

# Proposal for essential medicines for neonates

## Introduction

Despite great advances in medicine, including intensive care practices, child mortality rates are still high in many areas of the world. Under-five mortality, infant mortality and neonatal mortality rates are general indicators of child health and are the main indicators for Millennium Development Goal 4. Estimates for some of these indicators are shown below.<sup>1</sup>

	Neonatal mortality as % of under-five mortality (2000)	Neonatal mortality as % of infant mortality(2000)	Early neonatal mortality as % of neonatal mortality(2000)
World	36 (in 1995: 46)	53 (in 1995: 61)	75
Less developed regions	52	63	79

The largest fraction of deaths in under 5's occur in developing countries, and the majority are due to conditions that could be prevented or treated if there were appropriate interventions and medicines. The six main causes for death in children under-five years of age are: neonatal problems, pneumonia, diarrhea, malaria, measles, and HIV/AIDS. Neonatal problems account for the largest proportion, about 37% of all deaths. Within this group, the problems of prematurity and low birth weight make up about 27% of deaths, sepsis/pneumonia 26%, asphyxia 23%, congenital anomalies 9%, tetanus 7%, diarrhoea 3% and other reasons 7%.<sup>2</sup> Although there has been some improvement in under-five mortality and infant mortality rates overall, neonatal mortality rates remain very high.

The majority of newborns who die do so during the first day after the birth. This has implications for service design and delivery and makes delivery of effective neonatal health care highly demanding in terms of health care workforce and resources. For management of severe and progressive diseases in neonates, neonatology has been developed mainly as a hospital-based specialty. In developed countries, care is often delivered in secondary or tertiary neonatal intensive care units, and these have now been established in many developing countries. However, the cost of this specialized care is substantial and there is only uncertain evidence of the cost-effectiveness of some interventions used in these units.<sup>3</sup>

Despite the enormous attention paid to this group of vulnerable patients and the technical advances that have been achieved, globally there are still many gaps related to neonatal health care. These include:

- Lack of clear recommendations about appropriate and cost-effective systems for providing neonatal care. This includes a definition of required competencies and responsibilities for levels of care within a neonatal health care service, as well as recommendations for delivery of care at regional versus sub-regional levels. While there appear to be clear advantages for regionalization of specialized services, this approach has not been implemented everywhere and alternative systems can lead to confusion for patients, health workers and policy makers, decrease the efficacy of health care delivery, increase costs and cause duplication of services and decreased bed-utilization.<sup>4</sup>
- Inadequate numbers of health workers for the number of patients in specialized units and generally
- Lack of evidence-based practice: in neonatal care, many interventions and practices are used on the basis of expert opinion and experience only
- Lack of evidence for the efficacy and safety of many medicines used in treatment of newborns and thus high levels of 'off-label' use of medicines, with the associated risks.

The importance of implementing strategies for reduction of the morbidity and mortality in neonates was recognized during the First Meeting of the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines (July 2007).<sup>5</sup> The Subcommittee identified a number of gaps in the EML which required urgent attention and among the others, particular attention was given to medicines for neonates.

In developed countries, provision of specialist health care services for neonates on a regional basis is well accepted and there are generally clear policies and guidelines for admission of patients to different levels of facilities as well as transfer between them. This may include recommendations on what interventions are provided at each level of care. Ideally, this approach of a uniform classification of the functional capabilities of facilities that provide inpatient care for newborn infants should lead to the following benefits:

- Ensuring that each newborn infant is delivered and cared for in a facility appropriate for its health care needs, resulting in optimal health outcomes
- Prevention of unnecessary duplication of services
- Implementing appropriate Guidelines and recommendations for each level of care
- Creating uniform lists of medicines needed for each level of care and ensuring that those recognized as essential are accessible and affordable
- Allowing comparison of outcomes within and between countries.

Currently, the published WHO recommendations that define health care interventions to be provided by different levels of neonatal health care services are the new Integrated Management of Childhood Illness recommendations (2008) for care of children from 0-2 months and the Pocketbook Of Hospital Care For Children. These two publications cover primary care and second level health care respectively. There are numerous recommendations and guidelines from developed countries. Although there are some differences between countries in the definitions of each level of care, the majority are very similar. In developing this proposal for essential medicines for neonates, the recommendations are based mainly on guidelines from several developed countries with highly developed neonatal health care systems. However, countries need to make their own guidelines taking into account structures of specialist services, transfer and admission policies and available resources. Sources for guidelines used as the basis for this proposal, in addition to the WHO publications, are:

- National Guidelines Clearinghouse  
Web-site: <http://www.guideline.gov/sitemap/sitemap.aspx>
- The Guidelines and position statements of the Canadian Pediatric Society  
Web-site: <http://www.cps.ca/english/publications/FetusAndNewborn.htm>
- Neonatal Handbook-Victoria (Australia) (reference 14).  
Web-site: [http://www.netsvic.org.au/nets/handbook/about.cfm?doc\\_id=8837](http://www.netsvic.org.au/nets/handbook/about.cfm?doc_id=8837)
- British Association of Perinatal Medicine: Standards for Hospitals Providing Neonatal Intensive and High Dependence Care (Second Edition). 2001  
Web-site: [http://www.bapm.org/documents/publications/hosp\\_standards.pdf](http://www.bapm.org/documents/publications/hosp_standards.pdf)

