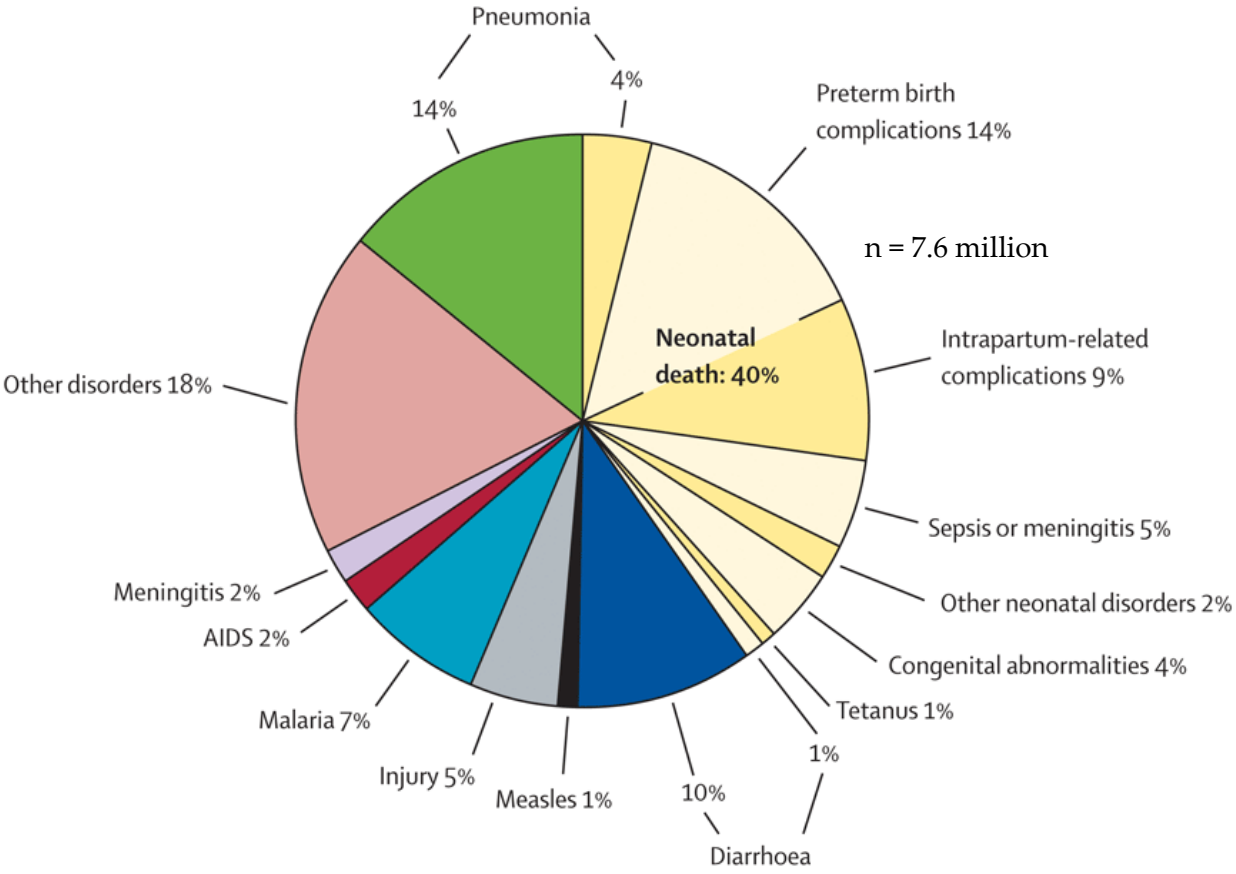
As a result of the 2008 updated Global Burden of Disease list released by the WHO and the 2010 Global Burden of Disease study published by the Lancet, neonatal conditions are now included in this report.[1,2] Related to the rising need for attention to neonatal conditions, other important reports such as *Born Too Soon: The Global Action Report on Preterm Birth* was published in 2012 in support of the Global Strategy for Women's and Children's Health and the efforts of the Every Woman Every Child campaign, led by the UN Secretary-General, Ban Ki-moon.[3]

In this paper, you will find the background on neonatal conditions including its disease burden, both globally and in Europe; the current control strategies via vaccinations, preventative approaches, and treatments; current research and development activities including the lessons learned from past research and the current pipeline. Most importantly, this paper will expose the pharmaceutical gaps that needs to be addressed and highlight opportunistic areas for research and development. This background paper will serve as the basis for the chapter to be found in the updated 2013 Priority Medicines report.

## 1.1 Background

Neonatal conditions are defined as conditions occurring during the first month after birth (0-28 days). Among many neonatal conditions; 1) premature birth, 2) neonatal infections, and 3) birth asphyxia, were identified as major contributors to the global burden of disease and will be the conditions focused on in this chapter.[1,2]

**Figure 6.23.1: Global causes of childhood deaths in 2010**




Source: Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Liu et al. The Lancet (May 11, 2012) [4]

### 1.1.1 Premature Birth

Premature birth is defined by the WHO as all births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period.[3] Causes of premature births are typically classified into two subtypes: 1) spontaneous preterm birth (spontaneous onset of labor or following pre-labor premature rupture of membranes (pPROM)) and 2) provider-initiated preterm birth (induction of labor or elective caesarian birth for maternal or fetal indications or other non-medical reasons).[3] Risk factors for spontaneous preterm birth has been identified such as age, multiple pregnancy, infection, maternal medical conditions and psychological health, nutritional, lifestyle, and genetic factors.[3]

Complications of premature birth are the single largest contributor to neonatal mortality. In addition to mortality outcomes, the implications of being born too soon extend beyond the neonatal period. Preterm babies lack the necessary physical development which often requires special care and they face greater risks of serious health problems in the future.[3] Survivors of premature birth may suffer lifelong effects such as impaired neurodevelopmental functioning, higher risk of non-communicable disease, and physical impairments in visual, hearing, lung function, and cardiovascular function.[3,5]

### 1.1.2 Neonatal Infections

The term "neonatal infections" in this background paper includes all infections except for diarrhoeal diseases and neonatal tetanus. Among the infections, sepsis and pneumonia account for the majority of the burden.[6] Neonatal pneumonia will be discussed in detail in Background Paper 6.22, while neonatal sepsis will be the focus of neonatal infections in this chapter.

Neonatal sepsis is a blood infection that can be caused by a number of different bacteria, including *Escherichia coli (E. coli)*, *Listeria*, and certain strains of *Streptococcus*.[7] *Streptococcus agalactiae* (Group B *Streptococcus*, GBS) is the most common cause of neonatal sepsis in many countries, though lower rates are reported from many low-income countries particularly in South Asia.[8]

Early-onset neonatal sepsis is seen within the first seven days of life and most often appears within 24 hours of birth where the baby is infected from the mother before or during the delivery.[7] Preterm delivery, rupture of membranes longer than 24 hours before birth, infection of the placental tissue and amniotic fluid (chorioamnionitis), and group B *Streptococcus* infection during pregnancy increases an infant's risk of early-onset sepsis.[7] Late-onset neonatal sepsis occurs after day eight of life and is acquired after delivery.[7] Having a catheter in a blood vessel and/or staying in the hospital for an extended period of time increases an infant's risk of sepsis after delivery.[7]

The chances of survival are reduced for newborns with a serious infection regardless of whether they are hospitalized or in the community.[9] Therefore, the complications of neonatal sepsis may be death or lifelong disability. Identifying and diagnosing neonatal sepsis is difficult because sick newborns often present with non-specific signs and symptoms that vary from changes in body temperature, breathing problems, diarrhea, low blood sugar, reduced movements and sucking, seizures, slow heart rate, swollen belly area, vomiting, and jaundice.[7,9]

### 1.1.3 Birth Asphyxia

One of the most common birth complications is RDS where babies struggle to breathe because their immature lungs do not produce enough surfactant, a protein that keeps small air sacs in the lungs from collapsing. Birth asphyxia, defined as the failure to establish breathing or perfusion at birth, accounts for an estimated 900 000 deaths per year.[10] Complications of low oxygen intake include damage to the brain tissues that can cause seizures and other neurological problems. The clinical presentation is not specific to birth asphyxia and the preferred term is "neonatal encephalopathy", where the precise cause is not implied.[11] Possible antecedents for neonatal encephalopathy include infection, cerebral infarction, intracranial haemorrhage, congenital brain malformations, inborn errors of metabolism, and genetic syndromes. However, the most likely antecedent is hypoxia-ischaemia (19 to 52%) that arise from birth asphyxia.[11] Neonatal encephalopathy is clinically assessed into three Sarnat staging where stage 1 may likely have unaffected outcome, stage 2 where 25% develop cerebral palsy, and stage 3 often results in disability or death.[11]

## 1.2 Neonatal Conditions: Burden of Disease

The neonatal period is only 28 days and yet accounts for 40% of all deaths in children younger than five years.[4] The average daily mortality rate during the neonatal period is almost 30-times higher than during the post-natal period.[6] Furthermore, there is still variation within the neonatal period such that mortality is very high in the first 24 hours after birth (25 to 45% of all neonatal deaths) while three quarters of neonatal deaths happen in the first week after birth.[6,12]

Neonatal conditions exert a heavy burden on families, society, and the health system. With the most potential for years lived with disability (YLD) and years of life lost (YLL), neonatal conditions are significant DALYs contributors.

## 1.3 Global Burden of Disease

Over past decades, neonatal mortality along with under-five mortality has been slowly decreasing. Globally, the number of neonatal deaths has decreased from 4 362 000 in 1990 to 2 955 000 in 2011.[13] However, all regions have seen slower reductions in neonatal mortality compared to under-five mortality resulting in an increased share of neonatal deaths among the under-five deaths. Neonatal deaths accounted for 36% of the under-five deaths in 1990 and rose to 40% in 2010.[4] This trend is expected to continue.[13]

The Millennium Development Goal (MDG) 4 calls for a reduction in the under-five mortality rate by two-thirds between 1990 and 2015.[3] Even with the visible progress, the rate of decline is insufficient to reach the set targets, particularly in sub-Saharan Africa and South Asia.[3] Child survival programs have primarily focused on causes of death after the neonatal period such as pneumonia, diarrhea, malaria, and vaccine-preventable diseases.[14] The lack of attention to neonatal conditions such as preterm birth, neonatal sepsis, and birth asphyxia, has resulted in it accounting for an increasing proportion of under-five deaths.[15] Unless actions are taken to reduce neonatal deaths, neonatal conditions will remain a barrier to progress on MDG 4.

An estimated 15 million babies in the world were born preterm in 2010, of which over one million children die each year due to complications of preterm birth.[3] For the newborns that survive this often means a lifetime of significant disability.[1] There is a dramatic survival gap for premature babies depending on where they are born. A 10:90 survival gap exists where over 90% of preterm babies born in low-income countries die within the first few days of life while less than 10% of babies of this gestation die in high-income settings.[3] Furthermore, over 60% of preterm births occur in Africa and South Asia and of the 11 countries with preterm birth rates of over 15%, all but two are in sub-Saharan Africa (Table 6.23.1).[3] The proportion of deaths due to prematurity drops with increasing neonatal mortality rate (NMR); however, this pattern is due to the large number of deaths from infection in high NMR settings.[12]

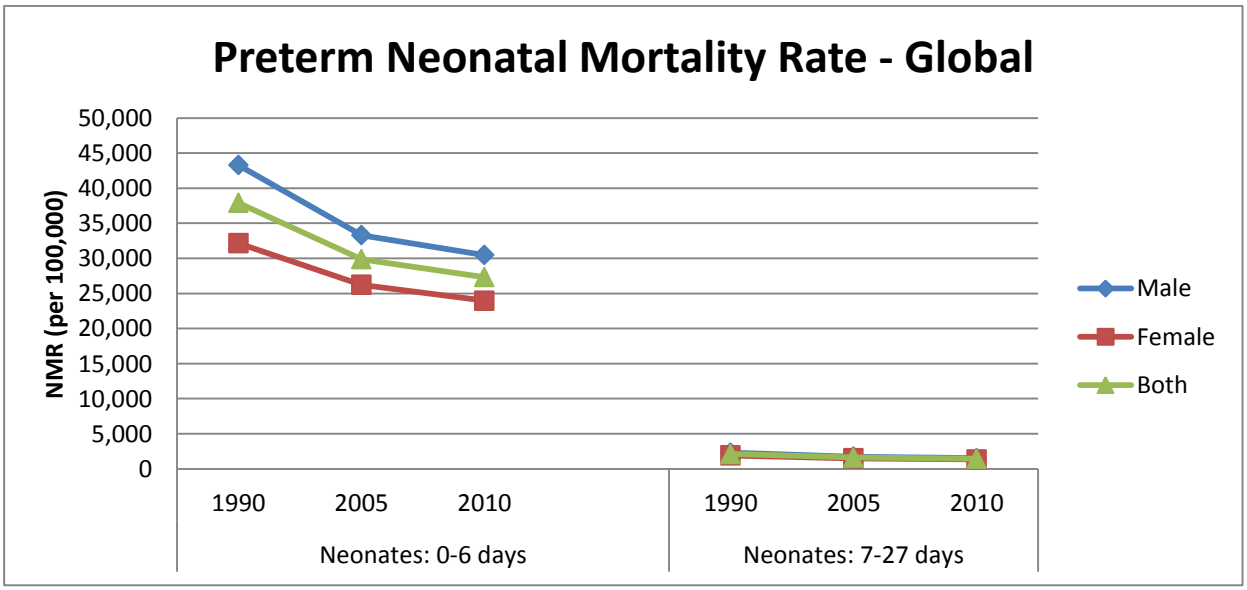
**Table 6.23.1. Neonatal deaths by region, 2011**

| Region | Number of neonatal deaths (thousands) | Neonatal deaths as a share of under-five deaths (%) |
|---|---|---|
| **Developed regions** | 53 | 55 |
| **Developing regions** | 2 902 | 43 |
| Northern Africa | 40 | 47 |
| Sub-Saharan Africa | 1 122 | 33 |
| Latin America & the Caribbean | 107 | 53 |
| Caucasus & Central Asia | 28 | 39 |
| Eastern Asia | 151 | 57 |
| Southern Asia | 1 216 | 52 |
| South-Eastern Asia | 155 | 50 |
| Western Asia | 77 | 49 |
| Oceania | 5 | 40 |
| **World** | 2 955 | 43 |

Source: Adapted from Born Too Soon Report**:** The Global Action Report on Preterm Birth[3]

Female neonates have a well-described biological survival advantage in the neonatal period.[13] This pattern is reflected in the mortality trends for preterm deaths, particularly in neonates aged 0-6 days (Figure 6.23.2). Not surprisingly, the NMR (neonatal mortality rate) for neonates aged 0-6 days is consistently higher compared to neonates aged 7-27 days. There has been progress in reducing the global deaths from complications of preterm birth from a million since 1990, particularly in neonates aged 0-6 days, but much progress still needs to be made.

