The impact of exogenous surfactant in neonatal Respiratory Distress Syndrome

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Declaration

I hereby declare that:

This thesis has been composed by the candidate.

The meta-analyses in this thesis are the candidate's own work but data has been obtained from published clinical trials.

The study in chapter 10 was carried out with the assistance of Drs Michael Beresford, David Milligan, Ben Shaw, Alan Fenton and Martin Ward Platt, and Professor John Matthews. The candidate was involved in the setting up of the study, responsible for the day to day running of the study with the collection of the data from enrolled infants in the former Northern region and participated in the analysis of the data.

The candidate was awarded the degrees of MB, ChB from the University of Edinburgh in 1988.

This thesis has not been submitted in candidature for any other degree, diploma or professional qualification.

Sean Brian Ainsworth

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Abstract

Among the many advances in neonatal intensive care over the past few decades, few changes can claim to have had an effect on outcomes in low birthweight infants as that of the introduction of exogenous surfactant therapy. Avery and Mead (1959) are generally credited with the discovery that surfactant deficiency leads to respiratory distress syndrome (RDS), but discoveries of the composition, function and physiology of surfactant span the whole of the 20th century.

This thesis reviews the current understanding of surfactant composition and function looking at the early discoveries to the first use of exogenous surfactant therapies and more recently the introduction of "designer" synthetic surfactants.

Several exogenous surfactants are currently available and whilst controlled trials have demonstrated surfactant therapy is better than placebo, there are several unanswered questions that this thesis addresses through a review of existing evidence;

1. Which surfactant preparation is clinically more efficacious
2. The choice between "rescue" (treatment after the development of RDS) or "prophylaxis" (prevention of RDS)
3. How many doses of surfactant are needed and what is the evidence for the size of the doses currently used

Four exogenous surfactant preparations – two synthetic and two animal-derived – have been licensed in the United Kingdom. The development of each surfactant is traced through a review of published trials. Current evidence from comparisons of synthetic and animal-derived surfactants is reviewed and evidence from comparative trials presented in an over-view using meta-analysis. This argument is further examined in a multi-centre randomised controlled trial looking at the effects of ***ALEC*** and ***Curosurf***, the two most commonly used synthetic and animal-derived surfactants used in the UK. The trial was terminated early because of a significantly higher mortality in the ***ALEC*** arm. Results of the trial are discussed in relation to previous synthetic versus animal-derived surfactant trials.

ALEC had been the most frequently used surfactant within the former Northern health region of England until publication of the study results and subsequent withdrawal of the ***ALEC*** by the manufacturer. The implications for neonatal service provision in the region in light of the

results of the ***ALEC*** versus ***Curosurf*** trial are explored using data from the region. This functions as a geographic cohort and has developed a centralised model of neonatal intensive care provision through a collaborative consortium. The impact of neonatal respiratory disease within it is examined with a survey of respiratory support and oxygen supplementation in neonatal provider and non-provider units. Using data from this survey and the ***ALEC*** versus ***Curosurf*** trial this thesis shows how a change in surfactant therapy can have widespread implications for service provision and funding in the region's neonatal units.

Ethics

Ethical approval for the randomised trial between ***Curosurf*** (poractant alfa) and ***ALEC*** (pumactant) was granted by the Northern and Yorkshire Multi-centre Research Ethics Committee, and by the Local Research Ethics Committees of all the hospitals involved in recruitment.

Abbreviations used in this thesis

BPD	Bronchopulmonary dysplasia
CBFV	Cerebral (arterial) blood flow velocity
CLD	Chronic lung disease
CPAP	Continuous positive airways pressure
DPPC	Dipalmitoylphosphatidylcholine
ECMO	Extracorporeal Membrane oxygenation
FiO_2	Fraction of inspired oxygen
HMD	Hyaline membrane disease
IVH	Intraventricular haemorrhage
MAP	Mean airway pressure
NEC	Necrotising enterocolitis
NGH	Newcastle General Hospital
$PaCO_2$	Arterial carbon dioxide concentration
PaO_2	Arterial oxygen concentration
PDA	Patent ductus arteriosus
PIE	Pulmonary interstitial emphysema
PMMH	Princes Mary Maternity Hospital
PPHN	Persistent pulmonary hypertension
PROM	Prolonged rupture of membranes
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
RVI	Royal Victoria Infirmary
TPN	Total parenteral nutrition

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Introduction

Exogenous surfactant therapy has been in widespread clinical use in neonates for nearly a decade. Its introduction was associated with a 30-40% reduction in neonatal mortality in infants at risk of respiratory distress syndrome (RDS) in a group of North American level III neonatal intensive care units (Schwartz *et al* 1994). Complications of RDS, such as pulmonary air leaks, are also reduced (Soll 1999a, Soll 1999b). When it is used in conjunction with antenatal steroids, there is a combined synergistic effect (Jobe *et al* 1993).

Several exogenous surfactants are currently available and are divided into two types according to their origins: animal-derived surfactant extracts and synthetic surfactants. Although all are designed to treat and prevent RDS, these products differ in several ways. Animal-derived surfactants contain proteins and lipids; whereas synthetic surfactants have until recently have been protein-free. Recent developments in molecular biology have led to the development of synthetic protein analogues and recombinant proteins that act in the same way as the naturally occurring surfactant proteins.

Whilst randomised controlled trials have demonstrated surfactant therapy is better than placebo, controversies remain regarding;

1. Whether one surfactant is better than another, in particular whether surfactants that are animal-derived offer clinically better outcomes than currently available protein-free synthetic surfactants
2. Whether there is a gestation or weight limit below which there is no or very little benefit from surfactant treatment
3. The choice between "rescue" (treatment after the development of symptoms of RDS) or "prophylaxis" (prevention of RDS by administering surfactant to all infants at risk of developing it)

This thesis begins with a review of the current understanding of surfactant; its composition, the function and the properties of its components, and the discoveries that led to its development as a therapeutic agent. This is followed by a review of placebo-controlled trials involving the four exogenous surfactant preparations that have been licensed in the United Kingdom. - Artificial Lung Expanding Compound (***ALEC***/pumactant), ***Exosurf*** (colfosceril), ***Curosurf*** (poractant) and ***Survanta*** (beractant). All four surfactants are demonstrably better than placebo but comparative trials between the different surfactants are limited.

The Scottish Health Purchasing Information Centre (SHPIC) had suggested ***ALEC*** should be the choice of surfactant for prophylaxis and ***Survanta*** the surfactant of choice for rescue therapy based published trials and the costs of surfactants (SHPIC report 1996). The report assumed no clinical differences between surfactant types however the fallacy of this view is examined using evidence from trials comparing synthetic and animal-derived surfactants in neonates and the results are presented in an over-view using meta-analysis. This area is further examined in a multi-centre randomised controlled trial looking at the effects of ***ALEC*** and ***Curosurf***, the two most commonly used synthetic and animal-derived surfactants used in the United Kingdom.

Neonatal care is provided in many ways; the former Northern region operates a consortium of neonatal intensive care (provider) units working with several special care baby (non-provider) units. The consortium provides long-term neonatal intensive care for the region's 33,000 livebirths per annum. How this organisation developed into its current status is explored and the impact of surfactant and respiratory distress syndrome within the region is examined. In addition this section examines whether in such an organisation place of birth influences mortality

The final section of this thesis re-examines the area of healthcare resources use in relation to surfactant therapy. ***ALEC*** was voluntarily withdrawn by the manufacturer following publication of the outcomes of the ***Curosurf*** versus ***ALEC*** trial (appendix 2). Using data extrapolated from the study and applying it to the geographically-defined population of the former Northern region of England, it illustrates the potential economic effects of the withdrawal of ***ALEC*** as well as resource implications for cot provision.

Chapter 1

Respiratory Distress Syndrome

1.1 Respiratory Distress Syndrome – an introduction

Surfactant deficiency lung disease in neonates is usually taken to be synonymous with respiratory distress syndrome (RDS). However as knowledge of the aetiology and pathogenesis of RDS have changed various terms have been used in medical literature. Initially RDS was called “hyaline membrane disease”. This is strictly speaking a pathological diagnosis and reflects the formation of a proteinaceous hyaline membrane in the alveoli of the lungs of affected infants. As the condition became increasing recognised as a distinct clinical entity with radiological and clinical features the name changed to idiopathic respiratory distress syndrome. The “idiopathic” part has since become superfluous with greater understanding of the disease and neonatologists use the term RDS to describe respiratory failure that results from a primary surfactant insufficiency.

Some older textbooks refer to two “types” of RDS – types I and II. Type I is that which is associated with surfactant deficiency in preterm infants whereas type II is that seen in more mature infants in whom a diagnostic label of transient tachypnoea of the newborn (TTN) may be used. Whilst the amount of surfactant in infants with TTN may be normal it may not be functioning properly.

A type of RDS also affects older children and adults. This has a different pathophysiology where there is surfactant dysfunction secondary to sepsis or multi-system organ failure. To distinguish the two types the two conditions are sometimes called adult respiratory distress syndrome (ARDS) and infant RDS. Just as with neonatal RDS there is some non-uniformity in nomenclature that can cause confusion, and some authorities use the term “acute” rather than “adult” reflecting the occurrence of the disease across the whole age spectrum.

This thesis concentrates on RDS in the newborn infant. This is an acute pulmonary condition usually, but not exclusively, found in preterm infants. Unless stated otherwise use of the term RDS in this thesis shall refer to this condition. Critical to the pathogenesis of RDS is deficiency of pulmonary surfactant (Avery & Mead 1959). Surfactant lowers alveolar surface tension and prevents alveolar collapse at the end of expiration. Deficiency, or dysfunction, of surfactant results in a reduced functional residual capacity, reduced lung compliance and ventilation perfusion mismatching.

Histologically respiratory epithelial injury occurs with exudation of an eosinophilic proteinaceous material into the alveolar airspaces. This triggers inflammatory cascades and the result is the classical "hyaline membrane disease" appearance (Lauweryns 1970). This hyaline membrane can still seen iin histological specimens despite the use of exogenous surfactant replacement therapy (Pinar *et al* 1994, Toti *et al* 1996). Structural immaturity, oxygen toxicity (free radical disease) and sometimes infection also contribute to the evolving clinical picture over the course of the illness (Jobe 1989).

Most infants with RDS require some respiratory support in the form of supplemental oxygen, continuous positive airways pressure (CPAP) or mechanical ventilation. The classical clinical course is one of deteriorating respiratory failure over the initial 48-72 hours after birth followed by a period of improvement. However this is seen only in infants of approximately 29-32 weeks gestation. In more immature infants, the disease tends to be more severe and mechanical ventilation is almost universally needed. These infants are also more likely to die or to have a prolonged course leading to chronic pulmonary insufficiency – variably called bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD).

1.2 Pulmonary Complications of Respiratory Distress Syndrome

Pulmonary complications of RDS can either be acute or long term. The acute problems are inadequate gas exchange and respiratory failure, pulmonary air leaks (pneumothoraces, pneumoperitoneum, pneumopericardium, pneumomediastinum and pulmonary interstitial emphysema) and death.

In the longer term CLD can be a major problem. Initialy called bronchopulmonary dysplasia (Northway *et al* 1967, Nash *et al* 1967), CLD has several definitions. A widely used definition is that of oxygen dependency at 28 days postnatal age, with (Heneghan *et al* 1986) or without (Tooley 1979) radiological changes. However a clinically more useful definition is that of oxygen dependency at 36 weeks corrected post-menstrual age (Shennan *et al* 1988), this is a better predictor of long-term oxygen dependency and respiratory insufficiency in infancy and later life (Gregoire *et al* 1998) because of the correction for gestation at birth. For example in the trial in reported in chapter 9 of this thesis, 60.4% of infants born between 25-29 weeks who survived to discharge were O_2 dependent at 28 days whereas only 53.8% were O_2 dependent at 36 weeks corrected gestational age.

CLD at 36 weeks predicts long-term respiratory morbidity (Coates 1997) and carries an increased respiratory mortality (Fillmore & Cartlidge 1998). Growth (Johnson *et al* 1998) and neurodevelopmental outcome (Hughes *et al* 1999) may also be adversely affected. Success of treatment strategies for RDS should be judged not only on the reduction of neonatal mortality but also the reduction in morbidity.

The incidence of CLD varies according to the definition used. Most early surfactant trials used a 28 day definition (see chapter 5), although more recent publications have included a 36 weeks corrected definition. This can make comparison over a long period of time difficult (Young *et al* 1999). There are also population differences in the prevalence of CLD; Fenton *et al* (1996a) reported a prevalence of 18.5% in one Canadian province and 6.4% in the Trent Health region in England whereas Young *et al* (1999) reported a prevalence of 25% in North Carolina in the USA. The differences in CLD between these populations may reflect differences in demography as well as medical care.

It is suggested that surfactant therapy and improved neonatal care may have led to an increase in CLD (Parker *et al* 1992, Fenton *et al* 1996b) as a result of increased survival although the proportion of surviving infants with CLD has remained unchanged.

1.3 The history of Respiratory Distress Syndrome

Hyaline membrane disease (HMD), the histopathological equivalent of RDS, was first described by Hockheim (1903), but its nature only became clear when Gitlin & Craig (1956) showed the membrane was formed as a result of exudation of proteinaceous material rather than inspissation of aspirated amniotic fluid.