In developing this proposal for essential medicines for neonates, the following assumptions are made:

1. All levels of care must be capable of performing resuscitation using the most evidence-based interventions, as the clinical condition of neonates can decline without warning and progress rapidly;
2. Each facility needs to be sufficiently specialized to support and stabilize the newborn until transfer to the next level (referral unit);
3. The most reasonable practice is to transport pregnant women with high-risk pregnancies to the most appropriate level of obstetric care, in order to ensure the most efficient, appropriate and safe delivery and postpartum care of the mother and baby.

The following classification of neonatal health care facilities is used:

- Level I - basic health care services, distributed throughout all countries
- Level II -specialty health care services; mostly in hospitals in the majority of countries, the first referral level of care;
- Level III - subspecialty health care services: a hospital neonatal intensive care unit (NICU) organized with personnel and equipment to provide continuous life support and comprehensive care for extremely high-risk newborn infants and those with complex and critical illness. Mostly available in high and middle-income countries. .

The definition of neonate for this document includes babies from 0-28 days of age, AND pre-term babies up to 3 months of age. Because premature newborns have slowed maturation of the liver and kidney as well as different body composition, the pharmacokinetics of medicines used in this group of patients are quite different, even when compared to full term newborns. In settings with an increasing prematurity rate, with an extended period of hospital stay, it is important to ensure that appropriate medicines are available for this group as well as normal newborns.

## Objectives

The objectives of this proposal are:

1. to identify the clinical problems treated in each level of neonatal care
2. to identify the appropriate medicines used for each of these problems
3. to develop a preliminary list of essential medicines for neonates, based on 1 and 2, divided into 'Core' and 'Complementary' medicines according to the standard definition of these terms for the Model List of Essential Medicines

4. to compare the existing List of Essential Medicines for Children with the list for neonates and identify discrepancies
5. to identify clinical evidence to support the use of the medicines on the preliminary list, using tertiary sources
6. to define the regulatory status of these medicines with respect to use in neonates
7. to identify prices of the each of the medicines
8. to develop a list of priority medicines for applications for addition to the EML

## Methods

1. Identification of neonatal problems and conditions according to the level of neonatal care was done based on a review of clinical guidelines identified above. The health conditions presented for each of the levels of care are derived from the guidelines listed above and for Level I and II, the list of health conditions was harmonized with WHO guidelines.
2. Identification of the medicines used in primary and secondary level of neonatal care for each of the problems.  
For this purpose four WHO published Guidelines were reviewed:  
**Pregnancy, Childbirth, Postpartum and Newborn Care: a guide for essential practice** 2003  
**Integrated Management of Childhood Illness** for 0-2 month old infants, 2008  
**Managing newborn problems: A guide for doctors, nurses and midwives**, WHO 2003;  
**Pocket book of Hospital care for children**, Chapter 3: Problems of the neonate and young infant, WHO 2005  
All medicines recommended in these guidelines were classified according to the clinical condition for which they were recommended. The EML for Children (EMLc) was reviewed to see if the dosage and strength of medicines included in it were appropriate for neonates. This was used as the basis for determining whether a new application for a medicine, form or strength was needed.
3. Preliminary identification of the medicines used in Neonatal Intensive Care Units for each of the problems. For this purpose, several guidelines were identified and reviewed, from different countries. The guidelines were selected because they represent several parts of the world and these institutions provide evidence based sources of data and information.
  - National Guidelines Clearinghouse, <http://www.guideline.gov/sitemap/sitemap.aspx>
  - The American Academy of Pediatrics, <http://www.aap.org/visit/cmte17.htm>
  - Neonatology on the web, <http://www.neonatology.org/neo.clinical.html>
  - The National Institute for Health and Clinical Excellence (NICE), <http://www.nice.org.uk/>
  - The Canadian Pediatric Society guidelines, <http://www.cps.ca/english/publications/FetusAndNewborn.htm>
  - NICU-WEB, Division of Neonatology at the University of Washington, <http://depts.washington.edu/nicuweb/>

