Proposal for the inclusion of surfactant in the WHO model list of essential medicines

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1. Synopsis

Surfactant is proposed for the care of the newborn infant. It is specifically proposed for the prophylaxis and/or treatment of respiratory distress syndrome (RDS) since there is robust evidence that surfactant reduces mortality and pulmonary air leaks in preterm infants with or at high risk for RDS. Surfactant may also be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (e.g., meconium aspiration syndrome, sepsis/pneumonia, and pulmonary hemorrhage).

Some differences between natural and synthetic surfactant have been highlighted, for example a difference in terms of reduction in the risk of death and pneumothorax, favoring the former. However, both animal-derived and synthetic surfactants are beneficial for prophylaxis and rescue treatment of RDS in preterm infants and therefore listing in the World Health Organization (WHO) Model List of Essential Medicines is requested as a group and not as an individual preparation.

At present, neither early nasal continuous positive airway pressure (nCPAP) nor mechanical ventilation and surfactant can be said to be superior for the prevention of death or bronchopulmonary dysplasia (BPD) in very preterm infants. The methods complement each other but the question regarding an optimal approach remains yet to be answered in future studies. The ability to administer surfactant during nCPAP appears to be important in Extremely Low Birth Weight (ELBW) infants and more mature infants with established RDS. New modalities of surfactant administration (e.g., aerosolized surfactant; surfactant via nasogastric tube) may in the future help to combine nCPAP and surfactant therapy more effectively and safely.
2. Summary statement of the proposal
Surfactant is proposed for the inclusion in the WHO Model List of Essential Medicines for the care of preterm infants with or at high risk for RDS, since both animal-derived and synthetic surfactants have been shown to be beneficial for prophylaxis and rescue treatment of RDS in preterm infants.

3. Name of the organization(s) consulted and/or supporting the application
University Children's Hospital of Tuebingen, Department of Neonatology, Calwerstr. 7, 72076 Tuebingen, Germany

4. Examples of surfactant preparations by generic names
Pumactant, Bovactant, BLES, Poractant alfa, Colfosceril palmitate, Calfactant, Surfactant-TA, Lucinactant, Beractant etc.

5. Formulation proposed for inclusion
The optimum dose of surfactant varies between different surfactant preparations and generally is between 50 and 200 mg/kg (see table 1, page 7). Since the primary target population consists of ELBW infants, a vial size for an anticipated body weight of 500g / 1000g would be desirable, although this cut-off is somewhat arbitrary.

6. Whether listing is requested as an individual preparation or as a group
Listing is requested on the WHO Model List of Essential Medicines as a group of different surfactant preparations (natural and synthetic).

7. Definition of RDS
RDS is mainly a problem of prematurity and it is caused by insufficient production of surfactant and structural immaturity of the lungs or, very rarely, by a genetic problem with the production of surfactant associated proteins.
RDS was previously called hyaline membrane disease due to the characteristic pathological finding seen in babies who died from RDS, "hyaline membranes", waxy-appearing layers that line the collapsed alveoli of the lung.
The clinical course of RDS is characterized by early tachypnea, tachycardia, chest wall retractions, expiratory grunting, flaring of the nostrils and cyanosis during breathing efforts. As the disease progresses, infants may develop respiratory failure and apnea, requiring positive pressure support and/or full mechanical ventilation.
Avery and Mead established the causal relationship of surfactant deficiency and RDS in 1959. Four years later, a baby boy born to then-President and Mrs. John F. Kennedy died of
RDS. Research into active treatment options for RDS was enforced and in 1980 the first successful use of exogenous surfactant therapy in preterm infants was reported (Fujiwara 1980). Since then randomized controlled trials (RCTs) have demonstrated that surfactant therapy is not only well tolerated but also significantly reduces both neonatal mortality and pulmonary morbidity.