The diagnosis of HMD/RDS remained primarily pathological until the 1950's when attempts were made to provide a clinically more useful definition. Some infants were noted to be dying from an HMD-like illness yet their autopsies failed to reveal a typical hyaline membrane (Briggs & Hogg 1958). These infants had RDS but were not old enough to have the alveolar leak and transudation that leads to hyaline membrane formation that was suggested as essential for the disease by Blystad *et al* (1951) and Miller & Jennison (1950).

Radiological features of RDS were outlined by Donald & Steiner (1953) as the emphasis changed to clinical and radiological diagnosis, however the term respiratory distress syndrome did not appear until the end of the decade (James 1959). Even then the two terms of HMD and RDS have continued to be used synonymously. Although discoveries regarding the aetiology were beginning to appear Rudolph & Smith (1960) suggested the condition be called "idiopathic" RDS and suggested clinical criteria that would fit the diagnosis.

RDS is a major cause of mortality and morbidity in preterm infants. It affects approximately 1 in 3 infants born before 34 weeks gestation (Roberton 1982). In the former Northern region of England 66% of infants born <32 weeks gestation were ventilated and a further 14% required other respiratory support in the form of continuous positive airway pressure (chapter 10). In 1988 it was estimated to cause over 3000 deaths per year in the USA (Wegman 1989).

Although surfactant is seen to be one of the most important advances in neonatology, there were improvements in mortality that preceded the introduction of surfactant and these probably reflect improvements in both antenatal and postnatal care (Swyer 1993, Schwartz *et al* 1994, Lee *et al* 1999). Antenatally these include improvements of obstetric care (Richardson *et al* 1998), regionalisation of resources (Paneth *et al* 1982, Verloove-Vanhorick *et al* 1988), use of tocolytic agents (largely to delay preterm labour long enough to allow the administration of steroids – Palta *et al* 1998) and antenatal steroids (Crowley 1999).

Postnatal care has been improved by the better understanding of homeostasis, nutrition, respiratory support and surfactant therapy. Successful respiratory support using mechanical ventilators and, later, continuous positive pressure appeared in the late 1960's and early 1970's. However it was not until 1980 that the first report of successful surfactant replacement appeared (Fujiwara *et al* 1980). Even though general improvements in perinatal care were reducing mortality in infants with RDS as shown by Lee *et al* (1999), the widespread introduction of surfactant in America led to a statistically significant drop in mortality in infants who were 750-1749 grams at birth (Schoendorf & Kiely 1997).

1.4 Risk factors for and antenatal influences on RDS

Surfactant deficiency or dysfunction causes disturbance of alveolar gas exchange. This is seen in the various forms of RDS. In the neonatal RDS, surfactant deficiency is a primary problem whereas in adult or acute RDS various disease processes interfere with surfactant production and function (the surfactant dysfunction is secondary to these processes). This explains why exogenous surfactant therapy is less effective in ARDS (Cawley *et al* 1998).

It is recognised that certain risk factors predispose to the development of RDS and that some infants are more at risk than others are. The following have been found to have either a positive or negative influence on RDS:

1.4.1 Prematurity

The biggest factor that predisposes to RDS is prematurity (defined as delivery before 37 weeks post-conception); the more immature the infant the greater the risk of RDS (Farrell & Avery 1975). The influence of prematurity on RDS is multifactorial with immaturity of the lung architecture and cells, as well as immaturity of surfactant production (Holm 1993). Even Avery & Mead (1959) acknowledge this in their important paper.

The lung develops in a series of stages (Hallman & Gluck 1977, Jobe 1997). The embryonic stage (0-5 weeks post-conception) sees budding of the lung from the foregut and formation of the early branches. The fetal stage occurs between 5 weeks to full term. Lungs become potentially viable gas exchange units during the canalicular phase (weeks 16-25) as airways and capillaries develop (Hislop & Reid 1974). Saturated phosphatidylcholine is produced from type II cells with functional lamellar bodies around 20 weeks gestation. Alveoli increase from around 30×10^6 at 28 weeks gestation to 150×10^6 at term during the terminal sac stage (Hislop *et al* 1986). Surfactant replacement therapy is also less effective at lower gestation (Battin *et al* 1998) suggesting that overall immaturity of lungs plays an important role in the morbidity and mortality in these infants.

The composition of surfactant changes with increasing fetal maturity and this is reflected in the declining incidence of RDS as the fetus approaches term (Farrell & Avery 1975). Changing surfactant composition can be observed through analysis of fetal lung fluid and amniotic fluid; these may be used clinically to estimate fetal lung maturity (Field & Gilbert

1997). The lecithin/sphingomyelin (L/S) ratio reported by Gluck & Kulovich (1972) remains the commonest used.

Lecithin (phosphatidylcholine) levels are measured relative to sphingomyelin, which is a general membrane lipid. Sphingomyelin levels remain relatively constant throughout fetal development until 32 weeks gestation when they fall, while lecithin levels rise. A value of 2.0 for the L/S ratio (normally achieved from 35 weeks gestation) is generally taken to equate to "mature" surfactant and RDS is unlikely, between 1.5 to 2.0 surfactant is "immature" but the risk of RDS is low. Below 1.0 the risk of RDS increases (Gluck *et al* 1974). Developmental changes in other surfactant phospholipids and proteins have also been documented both in normal (Kulovich *et al* 1979) and complicated pregnancies (Kulovich & Gluck 1979).

1.4.2 Gender

Male fetuses are at higher risk (1.4:1) of developing RDS than females of the same gestation, and are more likely to die as a result (Farrell & Avery 1975, Perelman *et al* 1986, Schwartz *et al* 1994). There is a relative delay in the maturation of surfactant in the male fetus reflected in the L/S ratio and appearance of phosphatidylglycerol (Fleisher *et al* 1985, Zachman *et al* 1989). In rabbits this delay in maturation is thought to be related to androgens in the male fetus (Kotas & Avery 1971).

1.4.3 Ethnicity

There is evidence particularly from multiracial areas that ethnic origin may affect both the risk of and outcomes from RDS. It has long been recognised that Afro-Caribbean infants have a lower incidence of RDS than Caucasian infants (Fujikura *et al* 1966). It appears that compared to Caucasian infants, they have a faster rate of lung maturation (Olowe *et al* 1978) although there is some question of whether this is true for very preterm infants (Robillard *et al* 1994).

The issue is complicated by the fact that Afro-Caribbean infants have a systematic tendency to be born at lower gestational ages and to weigh less at birth than Caucasian infants (Kleinman & Kessl 1987, Lyon *et al* 1994). When these factors are taken into account, blacks of African but not Caribbean descent have a lower incidence of RDS than Caucasian infants (Kavvadia *et al* 1998). It is possible that racial differences in the incidence of RDS may reflect genotype susceptibility (section 1.4.7).

1.4.4 Method of delivery

The influence of delivery method is somewhat controversial particularly with regard to the preterm infant. Most early studies (Usher *et al* 1964, Fedrick & Butler 1970, Usher *et al* 1971) but not all (Strang *et al* 1957) support the view that caesarean section performed without labour increases the risk of RDS.

Data on infants of gestations greater than 32 weeks also support this view (Cohen & Carson 1985, Morrison *et al* 1995, Shrivastava *et al* 1999). Confounding variables, such as maternal illnesses, premature rupture of membranes and infection make data on immature infants of ≤32 weeks gestation less clear. But when taking these variables into account it would seem that caesarean section without labour increases the risk of RDS in the very preterm infant (White *et al* 1985, Bryan *et al* 1990).

There are two main physiological reasons for an association between caesarean section and RDS. Firstly, immediately prior to the onset of labour there is a surge in adrenaline in the fetus (Faxelius *et al* 1983), leading to a reduction in the amount of lung fluid (Walters & Oliver 1978) and an increase in both production and secretion of surfactant (Corbet *et al* 1977, Enhörning *et al* 1977, Kanjanapone *et al* 1980). Secondly, during labour itself there is release of surfactant into the airways (Callen *et al* 1979).

Infants born by elective caesarean section have a lower L/S ratio in pharyngeal aspirates (Whittle & Hill 1980), have larger residual volumes of lung fluid (Milner & Vyas 1982) and secrete less surfactant in the period following delivery (Lawson *et al* 1977). With a smaller reserve of endogenous surfactant these infants are therefore potentially more susceptible to insults that affect surfactant function.

1.4.5 Perinatal asphyxia

Infants who are compromised at birth are at increased risk of RDS (Linderkamp *et al* 1978, Thibeault *et al* 1984). Even in the absence of RDS, severe perinatal asphyxia adds to respiratory morbidity (Thibeault *et al* 1984). The acidosis of perinatal asphyxia does not cause RDS (Kenny *et al* 1976), but increasing acidosis affects choline synthesis and reduces surfactant phospholipid metabolism (Merritt & Farrell 1976).

In preterm infants the combination of an immature L/S ratio and asphyxia are more predictive of RDS, than an immature L/S ratio alone. A 5-minute Apgar score ≤5 (Jones *et al* 1975) and a poor umbilical arterial pH (Tejani & Verma 1989), both markers of perinatal asphyxia, are associated with a higher risk of RDS in preterm infants. In preterm infants with a mature L/S ratio asphyxia can precipitate RDS (Worthington & Smith 1978).

Hypoperfusion-reperfusion injury is thought to be the mechanism behind asphyxia and surfactant dysfunction. Hypoperfusion leads to ischaemia of the fetal lung and is followed by hyperperfusion after delivery and resuscitation (Dawes & Mott 1962). The alveolar capillaries become damaged and proteinaceous fluid leaks into the alveolar space (Davis & Stafford 1964, Jeffries *et al* 1984). Thus asphyxiated infants respond less well following exogenous surfactant (Skelton & Jeffrey 1996).

1.4.6 Maternal diabetes mellitus

A widely held, but not universal (Usher *et al* 1971), view is that maternal diabetes increases the risk of RDS (Robert *et al* 1976). Evidence of delayed maturation of surfactant, particularly of phosphatidylcholine (Cunningham *et al* 1978, Ojomo & Coustan 1990) and the L/S ratio (Kulovich & Gluck 1979) support this view. More recent data shows that strict diabetic control reduces the incidence of RDS to that seen in non-diabetic controls (Mimouni *et al* 1987).

Analysis of surfactant components provides conflicting evidence. Lung phospholipids in amniotic fluid from both term diabetic and non-diabetic pregnancies are not different (Amon *et al* 1986). However even when the phospholipids are normal, abnormalities of the surfactant proteins may occur (Katyal *et al* 1984). All this suggests that the influences of maternal diabetes on surfactant maturation are at very best incompletely understood.

Malformations rather than RDS are currently the largest cause of death in the infant of a diabetic mother (Gabbe *et al* 1978). Whilst the mortality rate of infants of diabetic mothers has declined from 250 per 1000 live births in the 1960s to a 20 per 1000 live births in the 1980s. Major congenital malformations are found in 5-8% of infants of diabetic mothers, and these are responsible for 50% of perinatal deaths (Weintrob *et al* 1996).

1.4.7 Familial and genetic factors

Familial factors play a role in several ways. Inherited deficiency of surfactant protein B (SP-B) has been reported in term infants with alveolar proteinosis (Nogee *et al* 1993, Ball *et al* 1995). A number of different gene mutations have been recognised (Nogee *et al* 1994, Nogee 1998) and can cause either a full or partial deficiency of this important surfactant protein (Klein *et al* 1998). Affected infants present at all gestations with a severe and intractable RDS-like illness that responds poorly to exogenous surfactant.

Even without SP-B deficiency, up to 19% of infants with RDS have a sibling who was also affected (Lankenau 1976). This does not just reflect gestation at birth; infants of the same gestation are more likely to have RDS if their sibling also had RDS (Nagourney *et al* 1990). Evidence from linkage studies suggests that there is a "susceptibility" gene for RDS that is linked to the HLA antigens HLA-A3 and HLA-B14 (Hafez *et al* 1989), and it is this that may account for interracial differences in the incidence of RDS.

From a maternal point of view, a woman who has had one previous preterm infant is at an increased risk of subsequent pregnancies terminating prematurely (Graven & Misenhiemer 1965, Basso *et al* 1999). The risk is also increased after a previous spontaneous abortion (Basso *et al* 1998) or if the mother herself was premature (Porter *et al* 1997). Some of this may be attributable to a short cervix and cervical incompetence (Goldenberg *et al* 1998).

The locus for human surfactant protein A has been mapped to chromosome 10 and consists of two classes of functional genes (White *et al* 1985, Katyal *et al* 1992) and one pseudogene sequence (Korfhagen *et al* 1991). The product of each functional SP-A gene appears to be required for stable mature SP-A (Voss *et al* 1991); the DNA sequences for these have been denoted 6A and 1A. There are several allelic variants of the SP-A 6A (gene 1) and some appear to be important in the predisposition to RDS (Ramet *et al* 2000).

1.4.8 Multiple pregnancy

Infants born as a result of a multiple pregnancy are likely to be more immature and generate a disproportionately greater workload for obstetricians and neonatologists than singletons (Nielsen *et al* 1997).

There seems to be some disagreement whether individuals from the same multiple pregnancy are at greater risk of RDS. Wolf *et al* (1992) and Gardner *et al* (1995) could not find any increased RDS compared to singletons. On the other hand, Caspi *et al* (1980) suggested both twins are at greater risk than singletons, whereas others (Weller *et al* 1976, Dobbie *et al* 1983, Leveno *et al* 1984) have argued that only the second twin is at increased risk of RDS. Surfactant maturation is accelerated in the presenting twin and may explain the increased risk in the second twin (Obladen & Gluck 1977).