- The RPA Newborn Care Guidelines and Protocols, <http://www.cs.nsw.gov.au/rpa/neonatal/default.htm>
  - Auckland District Health Board Guidelines and Drug Protocols (National Women's Health and Newborn Intensive Care Unit), New Zealand, <http://www.adhb.govt.nz/newborn/Guidelines.htm> and <http://www.adhb.govt.nz/newborn/DrugProtocols/>
  - Iowa Neonatology Handbook, Division of Neonatology at the University of Iowa Children's Hospital. <http://www.uihealthcare.com/depts/med/pediatrics/iowaneonatologyhandbook/index.html>
  - Neonatal Handbook-Victoria (Australia), <http://www.netsvic.org.au/nets/handbook/about>
  - University of California, San Francisco Children's Hospital Guidelines, [http://www.ucsfhealth.org/childrens/medical\\_services/critical/](http://www.ucsfhealth.org/childrens/medical_services/critical/)
  - The Health Evidence Bulletins - Wales, <http://heb.w.cf.ac.uk/maternal/index.html>
4. Information about medicines included on the Model List of Essential Medicines for children was extracted from the WHO publication and websites [http://www.who.int/childmedicines/publications/EMLc%20\(2\).pdf](http://www.who.int/childmedicines/publications/EMLc%20(2).pdf) and <http://www.who.int/medicines/publications/EML15.pdf>
5. Prices of medicines were assessed from the International Drug Price Indicator Guide.<sup>6</sup> For medicines not included in the guide, prices from the BNF-C 2006 were used as indicative prices, although British prices are not globally applicable.
6. The regulatory status of medicines used for treatment of neonatal health problems was checked with the Food and Drug Agency of the USA, the Medicines Evaluation Board of the Netherlands and the European Medicines Agency (EMeA) as these sources were readily available.
7. To identify clinical evidence for each of the medicines, the following sources were used to retrieve reviews and summaries of evidence. A search of the primary literature was not carried out.
- Cochrane Database of Systematic Review, <http://www.cochrane.org/reviews/index.htm>
  - BNF for Children, <http://bnfc.org/bnfc/>
  - The Neonatal Formulary (NNF5), <http://www.blackwellpublishing.com/medicine/bmj/nnf5/default.asp>
  - E-Medicine, <http://www.emedicine.com/> and for neonatal topics, <http://www.emedicine.com/ped/cardiac.shtml>
  - Database of Abstracts of Reviews of Effects, Centre for Reviews and Dissemination, University of York, UK, <http://www.york.ac.uk/inst/crd/crddatabases.htm>
  - International Child Health Collaboration, <http://www.ichrc.org/>
  - RxList-The internet Drug Index for prescription drugs and medications, <http://www.rxlist.com/script/main/hp.asp>
  - Centers for Disease Control and Prevention, Atlanta, <http://www.cdc.gov/DiseasesConditions/>

## Results

1. **Neonatal conditions and clinical disorders** are listed according to the level of neonatal care in Tables 1, 2 and 3.

2. **Provisional list of essential medicines for neonates**

Table 4 lists the provisional list of essential medicines for neonates for Level I and II facilities, including all medicines that are currently included in the EMLc in an appropriate dosage form and strength. This is the list of potential 'core' essential medicines; note that the usual 'default' is that all medicines should be included on the 'core' list unless there are clear reasons to list them on the 'complementary' list. All medicines used in levels I and II can be used in Level III facilities. Medicines in Table 4 are therefore not duplicated in Table 5.

Table 5 lists medicines that are already on the EMLc and are essential for Level III facilities. These medicines used in third level care would be included in 'complementary list', as their use requires skilled personnel and facilities.

If the current EMLC only specifies a solid oral dosage form of a medicine, it has been assumed that it is *not* suitable for neonates.

3. **Missing essential medicines for neonates**

'Missing' essential medicines have been categorised in a number of ways, and are listed in the tables below. Table 6 lists medicines that are on the EML, but not in appropriate dosage forms and strengths for neonates. Table 7 lists medicines recommended in evidence based guidelines, for which there is adequate evidence of effectiveness and safety. These would be potential essential medicines and proposals for the consideration by the Expert Committee are required.

4. **Missing information**

As a result of this review and the review carried out by the Expert Subcommittee, additional questions and need for information have been specified for some medicines currently on the list for children generally. Table 8 lists these medicines and specifies the questions that would need to be answered before they could be confirmed as essential medicines for neonates.

5. **Medicines requiring substantial review before proposals could be considered.**

A number of medicines were recommended in guidelines, for which there is limited evidence to support their inclusion as essential medicines. Table 9 lists these medicines and the questions that would need to be evaluated.

6. **Medicines not recommended**

Based on the review of the guidelines and evidence sources, the medicines in Table 10 are those medicines that although recommended, do not have supporting evidence, or for which there are more effective and safer alternatives.

Additional information including prices, regulatory status, and the evidence reviewed for each medicines can be made available as supplementary annexes.

## References

1. <http://www.who.int/whosis/indicators/2007compendium/en/index.html>, accessed Jan 9 2008
2. [http://www.who.int/child-adolescent-health/OVERVIEW/CHILD\\_HEALTH/map\\_00-03\\_world.jpg](http://www.who.int/child-adolescent-health/OVERVIEW/CHILD_HEALTH/map_00-03_world.jpg).
3. <http://pediatrics.aappublications.org/cgi/content/full/114/5/1341>
4. Committee on Fetus and Newborn Levels of Neonatal Care. *Pediatrics* 2004; 114:1341-1347.
5. [http://mednet3.who.int/EML/expcom/expcom16/INDEX\\_expcom16.htm](http://mednet3.who.int/EML/expcom/expcom16/INDEX_expcom16.htm)
6. International Drug Price Indicator Guide. 2006 Management Sciences for Health.