8. RDS: epidemiological information on disease burden

RDS has been reported in all races worldwide although there is a paucity of population-based epidemiological studies. According to the few published studies, the overall incidence of RDS is about 1% (Field 1987, Rubatelli 1998).

In the United States, RDS occurs in approximately 20,000-40,000 infants each year. In 4438 infants weighing between 501 and 1500 g, and 195 infants weighing 401 to 500 g born at the 14 participating centers of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network very low birth weight (VLBW) registry between January 1, 1995 and December 31, 1996, RDS was the most frequent acute pulmonary disease (50% of all VLBW infants). It was diagnosed in 78% of infants weighing 501 to 750 g and 26% of infants weighing 1251 to 1500 g. Fifty-two percent of this cohort received surfactant therapy (Lemons 2001).

In comparison, RDS for VLBW infants was diagnosed in 71% of infants weighing 501 to 750 g and 23% of infants weighing 51 to 1500 g born in the NICHD Neonatal Research Network between Jan. 1, 1997 and Dec. 31, 2002 (Fanaroff 2007). Fifty-eight percent of the entire cohort were treated with surfactant. For the purpose of the study, an infant was determined to have RDS if each of the following was true: required oxygen at 6 hours of life continuing to age 24 hours, demonstrated clinical features within age 24 hours, need for respiratory support to age 24 hours, and an abnormal chest x-ray within age 24 hours (Fanaroff 2007).

Several risk factors for RDS have been identified. Multivariate regression analysis of maternal and perinatal data demonstrated that gestational age, birth-weight, maternal age, elective and emergency caesarean section (CS), and male sex were risk factors for RDS (Dani 1999). Most importantly, the incidence of RDS increases with decreasing gestational age and birth weight (Chard 1997).

Epidemiological data on the frequency of RDS in developing countries is difficult to obtain for various reasons: most deliveries occur at home, accurate records are often unavailable and epidemiological studies are sparse. Some believe that RDS is encountered less frequently in developing countries than elsewhere, because premature infants might be more often small
for their gestation and stressed in utero due to malnutrition or pregnancy-induced hypertension. Other studies have reported a comparable or even higher incidence of RDS than in the western world. In a prospective study of the prevalence of RDS in a consecutive 10,134 births at the Aga Khan University Hospital in Karachi, RDS was documented in 127 infants (1.2% births), with a prevalence of 12.8% among low birth weight infants (Bhutta 1997). The overall mortality for this group was 39%, with the highest mortality rate (68%) among newborn infants < or = 1000 g birth weight. The data from Pakistan suggest that RDS is a significant cause of morbidity and mortality in preterm infants with a comparable prevalence rate to western figures. However, these findings might not be representative for all developing countries since the data were obtained from a relatively well-nourished hospital-born population (Bhutta 1997). Another prospective hospital-based study from Pakistan reported a higher incidence of RDS than documented in studies from the Western world (Ghaffor).

In a prospective unmatched case-control study of 256 neonates with RDS and 256 controls that was conducted at the 70-bed Neonatal Unit of Muhimjibi Medical Centre in Dar es Salaam in Tanzania to study risk factors and outcome during March to November 1995, RDS contributed 6 per cent of all neonatal admissions. RDS was significantly associated with lower birth weight, gestational age, birth asphyxia and male sex. Maternal hypertension with or without albuminuria was inversely related to RDS. There was no significant association between RDS and mode of delivery, antepartum hemorrhage or premature prolonged rupture of membranes of more than 24 h. A total of 134 (52%) neonates with RDS died, 88% of which occurred in the first 7 days of life, thus significantly contributing to perinatal mortality (Mlay 2000).

Although neonatal care has changed dramatically over the last decades (introduction of antenatal steroids, exogenous surfactant replacement, improved ventilatory support etc.), the overall incidence of RDS remains relatively stable at about 1% (Field 1987, Rubatelli 1998). This might be due to the increased number of viable ELBW infants (Koivisto2004) and underlines the importance of RDS as a major neonatal morbidity.