The second twin is also more likely to be intubated, to need resuscitation, to have lower 5 minute Apgar scores, and to have more nursery complications (Prins 1994). However the increased risk of RDS in the second twin, if there is one, cannot be entirely explained by perinatal asphyxia (Arnold *et al* 1987). Triplets seem to be at no further risk than twins of the same gestation (Sassoon *et al* 1990).

Multiple pregnancies resulting from in-vitro fertilisation (IVF) techniques generate even more problems than spontaneous multiple pregnancies; IVF mothers had more pregnancy-induced hypertension, premature labour and preterm delivery; IVF infants had lower birthweights and shorter gestations (Tallo *et al* 1995). Much of the increased workload relates to the multiplicity of the pregnancy than the fact it was IVF (Wisanto *et al* 1996). Surviving IVF infants had longer hospitalisations, more days of oxygen therapy, more days of continuous positive airway pressure, and increased prevalence of respiratory distress syndrome, patent ductus arteriosus, and sepsis (Tallo *et al* 1995). Beyond the neonatal period, surviving IVF infants are no more likely to use, or importantly overuse, healthcare resources than other infants (Leslie *et al* 1998).

Antenatal steroids, used to good effect in reducing the severity of RDS (see below) appear to be less beneficial in twins (Turrentine *et al* 1996). The reasons for this are not clear.

1.4.9 Hypothermia

A major danger following preterm delivery is rapid heat loss from a small wet body with a large surface area-volume ratio. Despite textbooks on neonatal resuscitation emphasising thermoregulation in the preterm infant (Royal College of Paediatrics & Child Health 1997), hypothermia (temperature $<35^{o}C$) on admission to neonatal units has always been problematic (Stanley & Alberman 1978, Loughead *et al* 1997). Hypothermia independently increases the risk of RDS in an "at risk" population (Stanley & Alberman 1978), and increases the risk of complications of prematurity among RDS-affected infants (Herting *et al* 1992).

1.4.10 Prolonged rupture of membranes

Yoon & Harper (1973) first proposed the protective nature of prolonged rupture of membranes (PROM) in RDS, and a number of studies (Chiswick 1976, Sell & Harris 1977, Curet *et al* 1984, Bryan *et al* 1990, Suidan & Baassiri 1990) have supported their findings. Acceleration of the maturation of the surfactant surface tension reducing properties occur within 72 hours of membrane rupture in most infants with PROM between 29-37 weeks gestation (Salzer *et al* 1980).

Other studies have disagreed with the findings. James *et al* (1975) and Papageorgiou *et al* (1981) could find no evidence of an effect on either the incidence of RDS or its severity. Berkowitz *et al* (1976) found a reduction of RDS in infants ≤32 weeks gestation born ≥16 hours after the rupture of membranes but not in infants >32 weeks. The same investigators later refuted this finding and decided there did appear to be a protective effect in the more mature infant (Berkowitz *et al* 1978). Hallak & Bottoms (1993) suggested that PROM was associated with increased risk of RDS, especially if there was co-existing chorioamnionitis, but pointed out that gestational age, gender and birthweight were more important determinants than PROM. Overall evidence suggests PROM in the absence of infection having a protective affect against RDS, although the effect is small and other factors, such as gender and gestation, have a much greater influence (Mead 1980).

Very prolonged rupture of membranes presents problems other than RDS, particularly if the period between rupture and delivery extends for several days, as hypoplasia of the developing lungs may intervene. Wigglesworth *et al* (1981) reported that lungs which are hypoplastic as a result of oligohydramnios are also structurally and biochemically immature for gestational age. The authors suggest that the maturation arrest may be specifically related to failure of retention of fetal lung liquid and the earlier the rupture occurs the greater the likelihood of severe maturation and growth arrest.

The time from rupture of membranes to delivery is usually less than 48 hours at term, however in preterm fetus this period is inversely related to gestational age (Merenstein & Weisman 1996). Mid-trimester premature rupture of the membranes is uncommon (approximately 0.65% of all pregnancies) yet is associated with high perinatal morbidity (Schucker & Mercer 1996). The subsequent neonatal course may be very variable. Oligohydramnios with <1cm vertical pocket of amniotic fluid for 14 days is associated with >90% mortality (Kilbride *et al* 1996). Death from pulmonary hypoplasia is more a problem following preterm prolonged membrane rupture than ascending infection. (McIntosh & Harrison 1994).

Pulmonary hypoplasia is not inevitable even after prolonged periods of membrane rupture (McIntosh & Harrison 1994), and the major determining factor is whether or not the amniotic fluid pool is large enough to prevent it. The more immature the fetus at the time of membrane rupture the greater the risk of oligohydramios (Lauria *et al* 1995).

1.4.11 Chorioamnionitis

Recent evidence focussing on the presence of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), the interleukins IL-1 and IL-8 (Kotecha 1996, Jonsson *et al* 1997, Hallman 1999, Speer 1999) and low-grade infection of the chorion with organisms such as *Ureaplasma urealyticum* (Patterson *et al* 1998) suggests that these have a protective effect against RDS. However the initiation of inflammatory cascades leads ultimately to CLD that is out of proportion to the severity of the RDS (Watterberg *et al* 1996). As a result the infants seem to have mild to moderately severe RDS and require little in the way of respiratory support but then develop severe CLD. This pattern of CLD has a very different aetiology compared to that described by Northway *et al* (1967) when positive pressure ventilation was a major factor.

1.4.12 Antenatal steroid therapy

While investigating the physiology of parturition, Liggins (1969) was the first to observe the acceleration of lung maturity following administration of glucocorticoids to fetal lambs. This observation led to the first randomised-controlled trial of antenatal steroids in humans (Liggins & Howie 1972). Two hundred and eighty two mothers were enrolled in threatened preterm labour at 24-37 weeks gestation. Neonatal mortality was reduced from 11.2% in the control group to 6.0% in the treatment arm, and the incidence of RDS among infants <32 weeks gestation reduced from 69% to 11%.

Many more trials of antenatal steroids have followed. But despite evidence from these and several excellent systematic reviews (Sinclair 1995, Crowley 1995) and the NIH Consensus Conference (1995) obstetricians have been slow to adopt this beneficial treatment. The reasons behind this were unclear (Crowley 1999).

Antenatal steroids act by triggering surfactant maturation. All components of surfactant are induced by antenatal steroid therapy (Ballard 1989), and antenatal steroids enhance the maturation of type II pneumocytes (Snyder *et al* 1981). There appears to be a synergistic effect between antenatal steroids and postnatal surfactant (Jobe *et al* 1993) and protein leakage into alveoli is diminished (Ikegami *et al* 1987).

Antenatally endogenous cortisol levels rise progressively during the last trimester (Donaldson *et al* 1991), and appear to parallel the changes in L/S ratio (Murphy *et al* 1978). Infants with RDS frequently show an improvement in their lung function after 48-72 hours, a timing consistent with accelerated surfactant production in response to a stress-mounted cortisol surge. Despite this postnatal hydrocortisone failed to show any benefit (Baden *et al* 1972), suggesting that antenatal influences are more important in determining outcome from RDS.

The main problem is getting steroids to the "at risk" population in time. Many women do not reach maternity units in time for the antenatal steroid to be of benefit (Golden *et al* 1998). In addition there has been a reluctance of obstetricians to routinely administer steroids in the face of ruptured membranes (Gardner *et al* 1997).

The other major question regarding antenatal steroids centres around their effect on fetal growth, particularly whether more than one course of steroids has a greater impact on long-term outcome. As a result there is a wide variation in obstetric practice across the country (Brocklehurst *et al* 1999).

1.4.13 Antenatal thyrotropin-releasing hormone (TRH) therapy

Liggins was also instrumental in the discovery and development of antenatal thyrotropin-releasing hormone (TRH) in prevention of RDS. Using preterm lambs, Liggins and his co-workers demonstrated an increase in lung phospholipids after antenatal TRH administration (Schellenberg *et al* 1988) and that TRH could work synergistically with antenatal steroids

(Liggins *et al* 1988).

Since then a number of trials examining TRH, both alone and in conjunction with antenatal steroids, in a human population have been performed (Morales *et al* 1989, Ballard *et al* 1992, Knight *et al* 1994, The ACTOBAT Study Group 1995, Ballard *et al* 1998, Collaborative Santiago Surfactant Group 1998). However in a recent Cochrane meta-analysis (Crowther *et al* 2000), the view was that currently TRH could not be recommended for clinical practice. The meta-analysis demonstrated neither a reduction in neonatal mortality nor a reduction in the incidence of chronic lung disease, whereas side-effects were frequently reported in the mothers.

1.4.14 Antenatal ambroxol

Ambroxol, a metabolite of bromhexine (an anti-histamine used in older children and adults as an expectorant or mucolytic drug) has been used predominantly in centres across Europe to promote fetal lung maturation. Animal models had suggested that this drug was a suitable alternative to antenatal steroids (Egberts *et al* 1976, Van Petten *et al* 1978). It appears to work by causing an increase in the amounts of dipalmitoylphosphatidylcholine (DPPC), however later work suggests that the increase may be small (Sun *et al* 1992).

Several studies have examined the effects of ambroxol in a human population. Some of the studies that have shown benefit have either included mature infants (Wauer *et al* 1982) or involved small numbers of infants (Kimya *et al* 1995). In a later, and larger, trial (Wauer *et al* 1992) ambroxol reduced the 28 day incidence of CLD and intraventricular haemorrhage. Luerti *et al* (1987) demonstrated that ambroxol may be as effective as antenatal steroids in singleton pregnancies and may be more beneficial in twin pregnancies. On the other hand Dani *et al* (1997) could not demonstrate any benefit in their trial.

Overall it would appear that ambroxol has yet to be shown to be more beneficial that antenatal steroids. Ambroxol does have one major drawback in comparison to steroids in that 5 days of treatment are required compared to 2 days for steroids.

1.4.15 Antenatal aminophylline

Animal models had suggested that antepartum administration of aminophylline might be as effective as antenatal steroids in the prevention of RDS and two randomised trials showed a reduction in the incidence of RDS (Hadjigeorgiou *et al* 1979) and in perinatal mortality (Granati *et al* 1984). However later studies suggested that the beneficial effect of aminophylline can be attributed largely to a combination of accelerated fetal growth and improved postnatal regulation of breathing rather than a specific influence on the biochemical and functional maturation of the lung (Cosmi *et al* 1986). Furthermore concerns regarding the narrow therapeutic index of aminophylline have led to this therapeutic approach being abandoned (Papageorgiou & Stern 1986).

1.5 Conclusion & summary

Surfactant deficiency in the neonate manifests clinically as respiratory distress syndrome (RDS). This was previously known as hyaline membrane disease (HMD) because of the histopathological findings in affected infants who died. It is a major cause of respiratory morbidity in infants born before 30 weeks post-conception, leading to both acute and chronic complications.

There are many antenatal and perinatal influences that affect RDS, but the primary problem is one of insufficiency and immaturity of surfactant production in affected infants. The observation of acceleration of lung maturity following administration of glucocorticoids in preterm lambs by Liggins (1969) led to one of the major therapeutic interventions in treatment of RDS.

The other therapeutic intervention, exogenous surfactant therapy, although commonplace in neonatology today, came about because of discoveries that span most of the 20th century. These are recounted in the next chapter. This discusses early papers leading to the landmark study of Avery & Mead (1959) that linked surfactant deficiency and RDS; through the unsuccessful trials in the 1960's of simple surfactants; culminating in the report by Fujiwara *et al* (1980) of the first successful use of exogenous surfactant in a neonate.

Chapter 2

Surface tension, surfactant and the lung

2.1 Surface tension in the lung

It is the presence of a large air-tissue interface in the lungs that leads to tension at that interface and causes the lung to collapse. This interface occupies an area of $2.8m^2$ in the term newborn infant, and increases proportionally to growth so that by adulthood it occupies $75m^2$ (Dunnill 1962). The area is also affected by the number of alveoli, which number around 24×10^6 at birth, increasing to 300×10^6 in the adult. There is however wide variation in alveolar numbers among individuals, related to height and genetic factors (Dunnill 1962, Angus & Thurlbeck 1972).

Surfactant accumulates at the air-tissue interface. Surfactant reduces the surface tension, thereby stabilising alveoli and small airways against collapse and atelectasis on expiration (helping to maintain the residual volume of the lung) and promoting expansion on inspiration (reducing the work of breathing). Reduction of surface tension is the primary, but not only, role of surfactant (these roles are discussed, particularly in relation to the surfactant proteins, in chapter 3).

When alveoli collapse an increasing amount of pressure is required to open them again; this leads to the genesis of shearing forces at the air-liquid interface within the walls of the airways causing inflammation and tissue damage. As a result of tissue damage there is leakage of a pink staining proteinaceous material into the epithelial lining and the airways. This material forms a "hyaline membrane" and led to the alternative term for RDS of hyaline membrane disease (or HMD).

2.2 Surface tension and the law of Laplace

The relationship between surface tension, the size of the airspace (alveolus) and the pressure needed to maintain the shape may be demonstrated using the law of Laplace for thin walled spheres:

$$P = 2\delta / r$$

Where: δ is the surface tension
r is the radius of the bubble
P is the pressure required to maintain a radius of r in the bubble.