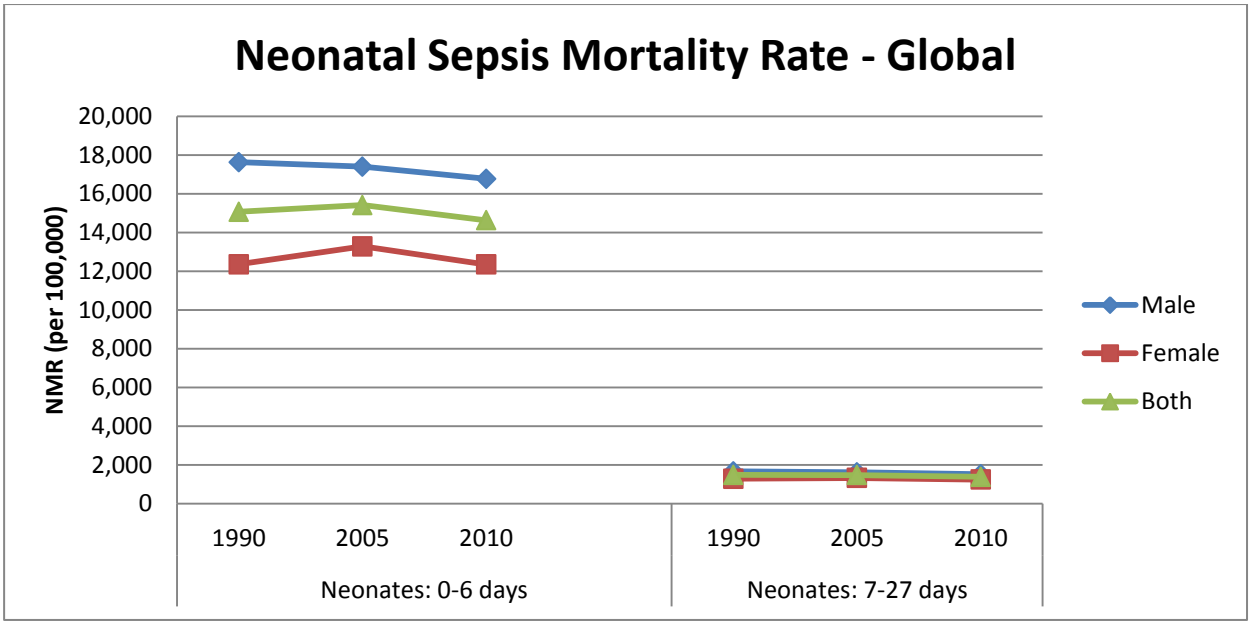
**Figure 6.23.2. Global neonatal mortality rates from complications of preterm birth**




Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010[16]

More than one-third of the estimated four million neonatal deaths each year are caused by severe infections, and a quarter, an equivalent of one million neonatal deaths, are due to neonatal sepsis and pneumonia alone.[9] The risk of dying due to severe infection in high mortality countries (NMR >45) is roughly 11-fold the risk in low-mortality countries (NMR <15).[6] The under-recognition of neonatal sepsis, delay in care seeking by the family, and lack of access to appropriate services means that not much progress has been made since 1990 (Figure 6.23.3).[9]

**Figure 6.23.3. Global neonatal mortality rates from neonatal sepsis**

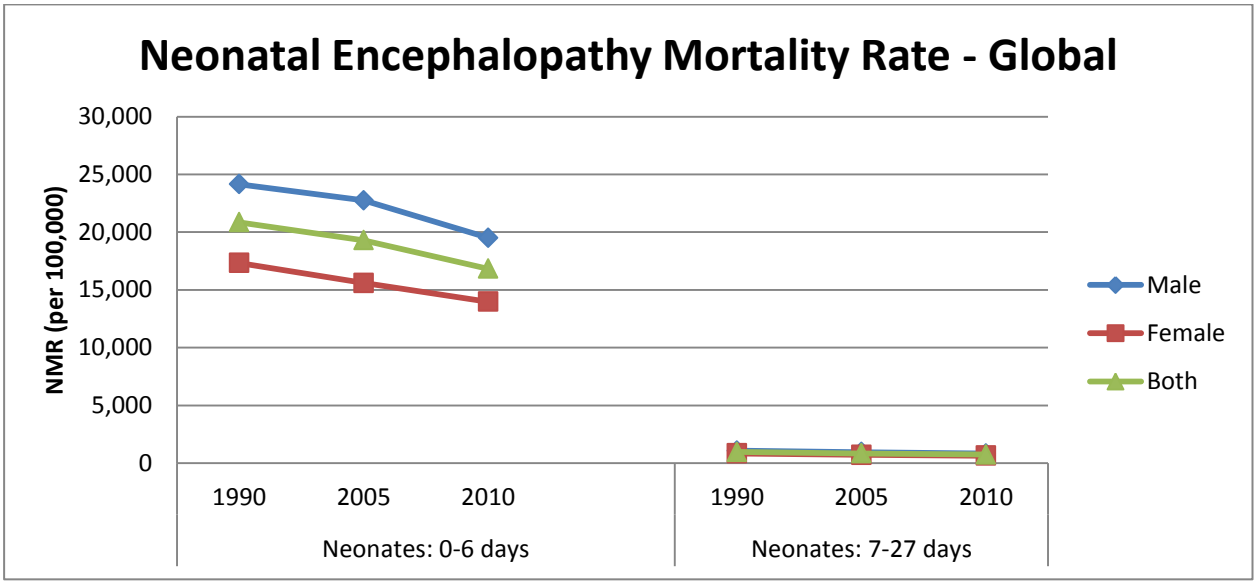



Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010[16]

Neonatal deaths from birth asphyxia are the fifth most common cause of under-five child deaths after pneumonia, diarrhea, preterm birth complications, and neonatal infectons.[4] The Global Burden of Disease 2004 report allocated 42 million DALYs to birth asphyxia, which is twice the number of DALYs allocated to diabetes and around 75% of the DALYs allocated to HIV/AIDS.[1] The risk of dying due to birth asphyxia is roughly eight-fold for babies in countries with very high NMRs, even though the proportion of neonatal deaths is fairly constant across mortality levels.

Consistent with the other neonatal conditions, NMR are much higher in boys than in girls (Figure 6.23.4). This gender gap is more prominent in neonates aged 0-6 days compared to neonates aged 7-27 days. Not surprisingly, the overall NMR for neonates aged 0-6 is consistently higher compared to neonates aged 7-27 days. There has been progress in reducing the global DALY from complications of preterm birth from a million since 1990, particularly in neonates aged 0-6 days, but much progress still needs to be made.

**Figure 6.23.4. Global neonatal mortality rates from encephalopathy as a result of birth asphyxia and birth trauma**




Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010[16]

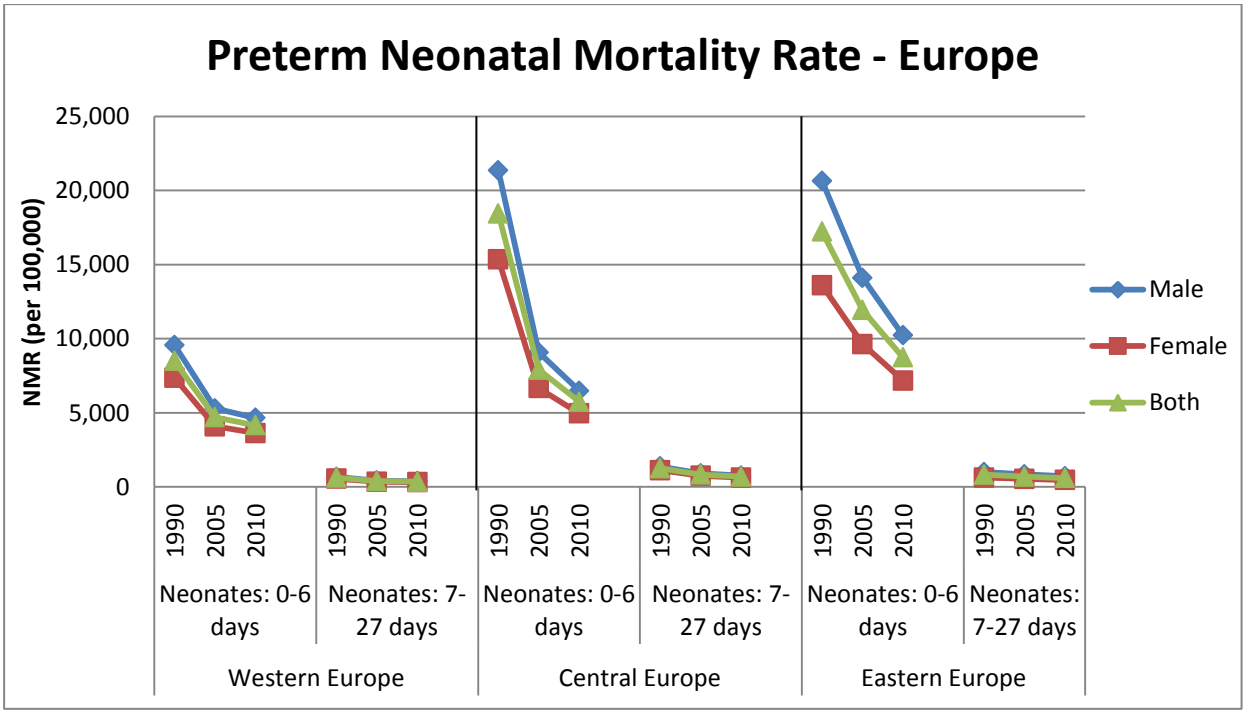
## 1.4 EU/EEA Burden of Disease

The number of neonatal deaths in the EU has decreased from 169 999 in 1990 to 70 000 in 2011.[13] However, there are large disparities even within the region where the highest national mortality rate is estimated to be 40 times the lowest.[17] Eastern Europe consistently has higher mortality and DALYs in comparison to Western and Central Europe across all three neonatal conditions, particularly neonatal sepsis and neonatal encephalopathy (Figure 6.23.5-7). The greatest progress from 1990 to 2010 was seen in neonates aged 0-6 days compared to neonates aged 7-27 days across the neonatal conditions. However, the number of deaths and DALYs in neonates aged 0-7 days were much higher when compared to neonates aged 7-27 days. The gender survival gap is still consistent with the European data which show that girls have a survival advantage compared to boys.[16]

### 1.4.1 Preterm birth

In a systematic review study, Europe was found to have the lowest rate of preterm birth (6.2% of all births) compared to all other regions.[3] However, mortality rates vary even within the region. An estimated 4 506 deaths due to preterm birth complications occurred in Western Europe, 4 835 deaths in Eastern Europe, and 1 876 deaths in Central Europe in 2010.[16]

**Figure 6.23.5. Neonatal mortality rates from complications of preterm birth in Europe**

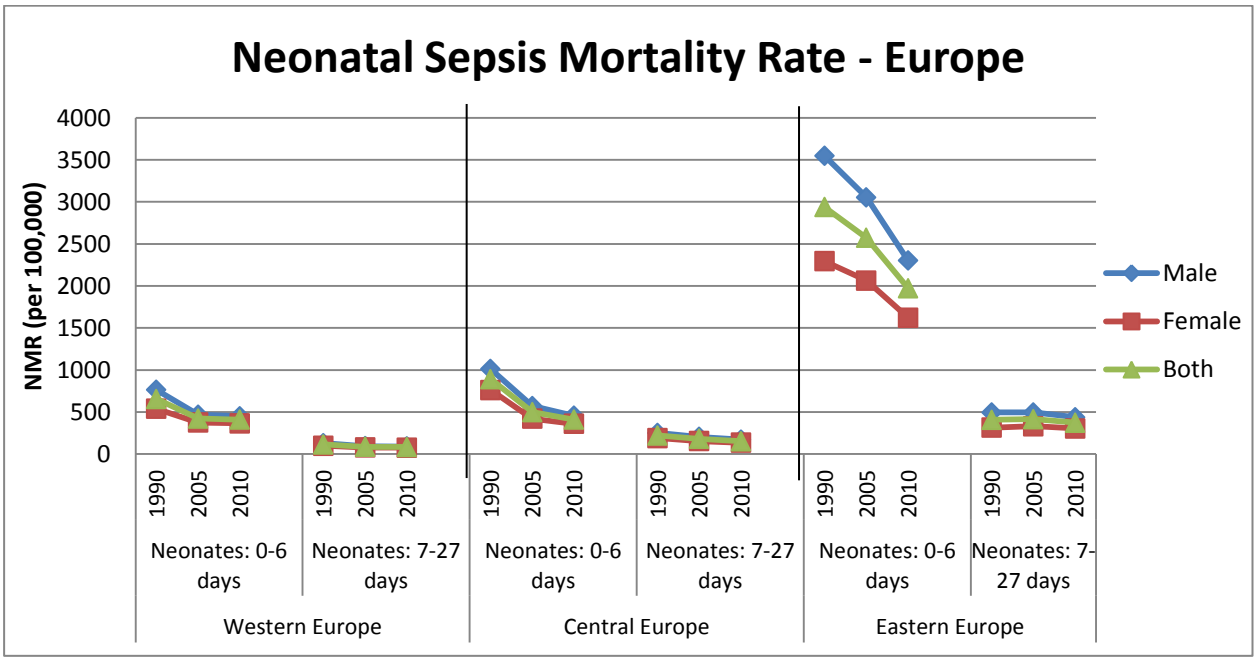



Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010[16]