9. Surfactant composition and function
Pulmonary surfactant is essential for normal lung function and survival at birth. It has surface tension-lowering properties, by which alveolar collapse is prevented and gas exchange is facilitated. It has also been shown to play an important role in innate defense of the lung (Haagsman 2008).
Surfactant is synthesized by alveolar type II cells, stored in lamellar bodies that are exozytosed and taken up into the monolayer lining the epithelial surface of the lung.

Surfactant is a complex mixture of interacting lipids and proteins. The lipid fraction is mainly (60%) comprised of saturated phosphatidylcholine. Twenty-five percent of phospholipids are unsaturated phosphatidylcholine species, whereas the remaining 15% are phosphatidylglycerol and phosphatidylinositol (Jobe 1993). The protein fraction is made up by four different types of apoproteins: the hydrophobic surfactant protein B (SP-B) and SP-C and the hydrophilic SP-A and SP-D. SP-B and SP-C are lipophilic surfactant-associated proteins that facilitate adsorption and spread of phospholipids to form a monolayer at the air–liquid interface. SP-A and D are members of the collectin family of proteins, containing a collagen-like domain as well as a carbohydrate-binding region. They are present in both pulmonary and extrapulmonary tissue. Among their functions are binding, opsonisation and clearance of microbes from the lung and regulation of immune cell activity (Kingma 2006). It has recently been proposed that SP-B and SP-C may be involved in modulation of pulmonary inflammation as well (Ryan 2006, Ikegami 2005).

The essential pulmonary role of surfactant is highlighted by the pathophysiology of RDS seen in preterm infants (see chapter 7). The first successful trial of surfactant treatment for RDS was reported in 1980 followed by numerous RCTs demonstrating the efficacy of surfactant treatment in reducing pulmonary air leaks and mortality. The introduction of exogenous surfactant administration for infants with RDS is generally considered one of the most important advancements in the field of neonatology. Nowadays, the potential benefit of surfactant therapy is evaluated in a wide range of respiratory disorders in both neonates and pediatric as well as adult patients. Moreover, several disease entities of formerly unknown origin have recently been linked to genetic disorders of surfactant metabolism.

10. **Commercially available surfactant preparations**
Surfactants may be of animal or synthetic origin. Both types of surfactants have been extensively studied in animal models and in clinical trials to determine the optimal timing, dose size and frequency, route and method of administration. There are several different types of surfactant preparation licensed for use in neonates with RDS (see table 1) including synthetic and natural surfactants. The following table does not claim to be complete; it was adapted from the European consensus guidelines on the management of neonatal RDS that were published in 2007 (Sweet 2007).
Table 1: Surfactant preparations (2007); adapted from the European consensus guidelines on the management of neonatal respiratory distress syndrome (Sweet 2007)

<table>
<thead>
<tr>
<th>Generic name / Trade name</th>
<th>Source</th>
<th>Dose (volume)</th>
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<tbody>
<tr>
<td>Bovactant / Alveofact</td>
<td>Bovine</td>
<td>50 mg/kg/dose (1,2 ml/kg)</td>
</tr>
<tr>
<td>BLES / BLES</td>
<td>Bovine</td>
<td>135 mg/kg/dose (5 ml/kg)</td>
</tr>
<tr>
<td>Calfactant / Infasurf</td>
<td>Bovine</td>
<td>105 mg/kg/dose (5 ml/kg)</td>
</tr>
<tr>
<td>Surfactant-TA / Surfacten</td>
<td>Bovine</td>
<td>100 mg/kg/dose (3,3 ml/kg)</td>
</tr>
<tr>
<td>Beractant / Survanta</td>
<td>Bovine</td>
<td>100 mg/kg/dose (4 ml/kg)</td>
</tr>
<tr>
<td>Poractant alfa / Curosurf</td>
<td>Porcine</td>
<td>100-200 mg/kg/dose (1,25-2,5 ml/kg)</td>
</tr>
<tr>
<td>Pumactant / ALEC</td>
<td>Synthetic</td>
<td>No longer manufactured</td>
</tr>
<tr>
<td>Colfosceril / Exosurf</td>
<td>Synthetic</td>
<td>64 mg/kg/dose (5 ml/kg)</td>
</tr>
<tr>
<td>Lucinactant / Surfaxin</td>
<td>Synthetic</td>
<td>Not licensed</td>
</tr>
</tbody>
</table>