In circumstances where surface tension is high, a higher pressure is required to produce the same size sphere. Applying this model to the alveolus in the absence of surfactant where the surface tension is 72 mN/m^2, a trans-surface pressure of approximately 28cm H_2O is required to maintain a radius of 50 micrometers. Translated to a human lung this means that in the absence of surfactant it would be necessary to apply 28cm H_2O of positive end expiratory pressure to maintain an adequate functional residual capacity (Figure 1).

Using the law of Laplace like this is an over-simplification. Because of interconnections in the interstitium, collapse of one alveolus leads to the expansion of other alveoli in the vicinity. It is however a useful concept to think in terms of what happens at single alveolar level and one that is used in the *in vitro* comparisons of surface tension reduction between various surfactants (chapter 7).

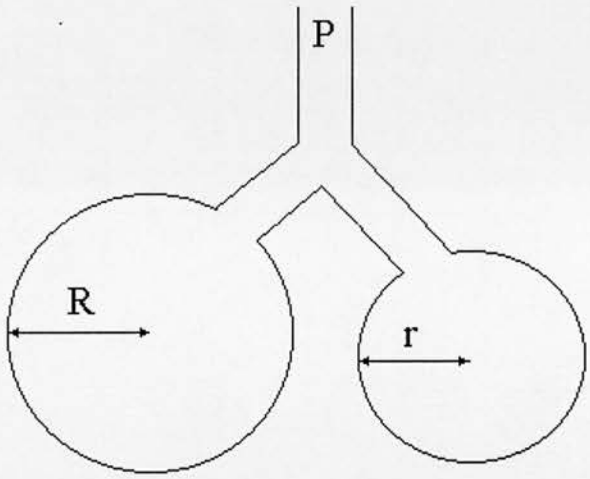
2.3 Early discoveries of surfactant

The discoveries that led to the development of surfactant and its use in neonatal respiratory distress syndrome span most of the twentieth century.

In the 1920's the Swiss scientist Kurt von Neergaard demonstrated the importance of surface tension in the expansion of lungs of newborn infants. His work, entitled "*New notions on a fundamental principle of respiratory mechanics: the retractile force of the lung, dependent on the surface tension in the alveoli*" (von Neergard 1929) was the first to suggest that surface tension played a role in the lungs. Using dog and pig lungs he demonstrated that the pressure required to inflate an atelectatic lung was greater if a gas, such as air or oxygen, was used than if the lung was inflated using saline or another liquid.

von Neergard explained his findings by saying there was surface tension at the air-tissue interface developing menisci that prevented the air passing into the alveoli: using a liquid abolished the air-tissue interface. Gruenwald (1946), using lungs from fresh stillborn human infants and infants who died within three days of birth, repeated this experiment and reached a similar conclusion.

Figure 1: The alveolus and the law of Laplace ($P = 2\delta / r$)



The pressure (P) required to keep the alveolus of radius r open, is inversely proportional to the radius (r) and is directly proportional to the surface tension (δ). Although the law of Laplace is useful to understand the relationship between pressure and surface tension, it must be remembered alveoli are not spherical and are connected to other alveoli and other structures. Collapse of one alveolus will have an effect on the neighbouring alveoli causing these to expand, which then reduces the tendency to collapse in the original alveolus.

In this idealised diagram of two alveoli, it can be demonstrated that using the law of Laplace the pressure required to keep the large alveolus (with radius R) open is less than that required to keep the small alveolus open. Consequently with a pressure of P in the absence of surfactant there is a tendency for small alveoli to collapse and larger alveoli to hyperinflate.

Surfactant reduces the surface tension in smaller alveoli to prevent some of the atelectasis that would otherwise occur. Smaller air sacs are comparatively stable during expiration and are recruited effectively during inspiration. This implies that alveolar surface tension is not constant but instead varies as a function of alveolar radius during respiration.

There followed a number of discoveries regarding alveolar lung fluid, both in terms of its composition, and in terms of differences between infants who died from RDS and those who died of other causes. However it was not until much later that Avery & Mead (1959) unified the various discoveries.

Thannhauser *et al* (1946) reported that lung fluid contains a high proportion of dipalmityl lecithin (dipalmitoylphosphatidylcholine or DPPC). However no connection was made regarding the presence of DPPC and alveolar stabilisation. Later Pattle (1955) was to demonstrate that alveolar fluid bubbles from cut surfaces of lungs taken from infants dying of non-respiratory causes shrank and then stabilised for a period of time. The alveolar fluid bubbles from infants who died after developing RDS were different: these failed to last as long in a stable state before disintegrating.

Using the Wilhelmy-Langmuir balance to measure surface tension-lowering properties of surfactant films, Clements (1957) showed that when compressed to a small volume, lung fluid molecules exerted a high surface pressure preventing further compression. In turn this meant that surface tension was very much reduced. He and his colleagues also suggested that the surface tension of surfactant varied according to the compression (Clements *et al* 1957).

The Enhörning Pulsating-Bubble Surfactometer, developed in the 1960's, offered an alternative to the Wilhelmy-Langmuir method for analysing surface tension reduction by pulmonary surfactant (Enhörning *et al* 1965). This was devised as a model of the alveolus and used the measured pressure difference across a spherical air bubble of a known radius to calculate surface tension. The bubble is then pulsated (typically at a speed of 20 cycles per second) between a maximum and minimum pressure that cause a 50% change in surface area. It is possible to calculate the surface tension (δ) using the law of Laplace ($P = 2\delta/r$). A similar surfactometer was devised by Boyle & Mautone (1982) and was used by Scarpelli *et al* (1992) to compare different surfactants (chapter 7).

Avery & Mead (1959) are generally credited with the discovery that surfactant deficiency is central to the pathogenesis of RDS. They also used the Wilhelmy-Langmuir balance. They found that the surface tension reducing property of surfactant obtained from infants dying from RDS was less than if the surfactant had been obtained from an infant dying from non-respiratory causes. This difference between extracts from the lungs of infants with and without RDS was not limited to those who died but also those who had respiratory failure (Reynolds *et al* 1965).

2.4 Early trials of exogenous surfactant

Following on from the findings of Avery & Mead (1959), and their own earlier work, Clements and co-workers organised a clinical trial measuring various aspects of lung function in infants with respiratory distress syndrome. They looked at DPPC as a surfactant replacement. This was aerosolised into the lungs of the affected infants. The results of the study were disappointing. Chu *et al* (1967) reported, "*our findings do not agree well with the suggestion that the syndrome results from the primary lack of pulmonary surface-active material*".

The lack of success in this trial and an earlier Canadian trial (Robillard *et al* 1964) was due to the use of pure DPPC. It was not realised that DPPC requires other phospholipids in order to function as a surfactant in humans. DPPC used in these trials simply lacked appropriate additives to address this problem. Later research found that:

- At body temperature, DPPC is a gelatinous solid (Morley *et al* 1978).
- Nebulisation of surfactants causes the formation of micelles that do not release their phospholipids well (Morley *et al* 1978).
- Pure DPPC requires too long to form a monolayer at the air-liquid interface (Bangham *et al* 1979).
- When it does, the monolayer gives a surface tension reading greater than natural surfactant (Bangham *et al* 1979).

A later trial of nebulised surfactant involving the addition of phosphatidylglycerol (PG) to the aerosolised solution of DPPC in a ratio of 1:9 did however produce improvements in gas exchange of treated infants (Ivey *et al* 1976). Research into nebulised surfactant still continues; Dijk *et al* (1997) suggest that this route lessens the risk of hypotension and reduced cerebral blood flow seen after intratracheal boluses of surfactant. However Fok *et al* (1998) argue that so little surfactant reaches the alveoli after nebulisation that there is no clinical effect, and hence no effect on blood pressure.

Despite the lack of success in these early surfactant trials there was increasing evidence that surfactant deficiency was indeed central to the pathogenesis of respiratory distress syndrome. Gluck *et al* (1967) showed DPPC was produced in increasing quantities in the developing lung and that it was secreted into the alveolar space. King & Clements (1972) analysing canine surfactant found DPPC is the major component of surfactant lipid.

After the failure of nebulised artificial surfactant in the 1960's work concentrated on finding other ways to administer surfactant, initially in experimental animals, and later in human infants. Enhörning & Robertson (1972) reported the first successful exogenous surfactant. They instilled surfactant, obtained from the alveolar washings of adult rabbits, in the trachea of prematurely delivered rabbit pups and measured airway pressures and volumes. Treating the rabbits with this surfactant produced pressure-volume curves that resembled those obtained from mature lungs.

Enhörning *et al* (1975) later showed deposition of small volumes of adult rabbit surfactant in the pharynx of premature rabbit pups improved both survival and lung expansion (shown radiologically). Twenty-one of 26 treated rabbits survived compared with only 4 of 23 controls. Of the four surviving controls there was poor lung expansion in two animals whereas in the surfactant treated group lung expansion was generally good.

The first successful use of exogenous surfactant therapy in human infants was reported by Fujiwara *et al* (1980). A modified bovine lung extract made from minced lung tissue was administered endotracheally to preterm infants with RDS between 4 and 33 hours of age (mean age at administration 12 hours). All ten infants in this uncontrolled trial showed improved oxygenation and a shortened duration of radiologically apparent RDS compared to untreated historical controls. Eight of the ten infants survived. Of the deaths, one occurred at 36 hours of age, the other at 30 days of age (due to chronic lung disease and sepsis).

2.5 Conclusion

The 20th century has seen many advances in the understanding of surfactant composition and how the components interact to give surfactant its wide range of biological functions. The composition and function of the components of surfactant are discussed in chapter 3. The development of exogenous surfactants as therapeutic agents arose following the work of Avery & Mead (1959) that linked surfactant deficiency and RDS and although Fujiwara *et* *al* (1980) published the first report of successful endogenous surfactant in a neonatal population several groups of investigators had independently developed exogenous surfactants from a variety of sources. These preparations and their origins are discussed in chapter 4.

Chapter 3

The composition of surfactant

Introduction

Studies of surfactant composition in reptiles (Daniels *et al* 1995) and air-breathing fish (Smits *et al* 1994) show some similarities. Surfactants in these animals are, like mammalian surfactant, phospholipid-based and suggest a common evolutionary pathway. The exact phospholipids however differ, reptiles having phosphatidylcholine (DPPC) but no phosphatidylglycerol (PG), whereas the air-breathing fish have higher cholesterol contents. Lung surfactant is very similar but not identical across several mammalian species (Possmayer *et al* 1984). This has allowed researchers to extrapolate their findings from animal models of RDS to the human infant.

There are two main fractions of surfactant: lipids and surfactant-specific proteins. In mature human surfactant lipids account for approximately 90%, and of these the majority are phospholipids. This chapter examines the composition and functions of both these surfactant components, however it begins by looking at the cells that are responsible for the production of surfactant within the lungs – the type II pneumocyte.

3.1 The type II pneumocyte

Macklin (1954) postulated that these cells, which he called "granular pneumocytes", secreted material that reduced the surface tension at the air-surface interface, enhanced the clearance of inhaled particles, was bacteriostatic and helped in the prevention of transudation of proteinaceous fluids into the alveolus. Although he did not realise it at the time these are some of the functions of surfactant as they are currently understood.

The major function of type II pneumocytes is the synthesis and secretion of surfactant. Lamellar bodies of type II cells contain all the lipid and protein components of surfactant (Barritussio *et al* 1994). There is a constant re-cycling process involving type II cells involving both the intracellular (lamellar bodies) and extracellular pools of surfactant (Hallman *et al* 1981).

A lesser known function of type II cells is that of regeneration of a continuous epithelium after alveolar injury. Type II cell hyperplasia occurs after a variety of injuries, all of which damage type I pneumocytes (Adamson & Bowden 1974, Evans *et al* 1975). Type I cells are larger than type II cells (810 μm^3 versus 340μm^3) and also have a greater (4000 μm^2 versus

70 μm^2) luminal surface area (Weibel 1974). This makes the type I cell ideal for gas exchange but very vulnerable to damage. In addition type I cells are devoid of ribosomes and mitochondria which are necessary for most cellular repair processes.

3.2 Surfactant phospholipids

Phosphatidylcholine is the most abundant phospholipid and comprises 70-80% of the total amount of lipid in surfactant (Batenburg 1992). Most phosphatidylcholine is saturated with one or two palmitic acid chains. The disaturated form DPPC accounts for 54.7 ± 3.9% of mature surfactant in infants without RDS (Poets *et al* 1997).

Phosphatidylglycerol (PG) is the next most abundant lipid in mature human surfactant, accounting for approximately 8% of the phospholipid (Poets *et al* 1997). This is a relatively high concentration of this substance that is otherwise only present in tissues as a low concentration substrate for cardiolipin (diphosphatidylglycerol) production. Cardiolipins are phospholipids that are found throughout the body, especially in muscles and the heart (Hatch 1996). Cardiolipin is localised primarily in the mitochondria and appears to be essential for the function of several enzymes of oxidative phosphorylation (Hoch 1992).

Other surfactant phospholipids are phosphatidylethanolamine (5% of phospholipids), phosphatidylinositol (3%), and small quantities of sphingomyelin, phosphatidylserine and lysophosphatidylcholine (Goerke 1974). Cholesterol accounts for 2.4% of surfactant composition by weight (Possmayer *et al* 1984). The phospholipid composition of the intracellular pool of surfactant is very similar to that in the extracellular compartment (Jobe *et al* 1980, Oulton *et al* 1986, Adachi *et al* 1989). This would suggest that there are no major alterations of the composition of the surfactant once it is extruded into the alveolus from the type II pneumocyte.