### 1.4.2 Sepsis

Most neonatal sepsis deaths are in Eastern Europe, both in neonates aged 0-6 days and neonates aged 7-27 days. With neonatal sepsis, the survival rate of girls is much higher than boys. The largest gender difference in survival rates is seen in neonatal sepsis compared to preterm birth and birth asphyxia. Mortality rates vary even within the region. An estimated 571 deaths due neonatal sepsis occurred in Western Europe, 1 417 deaths in Eastern Europe, and 208 deaths in Central Europe in 2010.[16]

**Figure 6.23.6. Neonatal mortality rates from neonatal sepsis in Europe**

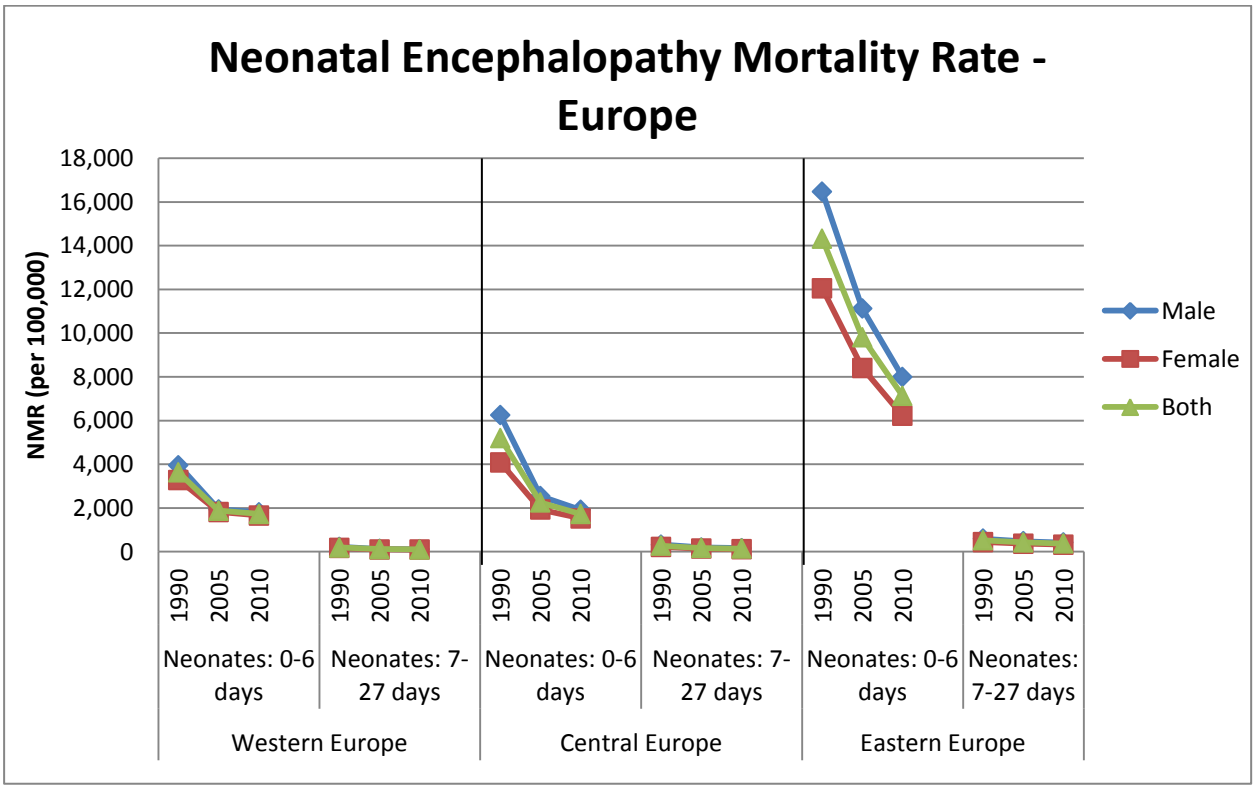



Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010[16]

### 1.4.3 Encephalopathy

The DALY burden from neonatal encephalopathy is disproportionately heavy in Eastern Europe compared to Western and Central Europe such that despite having the largest progress in neonates aged 0-6 days, Eastern Europe still has the highest DALY burden with 325 898.[16] Central Europe has the lowest DALY burden of 44 455, while Western Europe has a DALY burden of 153 542.[16]

**Figure 6.23.7. Neonatal mortality rates from neonatal encephalopathy as a result of birth asphyxia and birth trauma in Europe**




Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010[16]

# 2. Control Strategy

## 2.1 Vaccination (Prevention)

Neonatal immunization has long been considered as a method for reducing neonatal infections. However, the response varies according to the antigen and maternal antibodies often interfere with a neonate's response to the vaccine when administered under six months.[8] Protein antigen vaccines given at birth show poor responses compared to the same antigen given at two months of age.[18] Vaccines targeting *S. agalactiae* and *Streptococcus pneumonia* are shown to be ineffective when given in the neonatal period.[19] However, herd immunity effects have been seen in infants too young to receive when the heptavalent pneumococcal conjugate vaccine (PCV7) was recommended for all children aged 2 to 23 months.[20]

There are no available vaccines for premature birth, neonatal sepsis, or neonatal asphyxia for neonates, but some preventative recommendations include vaccinating the mother-to-be by promoting vaccination of all children and adolescents.[3] Infections transmitted around the time of conception may result in preterm birth.[21] Maternal immunization can provide neonates with the appropriate antibodies as soon as they are born.[18] For example, studies of maternal immunization with *S. agalactiae* type III conjugate vaccine have demonstrated effective placental transfer and persistence of protective levels in two-month old infants.[18] Through a recent modeling study, maternal immunization with *S. agalactiae* vaccine would prevent 60-70% of neonatal *S. agalactiae* infections within the United States context alone.[22] Encouraging results and promising safety profiles are also emerging from preliminary studies of maternal immunization with pneumococcal polysaccharide and conjugate vaccines.[18,23] Furthermore, Novartis have recently completed a Phase II GBS vaccine which is being trialed in the second trimester to prevent neonatal infection.[24] The study is to evaluate the safety and immunogenicity of GBS vaccine at one dose in healthy non-pregnant women and eventually in three different doses in healthy pregnant women.[24] However, barriers to maternal immunization still exists, including liability issues for vaccine manufacturers in developed countries, education of the public and health care providers regarding the benefits of maternal immunization and poor ascertainment of data from low-income countries.[18]

**Box 6.23.1: Maternal and Neonatal Tetanus elimination**

Maternal and neonatal tetanus deaths were among the most common lethal consequences of unclean deliveries and umbilical cord care practices. Mortality rates are extremely high once tetanus is diagnosed, especially when appropriate medical care is not available.

In 1988, WHO estimated that 787 000 newborns died of neonatal tetanus, roughly 6.7 deaths per 1 000 live births. Being a substantial public health problem, neonatal tetanus elimination was listed as one of the goals at the 1990 World Summit for Children and again at the 44th World Health Assembly in 1991. Through immunization of pregnant and child bearing age women and promotion of hygienic deliveries, WHO estimates that only 58 000 newborns died from neonatal tetanus in 2010 – a 93% reduction from the 1980s.

**Source:** Maternal and Neonatal Tetanus (MNT) elimination. [Internet]. [cited 14 February 2013]. Available from: http://www.who.int/immunization_monitoring/diseases/MNTE_initiative/en/index.html

## 2.2 Other Preventative Approaches

### 2.2.1 Preterm birth

Alternative methods have been developed to help prevent preterm birth targeting from preconception to antenatal care. This includes a preconception care package that includes family planning (e.g. birth spacing and adolescent-friendly services), education and nutrition especially for girls of child bearing age, and STI prevention.[3] An antenatal care package is recommended for all women that includes screening for and management of STIs, high blood pressure, and diabetes; behavior change for lifestyle risks; and targeted care of women at increased risk of preterm birth.[3] Preconception care services for prevention of preterm birth recommended for all women include:[3]

- **Prevent unintended pregnancies and promote optimal birth spacing** – Women who have very closely spaced pregnancies (within six months of a previous live birth or pregnancy) are at higher risk of a preterm or low-birthweight babies.[25] Correct and consistent use of family planning and contraceptive methods (hormonal and barrier methods) leads to more women spacing their pregnancies 18 to 24 months apart, which is ideal.[26] Breastfeeding is an underused method for preventing closely spaced pregnancies and should be promoted for 24 months. Twelve months of contraceptive use along with breastfeeding reduces the risk of mortality for the next newborn by 68.4%.[26]
- **Optimize pre-pregnancy weight** – Women who are underweight before pregnancy (body mass index less than 18.5 kg/m$^2$) and women who are overweight/obese (body mass index greater than 25 kg/m$^2$) are at significantly greater risk of having premature, low birth weight newborns.[27,28] Improving food security particularly in impoverished nations, and achieving a healthy maternal weight could reduce the rates of preterm birth.
- **Promote healthy nutrition including supplementation/fortification of essential foods with micronutrients** – Studies of the biological mechanisms leading to preterm birth suggest that more severe congenital disorders such as neural tube defects, might result in preterm delivery.[28] Consuming multivitamins in the preconception period has been shown to help prevent neural tube and other birth defects.[29] Iron and folic acid fortification of foods for mass consumption is considered an important strategy to increase micronutrient levels in that population.[3]
- **Promote vaccination of children and adolescents** – Infections transmitted around the time of conception or during pregnancy may result in preterm birth.[30] Many infections, such as rubella, could be prevented through routine childhood vaccinations.[3]

In addition to the following care services, women with special risk factors that increase the risk for preterm birth should also be recommended[3]:

- **Screen for, diagnose and manage mental health disorders and prevent intimate partner violence** – Maternal stressors including depression, socioeconomic hardship and intimate partner violence have been linked to preterm birth.[31,32] Studies suggest that stress acts through inflammatory pathways involving maternal cortisol which causes premature birth.[33,34] Furthermore, women with stressors have a greater likelihood to engage in risky behaviors such as smoking and alcohol use.[35]
- **Prevent and treat sexually transmitted infections (STI)s, including HIV/AIDS** – Reducing infectious diseases, particularly syphilis, can lower the rates of stillbirths

and preterm birth.[36] Behavioral, counseling, and mass treatment interventions with antibiotics have been shown to decrease the prevalence of STIs.[37],[38]

- **Promote cessation of tobacco use and restrict exposure to secondhand smoke** – Cigarette smoking roughly doubles the risk of preterm birth.[39] Tobacco cessation interventions and preconception counseling involving the husbands or partners can increase the number of women who quit smoking and reduce the exposure to secondhand-smoke.[40]

As of February 2011, Makena® (17-alpha-hydroxyprogesterone caproate or 17P) was approved by the US FDA as a pharmaceutical drug for the reduction of the risk of certain preterm births in women who have had at least one prior preterm birth.[41] Weekly injections of 17P resulted in significant reduction in the risk of delivery at less than 37 weeks of gestation (RR=0.66, 95% CI: 0.45 to 0.81), delivery at less than 35 weeks of gestation (RR=0.67, 95% CI:0.48 to 0.93), and delivery at less than 32 weeks of gestation (RR=0.58, 95%CI:0.37 to 0.91).[42] So far, this is the only pharmaceutical drug available in preventing preterm birth and has only been approved in the United States.

### 2.2.2 Sepsis

Although there is no way to prevent all types of sepsis, the transmission of Group B streptococcal (GBS) bacteria from mother to child could be prevented.[43] If a woman tests positive for GBS, she can receive intravenous antibiotics during labor, optimally at least four hours before delivery.[43]

In addition to maternal treatments, prophylactic approaches have also been considered. Any women with a fever during labor, pPROM, or if they had other children with sepsis or other diseases triggered by GBS are recommended to receive intravenous antibiotics during labor to lower the risk of transmission to the child.[22] Intrapartum antibiotic prophylaxis has been highly effective in reducing both early-onset neonatal bacterial and maternal sepsis in developing countries.[44] For example, chemoprophylaxis has halved the incidence of early-onset neonatal *S. agalactiae* sepsis from 1.7 per 1 000 live births in 1993 to 0.6 per 1 000 in 1998 in the United States.[45]

In addition, hand washing and ensuring that those who come in contact with the newborn are not sick and have been fully vaccinated can also prevent infection in both home and health facility settings.[19] Although, both important, there is stronger evidence for hand washing by health care providers after delivery for reducing neonatal sepsis and infection rates in hospitals compared to hand washing in mothers of their own infants.[46],[47] There is emerging evidence that neonatal skin antisepsis preparations, such as sunflower seed oil and chlorhexidine, provides cheap, safe, and effective protection against nosocomial infections in hospitalized preterm neonates in studies in South Asia.[8],[48],[49]

Lastly, neonatal nutrition can be a protective factor in neonatal infections. Breast milk contains secretory IgA, lysozymes, white blood cells, and lactoferrin and has been shown to promote the growth of healthy *Lactobacilli* and reduce the growth of *E. coli* and other Gram-negative pathogenic bacteria.[19] Early initiation and exclusive breastfeeding is associated with significant reductions in diarrhea and acute respiratory infections in neonates while other observational studies have demonstrated impact on infection specific mortality rates during the neonatal period.[50,51,52] Trials of parenteral vitamin A supplementation have also shown

significant reductions in respiratory disease in low birth-weight infants and reductions in neonatal mortality.[53,54]

## 2.3 Diagnostic Testing

### 2.3.1 Sepsis

Neonatal clinical sepsis syndrome identification is difficult since the symptoms are often very similar to other life-threatening diseases such as necrotizing enterocolitis, perinatal asphyxia, and hyaline membrane disease.[55,56] Seven danger signs have been identified to be used to diagnose infants with very severe disease including neonatal sepsis (Table 6.23.2) and have now been incorporated into the new neonatal WHO Integrated Management of Childhood Illness guidelines.[56] These signs provide high sensitivity and moderate specificity for detecting serious illness.