**Table 1: Clinical problems treated at first level of care**

<b>Clinical condition or problem</b>	<b>Management</b>
Normal birth	Essential newborn care: drying, warmth, cord care, early initiation of breastfeeding, eye prophylaxis
Perinatal asphyxia	Neonatal resuscitation: bag and mask ventilation
Hypoglycaemia	Prevention through early and frequent breastfeeding, or by feeding expressed breast milk or sugar water
Feeding problems	Support for exclusive breastfeeding
Vaccine preventable diseases	Immunization
Low birth weight (>1750 g), Premature babies of gestational age of >34 weeks	Warmth (Kangaroo Mother Care), breastfeeding support
Premature babies of gestational age of <34 weeks	Stabilization and referral
Anemia	Prevention of anaemia in preterm babies by iron supplementation starting at 8 weeks of age
Jaundice	Identification of severe jaundice and referral
Diarrhoea	Oral rehydration treatment
Hypothermia	Skin-to-skin contact with the mother
Risk of bacterial infection	2 intramuscular antibiotics for 5 days
Risk of HIV transmission	ARVs for mother and baby safer infant feeding , co-trimoxazole prophylaxis
Risk of tuberculosis	Isoniazid prophylaxis
Skin, umbilical or eye infections, thrush	Local treatment
Suspected severe infection	First dose of 2 IMI antibiotics and referral

**Table 2: Clinical problems treated at second level of care**

<b>Clinical condition or problem</b>	<b>Management</b>
Perinatal asphyxia	Neonatal resuscitation, oxygen, fluids, anti-convulsant therapy as needed
Low birth weight (>1250 g), Premature babies of gestational age of >32 weeks	Kangaroo Mother Care, cup feeding and gastric tube feeding of expressed breast milk, management of apnoea and other respiratory problems
Premature babies of gestational age of <32 weeks	Stabilization and referral
Severe jaundice	Phototherapy and exchange transfusion
Diarrhoea	Oral rehydration treatment, intravenous fluids for severe dehydration
Sepsis and meningitis	Intravenous or intramuscular antibiotics, oxygen, fluids, anticonvulsants as needed
Neonatal abstinence syndrome	Naloxone treatment
Feeding problems	Breastfeeding support, cup feeding and gastric tube feeding of expressed breast milk, partial parenteral nutrition
Hypoglycaemia	Prevention, treatment with 10% glucose
Hypocalcaemia	Treatment with intravenous calcium gluconate
Electrolyte disturbances	Correction of electrolyte imbalance

**Table 3: Clinical problems treated at third level of care -Neonatal Intensive Care Units**

<b>Underlying problem</b>	<b>Clinical problem</b>
Prematurity	Respiratory distress syndrome
	Necrotizing enterocolitis
	Patent ductus arteriosus
	Intraventricular hemorrhage
	Apnea of prematurity
	Chronic lung disease
	Retinopathy of prematurity
Cardiovascular	Hypotension
	Hypertension
	Cardiac failure
	Duct-dependant cardiac anomalies
	Tachyarrhythmias
Infections	Early onset bacterial infections (in the first 48/72 hours after delivery)
	Late onset bacterial infections (after 48-72 h after delivery)
	Fungal infections
	Congenital infections and sexually transmitted diseases
	Mother-to-child transmission HIV
	Viral infections
	Skin infections
	Eye infections
	Umbilical infections
Perinatal asphyxia	Birth asphyxia
	Hypoxic-ischaemic encephalopathy
	Seizures
	Meconium aspiration syndrome
	Persistent pulmonary hypertension of the neonate
Severe pain	Pain relief
Mother's substance abuse	Neonatal abstinence syndrome
Metabolic disturbances	Acidosis
	Hypoglycaemia
	Hyperglycaemia
	Hypokalaemia
	Hypocalcaemia
	Genetic metabolic disorders
Anemia	Iron-deficiency anemia
	Hypoplastic anaemia