There is general consensus that DPPC is the primary surface-active component (Ikegami *et al* 1979, Batenburg 1992). It is thought to exert its physiological function by lowering surface tension at the end of expiration to values <10 mN/m^2 (Clements 1977). Pure DPPC does not adsorb rapidly to the air-tissue interface at physiological temperatures (Notter *et al* 1982, King & Clements 1972) nor does it spread well (Bangham *et al* 1979, Notter *et al* 1980) and the other phospholipids may improve these functions *in vivo*.

The role of other phospholipids is less certain. Unsaturated phosphatidylcholine may aid in spreading and rapid adsorption at the air-tissue interface (King & Clements 1972). It is suggested that the DPPC component of surfactant changes throughout each compression and expansion cycle (Holm *et al* 1996) and that the more "fluid" components (predominantly unsaturated phosphatidylcholine and other phospholipids) are preferentially "squeezed out" to further reduce surface tension at small volumes (Notter & Finkelstein 1984, Yu & Possmayer 1992a). The surfactant proteins SP-B and SP-C are involved in the cyclical changes of phospholipid concentrations that occur during the respiratory cycle, although the nature of the involvement has not been fully explained (Taneva & Keough 1994, Putz *et al* 1999).

The anionic phospholipids, phosphatidylinositol (PI) and phosphatidylglycerol (PG), appear to have similar functions but their quantitative contributions to the surface active function of surfactant is unclear (Beppu *et al* 1983, Hallman *et al* 1985a). Low PG levels are found in immature surfactant of humans (Hallman *et al* 1976) and rats (Egberts & Noort 1986). Newborn term rabbits have very little PG, this appears shortly after birth, and coincides with a decline in the amount of PI, yet these rabbits do not get RDS (Hallman & Gluck 1980).

In preterm human infants PI is produced in preference to PG, and PG levels increase with increasing maturity (Hallman & Gluck 1976). The situation is not uniform among all species. Levels of PI remain high in mature surfactant of the rhesus monkey (Egberts *et al* 1987), guinea pig (Khan *et al* 1985) and cat (Shelley *et al* 1984). Despite the differences with regards to the relative amounts PI and PG levels, surface tension-lowering properties of surfactants *in vitro* containing one but not the other are similar (Hallman *et al* 1985a).

3.3 Surfactant-associated proteins

Four surfactant-associated proteins have been described. These can be usefully divided into two groups: the hydrophilic surfactant proteins SP-A and SP-D, and the hydrophobic surfactant proteins SP-B and SP-C. These are described in detail below.

The importance of these proteins is probably best emphasised by the lethal nature of SP-B deficiency (Nogee *et al* 1994, Ball *et al* 1995) and that experimental knockout of the SP-B gene in transgenic mice produces respiratory distress syndrome (Clark *et al* 1995). Nonetheless the currently available synthetic surfactants do not contain any surfactant proteins, yet are seen to be clinically effective in preterm infants. The endogenous surfactant that is present, albeit in smaller amounts than in term infants, presumably supplements the exogenous surfactant and enhances the surface-active properties *in vivo* (Holm 1993).

To explore the interaction between the biological system and exogenous surfactant Ikegami *et al* (1993) instilled ***Exosurf***, ***Survanta*** and a non-commercial protein-free surfactant in the lungs of preterm lambs. After 5 hours surfactant was recovered by lavage and analysed. It was composed of a mixture of exogenous and endogenous surfactant. In all cases, recovered surfactant was more effective when instilled in experimental rabbits compared with the original surfactant. This reinforces the notion that endogenous surfactant systems need to be taken into account when studying experimental therapeutics, for example in comparisons between different surfactants.

Although there is great structural and compositional similarity between surfactants of different species there remains the potential for immunological reactions when giving exogenous surfactant to preterm infants (Merritt *et al* 1988, Strayer *et al* 1989, Strayer & Robertson 1992). However to date there has been no evidence of disease that can be attributed to the surfactant-anti-surfactant complexes that are known to be formed (Strayer *et al* 1986).

3.3.1 Surfactant-associated protein A (SP-A)

SP-A was the first surfactant-associated protein to be discovered (King & Clements 1972) but it was not isolated until much later (Phizackerley *et al* 1979). It is the most abundant of the surfactant proteins accounting for approximately 50% (Sueishi & Benson 1981).

SP-A and SP-D are members of the family of C-type (calcium-dependent) lectins, or collectins (collagenous lectins). The collectins are a group of soluble multimeric lectins, which contain collagenous segments, and resemble the complement protein C1q in aspects of their structures and functions. This group of proteins, which includes mannose binding protein, SP-A, SP-D, conglutinin and CL-43, are known to act as opsonins in various circumstances, and are likely to have roles in innate immunity (Malhotra *et al* 1994).

The common structural feature of the collectins is that they are composed of an elongated collagen-like part with a globular head containing a carbohydrate recognition domain. The genes for the human collectins are found in a cluster on chromosome 10 (Crouch *et al* 1993, Fisher *et al* 1987). There are two functional SP-A genes (Katyal *et al* 1992) and both appear to be required for the formation of mature SP-A (Voss *et al* 1991). SP-A can be detected in endogenous surfactant from as early as 16 weeks gestation (Ballard *et al* 1986) and however its levels begin to increase proportionate to gestation after 28 weeks (Batenburg & Hallman 1990).

SP-A is a large octadecameric protein with a total molecular weight of about 650 kDa (Voss *et al* 1988). It is composed of a hexameric structure where each monomer is composed of three polypeptide chains. There is a short cysteine-containing part at the N-terminus that is involved in interchain disulphide bonding (Ross *et al* 1991). This is connected to a collagen-like segment, a short neck region and then the carbohydrate recognition domain. The carbohydrate recognition domain contains two interchain disulphide bridges (Haagsman *et al* 1989) forming two disulphide-dependent loops. The octadecameric SP-A molecule is about 20 nm from the N-terminus to the peripheral parts of the carbohydrate recognition domain, and these are separated by up to 28 nm (Voss *et al* 1988).

The putative functions of SP-A are summarised in Table 1. SP-A is not directly involved in the surface tension lowering role of surfactant, but it may be involved in the regulation of this (Schürch *et al* 1992). Although SP-A does not appear to have a function in the spreading and adsorption of the monolayer, there is evidence that it is important in the formation of tubular myelin (de Mello *et al* 1993). Tubular myelin is a distinctive cross-hatched bilayer microstructure that is seen when aqueous suspensions of surfactant are examined using electron microscopy. It is formed by interaction between phospholipids and surfactant associated proteins. Tubular myelin is thought to give the maximal adsorption of endogenous surfactant to the air-liquid interface (Magoon *et al* 1983). The formation of tubular myelin is also thought to be central to the regulation of lipid insertion into the monolayer. These properties of SP-A are dependent on the presence of calcium (Haagsman *et al* 1990).

Table 1: Summary of the putative functions of surfactant-associated protein A (SP-A).

Formation of tubular myelin
Regulation of phospholipid insertion into the surfactant monolayer
Modulation of uptake and secretion of phospholipids by type II pneumocytes
Activation of alveolar macrophages
Binding and clearance of bacteria
Binding and clearance of viruses
Chemotactic stimulation of alveolar macrophages

Table 2: Summary of the putative functions of surfactant-associated protein D (SP-D).

Activation of alveolar macrophages
Agglutination of bacteria
Protection again non-bacterial micro-organisms and viruses
Regulation of phospholipid homeostasis
Role in phosphatidylinositol metabolism

SP-A is located at the corners of the structural lattice of tubular myelin (Voorhout *et al* 1991) and the formation of the lattice is dependent on SP-A (Suzuki *et al* 1989). Transgenic mice with SP-A deficiency showed normal respiratory function and survival but no tubular myelin (Korfhagen *et al* 1996).

The addition of SP-A to hydrophobic surfactant enhances *in vitro* phospholipid adsorption (Chung *et al* 1989); in particular SP-A has a high affinity for DPPC (Kuroki & Akino 1991). Addition of SP-A to ***Curosurf*** did not improve the *in vitro* biophysical surface tension lowering properties, however when this modified surfactant was given to experimental rabbits in a dose of 100mg/kg there were improvements in the lung-thorax compliance that were only seen when twice the dose of non-modified surfactant was used (Sun *et al* 1997). Clearly there is some interaction between SP-A and the surface-active components of surfactant that cannot be demonstrated in an *in vitro* setting (Hallman *et al* 1991).

Tubular myelin and SP-A may be important in preventing the inactivation of surfactant by serum proteins. SP-A has been shown to reverse the inhibition of surface activity of phospholipids *in vitro* (Cockshutt *et al* 1990). ***Curosurf*** with added SP-A was more resistant to inactivation by meconium, fibrinogen, albumin and serum proteins than unmodified ***Curosurf*** (Sun *et al* 1997). Bruni *et al* (1996), comparing ***Survanta***, ***Exosurf*** and a porcine-derived surfactant containing surfactant proteins SP-A, SP-B and SP-C, found ***Survanta*** and ***Exosurf*** were inactivated to a greater extent after exposure to human serum than the porcine-derived surfactant.

It appears that SP-A also has a role in the modulation of uptake and secretion of phospholipids by type II cells. SP-A binds specifically to these cells (Kuroki *et al* 1988) and has been shown to inhibit secretion of phosphatidylcholine from them (Rice *et al* 1987). Re-uptake of phospholipids in isolated type II cells also appears to be regulated by SP-A (Bates *et al* 1994) although it appears that this process may be dependent on local concentrations of phospholipids and SP-A than on a specific phospholipid receptor on the type II cell (Haagsman *et al* 1993). Clearance of surfactant is also undertaken by alveolar macrophages and this too is mediated by SP-A (Wright & Youmans 1995).

That SP-A is involved in lung defence is demonstrated by the fact human SP-A obtained from lavage of lungs affected by alveolar proteinosis enhances the host defences of rat alveolar macrophages (van Iwaarden *et al* 1990). SP-A surface interactions are also required to release oxygen radicals from the alveolar macrophages (Weissbach *et al* 1994) and SP-A has also been shown to act as a chemotactic factor for alveolar macrophages (Wright & Youmans 1995).

The role of SP-A in host defence is further shown by its ability bind to some bacterial pathogens that infect lung tissue. SP-A acts as an opsonin through the carbohydrate binding region. The opsonisation process is selective; *Staphylococcus aureus* is opsonised but not *Streptococcus pneumoniae* (McNeely & Coonrod 1993). In the absence of opsonisation SP-A also potentiates the antimicrobial activity of the alveolar macrophages (Kremlev *et al* 1994) through the stimulation of cytokines modulating inflammatory cell function in the lung and immunoglobulin production (Kremlev & Phelps 1994). Opsonisation of viruses has also been reported (van Iwaarden *et al* 1991, Benne *et al* 1995).

SP-A may also be protective against chronic lung disease as baboons with hyperoxic and infection induced chronic lung disease were found to have a relative SP-A deficiency (King *et al* 1995).

3.3.2 Surfactant -associated protein D (SP-D)

SP-D was the most recently identified of the surfactant-associated proteins. There has been some debate whether it should be considered a true surfactant protein or not; it has no known role in lung surfactant biophysics although it plays an important role in lung defence. About 70% of the SP-D is recovered from the supernatant of lavaged lung surfactant whereas the other proteins are recovered from the lipid-containing surfactant pellet (Kuroki *et al* 1991). SP-D has also been detected (along with SP-A and SP-B) in gastric mucosa, which is also known to secrete a surface-active material (Eliakim *et al* 1989, Eliakim *et al* 1991, Fisher & Mason 1995).

SP-D is a C-type lectin like SP-A, and shares many structural similarities. The gene for SP-D is found on chromosome 10 (Crouch *et al* 1993). Mature human SP-D contains 355 amino acids and weighs 43 kDa (Lu *et al* 1993). Electron microscopy suggests SP-D has a homogeneous quaternary structure in the form of a cross (Crouch *et al* 1994). Four identical rods of triple collagen-like helices emanate from the central point and terminate in the carbohydrate recognition domain (Lu *et al* 1993). Thus SP-D is essentially a tetramer consisting of twelve polypeptide chains with a total molecular mass of 630 kDa.

The functions of SP-D within the surfactant system have not been fully elucidated. It does not seem to have a role in the surface tension lowering effect of surfactant and most of its putative functions relate to lung defence (Table 2).

It has been demonstrated that SP-D binds to the lipopolysaccharides of several bacteria (*Escherichia coli*, *Klebsiella pneumonia*, *Salmonella paratyphi* and *Pseudomonas aeruginosa*) but not to *Staphylococcus aureus* (Kuan *et al* 1992, Lim *et al* 1994). The shape of SP-D gives it the ideal configuration for binding to bacteria with the carbohydrate recognition domains spanning a long distance (Kuan *et al* 1992). It can also bind to alveolar macrophages and induce the production of free oxygen radicals (Miyamura *et al* 1994).

Evidence that SP-D may play a role in non-bacterial lung defence has come from patients suffering from human immunodeficiency virus (HIV) infection where pulmonary surfactant abnormalities can be found. These are worsened by co-infection with *Pneumocystis carinii* infection (Escamilla *et al* 1992). During *P. carinii* infection SP-D accumulates in the lung (Limper *et al* 1994), and augments the binding of the *P. carinii* organism to alveolar macrophages (O'Riordan *et al* 1995).