**Table 6.23.2. Clinical symptoms and signs of severe neonatal illness including sepsis**

| |
|---|
| History of difficulty feeding |
| History of convulsion |
| Movement only when stimulated |
| Respiratory rate ≥60 breaths per minute |
| Severe chest indrawing |
| Axillary temperature ≥37.5˚C |
| Axillary temperature <35.5˚C |

Source: Adapted from Clinical signs that predict severe illness in children under age two months[56]

Laboratory tests can help diagnose neonatal sepsis and identify the specific bacteria causing the infection. Blood tests may include blood culture, C-reactive, protein, and complete blood count.[7] If necessary, a lumbar puncture will be done to examine the cerebrospinal fluid for bacteria.[7] If the baby has a cough or issues breathing, a chest x-ray will be taken and urine culture tests can be done if the baby is older than several days.[7] However, identification of pathogenic organisms remain difficult because bacterial load in neonates may be low due to mothers receiving antepartum or intrapartum antibiotics and also because only small amounts of blood can often be taken from newborns.[57] Contamination rates may also be high due to difficulties of performing sterile venipuncture in small babies.[8]

Conventional assays are being replaced by newer "real-time" systems that are faster and associated with lower contamination rates because amplification and detection occur simultaneously in a closed system.[58] The real-time polymerase chain reaction (PCR) produces quantitative results within 30 minutes and calculates bacterial load by using a single primer to detect the universal bacterial genome (16S RNA or 23S RNA).[59] Broad-range real-time PCR can distinguish bacterial septicaemic disease from other causes of neonatal illness with similar symptoms such as asphyxia or premature complications.[59] Alternatively, multiplex PCR amplifies different targets, but is focused only on specific pathogens.[60] However, real time PCR requires the specimen to be collected with a sterile venipuncture which may be difficult in neonates. Typically, the specimen is collected via capillary heel prick due to its

ease, but also has the highest potential for contamination by skin flora.[8] Furthermore, real-time PCR technolgoies are expensive and can only be used by highly trained staff.[8]

Antigen detection techniques allow for rapid detection and identification without culturing.[8] The most commonly used commercially available test is the latex agglutination assay which is dependent on specific agglutination by bacterial cell wall antigens of antibody-coated latex particles.[8] However, these tests are reliable in detecting limited organisms such as *S. agalactiae* and are associated with high false positive and negative rates.[61]

Despite diagnostic advances, none of these diagnostic tests are ideal with results of blood culture being delayed up to 48 hours.[3] Since the condition of a neonate with true sepsis can deteriorate quickly, broad-spectrum antibiotic therapy are often prescribed even before the test results are available.[22,56] This often results in unnecessary antibiotic use, which may contribute to the emergence of antibiotic resistance.[22]

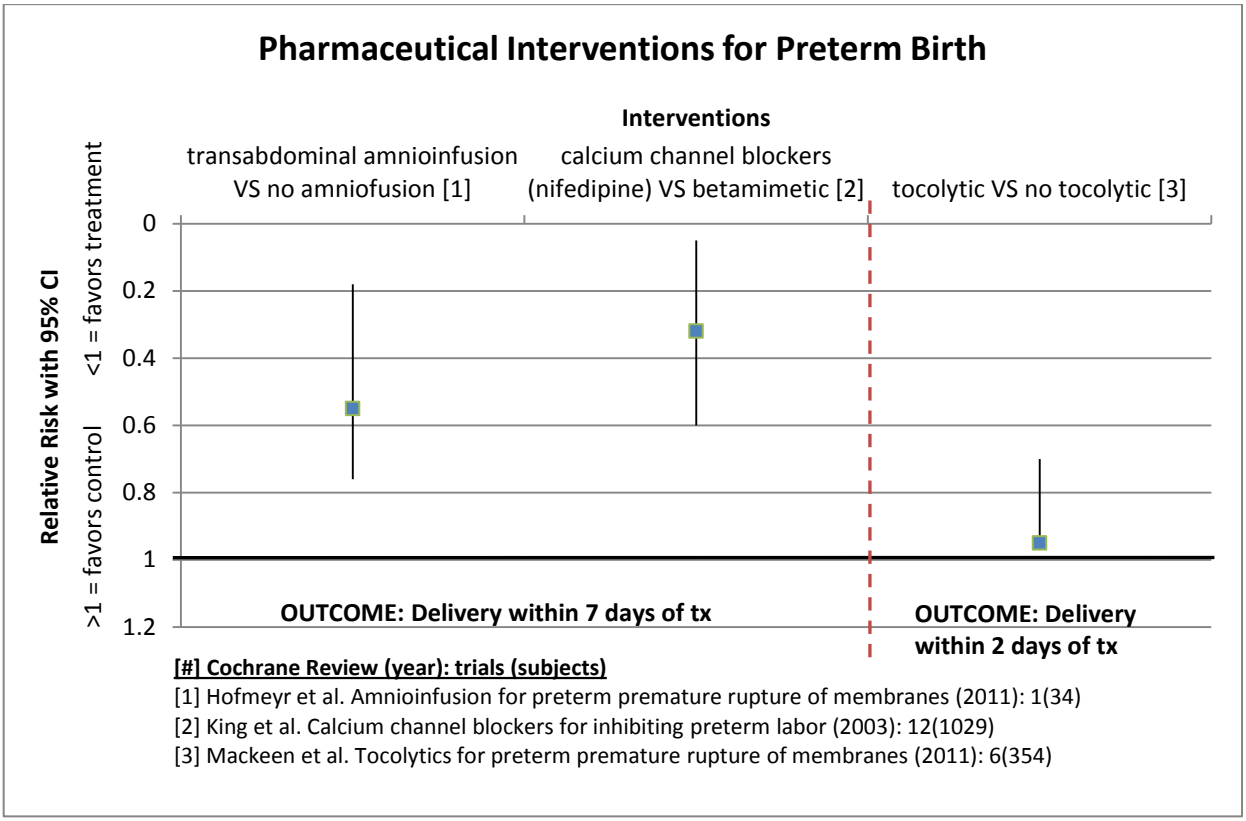
## 2.4 Treatment

### 2.4.1 Preterm birth

In women with preterm labor, tocolytics are drugs used to suppress uterine contractions and are often given to delay birth by inhibiting uterine contractions. Several tocolytics are available that work to inhibit preterm labor via different mechanisms including oxytocin antagonists, betamimetics, calcium channel blockers, and magnesium sulphate.[3] The provision of tocolytics has been shown effective in suppressing labor to allow enough time for antenatal corticosteroid treatment for fetal lung maturation prior to delivery and/or to transfer mother and baby to a higher-level facility where appropriate care may be available.[3, 62] Although betamimetics have been shown to delay delivery, its effects on neonatal outcomes and fetal maternal side effects have not been shown to improve perinatal outcome and have high frequency of unpleasant and sometimes fatal maternal side effects.[63] Any use of strategies to prolong labor must be evaluated against the potential risk of prolonged exposure of mother and fetus to sub-optimal conditions that may result in harm.[3]
According to Cochrane systematic reviews, there are several pharmaceutical interventions which are effective in delaying delivery by at least two days after the initiation of preterm labor (Figure 6.23.8). Trans-abdominal amnioinfusion reduces the risk of delivery within seven days of treatment compared with the control group in women with pPROM (Relative risk (RR) = 0.18, 95% confidence interval (CI): 0.05 to 0.7).[64] The most common drugs used to stop preterm labor are betamimetics such as ritodrine and terbutaline, as well as magnesium sulphate.[65] However, another Cochrane Review showed that calcium channel blockers, such as nifedipine and nicardipine, may be more effective in delaying delivery within seven days of treatment compared with other more commonly used betamimetics (RR=0.76, 95% CI: 0.6 to 0.97).[65] Lastly, any tocolytic administration seem to reduce births within 48 hours of treatment compared to no treatment at all (RR=0.55, 95% CI: 0.32 to 0.95).[66] All these pharmaceutical interventions seem to be effective in delaying delivery long enough to allow for a 48-hour corticosteroid treatment for fetal maturation, hopefully, reducing the morbidity and mortality associated with prematurity. A recent systematic review and network meta-analysis conducted by Haas et al. showed that prostaglandin inhibitors (OR=5.39, 95% CI: 2.14 to 12.34) followed by magnesium sulfate (OR=2.76, 95% CI: 1.58 to 4.94), calcium channel blockers (OR=2.71, 95% CI: 1.17 to 5.91), beta mimetics (OR=2.41, 95% CI: 1.27 to 4.55), and

oxytocin receptor blocker (OR=2.02, 95% CI: 1.10 to 3.80) delayed delivery best by 48 hours when compared with placebo.[67]

**Figure 6.23.8. Pharmaceutical interventions for delaying delivery by at least two days.**

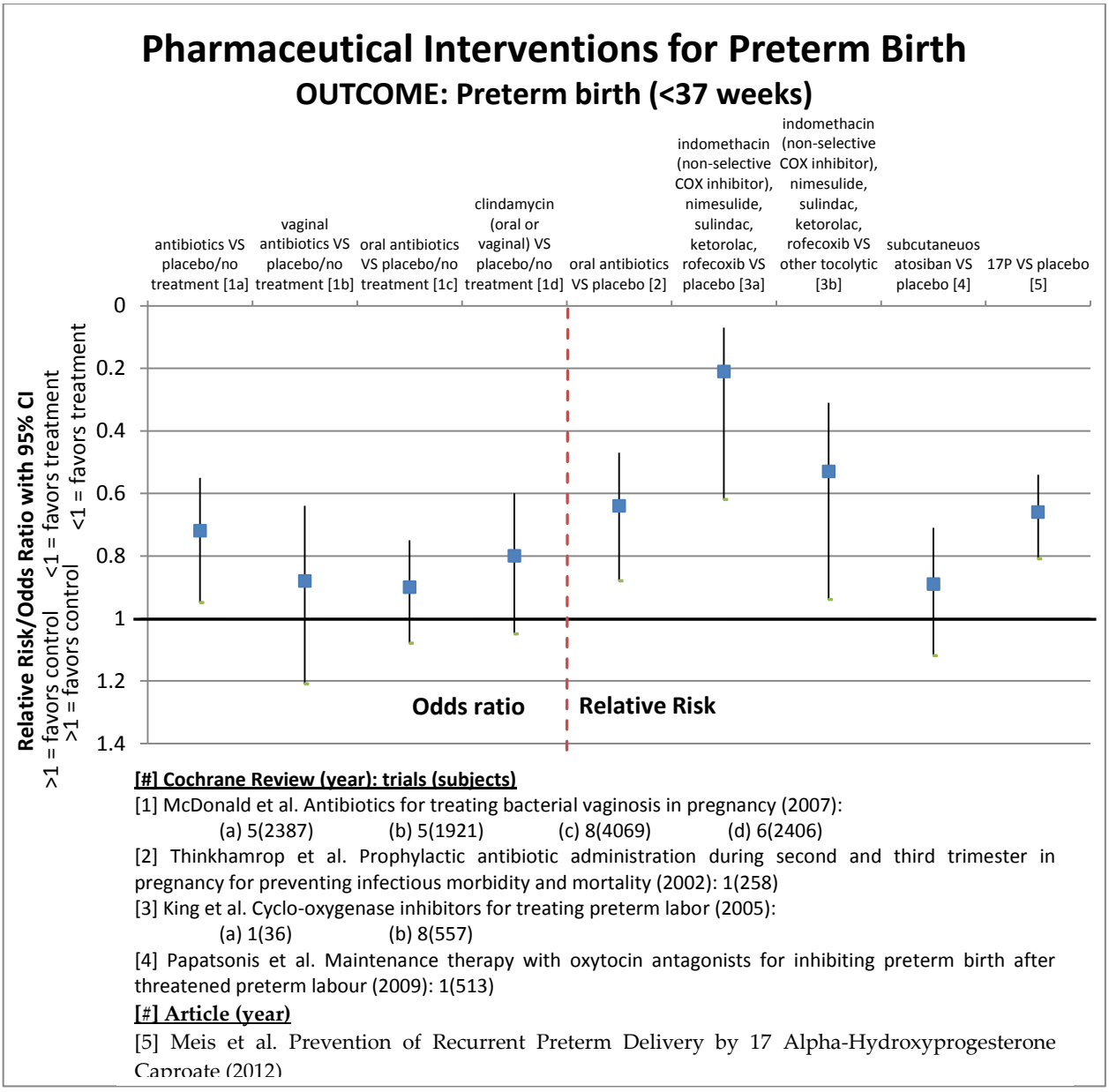



In contrast to interventions given after the initiation of preterm labor, several pharmaceutical interventions exist in preventing delivery prior to 37 weeks of gestation (Figure 6.23.9). The treatment methods vary depending on the potential risk of preterm birth. A Cochrane Review of antibiotic treatment for bacterial vaginosis before 20 weeks of gestation suggest reductions in the risk of preterm birth (OR=0.72, 95% CI: 0.55 to 0.95).[68] However, there is little evidence that treating all pregnant women with bacterial vaginosis, including those beyond 20 weeks of gestation, is effective in preventing preterm birth. Vaginal antibiotic treatments, oral antibiotic treatments, and clindamycin (oral or vaginal) treatments did not show significant reduction in the risk of preterm birth compared to no treatment (OR=0.88, 95% CI: 0.64 to 1.21; OR=0.9, 95% CI: 0.75 to 1.08; OR=0.8, 95% CI: 0.6 to 1.05; respectively).[68]

Another Cochrane Review of prophylactic antibiotic treatment during the second or third trimester of pregnancy reduced the risk of preterm delivery compared to the placebo group (RR=0.64, 95% CI: 0.47 to 0.88).[69] However, there was substantial bias in the review's results, warranting further research. Furthermore, a Cochrane Review compared non-selective cyclo-oxygenase (COX) inhibitors, such as indomethacin, with either placebo and other tocolytics. The results suggest reduced risk of preterm labor using COX inhibitor compared to both placebo and other tocolytics (RR=0.21, 95% CI:0.07 to 0.62; RR=0.53, 95% CI: 0.31 to 0.94; respectively).[70] It should be noted, however, that trial size was small and that the results, as well as the potential adverse effects of COX inhibition could not be adequately assessed.[70] For some women, an episode of preterm labor settles and does not result in immediate

birth.[71] Maintenance therapy with oxytocin receptor antagonist such as atosiban may have the potential to prevent premature birth. However, Cochrane Reviews of this treatment compared to placebo or no treatment did not provide enough evidence that maintenance treatment reduced the risk of preterm birth (RR=0.89, 95% CI:0.71 to 1.12).[71] Lastly, a double-blind, placebo-controlled trial showed that treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (RR=0.66, 95% CI: 0.54 to 0.81).