11. Summary of comparative effectiveness

11.1 Surfactant replacement for RDS

The European consensus guidelines on the management of neonatal RDS recommend that infants with or at high risk of RDS should be given surfactant as this reduces mortality and pulmonary air leak (Sweet 2007). In the following chapter we will review the supporting evidence separately for different indications, administrations, and formulations.

11.1.1 Prophylactic versus rescue surfactant

The prophylactic surfactant approach aims at delivering surfactant before the onset of respiratory symptoms. This approach offers the theoretical advantage of a more homogeneous surfactant distribution, a decrease in need for mechanical ventilatory support thus minimizing barotrauma and lung injury. This approach has mainly been operationalized in clinical studies as surfactant administration within a time frame of up to 30 minutes after birth.

The rescue surfactant approach reserves surfactant for infants with established RDS, most commonly within the first 12 hours after birth when prespecified threshold criteria for RDS are met. This approach offers the theoretical advantage of only treating infants with clinical disease thus eliminating the potential risks and costs of treating infants that would not need to be treated.

Using either approach (prophylactic and rescue) has been demonstrated to improve clinical outcome (Soll 2001, Soll 1998). Infants who receive prophylactic natural or synthetic
surfactant extract have a decreased risk of pneumothorax, a decreased risk of pulmonary interstitial emphysema, and a decreased mortality. In addition infants receiving prophylactic natural surfactant have a decreased risk of the combined outcome of bronchopulmonary dysplasia (BPD) or death (Soll 1997).

In a meta-analysis of 8 studies from the Cochrane Collaboration comparing prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants, significant improvement in clinical outcomes was noted with the prophylactic approach. The meta-analysis supports a decrease in pneumothorax (Relative Risk (RR) 0.62; 95% Confidence Interval (CI) 0.42-0.89), a decrease in the incidence of pulmonary interstitial emphysema (RR 0.54; 95% CI 0.36-0.82), a decrease in mortality (0.61; 95% CI 0.48-0.77) and a decrease in the incidence of BPD or death (RR 0.85; 95% CI 0.76-0.95) (Soll 2001).

Based on the available evidence, the European consensus guidelines on the management of neonatal respiratory distress syndrome recommend that prophylactic surfactant (within 15 min of birth) should be given to almost all babies under 27 weeks’ gestation (Sweet 2007). Prophylaxis should be considered for babies over 26 weeks but < 30 weeks’ gestation if intubation is required in the delivery room or if the mother has not received prenatal corticosteroids (Sweet 2007). According to these guidelines untreated babies should receive early surfactant if there is evidence of RDS such as increasing requirements for oxygen. However the timing for intervention or when to intervene as RDS progresses is not specified in these guidelines and the decision is left to the individual clinicians. The most recent statement of the American Academy of Pediatrics (AAP) concludes that surfactant should be given to infants with RDS as soon as possible after intubation irrespective of exposure to antenatal steroids or gestational age (Engle 2008). Prophylactic surfactant replacement is suggested to be considered for extremely preterm infants at high risk of RDS, especially in infants who have not been exposed to antenatal steroids (Engle 2008).