**Table 4 Essential Medicines for Levels I and II: Core**

Medicine	Dosage form and strength
Aciclovir ointment 3%	Ointment 3% W/W.
Amoxicillin as trihydrate (as sodium salt)	Powder for oral solution: 125 mg (anhydrous)/5-ml Powder for oral solution: 250 mg (anhydrous)/5-ml
Amphotericin B	Injection: 50 mg in vial
Ampicillin	Injection: (500 mg; 1g) as sodium salt in vial
Benzathine benzylpenicillin	Powder for injection: (900 mg benzylpenicillin = 1.2 million IU; 1.44 g benzylpenicillin = 2.4 million IU) in 5 ml vial
Benzylpenicillin (penicillin G)	Powder for injection: (600 mg = 1 million IU ; 3g = 5 million IU) as sodium or potassium salt in vial.
Caffeine citrate	Injection: 20 mg/ml ( equivalent to 10 mg caffeine base/ml). Oral liquid: 20 mg/ml ( equivalent to 10 mg caffeine base/ml)
Calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule
Ceftriaxone	Powder for reconstitution: (250 mg, 1g) as sodium salt in vial
Chloramphenicol	Oral liquid:150 mg/5-ml as palmitate Oily suspension for injection: 1g as sodium succinate in vial
Chlorine base compound	Powder: 0,1% chlorine for solution.
Cholecalciferol	Oral liquid: 400 IU/ml
Cloxacillin	Injection: 500 mg as sodium salt in vial
Diazepam	Injection: 5 mg/ml in 2-ml ampoule
Epinephrine	Injection: 1 mg as hydrochloride or hydrogen tartrate in 1-ml ampoule
Erythromycin	Powder for oral liquid: 125 mg as stearate or ethyl succinate Powder for injection: 500 mg ( as lactobionate) in vial
Ethanol	Solution: 70% (denatured)
Fluconazole	Oral liquid: 50 mg/5 ml Injection: 2 mg/ml in vial
Gentamicin	Solution (eye drops): 0,3% as sulfate.  Injection: (10 mg; 40 mg)/ml as sulfate in 2-ml vial
Glucose	Injectable solution 10% (75 mEq)

Medicine	Dosage form and strength																														
Glucose with sodium chloride	Injectable solution: 4% glucose, 0,18% sodium chloride (75 mEq and 2.6 g/l)																														
Glutaral	Solution: 2%																														
Isoniazid	Oral liquid: 50 mg/5 ml																														
Lidocaine	Injection: 1%, 2% ( hydrochloride) in vial Topical forms: 2% to 4 % (hydrochloride)																														
Methylrosanilinium chloride (gentian violet)	Aqueous solution: 0,5%																														
Morphine	Injection: 10 mg as morphine hydrochloride or morphine sulfate in 1 ml ampoule Oral liquid: 10 mg as morphine hydrochloride or morphine sulfate/5 ml																														
Naloxone hydrochloride	Injection: 400 micrograms as hydrochloride in 1-ml ampoule																														
Nevirapine	Oral suspension: 50 mg/5 ml																														
Nystatin	Oral suspension: 50 mg/5 ml; 100 000iu/ml																														
Oral rehydration salts	<table> <tr> <td>glucose:</td> <td>75</td> <td>mEq</td> </tr> <tr> <td>sodium:</td> <td>75</td> <td>mEq or mmol/l</td> </tr> <tr> <td>chloride:</td> <td>65</td> <td>mEq or mmol/l</td> </tr> <tr> <td>potassium:</td> <td>20</td> <td>mEq or mmol/l</td> </tr> <tr> <td>citrate:</td> <td>10</td> <td>mmol/l</td> </tr> <tr> <td>osmolarity:</td> <td>245</td> <td>mOsm/l</td> </tr> <tr> <td>glucose:</td> <td>13.5</td> <td>g/l</td> </tr> <tr> <td>sodium chloride:</td> <td>2.6</td> <td>g/l</td> </tr> <tr> <td>potassium chloride:</td> <td>1.5</td> <td>g/l</td> </tr> <tr> <td>trisodium citrate dihydrate+:</td> <td>2.9</td> <td>g/l</td> </tr> </table> <p>+ trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.</p>	glucose:	75	mEq	sodium:	75	mEq or mmol/l	chloride:	65	mEq or mmol/l	potassium:	20	mEq or mmol/l	citrate:	10	mmol/l	osmolarity:	245	mOsm/l	glucose:	13.5	g/l	sodium chloride:	2.6	g/l	potassium chloride:	1.5	g/l	trisodium citrate dihydrate+:	2.9	g/l
glucose:	75	mEq																													
sodium:	75	mEq or mmol/l																													
chloride:	65	mEq or mmol/l																													
potassium:	20	mEq or mmol/l																													
citrate:	10	mmol/l																													
osmolarity:	245	mOsm/l																													
glucose:	13.5	g/l																													
sodium chloride:	2.6	g/l																													
potassium chloride:	1.5	g/l																													
trisodium citrate dihydrate+:	2.9	g/l																													
Oxygen	Inhalation (medicinal gas)																														
Paracetamol	Oral liquid: 125 mg/5 ml Suppository: 100 mg																														
Phenobarbital sodium	Injection: 200 mg/ml																														
Phenytoin	Injection: 50 mg/ml as sodium salt in 5-ml ampoule Oral liquid: (25 mg to 30 mg)/5 ml																														
Phytomenadione	Injection: 1 mg/ml, 10 mg/ml in 5-ml ampoule																														
Potassium chloride	Solution: Powder for solution																														
Retinol	Oral oily solution: 100 000 IU/ml as palmitate in multidose dispenser																														
Sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na + 154 mmol/l, Cl - 154 mmol/l)																														

Medicine	Dosage form and strength
Tetracaine	Solution (eye drops): 0,5% as hydrochloride
Vancomycin	Powder for injection: 250 mg as hydrochloride in vial
Water for injection	Liquid for injection: 2-ml; 5-ml; 10-ml ampoules
Zinc sulphate	Oral liquid: in 10 mg per unit dosage forms