**Figure 6.23.9. Pharmaceutical intervention for preventing preterm birth defined as 37 weeks of gestation.**




Currently, there are three key interventions that can be delivered during the pregnancy period with evidence of improving health outcomes in a premature baby: antenatal corticosteroids, antibiotics for pPROM, and magnesium sulphate (Table 6.23.3).[3]

Antenatal corticosteroids can be administered to women at high risk of preterm birth as early as 23 weeks and can significantly reduce the premature baby's risk of death, respiratory distress, and developmental problems.[3] The WHO lists antenatal corticosteroids (betamethasone and dexamethasone) as a priority intervention for the prevention of respiratory distress syndrome (RDS) in premature babies and considers antenatal corticosteroids as a priority medicine for reducing mortality among premature babies.[72] It should be noted that at the time of publication, dexamethasone was listed for treating allergies only. Despite the evidence of effectiveness, antenatal corticosteroid use remains low. In 2000, it was estimated that in the 42 countries with 90% of the world's childhood deaths, only 5% of appropriate candidates received the intervention.[73] This is a clear indication of missed opportunities for improving the survival chances of premature babies.

Premature rupture of the membranes is strongly associated with infection of the amniotic membranes contributing to preterm birth and other poor fetal outcomes such as cerebral palsy and chronic lung disease.[3] Antibiotic treatment for pPROM has been shown to suppress labor for up to 48 hours as well as reduce neonatal infections and abnormal cerebral ultrasound scans prior to hospital discharge.[3] However, due to increasing concern around bacterial resistance and the risk of maternal anaphylaxis with antibiotic use, its risks and benefits should be assessed to ensure judicious use of antibiotics.

Magnesium sulphate administration to women at risk of preterm birth reduces the risk of neurological disorders in their infants such as cerebral palsy and improve long-term neonatal health outcomes.[3,74] It is a safe and relatively inexpensive drug.[74] However, magnesium sulphate has a narrow safe dosage range and require close monitoring during treatment.[43] Further studies are needed to investigate the maternal side effects (e.g. flushing, sweating, nausea, vomiting, headaches, and a rapid heartbeat).[3]

**Table 6.23.3. Common medicines for preterm labor**

| | Medicine | Possible maternal side effects | Possible side effects in baby |
|---|---|---|---|
| **Corticosteroid** | Betamethasone | • Fluid build-up in the body<br>• Rising blood pressure<br>• Increased risk of infection<br>• Problems with wound healing | • Increased risk of infection |
| | Dexamethasone | • Fluid build-up in the body<br>• Rising blood pressure<br>• Increased risk of infection<br>Problems with wound healing | • Increased risk of infection |
| **Tocolytic** | Calcium channel blockers (nifedipine) | • Redness of the skin<br>• Headache<br>• Dizziness or feeling faint<br>• Nausea<br>• Low blood pressure<br>• Constipation or diarrhea | No known side effects |
| | Nonsteroidal anti-inflammatory drugs (indomethacin) | • Dizziness<br>• Nausea or throwing up<br>• Heartburn<br>• Vaginal bleeding<br>• Swollen stomach lining | • Oligohydramnios<br>• Ductus arteriosis<br>• Rising blood pressure in the lungs<br>• Kidney problems<br>• Bleeding within the brain or heart<br>• Jaundice<br>• Necrotizing enterocolitis |
| | Magnesium sulfate | • Fast or irregular heartbeat<br>• Fluid in the lungs<br>• Low blood pressure<br>• High blood sugar<br>• Low blood potassium<br>• Trouble breathing<br>• Chest pain<br>• Shaking or feeling nervous<br>• Seizure<br>• Nausea or throwing up<br>• Headache<br>• Dizziness<br>• Fever<br>• Diarrhea | • Fast heartbeat |

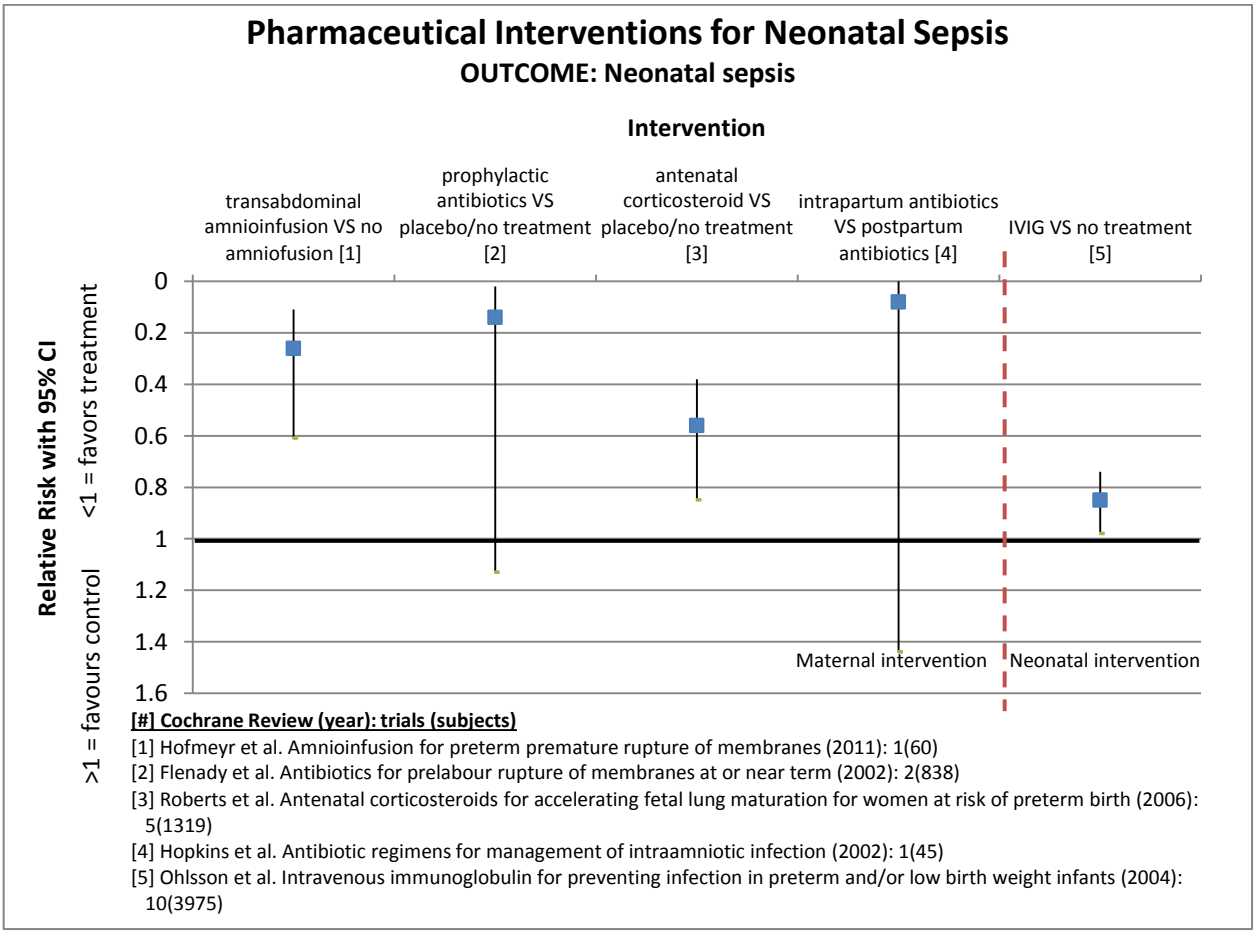
Source: Adapted from March of Dimes, Preterm labor[75]

### 2.4.2 Sepsis

Antibiotics are used to prevent life-threatening complications from infections for both the mother and the baby. Since early-onset neonatal sepsis is caused by infection from the mother before or during the delivery, antenatal and intrapartum interventions targeting the mother is common to reduce the risk of neonatal sepsis (Figure 6.23.10). Prelabour rupture of the membranes increases the risk of infection for the woman and her baby.[76] A Cochrane Review of amnioinfusion treatment for pPROM showed reduction in neonatal sepsis compared to no treatment in other women with pPROM (RR=0.26, 95% CI:0.11 to 0.61).[64] Antibiotic treatment is accepted as the standard of care, but routine use of prophylactic antibiotics for women at the time of pPROM raises concern due to the increasing problems with bacterial resistance and the risk of maternal anaphylaxis with antibiotic use.[76] It should be noted that reviews of prophylactic antibiotic use compared to placebo or no treatment was associated with a reduction in neonatal sepsis, but the results did not reach statistically significance (RR=0.14, 95% CI:0.02 to 1.13). [77] Antenatal corticosteroid treatment for accelerating fetal lung maturation for women at risk of preterm birth has been shown to reduce birth complications including the risk of neonatal sepsis (RR=0.56, 95% CI:0.38 to 0.85).[78] Intraamniotic infection is also associated with neonatal sepsis and studies have been conducted to examine the effectiveness of different antibiotic regimens to treat this infection. Intrapartum antibiotic treatment was associated with a reduction in neonatal sepsis compared to antibiotic treatment given immediately postpartum, but the results did not reach statistical significance (RR=0.08, 95% CI:0.0 to 1.44).[78]

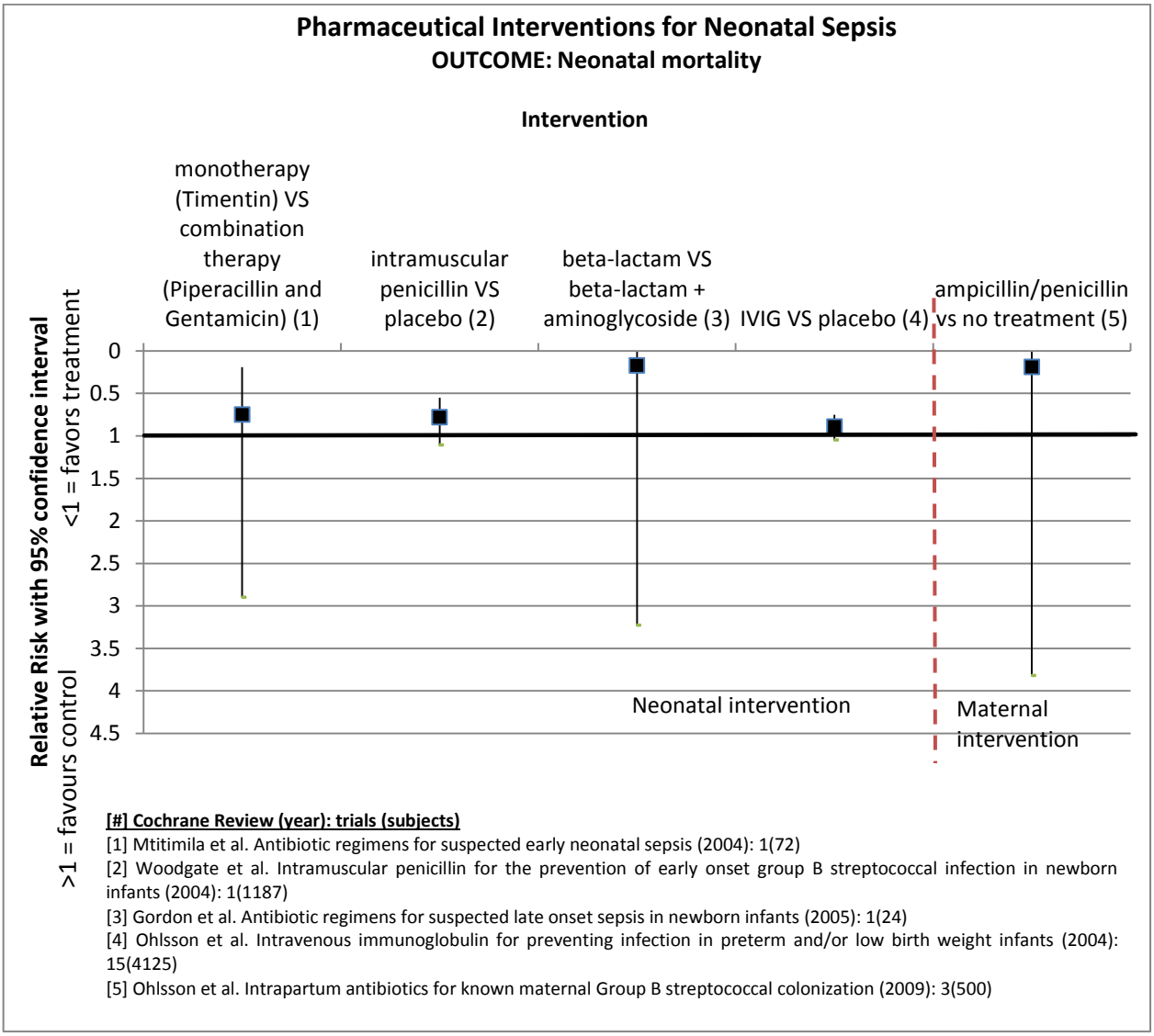
One intervention focused on the neonate exists in preventing neonatal infection in preterm and/or low birth weight infants (Figure 6.23.10). Preterm infants are deficient in immunoglobulin (IgG); therefore, prophylactic administration of intravenous immunoglobulin may have the potential of preventing infections.[79] According to a Cochrane systematic review, the use of prophylactic intravenous immunoglobulin was statistically significant for reducing sepsis (RR=0.85, 95% CI:0.74 to 0.98).[79]