Based on the above evidence and guidelines, the standard treatment for very preterm infants is/was with assisted ventilation and surfactant (Lindner 1999). However, with recent changes in neonatal care and insight that ventilation may be harmful to the lungs, it has been hypothesized that the avoidance of ventilation might lead to less BPD. In the COIN trial, an RCT in which 610 infants who were born at 25-to-28-weeks' gestation were assigned to either CPAP or intubation and ventilation at 5 minutes after birth, there was no statistical evidence of a difference in the combined outcome of death or BPD at 36 weeks' gestational
age between the groups (Morley 2008). However, at 36 weeks' gestational age, only 9% of infants in each group of survivors were receiving an oxygen concentration of 30% or more. The benefits of CPAP included a lower risk of the combined outcome of death or the need for oxygen therapy at 28 days and fewer days of assisted ventilation. A side effect of CPAP was an increase in the number of pneumothoraces. Overall, starting early CPAP treatment in very preterm infants was not detrimental.

At present, neither early nCPAP nor mechanical ventilation and surfactant can be said to be superior. The methods complement each other but the question regarding an optimal approach remains yet to be answered. The ability to administer surfactant during nCPAP appears to be important in ELBW infants and more mature infants with established RDS. New modalities of surfactant administration (e.g. aerosolized surfactant; surfactant via nasogastric tube) may in the future help to combine nCPAP and surfactant therapy more efficiently and safely.

11.1.2 Natural versus synthetic surfactant
A variety of surfactant preparations has been developed and tested in clinical trials, including synthetic surfactants and surfactants derived from animal sources. Both animal-derived and synthetic surfactants are beneficial for prophylaxis and rescue treatment of RDS in preterm infants. A systematic review from the Cochrane Collaboration comparing natural surfactant extract to synthetic surfactant in the treatment or prevention of RDS identified 11 trials that met the inclusion criteria (Soll 2001). The meta-analysis shows that the use of natural surfactant rather than synthetic surfactant results in a significant reduction in the risk of pneumothorax (RR 0.63; 95% CI 0.53-0.75) and mortality (RR 0.87; 95% CI 0.76-0.98). A trend towards an increase in overall intraventricular hemorrhage (IVH) incidence with natural surfactant was noted in the meta-analysis (RR 1.09; 95% CI 1.00-1.19).

The European Consensus Guidelines recommend that natural surfactants should be used in preference to synthetic as they are more effective in reducing pulmonary air leaks and mortality (Sweet 2007). In contrast, the most recent statement of the AAP emphasizes that both animal-derived and synthetic surfactants decrease respiratory morbidity and mortality in preterm infants with surfactant deficiency and that new synthetic surfactants with surfactant protein-like activity are promising new treatments for surfactant-deficiency disorders (Engle 2008). For the purpose of this proposal, listing in the WHO Model List of Essential Medicines is requested as a group of different surfactant preparations (natural and synthetic).

11.1.3 Surfactant administration
To optimize surfactant administration, controlled trials have compared different treatment procedures (bolus, infusion, multiple lumen endotracheal tube (ETT), side-hole adapter and number of doses).

**Bolus versus infusion**

Surfactant has been administered through an endotracheal tube either by bolus/fairly rapid installation or slow infusion. In animal studies bolus administration has been shown to be superior and lead to a more uniform distribution compared to infusion over 5, 30 or 45 minutes (Segerer 1996, Segerer 1993, Ueda 1994). Human data on this issue are sparse. A small clinical trial enrolling 299 infants showed no significant differences in outcome measures of fractional inspired oxygen, mean airway pressure, and arterial-alveolar ratio of partial pressure of oxygen at 72 hours of life, or in the incidences of air leaks, pulmonary interstitial emphysema, or death through 72 hours of life (Zola 1993). However, oxygen desaturation occurred more often when bolus administration was used, whereas reflux into the ETT occurred more often when the infusion technique was used.