**Table 5: Essential Medicines for Level III (Complementary List)**

Medicine	Dosage form and strength
Aciclovir	Powder for injection: 250 mg as sodium salt in vial Oral liquid: 200 mg/5 ml
Amikacin	Injection: 1000 mg in vial
Atropine sulphate	Solution (eye drops): 0.1%; 0.5%; 1% as sulfate Injection: 1 mg as sulfate in 1-ml ampoule
Chlorpromazine	Injection: 25 mg/ml as hydrochloride in 2-ml ampoule Oral liquid: 25 mg/ml as hydrochloride
Digoxin	Oral liquid: 50 micrograms/ml Injection: 250 mg micrograms/ml
Dopamine hydrochloride	Injection: 40 mg as hydrochloride in 5- ml vial
Flucytosine	Injection: 2.5 g in 250 ml infusion
Human normal immunoglobulins	Injection, intramuscular administration: 16 % protein solution Intramuscular administration: 5%; 10% protein solution Subcutaneous administration: 15%; 16% protein solution
Hydrocortisone	Powder for injection: 100 mg as sodium succinate in vial
Imipenem + cilastatin	Powder for injection: (250 mg as monohydrate + 250 mg as sodium salt; 500 mg as monohydrate + 500 mg as sodium salt) in vial
Insulin	Injection: 40 IU/ml in 10-ml vial Injection: 100 IU/ml in 10-ml vial
Metronidazole	Oral liquid: 200 mg/5-ml as benzoate Injection 500 mg in 100-ml vial
Neostigmine	Injection: 500 micrograms in 1-ml ampoule Injection: 2.5 mg in 1-ml ampoule as metilsulfate
Phenoxymethyl penicillin	Powder for oral liquid: 250 mg/5-ml as potassium salt
Ranitidine	Oral solution: 75 mg/5 ml Injection: 25 mg/ml in 2-ml ampoule
Salbutamol	Injection: 50 micrograms/ml as sulfate in 5-ml ampoule Respirator solution for use in nebulizers: 5 mg/ml as sulfate

**Table 6: Medicines on the EMLC but with inappropriate dosage form or strength**

<b>Level I and II</b>		
<b>Medicine Name</b>	<b>Dosage form Currently available</b>	<b>Comment</b>
Glucose	Solution 10%	A higher concentration form of 66.7% is needed for pain relief in simple procedures.
Lamivudine	Oral liquid	A more dilute form of the oral liquid is needed especially for preterm neonates. The strength of the existing form is too strong
Nystatin cream	Oral dosage forms	Application for cream may be useful
Phenobarbital	Elixir	A higher concentration of the oral form is needed. 15 mg/5ml is too diluted to be used for maintenance period following neonatal seizures.
Polyvidone iodine	Solution: 10%	A more dilute form of the solution is needed especially for preterm neonates. The existing strength of 10% is too strong
Sulfadiazine + pyrimethamine	Oral liquid form needed	An appropriate oral form needs to be considered for a new application for use in prophylaxis for Toxoplasmosis
<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage form Currently available</b>	<b>Comment</b>
Ciprofloxacin	Tablet	
Hydrochlorothiazide	Tablet	

**Table 7: Potential essential medicines for priority review**

<b>Level I and II</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Lidocaine + prilocaine	Gel or cream	If superior to lidocaine alone
Pyridoxine	Injection	Guidelines recommend it in the treatment of neonatal seizures.
<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Indomethacin	Injection	Indomethacin is recommended. for medical treatment for DAP
Prostaglandin E1 or Prostaglandin E2	Injection	A new application needs to be considered, for maintaining patency of patent ductus
Surfactant	Suspension	Evidence exists for effectiveness and safety in specific settings.

**Table 8: Medicines on the EMLc, but missing information to support use in neonates**

<b>Level I and II</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Ceftazidime	Injection as pentahydrate	Both cefotaxime and ceftazidime are alternatives to ceftriaxone which is already on the list with a square box. Needs confirmation of best choice in neonates
Chlorhexidine gluconate	Solution: 5% (digluconate) for dilution	More evidence is needed for the strength
d - Penicillamine	Oral Liquid or Injection.	Not used in children < 1month old. Evidence is required to support the IV form application.
Nitrous oxide	Solution, inhaled gas	Currently listed as anaesthetic.
Sulfamethoxazole + trimethoprim	Suspension and injection	Safety and efficacy data in neonates?
Trimethoprim	The oral liquid and tablet forms are listed on the EML.	Not licensed for use in neonates <6 weeks, indication?
Zidovudine	Oral Solution and Injection	Data too limited in neonates to provide specific dose recommendations, however 2mg/kg weight has been found to be effective.
Zinc oxide	Cream	It is recommended for excoriation of the skin and nappy rash, if not fungal. Evidence for this indication was not found.