SP-D also binds with phosphatidylinositol in a calcium-dependent manner (Ogasawara *et al* 1992). The importance of this interaction is unclear, in mature human surfactant phosphatidylinositol accounts for only 3% of the phospholipids. SP-D appears to play a role in the homeostasis of surfactant phospholipid; transgenic SP-D (-/-) mice have abnormal accumulations of surfactant phospholipid (Korfhagen *et al* 1998).

3.3.3 Surfactant-associated protein B (SP-B)

Phizackerley *et al* (1979) were the first to describe the presence of hydrophobic surfactant proteins in lung surfactant. Currently two proteins are known, SP-B and SP-C. Their structure and functions have been investigated in detail. They are soluble in organic solvents such as chloroform-methanol (Pérez-Gil *et al* 1993) and therefore are retained in the extraction processes of the animal-derived surfactants (chapter 4).

Both proteins are synthesised within the type II alveolar cells and undergo extensive intracellular modification because of their hydrophobic nature (Voorhout *et al* 1992, Beers & Lomax 1995). The close functional relationship of SP-B with SP-C is demonstrated by abnormal functioning of SP-C in congenital SP-B deficiency (Vorbroker *et al* 1995). The genes for SP-B are found on chromosome 2 (Pilot-Matias *et al* 1989) and SP-B deficiency may be due to a one of a number of SP-B gene mutations (Nogee *et al* 1994).

SP-B is a small protein of 79 amino acids with a high cysteine content (Curstedt *et al* 1990). The cysteine residues form a unique disulphide pattern of three intermolecular bonds and one intermolecular bond. These stabilise the protein and form a dimeric form of SP-B (Johansson *et al* 1991).

The most important function of SP-B is the enhancement of the surface tension reducing properties of the surfactant lipids, but other functions have been described (Table 3). SP-B greatly enhances the formation of a stable surface film (Oosterlaken-Dijksterhuis *et al* 1991a, Oosterlaken-Dijksterhuis *et al* 1991b). Positive charges within the SP-B protein are essential for this (Cochrane & Revak 1991) as it interacts with the negatively charged PG promoting adsorption of the phospholipids (Yu & Possmayer 1992b).

SP-B, together with SP-A, is necessary for the formation of tubular myelin (Poulain *et al* 1992). In SP-B deficiency there is an abundance of alveolar multilamellar structures but no tubular myelin (de Mello *et al* 1994). It is thought that SP-B promotes the formation of contact sites between bilayers in tubular myelin enabling flow of phospholipids between bilayers. SP-B may also protect against the inactivation of surfactant by serum proteins (Amirkhanian *et al* 1993).

Addition of SP-B increases the inter- and intra-molecular ordering of the phospholipid membranes (Cochrane & Revak 1991). A single monomeric SP-B molecule influences 50-70 phospholipid molecules (Shiffer *et al* 1993).

Table 3: Summary of the putative functions of surfactant-associated protein B (SP-B).

Promotion of phospholipid insertion into the air-tissue (liquid) interface
Formation of tubular myelin
Protection from inactivation by serum proteins
Influence on molecular ordering of phospholipid monolayer

Table 4: Summary of the putative functions of surfactant-associated protein C (SP-C).

Promotion of phospholipid insertion into the air-tissue (liquid) interface
Alteration of proportion of phospholipids components to alter surface tension lowering properties at smaller volumes
Regulation of phospholipid ordering

3.3.4 Surfactant-associated protein C (SP-C)

SP-C was the second hydrophobic surfactant protein to be identified. It is a small polypeptide of 35 amino acid residues. There are two genes for SP-C that can be found on chromosome 8 (Glasser *et al* 1988). It is highly hydrophobic due to the high content of valine residues (Johansson *et al* 1994a). These are present in two thirds of the molecule that forms a regular α-helix (Johansson *et al* 1994b), the long axis of this helix being orientated parallel to the acyl chains of the phospholipids (Vandenbussche *et al* 1992).

Both monomeric and dimeric forms of SP-C can be found in surfactant. The properties of the two forms are probably different (Karaborni *et al* 1994), although the exact role each form plays has not been clarified.

SP-C functions are broadly similar to SP-B (Table 4). Its major role is the stimulation of insertion of the phospholipids into the air-tissue interface in a calcium-dependent manner (Oosterlaken-Dijksterhuis *et al* 1991a). This process is preceded by the SP-C dependent binding of phospholipid to the monolayer (Oosterlaken-Dijksterhuis *et al* 1991b). At high pressures SP-C seems to be squeezed out of the monolayer (Keough *et al* 1994) and when this occurs each molecule of SP-C takes with it 8-10 phosphatidylcholine molecules. This raises the possibility that SP-C may alter the composition of the monolayer and thus alters surface tension according to volume (Taneva & Keough 1994).

In mixtures of SP-C and phospholipid the protein alters the arrangement of the lipid bilayers (Williams *et al* 1991), and monolayers (Pérez-Gil *et al* 1992). This probably helps the stabilisation of the phospholipids within the alveolus.

3.4 Other proteins/polypeptides in surfactant

Recently three heptapeptides have been isolated from ovine surfactant (Brogden *et al* 1996). These contain a core of several aspartate residues and are bactericidal to *Pasteurella haemolytica*. However the synthesis and exact functions of these small peptides have yet to be delineated although it is suspected that they interact with other lung defences (Brogden *et al* 1998). Similar polypeptides have been found to be present in porcine surfactant. These are the prophenins and are derivatives of the cathelicidin family of antibacterial peptides (Wang *et al* 1999). Interestingly these polypeptides are preserved by the usual methods for extracting the animal-derived lung surfactants and may be responsible for some of the antibacterial action seen with some exogenous preparations (Sherman *et al* 1994).

3.5 Conclusion

Endogenous surfactant is a complex mixture of substances and current understanding of it is incomplete. Surfactant has a role beyond reduction of surface tension. Knowledge of the role of the surfactant-associated proteins is increasing, and it may be possible that they have important roles to play in the prevention of chronic lung disease (King *et al* 1995).

Exogenous surfactant replacements are by contrast very simple, especially the synthetic surfactants ***ALEC*** and ***Exosurf***. It is unlikely that current exogenous surfactants replicate the full range of properties seen with endogenous surfactant. What appears to be more likely is that exogenous surfactant supplements the components of the endogenous surfactant.

The various surfactant preparations that have been reported in the literature are summarised in chapter 4, and those that have become available commercially in the United Kingdom examined in greater detail in chapter 5.

Chapter 4

The surfactant era

Introduction

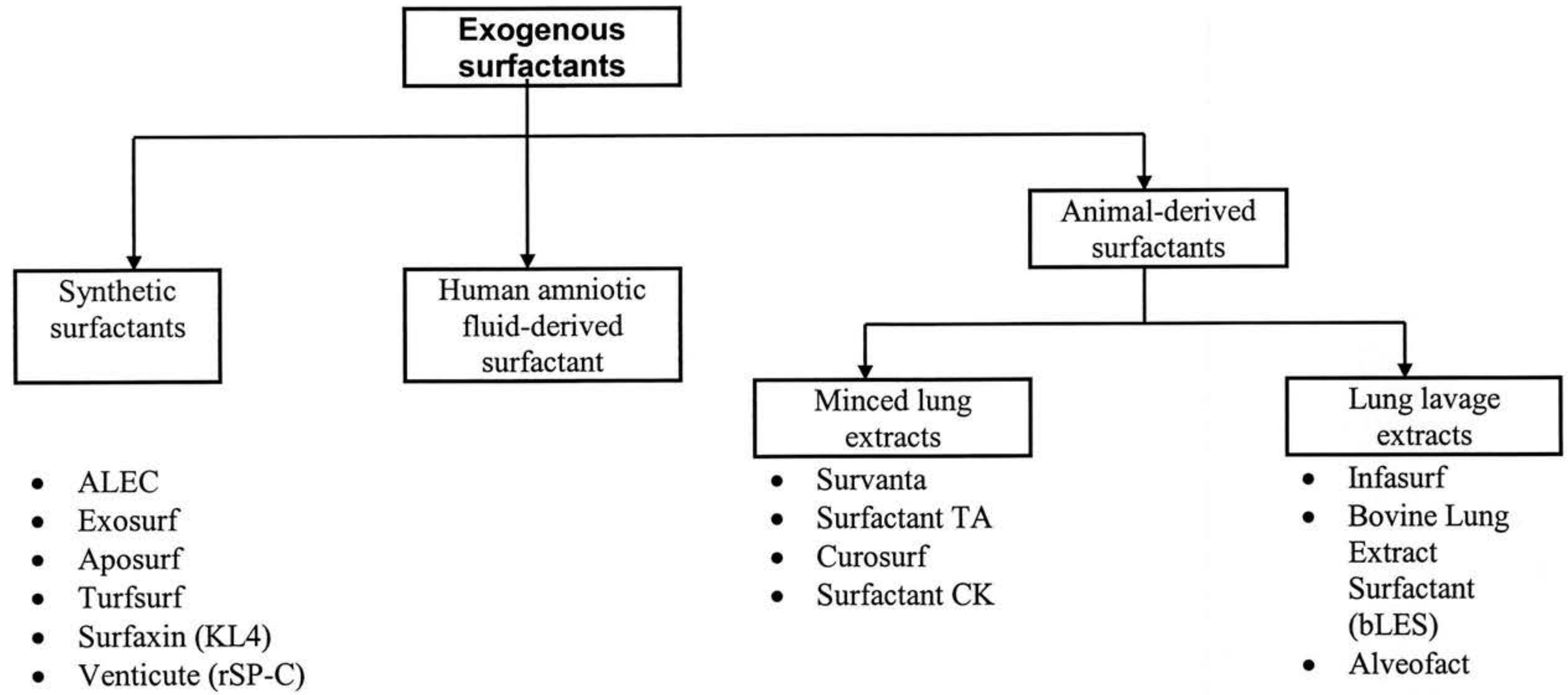
The work by Fujiwara *et al* (1980) had demonstrated that exogenous surfactant replacement could produce beneficial improvements in infants with RDS. During the early 1980's several groups of researchers developed exogenous surfactants and published their results. Surfactants can be classified as those of animal or human origin ("natural" surfactant extracts) or those that are wholly synthetic (Table 5).

4.1 Extracts of naturally-occurring surfactants

The modified bovine lung surfactant used by Fujiwara and co-workers has undergone several modifications since the original report and has been developed for clinical use as a lyophilised powder called ***Surfactant TA/Surfacten*** (Tokyo Tanabe, Tokyo, Japan). The surfactant extract is removed from finely ground bovine lung through a series of differential centrifugation and flotation steps. Neutral lipids (predominantly cholesterol) are removed by using ethyl acetate. The surfactant is then extracted using chloroform-methanol. This lung surfactant extract is then supplemented with synthetic phospholipids to give a final product that contains approximately 84% phospholipids, 7% tripalmitin, 8% palmitic acid and 1% protein (Fujiwara & Robertson 1992). This supplemented surfactant extract is then sterilised by high pressure filtration and lyophilised. The lyophilised ***Surfactant TA*** is reconstituted prior to use in saline to give a concentration of 30 mg/ml of phospholipids.

Following the report by Fujiwara *et al* (1980) Drs M Avery and W Taeusch visited Japan and took samples of ***Surfactant TA*** back with them to the United States of America. Following this ***Surfactant TA*** became available more widely as a result of licensing agreement between Tokyo Tanabe and Abbott Laboratories under the name ***Survanta*** (beractant, Abbott Laboratories, Chicago, USA). It was launched in the United Kingdom in 1993. Both ***Surfactant TA*** and ***Survanta*** are made in the same way and are similar in composition. It is important to note that both have additional phospholipids added after the extraction process thus they are essentially a "modified natural-derived surfactant" rather than a "natural surfactant". The only differences between ***Surfactant TA*** and ***Survanta*** are that the latter is available as a suspension of 25 mg/ml (and not 30mg/ml) of phospholipids and undergoes a terminal autoclave sterilisation process.

Table 5: Classification of exogenous surfactants by origin.



SF-RI 1 (***Alveofact***; Boehringer, Ingelheim, Germany) is another bovine surfactant extract. It was developed and tested in mainland Europe (Gortner *et al* 1990a, Gortner *et al* 1990b). It differs from beractant in that it is obtained lavage of intact rather than minced cow lungs. Nonetheless chloroform-methanol extraction features in its manufacturing process. It consists of approximately 99% phospholipids and neutral lipids (including 4% cholesterol) and 1% surfactant associated proteins SP-B and SP-C.

Two calf lung surfactant extract (CLSE) preparations have been developed. The first called ***Infasurf*** (Forrest Pharmaceuticals, St Louis, USA) was developed in the United States (Notter *et al* 1985). ***Infasurf*** is lavaged from the lungs of freshly killed calves and then extracted using chloroform-methanol. There is some variation in the composition of different batches of ***Infasurf***, and as a result reports of the composition do vary. A representative composition (expressed as a percentage of dry weight) is phospholipids 94% (of which 79% is phosphatidylcholine [63.2% DPPC] and 6% phosphatidylglycerol), cholesterol and cholesterol esters 4% and surfactant associated proteins SP-B and SP-C 1% (Kendig *et al* 1989).