**Single lumen ETT bolus installation vs. dual-lumen ETT**

An RCT including one hundred ninety-eight infants (birth weight 600-2000 g) with RDS needing mechanical ventilation with a fraction of inspired oxygen (FIO2) of 0.40 comparing 200 mg/kg of Curosurf, either by bolus instillation or by a simplified dosing technique (giving the full dose in 1 minute via a dual-lumen endotracheal tube without positioning, interruption of mechanical ventilation, or bagging) found fewer episodes of hypoxia and a smaller decrease in heart rate and oxygen saturation in the dual-lumen group. Infants in the dual-lumen group also had a lower total time exposure to supplemental oxygen but no difference in patient relevant long term outcomes was found (Valls-i-Soler 1998).

**Bolus vs. 1-minute infusion through a side-hole adapter**

Another RCT that compared the incidence of transient hypoxia and bradycardia, gas exchange, ventilatory requirements and 28 day outcomes of two different surfactant dosing procedures (bolus vs. surfactant given in 1 min via a catheter introduced through a side-hole in the tracheal tube adaptor) in infants with RDS found no differences between the two procedures (Valls-i-Soler 1997).

**Repeated doses**

Most RCTs evaluating the effectiveness of surfactant used single doses. Since surfactant was introduced in neonatal care, physicians have noted that some neonates respond only transiently to surfactant therapy and the question arose whether multiple doses of surfactant
might be more effective than a single dose. Individual trials have shown that repeated doses of surfactant (both natural and synthetic) given at intervals for predetermined indications have decreased mortality and morbidity compared with single surfactant doses or placebo (Hoeckstra 1991, Liechty 1991, Dunn 1990, Corbet 1995, Speer 1992). A systematic review from the Cochrane Collaboration that compared multiple versus single dose natural surfactant extract for severe neonatal RDS identified two RCTs (Dunn 1990, Speer 1992) including 394 patients. Meta-analysis of these trials suggests a reduction in the risk of pneumothorax (RR 0.51; 95% CI 0.3-0.88) and a trend towards a reduction in mortality (RR 0.63; 95% CI 0.39-1.02) (Soll 1999). At present there is insufficient evidence to recommend the optimal number of fractional doses of surfactant (Zola 1993), however, the OSIRIS trial, a large factorial RCT provided no evidence that a regimen including the option of a third and fourth dose of a synthetic surfactant when signs of RDS persisted or recurred was clinically superior to a regimen of two doses (OSIRIS Collaborative Group 1992).

The optimal method of surfactant administration remains yet to be clearly proven. New methods such as aerosolized surfactant and surfactant administered via a nasogastric tube need testing in future controlled trials.

11.2 Surfactant replacement for respiratory disorders other than RDS
11.2.1 Persistent pulmonary hypertension of the newborn (PPHN)
PPHN is the result of a failed normal circulatory transition after birth. It is a syndrome characterized by marked pulmonary hypertension that causes hypoxemia and right-to-left extrapulmonary shunting of blood. With inadequate pulmonary perfusion, neonates develop refractory hypoxemia, respiratory distress, and acidosis. PPHN is caused by a number of medical conditions, including meconium aspiration syndrome (MAS), pneumonia and sepsis and congenital diaphragmatic hernia (CDH). In some of these conditions surfactant has been shown in controlled trials to be beneficial.

11.2.2 Meconium aspiration syndrome (MAS)
The aspiration of meconium stained amniotic fluid before, during, and after birth can lead to unfavorable pulmonary symptoms in the neonate, a condition that is called meconium aspiration syndrome (MAS). Several constituents of meconium, especially the free fatty acids (eg, palmitic, stearic, oleic), have a higher minimal surface tension than surfactant and strip it from the alveolar surface. Thus MAS may lead to severe respiratory failure and secondary surfactant insufficiency. In a systematic review from the Cochrane Collaboration, surfactant replacement in full term/near term infants with severe MAS reduced the risk of requiring
extracorporeal membrane oxygenation (ECMO) (RR=0.64; 95%CI: 0.46-0.91) and the length of hospital stay (Median (MD) – 8 days; 95%CI: -14 to -3 days). (El Shaled 2007).