<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Amoxicillin as trihydrate + clavulanic acid as potassium salt	Oral suspension and injection	Safety of clavulanic acid is questionable in neonates.
Cefazolin	Injection	Is this the best choice for neonates?
Dexamethasone	Injection	The appropriate dosage form needs to be decided.
Folic acid	Oral liquid	A review is necessary before it can be confirmed for use in the neonates.
Furosemide	Oral Solution. Not licensed for use in children for hypertension.	Indication in neonates?

Level III		
Medicine Name	Dosage Form	Comment
Pyridostigmine	Tablet	It is less powerful and slower in action compared to neostigmine, but it has a longer duration. It is preferable to neostigmine because of its smoother action and the need for less frequent dosage. Would need a new dosage form if required.
Sodium nitroprusside	Injection	Safety and efficacy in neonates?
Spironolactone	Oral suspension	Indicated for use in children, however no specific information about use in neonates
Vecuronium	Powder for injection	It is listed on the EML, however no information is provided on its use in neonates

**Table 9: Medicines recommended in guidelines, but lacking evidence**

Level III		
Medicine Name	Dosage Form	Comment
Adenosine	Injection	Indicated as antiarrhythmic. Evidence for use in neonates?
Amiodarone	Injection	It can be used in VT and SVT not responsive to adenosine. Is use in neonates safe?
Captopril	Tablet	No ACE inhibitors currently listed on EMLc. Comparative effectiveness and safety would need to be established and a new dosage form listed if necessary.
Cefotaxime	Injection	Both cefotaxime and ceftazidime are alternatives to Ceftriaxone which is already on the list with a square box. Listing this as replacement or in addition would require evidence of superior comparative effectiveness and safety.
Clonazepam	Injection. The liquid form is not used in children < 1 month of age	There is a need for the review of benzodiazepines (clonazepam, diazepam, midazolam, lorazepam). Evidence to support the use of these medicines in neonates?
Dobutamine	Injection	Preference versus dopamine?
Enalapril	Tablet available	No ACE inhibitors currently listed on EMLc. Comparative effectiveness and safety would need to be established and a new dosage form listed if necessary.

<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Esmolol hydrochloride	Injection	Indication, efficacy and safety?
Fentanyl	Injection	Currently contraindicated in children < 12 years. Would need review of effectiveness and safety.
Flecainide acetate	Tablet and liquid and injection	Indication, efficacy and safety?
Ganciclovir	Injection	Evidence for use of ganciclovir in the treatment of cytomegalovirus infections in neonates?
Heparin	Injection	Insufficient evidence for its efficacy in continuous infusions for maintenance of I.V. access.
Ibuprofen	Injection	Evidence to support efficacy for closure of PDA?
Lorazepam	Injection/By rectum and by sublingual administration	There is a need for the review of benzodiazepines (clonazepam, diazepam, midazolam, lorazepam) in neonates.
Methadone	Oral solution	Evidence does not show its superior effectiveness over morphine and phenobarbital in the treatment of NAS.
Midazolam	Oral liquid and injection	There is little neonatal experience in the use of anticonvulsant medications (midazolam, lignocaine, benzodiazepines, lamotrigine, carbamazepine and valproate ) as second line agents for neonatal seizures.
Sodium hydrogen carbonate	Injection	It is identified in some guidelines, but the evidence does not support its inclusion on the list.
Sotalol hydrochloride	Tablet	It is used in refractory SVT combined with flecainide. Role in neonates uncertain.
Streptokinase	Injection not used in children < 1 month	No randomized controlled trials were identified from the Cochrane Reviews to provide evidence to support use in neonates.

Level III		
Medicine Name	Dosage Form	Comment
Tobramycin	Injection as sulphate	Should be used with caution in children because of their renal immaturity and the resulting prolongation of serum half-life of the drug. Amikacin and gentamycin are representatives of the same class.
Tocopheryl acetate	Injection	Evidence show effect in reducing IVH and retinopathy, but because of serious risks (NEC and sepsis ) it is uncertain whether there is a need for a new application. More evidence is needed.

**Table 10: Medicines from guidelines or the EMLc that are not recommended for review**

Level I and II		
Medicine Name	Dosage Form	Comment
Adenine arabinoside	Injection	It is recommended for the treatment of herpetic infections, but the evidence does not support its evidence in the treatment of neonates. Aciclovir is preferred over adenine.
Aminophylline	Injection	The evidence supports use of caffeine citrate in the treatment of apnea of prematurity, as superior to other methylxanthines or doxapram.
Amlodipine	Tablet in children > 1 month	Recommended in some guidelines. Evidence for safety and effectiveness in neonates lacking.
Methicilin	Now discontinued	It is recommended in some guidelines, but there is no evidence to support an application.
Paraldehyde	Enema by rectum	Recommended in some guidelines. There is a need for review of its efficacy and adverse events as well as availability.
Tetracycline hydrochloride	Eye ointment 1%	Evidence does not support use of topical ointments in premature neonates

Level III		
Medicine Name	Dosage Form	Comment
Acetazolamide	Injection. Powder for reconstitution as sodium salt.	Acetazolamide therapy is neither effective nor safe in the treatment of post haemorrhagic ventricular dilation. Acetazolamide can not be recommended as therapy for post hemorrhagic hydrocephalus
Allopurinol	Tablet	Not indicated for use in children < 1 month
Aminoacids	Powder	There are some recommendations for their use in the prevention of NEC. However the evidence does not support these either in