The other calf lung surfactant extract was developed in Canada. Its use was first reported by Smyth *et al* (1983) and later in a randomised clinical trial by Enhörning *et al* (1985). It is not available currently in the United Kingdom, but has been commercially developed in Canada by bLES Biochemicals Inc. (Ontario, Canada) and marketed under the name ***bLES*** (bovine lipid extract surfactant). It has recently been compared to ***Exosurf*** in a randomised trial (Peliowski *et al* 1998). Like ***Alveofact***, ***bLES*** is a chloroform-methanol extract of surfactant isolated after centrifugation of lung lavage from intact cows lungs. However an addition extraction step using acetone is used to reduce the amounts of cholesterol and other neutral lipids. After this acetone extraction step, ***bLES*** contains 98-99% phospholipids (79% of which is phosphatidylcholine) and 1% surfactant associated proteins SP-B and SP-C.

Poractant (***Curosurf***; Chiesi Farmaceutici S.p.A., Parma, Italy) has also been widely studied; this was developed in Europe and is isolated from minced porcine lungs by a process of washing, chloroform-methanol extraction and liquid gel chromatography (Noack *et al* 1987). Poractant contains 99% polar phospholipids and 1% surfactant-associated protein. Pursuant to a license agreement in 1991, Ares-Serono became the exclusive European licensee for ***Curosurf***, except in Italy where Chiesi markets the product itself. The composition of

Curosurf is shown more fully in chapter 5. It contains a higher percentage of tissue-derived phophatidylethanolamine and sphingomyelin, and less phosphatidylcholine than lavaged surfactant extracts.

A chloroform-methanol extract of lavaged porcine lung, ***surfactant CK***, was one of the first surfactants to be used clinically. It was shown to have beneficial effects on lung function when administered to preterm infants in uncontrolled studies in the early 1980's (Kobayashi *et al* 1981, Nohara *et al* 1983). It has never been developed commercially.

A homologous (human) surfactant has also been developed and tested (Hallman *et al* 1983, Hallman *et al* 1985b, Merritt *et al* 1986, Merritt *et al* 1991). This is derived from term amniotic fluid, which contains considerable amounts of surfactant. Amniotic fluid is collected and processed in a sterile fashion with the active surfactant fraction being obtained through density gradient separation and centrifugation. The final preparation contains 80-83% phospholipids and 5% surfactant-associated protein (Hallman *et al* 1983). This material currently represents the only surfactant replacement therapy of human origin and contains all the surfactant-associated proteins. The donors are tested to ensure human viral agents are not transmitted in the preparation. The major disadvantage of this type of surfactant is the difficulty in harvesting enough for widespread utilisation. Uncontaminated amniotic fluid from 100 births is required to make just 1 gram of surfactant phospholipids (Robertson 1987).

4.2 Synthetic surfactants

Pumactant (***Artificial Lung Expanding Compound*** or ***ALEC***; Britannia Pharmaceuticals, UK) is a synthetic surfactant containing only the phospholipids, DPPC and PG. It was developed and tested in the United Kingdom (Bangham *et al* 1984, Morley *et al* 1988, Ten Centre Study Group 1987). It is discussed in greater detail in chapter 5.

Colfosceril (***Exosurf neonatal***; Burroughs Wellcome Co, California, USA) another synthetic surfactant was developed in America by John Clements and co-workers. It is composed of DPPC (84.5%), with hexadecanol (9.5%) and tyloxapol (6%) added to facilitate dispersion within the lung. ***Exosurf*** has been widely tested in North America. These early trials are discussed in detail in chapter 5.

Turfsurf or the "Belfast surfactant" was reported (Halliday *et al* 1984). This was a mixture of DPPC and high density lipoproteins in a ratio of 10:1. It has not been developed commercially and is no longer in clinical use.

Aposurf was reported in a comparison with two porcine lung surfactant extracts (of which one was ***Curosurf***) in a rabbit model of RDS. ***Aposurf*** was "reconstituted" from isolated low molecular weight apoproteins, synthetic DPPC and dipalmitoylphosphatidylglycerol (DPPG). It was found not to be as effective in the animal model as the natural surfactant extracts and has not been made commercially (Robertson *et al* 1988).

A recent development in synthetic surfactants, ***Surfaxin*** (KL4 or lucinactant, Discovery Laboratories, Inc. Pennsylvania, USA.) has been reported (Revak *et al* 1996, Cochrane *et al* 1996) but has undergone only phase I and II clinical trials. KL4 refers to the 21 amino acid polypeptide sequence of lysine (K) and leucine (L) in a synthetic peptide that resembles the periodic pattern of hydrophobic and hydrophilic residues found in the N-terminal part of surfactant-associated protein B (SP-B) (Gustafsson *et al* 1996). KL4 is added to phospholipids (DPPC, palmitoyloleoyl phosphatidylglycerol and palmitic acid). This synthetic peptide forms a transmembrane α-helix in surfactant-like lipids and like SP-B accelerates the spreading of the surfactant.

With improvements in recombinant technology it has become possible to manufacture synthetic versions of SP-C. The most widely studied preparation contains a recombinant 34 amino acid analogue of human SP-C (Byk Gulden Pharmaceutical, Konstanz, Germany). Three amino acids differ in this analogue compared to human SP-C – phenylalanine is substituted for cysteine in positions 4 and 5, and isoleucine for methionine in position 32. The rSP-C is added to phospholipids (DPPC, palmitoyloleoyl phosphatidylglycerol and palmitic acid) to give 2% by weight in the final preparation. This surfactant has been shown to be as effective as the current animal-derived surfactants in a rat model of ARDS (Hafner *et al* 1998). A second recombinant SP-C that does not have the amino acid substitutions is also under investigation for clinical use, this is sometimes designated rSP-C$(Cys)_2$.

The major distinguishing feature between natural (animal- or human-derived) and synthetic surfactants is the presence of surfactant-associated proteins in the natural products. To some extent the synthetic peptide in ***Surfaxin*** and the recombinant SP-C in rSP-C surfactant mimic the structure and function of hydrophobic surfactant proteins. All animal-derived surfactants contain SP-B and SP-C. Human amniotic fluid-derived surfactant contains all the surfactant-associated proteins (SP-A, SP-B, SP-C and SP-D).

4.3 Conclusion

Several exogenous surfactant preparations have been developed and available commercially. Early placebo controlled trials (those relating to the four surfactants available in the United Kingdom are discussed in greater detail in chapter 5) showed surfactant therapy reduces neonatal mortality and early respiratory morbidity. Nationally a significant reduction in neonatal mortality in North America was attributed to the widespread introduction in surfactant at the beginning of the 1990s (Schoendorf & Kiely 1997). Nonetheless there are several outstanding questions regarding the use of surfactant therapy in neonates:

1. Which surfactant is best?

The main argument here revolves around whether animal-derived surfactants that more closely resemble human surfactant offer any advantages over synthetic surfactants. This question was first asked in the early 1990s and despite several large randomised controlled trials comparing animal-derived and synthetic products (reviewed in chapter 8), and meta-analyses of these trials (Halliday 1996, Soll 1999c), a clear answer has yet to emerge. However these trials between animal-derived and synthetic surfactants concentrated on the exogenous surfactants that are in widespread use in North America (namely ***Survanta*** or ***Infasurf*** against ***Exosurf***), whilst the market leaders for synthetic and animal-derived surfactants in the United Kingdom are ***ALEC*** and ***Curosurf***.

2. How much surfactant should be given?

In clinical trials of surfactant the dose of phospholipids used varies from as little as 25 mg irrespective of birth weight (Morley *et al* 1981) to 200 mg/kg (Collaborative European Multicenter Study Group 1988, Collaborative European Multicentre Study Group 1991, Bevilacqua *et al* 1993, Halliday *et al* 1993). These doses have very little scientific basis, although as research in surfactant and surfactant deficiency progressed it has become evident that a term infant who has been allowed to adapt to extra-uterine life has a surfactant pool size of approximately 100 mg/kg (Jackson *et al* 1986). Although there is some scientific basis for the dose of surfactants used (most use a phospholipid dose of 100mg/kg), only three clinical trials compare different doses. These are reviewed in chapter 6.

3. When should surfactant be given?

Evidence has emerged that early or prophylactic administration of surfactant is more efficacious than treatment given once RDS has become established. Evidence from animal studies and clinical trials is examined in chapter 6. It is becoming clearer that earlier treatment with surfactant, whether given prophylactically to every infant at risk of RDS or as early rescue therapy in those showing clinical signs of RDS, is associated with a better outcome in terms of mortality and short-term respiratory morbidity (Morley *et al* 1997, Soll & Morley 1999, Yost & Soll 1999).

Chapter 5

Surfactants available in the United Kingdom

Introduction

There are currently four exogenous surfactant preparations available commercially in the United Kingdom – ***ALEC*** (Britannia Pharmaceuticals Ltd.), ***Curosurf*** (marketed by Serono Laboratories Ltd. pursuant to a licensing agreement with Chiesi Farmaceutici SpA. of Italy), ***Exosurf*** (Wellcome Laboratories) and ***Survanta*** (Abbott Laboratories). These surfactants vary widely in their constituents (Table 6).

This chapter traces the development of each of these surfactants and the early trials that led to their widespread acceptance on neonatal units. The placebo-controlled trials of each surfactant are analysed in meta-analyses to give some idea of the benefits that may be expected with each surfactant.

5.1 Artificial Lung Expanding Compound (ALEC / pumactant) Britannia Pharmaceuticals

5.1.1 Development and early trials of ALEC

ALEC is a synthetic surfactant developed in Cambridge, England during the 1980's. The initial trials used dry powder consisting of dipalmitoylphosphatidylcholine (DPPC) and phosphatidylglycerol (PG).

To avoid the problems of using pure DPPC (a gelatinous solid at body temperature, liquefying only at 41°C), PG was added to give the desired properties of rapid spreading and reduction of surface tension (Bangham *et al* 1979). The dry powder was thought to be superior to a liquid formulation, as it was believed the phospholipids in the liquid would form micelles and not be released to the lung surface. In a separate study the in-vitro (physiological) surface properties of the dry surfactant were shown to be superior to the current reconstituted ***ALEC*** both when stored at 37°C and at 4°C (Takahashi *et al* 1994).

Table 6; Composition of surfactants available in the United Kingdom.

Surfactant	*ALEC*	*Curosurf*	*Exosurf*	*Survanta*
PHOSPHOLIPIDS	DPPC 70% Phosphatidylglycerol 30%	Phosphatidylcholine 60-80% (of which DPPC at least 40%) Acidic phospholipids 10-15% (Phosphatidylserine, phosphatidylinositol, phosphatidylglycerol) Lysophosphatidylcholine ≤ 4% Other phospholipids < 20%	DPPC 84% Hexadecanol Tyloxapol	88-90% phospholipids (of which DPPC approx. 57%) Free fatty acids6%
SURFACTANT ASSOCIATED PROTEINS	None	SP-B and SP-C proteins 1.0 ± 0.5%	None	SP-B and SP-C proteins 1.0%
OTHER		Phosphatidylethanolamine, sphingomyelin Cholesterol and triglycerides ≤ 2%		0.2% cholesterol and 3% triglycerides

An initial trial in preterm rabbits of dry powder DPPC and PG in a ratio of 7:3 compared effects with controls (no treatment) and adult rabbit surfactant (Morley *et al* 1980). Rabbits were delivered at 27 days post-conception (term being 31 days) and had a tracheostomy fashioned. After instillation of either adult rabbit surfactant, dry powder DPPC: PG or nothing the rabbits were ventilated for one hour. Improvements in static lung compliance were noted in both surfactant treated groups but the numbers of rabbits developing pneumothoraces were the same. Histological examination showed bronchiolar lesions of necrosis, desquamation and hyaline membrane formation in both treated and untreated animal lungs.

The first trial of the dry powder formulation of DPPC: PG in human neonates involved infants of <34 weeks gestation intubated and ventilated from birth (Morley *et al* 1981). Treatment with surfactant was only given if one of the investigators was able to attend the delivery. Controls did not receive any placebo treatment and the trial was not blinded. This trial was therefore open to criticism regarding treatment allocation and selection bias. Nonetheless 55 infants (22 treated and 30 controls) were enrolled. The groups were similar at entry in terms of gestation, birthweight and gender. Fewer infants in the treatment arm (9/30 versus 1/22) required supplemental oxygen or respiratory support and among infants that required ventilation, treatment with surfactant was associated with significantly lower mean ventilatory pressures and fewer deaths.

A second randomised non-blinded trial using the same dry powder of DPPC: PG followed (Wilkinson *et al* 1985). Infants were enrolled into one of two parallel trials: the first using surfactant as "prophylaxis", and the second "rescue" treatment in established respiratory distress syndrome. A total of 56 infants <31 weeks gestation were enrolled; 32 in the "prophylaxis" trial and 24 in the "rescue" trial. Surfactant was administered using capsules within a special adapter in a resuscitator bag, these were pierced to release the powder during inflations, and in the case of the control arm the capsule was not pierced. The trial could not demonstrate any difference in respiratory outcomes or survival.

The third trial of the dry powder was a sequential analysis of static compliance and blood gas parameters after surfactant or saline control (Milner *et al* 1983). Dry surfactant and saline were alternately insufflated at intervals of twenty minutes. Not surprisingly, given that later trials showed compliance improves only slowly after surfactant (Morley &

Greenough, 1991, Armsby *et al* 1992), there were no demonstrable differences in compliance, nor were there any differences in blood gas parameters.