**Figure 6.23.10. Pharmaceutical interventions to reduce risk of developing neonatal sepsis**




Several pharmaceutical interventions exist to treat neonatal sepsis once it develops. Prompt antibiotic treatment is necessary as newborn babies have an immature immune system and conditions can deteriorate quickly once sepsis is diagnosed.[9] Cochrane Reviews were gathered to assess the effectiveness of antibiotic regimens for treatment of neonatal sepsis and the results are limited (Figure 6.23.11). Two small studies compared monotherapy (ticarcillin or clavulanate) with combination therapy (piperacillin and gentamicin) and showed no significant difference in mortality outcomes from neonatal sepsis (RR=0.75, 95% CI:0.19 to 2.9).[80] Another review assessed the effectiveness of beta-lactam therapy compared with combination of beta-lactam plus aminoglycoside treatment and found that there was no significant difference in mortality outcome between these two therapies (RR=0.17, 95% CI:0.01 to 3.23).[81]

**Figure 6.23.11. Pharmaceutical interventions for neonatal sepsis**




Currently, parenteral (intravenous or intramuscular) regimens of a combination of penicillin/ampicillin and gentamicin or third-generation cephalosporins (e.g. ceftriaxone or cefotaxime) for 10 to 14 days is recommended by national paediatric associations and the WHO (Table 6.23.4).[8,82] These antibiotics are shown to be safe and retain efficacy when administered at extended intervals.[83] These treatments are effective against *Streptococcus*, but *Staphylococcus is highly resistant*.[84] Gram-negative antimicrobial susceptibility to ampicillin and gentamicin can also be poor, particularly for *Klebsiella*.[84] *E.coli* resistance to ampicillin, gentamicin, and third-generation cephalosporins in hospitals of both developed and developing countries is emerging and is raising concern. [85] Furthermore, parenteral administration requires health care professionals that are often lacking in lower-resource settings where the majority of births and neonatal deaths occur at home.[86,87]

**Table 6.23.4. Injectable antibiotics products for treating neonatal sepsis**

| **Drug** | Procaine benzylpenicillin | Gentamicin | Ceftriaxone |
|---|---|---|---|
| **Indication** | Neonatal sepsis, first-line | | Neonatal sepsis, second-line |
| **Formulation** | Powder for injection: 1 g (=1 mill IU); 3 g (=3 mill IU) in vial | Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial | Powder for injection: 250 mg and 1 g |
| **Dose** | Intramuscular injections 50 mg/kg of ampicillin (or comparable) every 6-8 hours – depending on age – divided 2x/day for at least 10 days | Intramuscular injection 7.5 mg/kg of gentamicin (or comparable) in addition to the benzylpenicillin injections – divided 2x/day for at least 10 days | 50 mg/kg once daily for all newborns (<1 week, <2 kg) 75 mg/kg once daily for 10 days (>1 week, >2 kg) |
| **Average Cost (per treatment)** | ~US$ 0.13-0.16 | ~US$ 0.17-2.03 | ~US$ 0.50-0.90 |
| | (dependent on weight and # days treated) | | |

Source: Every Woman Every Child – Injectable Antibiotics for Newborn Sepsis[88]

Despite the existence of effective antibiotics to treat neonatal sepsis, case-fatality rates for severe bacterial infections in developing countries remain high.[88] Although relatively low-cost treatments exist, properly trained care providers are required to administer them. There has been insufficient focus on optimizing innovative approaches to product formulation and packaging.[121] Gentamicin administration should be monitored closely as there are risks related to toxicity that could result in permanent hearing and kidney damage.[88] In both Asia and sub-Saharan Africa, where a large burden of neonatal sepsis lies, formulations at appropriate dosage may not be readily available. [88] It is difficult to develop alternative delivery mechanisms for these antibiotics as procaine benzylpenicillin and ceftriaxone powders must be reconstituted with sterile water and achieving appropriate volumes with the correct formulation remains a challenge.[88] The UN Commissioners' Report released in 2012 for life-saving commodities for women and children have identified and recommended simple potential product innovations that demand further research particularly in the administration of gentamicin (including fixed-dose presentations for needles and syringes, auto-disable syringes, and micro-needle patch technology for administering gentamicin) (Table 6.23.5).[89]

**Table 6.23.5. Potential product innovations for injectable antibiotics**

| **Commodity** | **Potential product innovations** |
|---|---|
| Injectable antibiotics | • Fixed-dose presentations for basic needles and syringes and pre-filled delivery devices for administering gentamicin<br>• Auto-disable syringes for administering gentamicin<br>• Micro-needle patch technology for administering gentamicin |

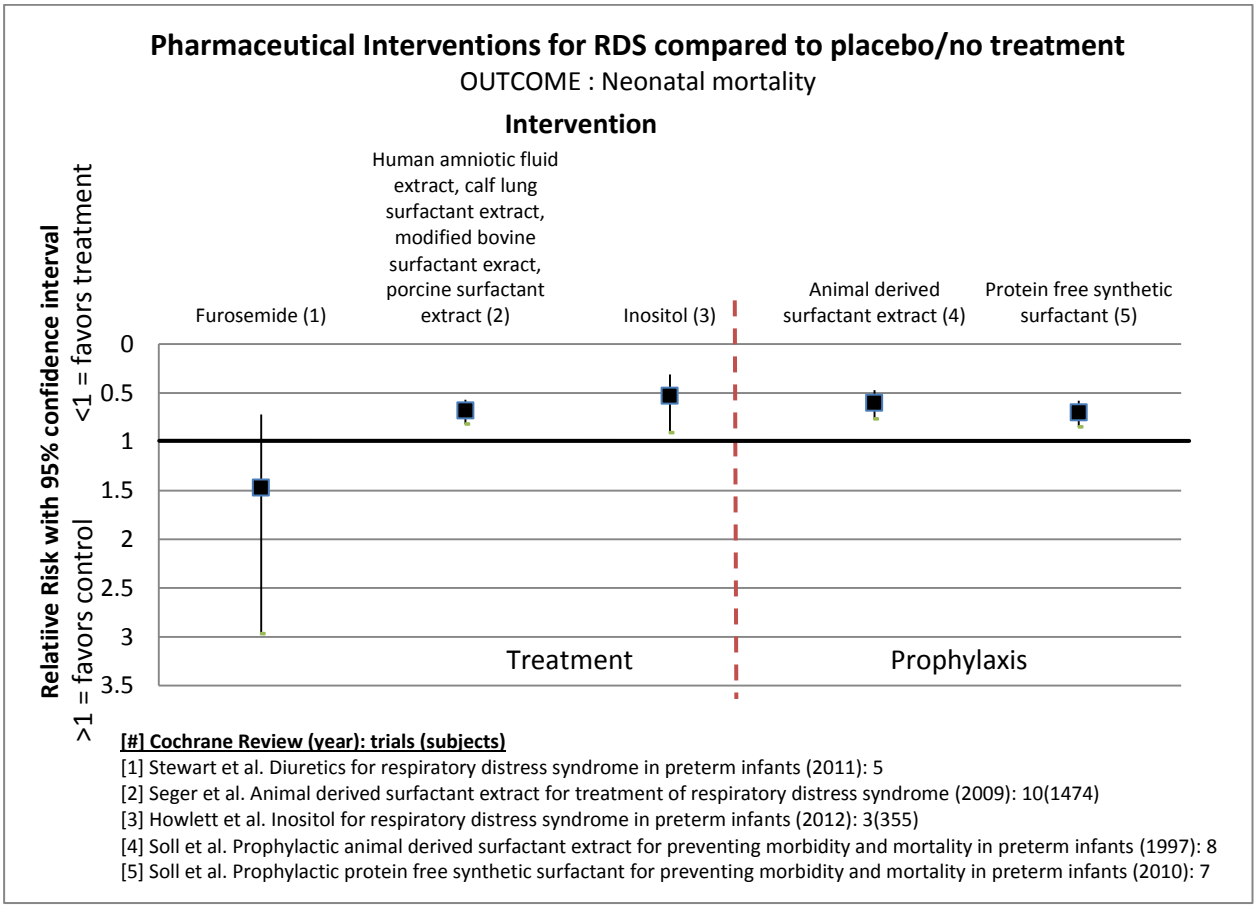
Source: UN Commission on Life-Saving Commodities for Women and Children[121]

### 2.4.3 Birth Asphyxia

Several pharmaceutical interventions have been identified to reduce the risk of neonatal mortality from respiratory distress syndrome (RDS) (Figure 6.23.12). Respiratory distress syndrome is associated with a deficiency or dysfunction of pulmonary surfactant that lines the alveolar surface and prevents atelectasis at the end of expiration. Surfactant therapy has been shown to improve the immediate need for respiratory support and the clinical outcome of very preterm newborns.[90,91] Studies have been conducted on a variety of surfactant preparations used to prevent (prophylactic or delivery room administration) or treat (very early, selective or rescue administration).[92,93] Use of surfactant therapy have demonstrated decreases in the severity of respiratory distress, decreases in the frequency of pneumothorax, increases survival without chronic lung disease, and decreases mortality.[91] Cochrane systematic reviews, show that the use of animal derived surfactant extract showed reduced risk of neonatal mortality from RDS (RR=0.68, 95% CI:0.57 to 0.82). Inositol is an essential nutrient which promotes maturation of several components of surfactant and may play a critical role in reducing neonatal mortality in neonates with RDS. Cochrane Reviews of inositol supplementation resulted in statistically significant reductions in neonatal mortality (RR=0.53, 95% CI:0.31 to 0.91).[94] Furthermore, lung edema may complicate RDS in preterm infants and for this reason, treatment with diuretics like furosemide may help remove the excess fluid from the lungs that can cause breathing problems.[95] However, the data did not support routine administration of furosemide in preterm infants with RDS as it did not reduce the risk of neonatal mortality (RR=1.47, 95% CI: 0.72 to 2.97) and furosemide-induced transient improvement in pulmonary function did not outweigh the increased risk for patent ductus arteriosus and hemodynamic instability.[95]

Prophylactic administration of pulmonary surfactant to newborns at risk of developing RDS is also another treatment option. The Cochrane Reviews of this intervention shows a decrease in the risk of neonatal mortality in infants who receive prophylactic animal derived surfactant extract compared to administration of normal saline or air placebo (RR=0.60, 95% CI:0.47 to 0.77).[96] A variety of synthetic surfactant products have also been developed and administered prophylactically. Cochrane Reviews, supports prophylactic administration of protein free synthetic surfactant in reducing the risk of neonatal mortality (RR=0.70, 95% CI:0.58 to 0.85).[97]

**Figure 6.23.12. Pharmaceutical interventions for preventing neonatal mortality from RDS**




A variety of surfactant preparations have been developed and tested including synthetic surfactants and surfactants derived from animal sources for treatment and prophylactic use in infants at risk for or having RDS (Figure 6.23.13). Although both surfactant preparations are effective, comparative reviews show that natural surfactants seem to have greater efficacy, perhaps due to the protein content that is lacking in synthetic surfactants.[96, 98] Cochrane Reviews comparing natural surfactant extract versus synthetic surfactant show that there is greater efficacy of natural surfactant products (RR=0.87, 95% CI:0.76 to 0.98).[96] Recent developments in synthetic surfactant preparations include peptides or whole proteins that mimic endogenous surfactant protein.[97] Comparisons of synthetic surfactant containing surfactant protein mimics compared to animal derived surfactant extract showed comparable results in reducing the risk of neonatal mortality (RR=0.79, 95% CI:0.61 to 1.02).[97] Furthermore, it has been suggested that multiple doses of surfactant may lead to improved outcome due to surfactant inactivation.[99] Meta-analysis of trials comparing multiple doses with only a single dose of animal derived surfactant extract as treatment in established RDS suggests a reduction in the risk of mortality, but did not reach statistical significance (RR=0.63, 95% CI:0.39 to 1.02). However, statistical significance was reached in a similar trial comparing multiple doses with a single dose of prophylactic exogenous surfactant in infants at high risk of RDS for reducing risk of neonatal death (RR=0.56, 95% CI:0.39 to 0.81).[99]

Although animal derived surfactant preparations seem to be the most effective in the treatment of premature infants with RDS, they are expensive to produce and supplies are limited.[100] Table 6.23.6 highlights the cost of the bovine lung extract, beractant, and the

