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6.23 Neonatal conditions

See Background Paper 6.23 (BP6_23Neonatal.pdf)

Background

The neonatal period is only the first 28 days of life and yet accounts for 40% of all deaths in children under five. Even within the neonatal period there is wide variation in mortality rates, with 75% of all neonatal deaths occurring in the first week of life – including 25% to 45% in the first 24 hours after birth. In 2010, neonatal conditions accounted for 3,072,000 deaths worldwide. Among the many neonatal conditions, the three major contributors to the global burden of disease are (in order of magnitude) premature birth, birth asphyxia, and neonatal infections.

Premature birth is defined 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. Complications of premature birth are the single largest contributor to neonatal mortality, due to the lack of necessary physical development. The survivors of premature birth may suffer lifelong effects. Neonatal sepsis is a blood infection that can be caused by a number of different bacteria. Neonatal sepsis can have an early-onset (within 24 hours of birth) or late-onset (after eight days of life). Birth asphyxia is defined as the failure to establish breathing or perfusion at birth.

Neonatal conditions exert a heavy burden on families, society, and the health system. Because they occur in the first few weeks of life, neonatal conditions are major contributors to the global toll of DALYs (having the most potential Years Lived with Disability (YLD) and Years of Life Lost (YLL)).

Developments since 2004

Although a regional survival gaps exist, depending on where a baby is born, neonatal conditions are an issue of global concern. All regions have seen slower reductions in neonatal deaths compared to overall deaths for children under five. This has resulted in an increased share of neonatal deaths among the under-five deaths – up from 36% of under-five deaths in 1990 to 43% in 2011, a trend that is expected to continue. Within Europe, Eastern Europe has consistently higher mortality rates and DALY burden for all three high-burden neonatal conditions (particularly neonatal sepsis and birth asphyxia-related neonatal encephalopathy) than Western and Central Europe.

Remaining challenges

At present, preventive methods, diagnostic tools, and treatments for neonatal conditions remain limited, due to the complex causes of these conditions. Many of the current preventive approaches focus on maternal health prior to the birth (for example, maternal immunization and efforts to ensure a healthy pregnancy). Furthermore,
encouraging results and promising safety profiles are emerging from preliminary studies of maternal immunization with pneumococcal polysaccharide conjugate vaccines.\textsuperscript{6} Alternative non-pharmaceutical prevention methods for pre-term birth include: birth spacing; optimizing pre-pregnancy weight; promoting healthy nutrition; promoting vaccination of children and adolescents; preventing sexually transmitted infections (STIs), and promoting cessation of tobacco use.\textsuperscript{7} Several treatments exist for neonatal conditions that can lower the risk of maternal and neonatal mortality. However, these treatments are still not ideal, due to their formulation, packaging, and/or accessibility (Table 6.23.1).\textsuperscript{8,9,10}

**Table 6.23.1: Pharmaceutical gaps of existing treatments for neonatal conditions**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Condition treated</th>
<th>Gaps</th>
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<tbody>
<tr>
<td>Tocolytics</td>
<td>Inhibit pre-term labour</td>
<td>- Associated with adverse effects to both mother and newborn</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Foetal lung maturation</td>
<td>- Associated with increased risk of infection to both mother and newborn</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Treat neonatal sepsis</td>
<td>- Non-ideal formulation and packaging for neonatal use</td>
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<tr>
<td></td>
<td></td>
<td>- Require a trained health worker to administer</td>
</tr>
<tr>
<td>Surfactant preparations</td>
<td>Treat respiratory distress syndrome</td>
<td>- Expensive to produce</td>
</tr>
</tbody>
</table>

Several tocolytics (for example, oxytocin antagonists, betamimetics, calcium channel blockers, and magnesium sulphate) are available and are effective in suppressing labour to allow enough time for antenatal corticosteroid treatment for foetal lung maturation prior to delivery and/or to transfer mother and baby to a higher-level facility where appropriate care may be available.\textsuperscript{7,11} However, the effects on neonatal outcomes and foetal/maternal side-effects have not been shown to improve the perinatal outcome.

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.\textsuperscript{12,13} 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 pharmaceutical companies to think strategically in terms of paediatric medicines.

The 2012 Report of the UN Commission on Life-saving Commodities for Women and Children recommended simple potential product innovations that need further research, particularly for the administration of gentamicin to treat neonatal infections.
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(including fixed-dose presentations for needles and syringes, auto-disable syringes, and micro-needle patch technology for administering gentamicin).[^10]

A variety of surfactant preparations have been developed and tested, including synthetic surfactants derived from animal sources, for treatment and prevention in infants at risk of respiratory distress syndrome. Although both surfactant preparations are effective, comparative reviews indicate that natural surfactants may have greater efficacy. However, these are expensive to produce and supplies are limited.[^10]

Meanwhile, the lack of rapid diagnostic tests often results in inappropriate use of antibiotics, thereby increasing the risk of the development of antimicrobial resistance. The symptoms of neonatal sepsis are often very similar to other life-threatening diseases (such as necrotizing enterocolitis and perinatal asphyxia), making it difficult to accurately diagnose and treat.[^14] Even with the few diagnostic tools that exist, pathogenic organisms remain difficult to identify. The bacterial load in neonates may be low because the mother is being treated with antibiotics and/or because only small amounts of blood can be taken from newborns.[^15] In addition, the results of these diagnostic tests take up to 48 hours, which is often too long to wait as the condition of a neonate with neonatal sepsis can deteriorate rapidly.[^7]

**Research needs**

In order to reduce neonatal mortality rates, there is a need to boost the number of innovative products in the R&D pipeline – especially new rapid diagnostic tools and appropriate treatments. More specifically, pharmaceutical gaps that offer research opportunities include:

**Pre-term birth:**
- Development of a more simplified dosing regimen and single dose packaging of tocolytics to prevent or delay premature labour.
- Development of tocolytics with fewer side-effects in mothers and newborns.
- Evidence-based protocols for the use of injectable antenatal corticosteroids to prevent respiratory distress syndrome.
- Clearly labelled, pre-packaged or pre-filled delivery systems for 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 to treat respiratory distress syndrome in newborns.
• Development of a more stable oral surfactant.

Efforts to address neonatal conditions need to be prioritized in order to help achieve the Millennium Development Goal 4 of reducing under-five mortality by two-thirds by 2015. This could have a major impact in reducing the global burden of disease as these conditions have the most potential YLL and YLD. Although the burden of neonatal disease is largest in developing countries, the proportion of neonatal deaths in under-five deaths is highest in developed countries, making this an issue of global concern. The development of innovative and more affordable pharmaceuticals and diagnostics for neonatal conditions require substantive investment and long-term support.

**References**


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