<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
		prevention or treatment of NEC.
Chloral hydrate	Solution for oral or rectum use	There is no evidence on the benefit/risk ratio of this medicine.
Chlorothiazide	Oral suspension	Hydrochlorthiazide is listed on the EML
Chromolyn sodium	Inhaler	There is currently no evidence from randomized trials that cromolyn sodium has a role in the prevention of CLD in preterm infants.
Cimetidine	Oral solution and injection, not for use in children under 1 year of age	Ranitidine is the representative of the same class and it has already been added to the list
Clindamycin	Liquid. injection not used in children < 1 month	Dose recommendation starts at > 1 month of age. It is contraindicated in preterm infants
Clonidine hydrochloride	Tablet and injection used in children < 2 years	No evidence of superior effectiveness over morphine and phenobarbital in the treatment of NAS (Neonatal Abstinence Syndrome )
Diazoxide	Injection for IV use and for administration by mouth as an extemporaneous formulation	Discontinued
Doxapram	Assumed injection	The evidence supports use of caffeine citrate in the treatment of apnea of prematurity
Epoprostenol	Infusion, powder for reconstitution	No evidence to support it application Prostacycline may be used in severe and refractory cases, although it is difficult to obtain and its use is controversial.
Flucloxacillin as sodium salt	Oral solution and injection	Cloxacillin is the representative of the same class, with less serious adverse effects.
Furosemide	Injection	There is not enough evidence to support use of furosemide in infants for DAP.
Human recombinant erythropoietine	Assumed injection	The evidence show no benefit in prevention and treatment of anaemia of prematurity
Hydralazine hydrochloride	Injection	No information about the indications or contraindications in children
Inositol	Tablet	Further investigations of inositol as a prophylactic nutritional supplement that can be used to reduce the severity of respiratory distress due to surfactant deficiency are needed.
Isoproterenol	Assumed injection	Needs review of evidenced on effectiveness and safety in neonates.
Isradipine	Assumed oral liquid	There are no clinical studies with calcium antagonists in neonates.
Kanamycin	Powder for injection	Gentamycin is already on the list representing aminoglycosides.

<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Labetalol hydrochloride	Injection	No information about the indications or contraindications in children
Magnesium sulphate	Injection	Evidence for efficacy and safety in the treatment of PPHN?
Meropenem	Injection, powder for reconstitution as trihydrate	Imipenem + cilastatin is in the same class of the penems; would need to have evidence of comparative efficacy in neonates
Methyldopa	Tablet used in children > 1 month	Recommended only in children > 50 kg
Metolazone	Tablets. It is not licensed for use in children.	Efficacy and safety in paediatric patients have not been established
Milrinone	Injection	Efficacy and safety in paediatric patients have not been established
Minoxidil	Tablet used in children > 1 month	Insufficient evidence to support use.
Neomycin	Ointment	Neomycin is associated with systemic toxicity and ototoxicity in neonates and children with renal impairment
Nicardipine	Injection	Efficacy and safety have not been established in patients < 18 years of age.
Pancuronium	Injection	Vecuronium is the representative in the same group. Is there any need for pancuronium?
Paragoric	Oral tablet	No evidence of efficacy compared to morphine and phenobarbital in the treatment of NAS (Neonatal Abstinence Syndrome).
Probiotics	Unknown	Dietary supplements are not listed on the EML
Procainamide	Assumed IV injection	Safety and efficacy in children have not been established
Propafenone	Tablet	Safety and efficacy in children have not been established
Propranolol	Tablet	Listed as tablets on the EML: 20 mg; 40 mg as hydrochloride, as an antimigraine medicine.
Pyrimethamine	Tablet available	Tablet listed on the EML. It is not licensed for use in children under 5 years.
Quinidine	Tablet	Safety and efficacy in neonates have not been established.
Recombinant human activated protein C	Appropriate form to be specified	Insufficient data to support the use of rhAPC for the management of severe sepsis in newborn infants
Sildenafil	Tablets	The safety and effectiveness of sildenafil in the treatment of PPHN has not yet been established
Superoxide dismutase	Unknown	Some evidence show benefit but it is insufficient to support need for a new application.

<b>Level III</b>		
<b>Medicine Name</b>	<b>Dosage Form</b>	<b>Comment</b>
Streptomycin	Injection, powder for injection as sulphate.	It is mentioned as a medicine included in EMLC, but not identified in the Guidelines. No indication in neonates.
Suxamethonium Chloride	Injection	May be contraindicated in preterm infants.
Tobramycin sulfate	Injection and nebuliser solution	Gentamicin is already included in the EMLC - representatives of the same class
Tolazoline	Injection	No evidence to support its use.
Trifluorothymidine	Ointment	It is recommended in some guidelines, but there is insufficient evidence to support its use in the treatment of herpes keratitis.