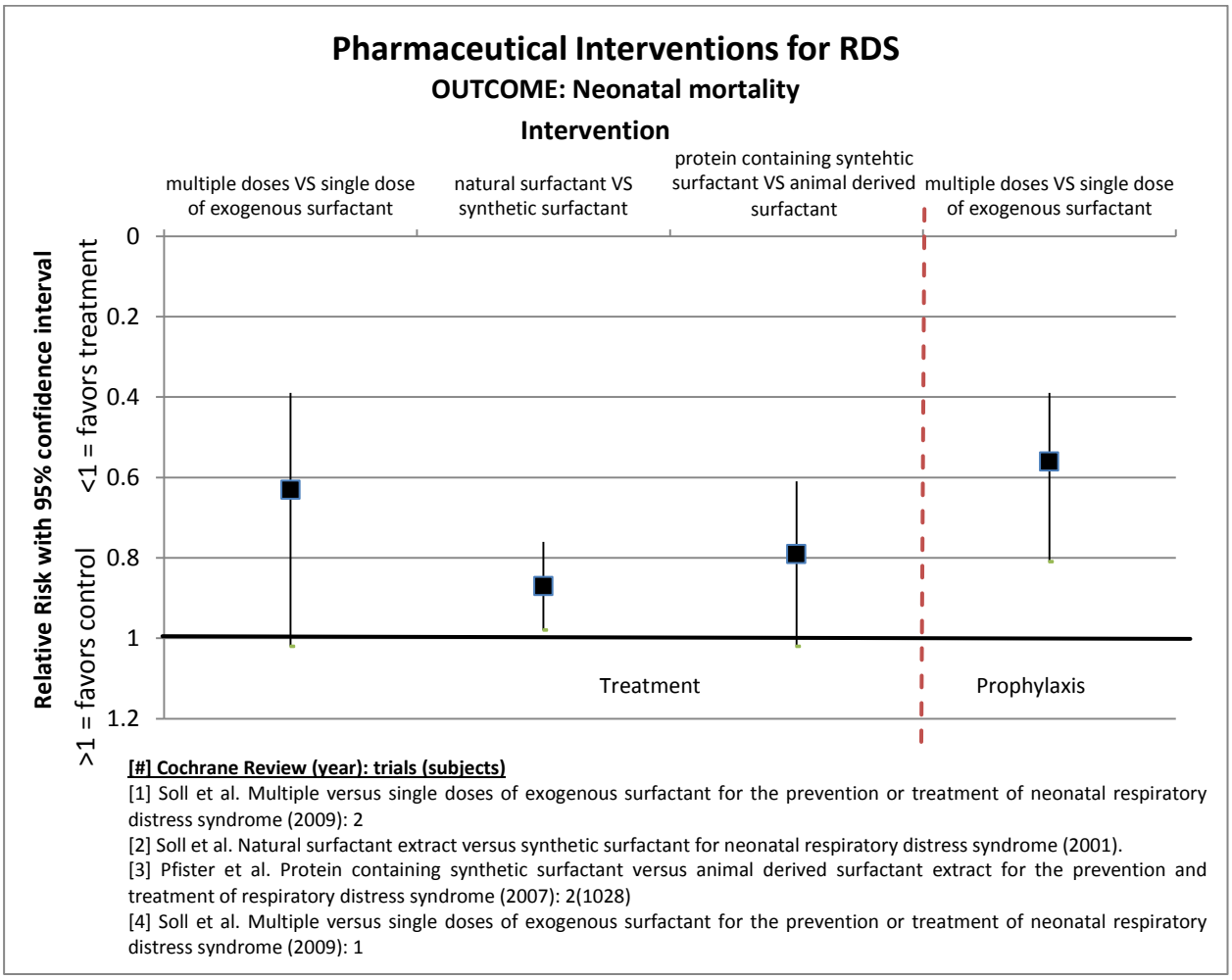
porcine lung phospholipid fraction, poractant alfa, in the United Kingdom in 2012.[101] Reimbursement prices for other European countries can be found in Annex 6.23.1.[102] In order to widen the availability of surfactant treatment, synthetic preparations need to be developed that can be produced in large quantities and at a reasonable cost. Although some effective synthetic surfactants have been developed, the development of the key hydrophobic surfactant proteins involved in increased alveolar stability, SP-B and SP-C, are too big to synthesize, structurally complex, or unstable in pure form.[100] Development of clinically active synthetic surfactants has turned out to be more complicated than initially anticipated and further research and development need to be undertaken.

**Table 6.23.6. The reimbursed price for animal derived surfactants in the United Kingdom in 2012**

| Molecule List | Pack | £ per unit |
|---|---|---|
| Poractant alfa | VIAL 80 MG 3 ML | 547.40 |
| Poractant alfa | VIAL 80 MG 1.5 ML | 281.64 |
| Beractant | VIAL 25 MG 8 ML | 306.43 |

Source: National Health Service England and Wales: Electronic Drug Tariff [101]

**Figure 6.23.13. Comparison of pharmaceutical surfactant interventions and regimens in reducing risk of neonatal mortality from RDS**




**[#] Cochrane Review (year): trials (subjects)**

[1] Soll et al. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome (2009): 2

[2] Soll et al. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome (2001).

[3] Pfister et al. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome (2007): 2(1028)

[4] Soll et al. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome (2009): 1

# 3. Research and Development

Neonatal conditions have multiple causes; therefore, solutions will not come through a single discovery, but will depend on an array of discoveries addressing multiple biological, clinical, and social-behavioral risk factors. The pipeline will need to address both the prevention of neonatal conditions and the care and survival gap. This will involve different approaches along the pipeline of innovation.

## 3.1 Pharmaceuticals

### 3.1.1 Preterm

The Global Action Report on Preterm Birth released by the WHO, emphasized descriptive and discovery learning to better understand preventative methods to preterm birth in various contexts while development and delivery research is emphasized for premature baby care.[3]

Based on the United States National Institutes of Health, 498 clinical trials were found for preterm and premature conditions in which 235 of them are open studies.[103] In 2005, the March of Dimes initiated the Prematurity Research Initiative which funds research into the causes and treatments of prematurity.[104] More than US$ 15 million have been awarded to 43 grantees over the past six years.[104]

Researchers are working to identify the causes of premature birth and new treatments to prevent or halt preterm labor. A recent development shows promise, but only for a minority of high-risk women with premature cervical shortening. Clinical trials suggest that progestational agents (PA) may modify the signal transduction pathways that are involved in cervical ripening.[105] Progestational agents seem to regulate pathways which prevent preterm birth, specifically claudin proteins.[105] However, how PAs helps prevent preterm labor and which forms of progesterone may be most effective is still to be determined.[104] It should be noted that Makena® (17-alpha-hydroxyprogesterone caproate) was approved by the FDA in the USA only in 2011 for women with a history of at least one previous spontaneous preterm birth.[41]

Several factors are hypothesized to help regulate the timing of labor including the drop in enzyme levels of caspase-3 triggering labor and the closing of SK3 (potassium) channels in the cell membranes preventing potassium flow out of the uterine muscle cells.[106,107] The enzyme, caspase-3, may help prevent contractions until term when levels drop sharply triggering labor. Prior to the onset of labor, active caspace-3 levels and fragmentation of the uterine myocyte contractile proteins decline suggesting that uterine caspase-3 acts as an anticontractile agent.[108] If this is true, it may be possible to develop drugs to regulate enzyme levels and prevent preterm labor. Additionally, the SK3 channels in cell membranes that allow potassium to flow out of the uterine muscle cells are believed to relax the uterus, allowing pregnancy to continue to term. These channels may close, prompting labor to begin.[106] If this proves correct, it could lead to the development of drugs that open the channels to prevent or half preterm labor.

A simple approach that is being investigated is the administration of vitamin D supplements for women with uterine infections. This may help prevent preterm labor by suppressing inflammation.[105]

### 3.1.2 Sepsis

Based on the US National Institutes of Health, 96 clinical trials were found for neonatal sepsis in which 38 of them are open studies.[87]

Many cases of neonatal sepsis never reach a health care facility and oral antibiotic therapy must be considered where no health care providers trained to give parenteral antibiotics are available.[83] The incremental benefit of injectable over oral antibiotics is not clear, but oral antibiotic therapy is certainly better than no antibiotic therapy at all.[8] A series of trials are evaluating the impact of home and clinic-based seven-day intramuscular and oral antibiotic therapy for neonatal sepsis in low-income countries.[83] The available data on the effect of oral cotrimoxazole in community-based treatment of serious neonatal bacterial infections are promising, but concerns of high resistance rates and side effects such as neonatal jaundice have been reported.[84]

New, better absorbed oral antibiotics should be considered. Second-generation cephalosporins (e.g. cefadroxil and cefuroxime) have shown excellent safety profile, a spectrum of activity similar to cotrimoxazole, and may be more effective given the high resistance of neonatal pathogens to cotrimoxazole.[8] Ciprofloxacin is also becoming increasingly accepted as safe for neonate use, but warrants further investigation for treatment of infections in newborns.[8] However, the current costs for these agents and the potential for exacerbating antimicrobial resistance may limit widespread use.[83] Newer antibiotics that are effective when given orally, as well as the safety and efficacy of oral plus injectable antibiotics were also identified as research priorities by technical experts to reduce global newborn infection-related mortality by 2015.[109]

### 3.1.3 Birth Asphyxia

Based on the United States National Institutes of Health, 39 studies were found for birth asphyxia in which 19 of them are open studies.[110]

One of the most common birth complications is RDS where babies struggle to breathe because their immature lungs do not produce enough surfactant, a protein that keeps small air sacs in the lungs from collapsing.[111] Since the introduction of surfactant therapy in 1990, deaths from RDS have been reduced by two-thirds.[111] Despite these advancements, about 20% of babies with RDS do not respond to surfactant treatment and further discovery and development is needed.[111] Natural surfactant contains four known proteins – SP-A, SP-B, SP-C, and SP-D – but surfactant treatments only contain SP-B and SP-C.[111] Research is being conducted to study the structure and function of SP-B to improve the synthetic surfactant to mimic the activity of the natural protein and be effective when the one currently available fails.[111, 112] Furthermore, a new generation of synthetic surfactants containing simplified phospholipid mixtures and small amounts of peptides replacing the hydrophobic proteins is currently under development and should be introduced into the market in the near future.[100]

In addition to surfactants, many newborns with RDS receive additional oxygen and mechanical breathing assistance. However, these treatments can contribute to lung injury and bronchopulmonary dysplasia.[111] Research is being done to see whether adding SP-D to commercial surfactant treatments can help the immune system fight off lung infections and prevent the inflammation that contributes to lung injuries and bronchopulmonary dysplasia.[111, 113]

Further research have been conducted in animals to test the effects of administration of caffeine on metabolic variables with peripartum asphyxia. Findings suggest that administering caffeine immediately after birth to neonatal pigs with severe oxygen restriction resulted in significant improvements in metabolic variables such as triglyceride and lactate concentrations.[113]

## 3.2 Diagnostics

### 3.2.1 Sepsis

Recent developments in microtechnologies, particularly microfluidics, have provided the greatest contribution to the diagnosis of neonatal sepsis. This technology uses the unique properties of continuous flow micro-volume channels to study the behavior, precise control, and manipulation of fluids.[8] When applied to bacterial DNA protein microarray hybridization, DNA probes specific to selected targets that are spotted on a glass or silicon slide in a known order.[114] Target DNA fragments are labeled with a reporter molecule, combined into a single hybrid, and measured using fluorescent signals to identify specific sepsis pathogen such as bacterial meningitis, acute viral respiratory tract infections, and neonatal sepsis.[60,115] This method has also been used to detect antimicrobial resistance and virulence genes in research settings.[79]

Microfluidic technology has also developed small, disposable, single-use diagnostic cartridges or cards that have been called "lab-on-a-chip" (LOC).[115] Some LOCs have combined sample preparation, biomarkers, real-time PCR, and DNA microarrays to determine indices of inflammation, pathogen identification, and antimicrobial susceptibility patterns at the point of care[115, 116] Its performance for sensitivity, specificity, and reproducibility levels are comparable to those of central laboratory analyzers and requires little user input other than the insertion of the sample.[8] Samples as little as a single drop of blood, faeces, and saliva have been tested with encouraging results.[8] Currently, LOCs are being evaluated for use in sepsis and are not yet in clinical use nor are they licensed by regulatory authorities.[8]

## 3.3 EC Framework Programme

There have been 13 projects on research and development for neonatal conditions funded by the EC Framework Programme since 2004.[117,118, 119] One project was funded by the Sixth EC Framework Programme (FP6) and 12 projects by the Seventh EC Framework Programme (FP7). The complete list of projects funded by the EC Framework Programme since 2004 is listed below sorted by each neonatal condition. Starred projects indicate an overlap between neonatal conditions and are listed in all relevant categories.