11.2.3 Neonatal pneumonia and sepsis
Like MAS pneumonia and sepsis cause surfactant inactivation, an influx of serum protein into the alveolar space and the formation of hyaline membranes. A study showed that surfactant therapy improved gas exchange in the majority of patients with GBS pneumonia, but the response to surfactant was slower than in infants with RDS (Herting 2000). This study recruited 118 infants with respiratory failure, clinical and/or laboratory signs of acute inflammatory disease, and Group B Streptococcus (GBS) infection proven by culture results retrospectively from a database of patients treated with surfactant at 28 neonatal units participating in European multicenter trials from 1987-1993 and prospectively from the same units in the following years using a nonrandomized control group of 236 noninfected infants from the same database. The beneficial findings of the study by Herting et al. have been confirmed in subgroups of RCTs of infants with severe respiratory failure and other beneficial findings (improved oxygenation and reduction in the need for ECMO) have been suggested in these subgroup analyses (Lotze 1998, Lotze 1993).

11.2.4 Congenital diaphragmatic hernia (CDH)
The term “congenital diaphragmatic hernia (CDH)” summarizes a variety of congenital birth defects that involve abnormal development of the diaphragm. This allows the abdominal contents to protrude into the chest thereby impeding proper lung formation. Newborns with CDH often have severe respiratory distress and CDH may be associated with surfactant insufficiency. However, the lungs of human infants with CDH show surfactant synthesis rates similar to those from infants without CDH, but contain less phospholipids and phosphatidylcholine per milligram of DNA than control infants and also show altered kinetics (Finer 2004, Cogo 2003, 2004). Small case reports have reported a benefit of surfactant for infants with CDH, but larger series of infants with CDH have not confirmed these findings and even point to an increased rate of negative outcomes (use of ECMO, BPD, mortality) (Finer 2004, Van Meurs 2004, Lally 2004).

11.2.5 Neonatal pulmonary hemorrhage
Neonatal pulmonary hemorrhage occurs mainly in preterm ventilated infants with severe RDS who often have a persistent ductus arteriosus (PDA). The cause of hemorrhage is thought to be due to a rapid lowering of intrapulmonary pressure, which facilitates left to right shunting across a PDA and an increase in pulmonary blood flow. As is the case with meconium, blood can lead to secondary surfactant inactivation. Due to the fact that neonatal
pulmonary hemorrhage is an unpredictable complication, RCTs investigating the role of surfactant are difficult to design and implement and a recent systematic review from the Cochrane Collaboration did not identify any randomized trials evaluating the role of surfactant in pulmonary hemorrhage (Azis 2008). However, evidence from observational studies points to a benefit of surfactant therapy in neonatal pulmonary hemorrhage (Pandit 1995, Amizuka 2003).

11.2.6 Acute lung injury and acute respiratory distress syndrome in adults
Adult respiratory distress syndrome (ARDS) is a diffuse pulmonary parenchymal injury associated with noncardiogenic pulmonary edema. It results in severe respiratory distress and hypoxemic respiratory failure with the pathologic hallmark being a diffuse alveolar damage. In a meta-analysis of nine trials randomizing 1441 adult patients, surfactant showed no effect on early mortality compared to control (RR 0.93; 95%CI: 0.77-1.12) in patients with ARDS (Adhikari).

12. Methodological quality of surfactant studies
12.1 Prophylaxis studies
The methodological quality of RCTs comparing prophylactic synthetic surfactant to control treatment (sham air treatment or instillation of normal saline) in premature infants thought to be at risk for developing RDS is generally high (Soll 1998). All studies included in the corresponding Cochrane review assigned treatments by random allocation and sealed enveloped were used in all seven studies. Investigators in these studies attempted to blind treatment with most studies relying on a resuscitation team not responsible for ongoing care of the infant to administer the intervention and control treatment. Most outcome assessors were blinded and minimal exclusions were noted after randomization (Soll 1998).