**Preterm (11 projects total)[117]:**

Treatment (8 projects)

- New approach to treatment of the blinding disease retinopathy of prematurity (ROP) (FP7)
- Efficacy and safety of inhale budesonide in very preterm infants at risk for bronchopulmonary dysplasia (FP7)
- Management of hypotension in the preterm extremely low gestational age newborn (FP7)
- Evaluation of antibiotics (ciprofloxacin and fluconazole) for the treatment of infections in preterm and term neonates (FP7)*
- No pain during infancy by adapting off-patent medicines (FP7)
- Documentation of lung growth after tracheal occlusion to reverse pulmonary hypoplasia in congenital diaphragmatic hernia. Experimental studies in the rat and clinical implications of fetal therapy (FP7)
- Treat Infections in Neonates 2 – Evaluation of an infective agent (azithromycin) for the treatment of infections in preterm and term neonates (FP7)*
- Does vascular endothelial growth factor gene therapy safely improve outcome in severe early-onset fetal growth restriction? (FP7)

Diagnostics (2 projects)

- Brain diagnostics and monitoring in early neonatal period (BraDiMo) (FP7)
- Special non-invasive advances in foetal and neonatal evaluation network (FP6)

Basic science and other fields of research (1 project)

- Effective perinatal intensive care in Europe: translating knowledge into evidence based practice (FP7)

**Sepsis (4 projects total)[118]:**

Treatment (3 projects)

- European multicenter network to evaluate pharmacokinetics, safety and efficacy of meropenem in neonatal sepsis and meningitis (FP7)
- Evaluation of antibiotics (ciprofloxacin and fluconazole) for the treatment of infections in preterm and term neonates (FP7)*
- Treat infections in NeoNates 2 – Evaluation of an infective agent (azithromycin) for the treatment of infections in preterm and term neonates (FP7)*

Diagnostics (1 project)

- Fast automated multiplex analysis of neonatal sepsis markers on a centrifugal microfluidic platform (FP7)

**Birth Asphyxia (0 projects total)[119]**

# 4. Existing Resource Flows

## 4.1 Finance for Research and Development

Global spending on maternal, newborn, and child health (MNCH) has been increasing from US$ 2.1 billion in 2003 to almost US$ 3.5 billion in 2006, with child health accounting for more than two-thirds of total aid to MNCH.[120] In 2006, the two leading contributors supporting MNCH were the United States government and the World Bank, which collectively contributed US$ 1.4 billion.[89] Although donor funding has increased for maternal, newborn, and child health, no analysis to date has disaggregated aid specifically for newborns.[121]

Based on the analysis of donor-reported data, donor attention to newborn survival has increased since 2002, but does not appropriately reflect the aid needed with over three million newborn deaths each year.[121] For low- and middle-income countries (LMIC), where the majority of total neonatal deaths occur, the investment in research funding for neonatal survival is extremely low. It is estimated that only around US$ 20 million per year is invested into research for neonatal survival.[122] Defining specific funding allocations for research on neonatal conditions is not possible in current research resource reporting for either high- or low-income countries.[120] The low investment suggests a large potential for public-private partnership (PPP) collaborations. Identifying incentives to foster research funding is recommended and necessary (See Chapter 8).

Currently, none of the neonatal conditions – preterm birth, neonatal sepsis, and birth asphyxia – are listed as one of the diseases on G-FINDER.[123] Donors interested in funding research and development for neonatal conditions need to be able to make substantial investment decisions based on accurate data regarding funding flows, gaps, and duplications. The inclusion of neonatal conditions on funding surveys such as G-FINDER can provide funders with better information and hopefully stimulate increased efficiency and investment to improve neonatal health.

According to a recent 2012 UN commission report on life-saving commodities for women and children, an investment of US$ 2.6 billion over five years to scale up 13 key commodities would cumulatively save over six million women and children.[89] The list includes a preliminary sample of overlooked life-saving commodities that represent common challenges and require a priority response, but are not exhaustive.[89] Of the 13 recommended commodities, four of them focus on interventions for newborn conditions that can have a large potential impact (Table 6.23.7).

Within the European Union, following the requirements of the Paediatric Regulation, the EMA produces a yearly updated "priority list" of medicines in need for children.[124,125] Neonates are included in these pan-European efforts. These Paediatric Regulations require that any new drug, whatever its main target, should also be considered for potential paediatric use which forces all pharma companies to think strategically in terms of paediatric medicines.

**Table 6.23.7. Newborn health commodities recommended in the 2012 Commissioners' Report**

| Newborn health commodity | Examples of key barriers | Potential 5-year impact |
|---|---|---|
| **Injectable antibiotics** – neonatal sepsis | Poor compliance by health workers | 1.22 million neonatal lives saved |
| **Antenatal corticosteroids** – preterm RDS | Low awareness of product impact | 466 000 neonatal lives saved |
| **Chlorhexidine** – newborn cord care | Limited awareness and demand | 422 000 neonatal lives saved |
| **Resuscitation devices** – newborn asphyxia | Requires trained health workers | 336 000 neonatal lives saved |

Source: Every Woman Every Child. UN Commision on Life-Saving Commodities for Women and Children: Commissioners' Report September 2012; 2012 Sept. [89]

Despite the large global burden from neonatal conditions, a recent global analysis suggests that newborn survival will remain vulnerable on the global agenda without adequate funding and without high-level engagement of policy-makers.[3] For this reason, it becomes imperative that more funding is allocated towards research and development addressing neonatal conditions.

## 5. Challenges and Research Opportunities

- Although the overall under-five mortality has been declining, neonatal mortality are lagging in improvements and is becoming a larger contributor in the under-five deaths
- The latest data in 2011 indicate that neonatal deaths account for 43% of under-five deaths worldwide. The highest share (55%) of neonatal deaths for under-five deaths is seen in developed regions
- Each neonatal condition has numerous confirmed and hypothesized etiology and contributing risk factors which makes addressing these conditions complex
- Pharmaceutical gap which presently exist offer research opportunities:

**Preterm Birth:**

- Development of a more simplified dosing regimen and single dose packaging of tocolytics to prevent or delay premature labour.
- Development of tocolytics with side-effects in mothers and newborns.
- Evidence-based protocols for use of injectable antenatal corticosteroids to prevent respiratory distress syndrome.
- Clearly labeled, pre-packaged or pre-filled delivery systems of antenatal corticosteroid products.

**Sepsis:**

- Rapid diagnostics for neonatal sepsis to prevent late or inadequate administration of necessary antibiotics.

  - Appropriate product formulation and packaging for treating neonatal sepsis, especially low-dose injectable gentamicin.
  - Development of shorter course antibiotics, oral antibiotics, and antibiotics with fewer side effects for newborns.
  - Development of diagnostic tools for neonatal conditions, which can help reduce the inappropriate use of antibiotics.
  - Development of new and effective antibiotics to treat bacterial infections that are or will soon become resistant to current antibiotics (see Chapter 6.1).

**Birth asphyxia:**

  - Development of effective and lower-cost synthetic surfactants
  - Development of a more stable oral surfactant

- Many of the current treatment regimens require properly trained care providers to administer these technologies. The best methods to train these providers need to be researched.

# 6. Conclusions

Neonatal conditions need to be prioritized to achieve MDG 4. Addressing neonatal conditions can have a major impact in reducing the global burden of disease as these conditions have the most effect on potential for years lived with disability (YLD) and years of life lost (YLL). Although the burden of disease is largest in developing countries, neonatal conditions are of a *global* concern as the share of neonatal deaths in under-five deaths are highest in developed countries.

Further research and development for rapid diagnostic tools and appropriate treatments should be prioritized. Simple product innovations such as fixed-dose technology for simple treatment administration can increase treatment usage in lower-resource settings, as well as the need for continuous innovation in developing new effective antibiotics to treat infections resistant to current antibiotics. A large challenge also remains that most of the current research and development are focused on treatments and not on prevention, in part due to the lack of understanding of the multiple etiology for each of these neonatal conditions. Furthermore, most published research has been conducted in high-income countries and research in developing, delivering, and testing community-based interventions in lower-resource settings are needed.

Research and development of new or more affordable pharmaceuticals, such as synthetic surfactants, to address neonatal conditions require substantive investment and long-term support. Increased support from the European Commission is imperative to reduce the burden of neonatal conditions such as preterm birth, neonatal sepsis, and birth asphyxia in Europe and the world.

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# Annex

## Annex 6.23.1: The reimbursed price for animal derived surfactants in European countries in 2012

Source: Pharma Price Information (PPI) service. Gesundheit Österreich GmbH (Austrian Health Institute); 20123. Available from: www.goeg.at/en/PPI

| Country | Product name | Package | Dosage form | ATC | Route of admin. | Inn. & Strength | No. of units | Manufacturer price/unit | Wholesale price/unit | Net retail price/unit | Gross retail price/unit |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Italy** | curosurf | 1fl 3 ml 80 mg/ml | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | 775.760000 € | - | 955.970000 € | 1280.320000 € |
| **Italy** | curosurf | 2fl 1.5 ml 80 mg/ml | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 2 | 387.880000 € | - | 581.965000 € | 640.160000 € |
| **Spain** | curosurf 120 ; 1 vial 1.5 ml | 1 | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | 259.560000 € | - | 310.470000 € | 322.890000 € |
| **Belgium** | curosurf 120 mg | 1.5 ml suspension pour instillation x 80 mg/ml surfactant pulmonaire porcin en 1 récipient unidose | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | 299.930000 € | 304.790000 € | - | - |
| **Greece** | curosurf 120 mg/1.5 ml btx1vialx1.5 ml | 1 | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | - | 211.230000 € | - | 256.910000 € |
| **United Kingdom** | curosurf 120 mg/1.5 ml endotracheopulmonary suspension vials (chiesi ltd) 1 vial | 1x | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | - | - | UK** 328.634772 € | UK** 328.634772 € |
| **Spain** | curosurf 240 ; 1 vial 3 ml | 1 | intratracheal suspension | R07AA02 | inhalation | natural phospholipids | 1 | 480.180000 € | - | 531.090000 € | 552.330000 € |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 240 mg | | | | | |
| **Belgium** | curosurf 240 mg | 3 ml suspension pour instillation x 80 mg/ml surfactant pulmonaire porcin en 1 recipient unidose | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | 419.600000 € | 425.540000 € | - | - |
| **United Kingdom** | curosurf 240 mg/3 ml endotracheopulmonary suspension vials (chiesi ltd) 1 vial | 1x | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | - | - | UK** 638.739790 € | UK** 638.739790 € |
| **Greece** | curosurf 240 mg/3 ml vial btx1vialx3 ml | 1 | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | - | 413.300000 € | - | 472.110000 € |
| **Denmark** | curosurf 80 mg/ml endotra.pulm.inst.su | 3 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | - | 1069.260049 € | 1165.582405 € | 1456.978007 € |
| **Denmark** | curosurf 80 mg/ml endotra.pulm.inst.su | 1.5 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | - | 615.148835 € | 671.507646 € | 839.384558 € |
| **Hungary** | curosurf 80 mg/ml endotracheopulmonális csepegtető szuszpenzió | 1x3 ml injekciós üvegben | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | 410.031820 € | 428.073220 € | 431.460636 € | 453.033154 € |
| **Hungary** | curosurf 80 mg/ml endotracheopulmonális csepegtető szuszpenzió | 2x1.5 ml injekciós üvegben | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 2 | 218.101413 € | 227.697882 € | 229.392343 € | 240.861190 € |
| **Norway** | curosurf 80 mg/ml endotrakeopulmonal instillasjonsvæske. suspensjon | 1.5 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | - | 611.470680 € | 639.745247 € | 799.681559 € |
| **Norway** | curosurf 80 mg/ml endotrakeopulmonal instillasjonsvæske. suspensjon | 1 x 3 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | - | 1222.942721 € | 1275.669202 € | 1594.586503 € |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Norway** | curosurf 80 mg/ml endotrakeopulmonal instillasjonsvæske. suspensjon | 1 x 1.5 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | - | 611.470680 € | 639.745247 € | 799.681559 € |
| **Norway** | curosurf 80 mg/ml endotrakeopulmonal instillasjonsvæske. suspensjon | 3 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | - | 1222.942721 € | 1275.669202 € | 1594.586503 € |
| **Iceland** | curosurf 80 mg/ml innöguf | 1 hgl x 1.5 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 1 | - | 547.987977 € | 557.187278 € | 699.270028 € |
| **Iceland** | curosurf 80 mg/ml innöguf | 1 hgl x 3 ml | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 240 mg | 1 | - | 1020.451478 € | 1029.653907 € | 1292.215679 € |
| **Slovenia** | curosurf 80 mg/ml suspenzija za endotraheopulmonalno vkapavanje | škatla z 2 vialama z 1.5 ml suspenzije | endotracheopulmonary instillation, suspension | R07AA02 | inhalation | natural phospholipids 120 mg | 2 | - | 472.355000 € | - | - |
| **Italy** | surfactal | iv fl 50 ml 1 g | solution for infusion | R07AA | parenteral | ambroxol 1000 mg | 1 | - | - | 16.040000 € | 17.640000 € |
| **United Kingdom** | survanta 200 mg/8 ml endotracheopulmonary suspension bottles (abbvie ltd) 1 bottle | 1 bottle | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 200 mg | 1 | - | - | UK** 357.561260 € | UK** 357.561260 € |
| **Greece** | survanta 200 mg/8 ml vial btx1 vialx8 ml | 1 | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 200 mg | 1 | - | 304.420000 € | - | 356.160000 € |
| **Spain** | survanta 25 mg/ml suspension para instilacion endotraqueopulmonar . 1 vial de 8 ml | 1 | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 200 mg | 1 | 268.580000 € | - | 319.490000 € | 332.270000 € |
| **Hungary** | survanta intratrachealis szuszpenzió | 1x8 ml injekciós üvegben | intratracheal suspension | R07AA02 | inhalation | natural phospholipids 200 mg | 1 | 276.788586 € | 288.967291 € | 292.352961 € | 306.969583 € |

UK** This is the reimbursement price to community pharmacies for dispensing the medicine against a NHS prescription. For branded medicines, the price is the NHS list price, set by the PPRS. For most generic medicines, this is the reimbursement price listed in Part VIII of the Drug Tariff. But where a supplier name is specified on the prescription e.g. omeprazole AAH or a product is not listed in Part VIII, the pharmacist is reimbursed the supplier's list price. The price includes

wholesaler and pharmacy margins that are not regulated. The United Kingdom does not hold information on the manufacturer or wholesale price. Community pharmacies and hospitals may be able to purchase medicines at a discount to these prices. (United Kingdom)