The eight RCTs that are included in the Cochrane review on natural surfactant for the prophylaxis of RDS are likewise of high methodological quality (Soll 1997). All studies allocated assigned treatment by randomization and either used sealed enveloped (7 studies) or coded vials (1 study). As in the studies using synthetic surfactant, blinding of treatment was attempted by relying on a resuscitation team, not otherwise responsible for ongoing care of the infants. Outcome assessors were mostly blinded and apart from one study (Kwong 1985), exclusion after randomization was minimal (Soll 1997).

12.2 Treatment studies
There are 6 studies included in the Cochrane Review on synthetic surfactant for RDS in preterm infants (Soll 1998). All included studies allocated treatment by randomization and
treatment assignments were provided to participating centers by sealed envelopes. Blinding of treatment and outcome assessment was mostly attempted by means of a resuscitation and assessment team not otherwise involved in the care of the study infants. Follow-up of short term (in hospital) outcomes was virtually complete while long-term follow-up rates ranged from 84% to 100% of surviving infants (Soll 1998).

13. Cost effectiveness of prevention and treatment of neonatal RDS with exogenous surfactant

There are several publications on the economics of neonatal care, including policies for surfactant use (for an overview of the surfactant economics literature see Mugford 2006). Models of cost-effectiveness showed surfactant to be an expensive but effective and cost effective treatment (Mugford 1993). However, these models were dependent on the neonatal technology in use and on the costs of neonatal care and prices of surfactant at the time. Most importantly, little information was available about long term pulmonary and neurodevelopmental outcomes. Despite being an effective therapy for RDS, surfactant has failed to have a significant impact on the incidence of chronic lung disease in survivors.

Paradoxically the cost of neonatal care has increased as surviving infants are more immature and consume a greater proportion of neonatal intensive care resources. Despite this, surfactant has been and still is considered a safe and cost-effective therapy for RDS compared with other therapeutic interventions in premature infants (Tubman 1990, Ainsworth 2002, Mugford 2006). Nevertheless, neonatal medicine has changed dramatically in recent years and the current most efficient policy for use of surfactant depends on the concomitant use of other therapies and technologies such as antenatal steroids and continuous positive airway pressure. Furthermore, since surfactant has been adopted into routine neonatal practice, the questions of economic impact have shifted to questions regarding the specific preparations, number of doses, modes of administration, concomitant use of new technologies such as nCPAP etc. Therefore, future economic studies addressing these new issues and new economic models are needed.
### 14. List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
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<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
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<td>CDH</td>
<td>Congenital Diaphragmatic Hernia</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>Caesarean Section</td>
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<td>Extremely Low Birth Weight</td>
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<td>Endotracheal Tube</td>
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<td>Phosphatidylcholine</td>
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<td>GBS</td>
<td>Group B Streptococcus</td>
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<td>IVH</td>
<td>Intraventricular Hemorrhage</td>
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<td>Meconium Aspiration Syndrome</td>
</tr>
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<td>MD</td>
<td>Median</td>
</tr>
<tr>
<td>nCPAP</td>
<td>Nasal Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>PDA</td>
<td>Persistent Ductus Arteriosus</td>
</tr>
<tr>
<td>PPHN</td>
<td>Persistent Pulmonary Hypertension</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SP-A</td>
<td>Surfactant Protein A</td>
</tr>
<tr>
<td>SP-B</td>
<td>Surfactant Protein B</td>
</tr>
<tr>
<td>SP-C</td>
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<tr>
<td>SP-D</td>
<td>Surfactant Protein D</td>
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<tr>
<td>VLBW</td>
<td>Very Low Birth Weight</td>
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<td>WHO</td>
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15. References


OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant--the judgment of OSIRIS. (open study of infants at high risk of or with respiratory insufficiency--the role of surfactant. Lancet 1992;340:1363-69.