The results of the last two trials suggested dry surfactant was not as effective as first thought and work began to look at alternative ways of administering the phospholipids. Simply dissolving the powder in saline did not work, ***ALEC*** stored at 37°C does not demonstrate any surface tension reducing properties (Takahashi *et al* 1994). The solution was to cool both the phospholipids and the medium used to administer them (Bangham *et al* 1984). ***ALEC*** that has been stored at 4°C and mixed with saline whilst still cold reduced surface tension (Takahashi *et al* 1994).

A randomised-controlled study using this formulation began in 1982 in Cambridge and Nottingham (Morley *et al* 1988). Enrolled infants of 23-34 weeks gestation received a pharyngeal deposition of 50mg of ***ALEC*** after birth with further doses at 10 minutes, 1 hour and 24 hours if they remained intubated. Controls received 1ml saline. The pharyngeal deposit prior to the first postnatal breath was used so that this would be inhaled and was intended to be quicker than after intubation.

Changes were made to the protocol after an interim analysis. It became evident that infants >30 weeks gestation had very little RDS. The trial then concentrated on infants of ≤30 weeks gestation. Concurrent with the change in gestation criteria was an increase in the dosage of ***ALEC*** from 50mg to 100mg.

Treatment and control groups were well matched at entry. Among infants >30 weeks differences in outcome were not significantly different however in the more immature group there were reductions in neonatal death, intraventricular haemorrhage and death/oxygen dependency at 28 days (Table 7).

The original two centre trial therefore enlarged to become a larger multi-centre trial to show conclusively whether surfactant was beneficial (Ten Centre Study Group 1987). This followed the protocol from the earlier trial (Morley *et al* 1988) but concentrated on infants of 25-29 weeks gestation. The primary outcome was mortality, irrespective of cause, with other complications of prematurity being analysed as a secondary outcome.

Table 7: Significant outcomes reported in controlled trials of ***ALEC***.

Study	Outcome	Surfactant treated infants	Placebo	Relative risk	95% CI	Risk difference	95% CI
Two centre study (Morley *et al* 1988)	IVH (all babies)	13 / 164 (8.0%)	29 / 163 (17.7%)	**0.45**	0.24 to 0.84	**-9.7%**	-16.9 to -2.5%
	Neonatal death (babies ≤30 weeks)	10 / 69 (14.5%)	21 / 67(31.3%)	**0.46**	0.24 to 0.91	**-16.9%**	-30.7 to -3.0%
	Death before discharge (babies ≤30 weeks)	12 / 69 (17.4%)	24 / 67 (35.8%)	**0.49**	0.26 to 0.89	**-18.4%**	-33.0 to -3.9%
	IVH (babies ≤30 weeks)	13 / 69 (18.8%)	27 / 67 (40.3%)	**0.47**	0.26 to 0.83	**-21.5%**	-36.4 to -6.5%
Ten Centre Study (1987)	Neonatal death	23 /159 (14.5%)	40 /147 (26.8%	**0.54**	0.34 to 0.85	**-12.8%**	-21.4 to -3.4%
	Death prior to discharge	30 / 159 (18.9%)	44 /147 (29.5%)	**0.64**	0.43 to 0.96	**-10.7%**	-20.2 to -1.1%

All infants in the treatment and placebo arms received at least one dose of their allocated surfactant/placebo. Seventeen infants (10.7%) in the treatment arm and 21 infants (14.1%) in the control arm were not intubated and received only the pharyngeal dose (*Personal communication* – Professor C Morley). Treatment or control arms were well matched. ***ALEC*** was found to reduce mortality both at 28 days and prior to discharge.

On the strength of the Ten Centre Study, ***ALEC*** was granted a licence. The dosing schedule has remained largely unchanged except for the pharyngeal deposit, which was dropped as there was insufficient data to support its use and very few infants in the 25-29 week gestation range did not get intubated. The consensus between the investigators and the company was that prescribers could not justify the cost in the absence of evidence of clinical efficacy (*personal communication* – Professor C Morley).

ALEC was also shown to be a safe drug. Adverse events associated with its use related largely to transient bradycardia and/or hypoxia during administration. Occasionally there is obstruction of the endotracheal tube requiring reintubation. None of these events are exclusive to ***ALEC*** and occur with a similar frequency with other surfactants (Ahluwalia & Morley 1995). Longer-term follow-up (Morley & Morley 1990) again suggested the drug is safe. In particular there was no increase in the numbers of handicapped children among the increased number of survivors.

Whilst the study of *in vitro* properties by Takahashi *et al* (1994) suggests that both synthetic surfactants ***ALEC*** and ***Exosurf*** have inferior surface active properties compared to the bovine-derived ***Survanta / Surfactant TA*** no trials comparing ***ALEC*** with another surfactant in a neonatal population have yet been published.

5.1.2 Meta-analysis of the randomised controlled trials of ALEC.

Method

The objective of this meta-analysis was to assess the effect of intra-tracheal administration of ***ALEC*** administered either prophylactically or in premature infants with established RDS. Searches were made of the Oxford Database of Perinatal Trials, Medline, BIDS (Embase), the National Research Register, previous reviews including cross references, abstracts, conference and symposia proceedings, expert informants, and hand-searching of journals written in the English language to find randomised controlled trials that compared the effect of ***ALEC*** to controls in preterm infants with RDS or at risk of RDS.

Data was collected regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials. Analyses of the data were performed using **relative risk** and **risk difference** (Bracken 1992).

Relative risk (also known as event rate ratio or incident rate ratio) is the traditional estimate of effect derived from prospective studies. In case controlled studies the relative risk is also approximated by odds ratio. It provides some idea as to the proportion of treated patients that experience an event (such as death, treatment of patent ductus, etc.) relative to the proportion of control patients that experienced the same event.

Relative risk is independent of the baseline rate of events (that is the rate of events seen in controls). In trials where there is no difference between event rates in treated and control arms the relative risk is 1.0, where the result favours treated groups the relative risk is less than 1.0 and greater than 1.0 when the result favours controls. A statistically significant result occurs when the 95% confidence interval does not cross unity.

Risk difference (also known as event rate difference) reflects the baseline event rate (seen in the control arm) and the reduction (or otherwise) seen in the treated arm. Therefore, it may have more relevance to the clinicians than relative risk or odds ratio. Where there is no difference between event rates in the treated and control arms the risk difference is 0.0%, where the result favours treated groups the risk difference is less than 0.0% (it achieves a negative value) and greater than 0.0% (remains positive) when the result favours controls. A statistically significant result occurs when the 95% confidence interval does not cross the zero value.

In meta-analyses/over-views of randomised clinical trials there are inherent biases (Egger & Smith 1998), not least depending on the data presented in the literature. Meta-analysis of published results with heterogeneity among the trials, possibly arising from differences among centres, populations, treatment protocols and different surfactants may lead to both an under- and over-estimation of the treatment effect and also the statistical significance (Thompson & Pocock 1991). One alternative is to retrieve the raw data; this has been done by Egberts *et al* (1997) in comparison of prophylactic versus rescue ***Curosurf***. Meta-analyses are not a substitute for properly conducted randomised controlled trials however the pooling of results may identify areas where research is lacking and prevent unnecessary new trials from being carried out. The uses and abuses of meta-analyses are reviewed by Petticrew (2001).

Studies were included only if they fulfilled the following criteria:

(a) Types of study - Randomised (or quasi-randomised) controlled trial comparing ***ALEC*** to control (placebo or no treatment).

(b) Types of participants – preterm neonates at risk of or with clinical and radiological evidence of RDS requiring assisted ventilation.

(c) Types of intervention - Infants randomised to receive ***ALEC*** versus control treatment (intratracheal administration of saline placebo).

(d) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, pulmonary air leak, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, bronchopulmonary dysplasia (at 28 days in survivors), bronchopulmonary dysplasia or death (at 28 days).

Where data were only available from a single study these are presented using risk difference and relative risk to allow comparisons to be drawn with outcomes after treatment with the other surfactants.

Results

Only two studies were identified. Morley *et al* (1988) Two Centre Study of ***ALEC*** and The Ten Centre Study (1987). Infants under thirty weeks gestation were enrolled in both studies but the data presented by Morley *et al* (1988) allows extraction of the outcomes for the more mature infants enrolled only in that trial. Summaries for these trials are shown in Table 8.

Other publications reporting outcomes with ***ALEC*** were excluded for the following reasons:

- Morley & Greenough (1991) – examined respiratory compliance in a subgroup of the Ten Centre Study infants
- Morley (1989) – reviews the two centre and ten centre trials, and also includes the results from the earlier non-randomised dry-powder trial

Table 8: Summaries of the randomised-controlled trials involving ***ALEC***

Study	Methods	Participants	Exclusions	Outcomes
Ten centre study (1987) - Ten centre study of ALEC (308 infants)*	Randomised (antenatal) Multicentre (10 centres) Blinded using drug administrators not involved in infant care Telephone randomisation (sealed envelopes) ALEC or saline placebo	Infants between 25-29 weeks gestation	Congenital malformation Stillbirths	Neonatal mortality Incidence of RDS Complications of prematurity
Morley *et al* (1988) - Two centre study of ALEC (327 infants)*	Randomised (antenatal) Two centres Attempted blinding using drug administrators not involved in infant care Randomised (sealed envelopes) ALEC or saline placebo	Infant <34 weeks' gestation	Congenital malformation (7 infants) Stillbirth (7 infants)	Respiratory support Duration of ventilation and oxygen therapy Complications of prematurity

*Note these two studies are not mutually exclusive. Babies of <30 weeks gestation enrolled in the Two Centre Study were also enrolled in the Ten Centre Study.

- Ahluwalia & Morley (1995) – examined oxygenation and heart rate changes after ***ALEC*** in a non-randomised cohort of infants
- The three dry powder ***ALEC*** trials (Morley *et al* 1981, Milner *et al* 1983, Wilkinson *et al* 1985) were excluded, as this preparation is considered ineffective. Morley (1989) is a review of the outcomes of infants in these trials treated prophylactically.

Treatment of premature infants with ***ALEC*** was shown to improve oxygenation and ventilatory requirements in treated infants. It has the following clinical impact (Figure 2):

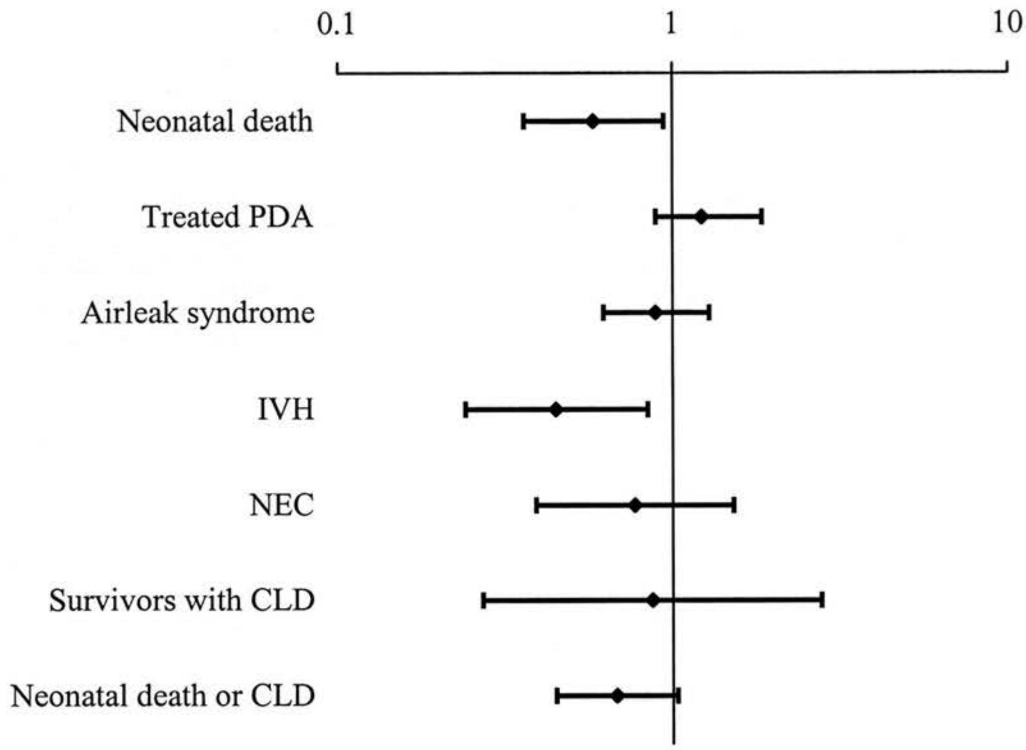
Neonatal Mortality: Both trials report on the risk of neonatal mortality. Both the Ten Centre Study and a subgroup analysis within the Two Centre Study of infants less than 30 weeks gestation reported a decrease in the risk of neonatal mortality associated with ***ALEC*** use. However when analysing the more mature infants in the Two Centre Study there is insufficient data due to the relative infrequency of both RDS and its complications in this gestation group. The typical estimate from the meta-analysis suggests a decrease in the risk of neonatal mortality associated with ***ALEC*** (typical relative risk 0.58, 95% CI 0.36 to 0.94; typical risk difference –6.8%; 95% CI –12.6 to –0.9%).

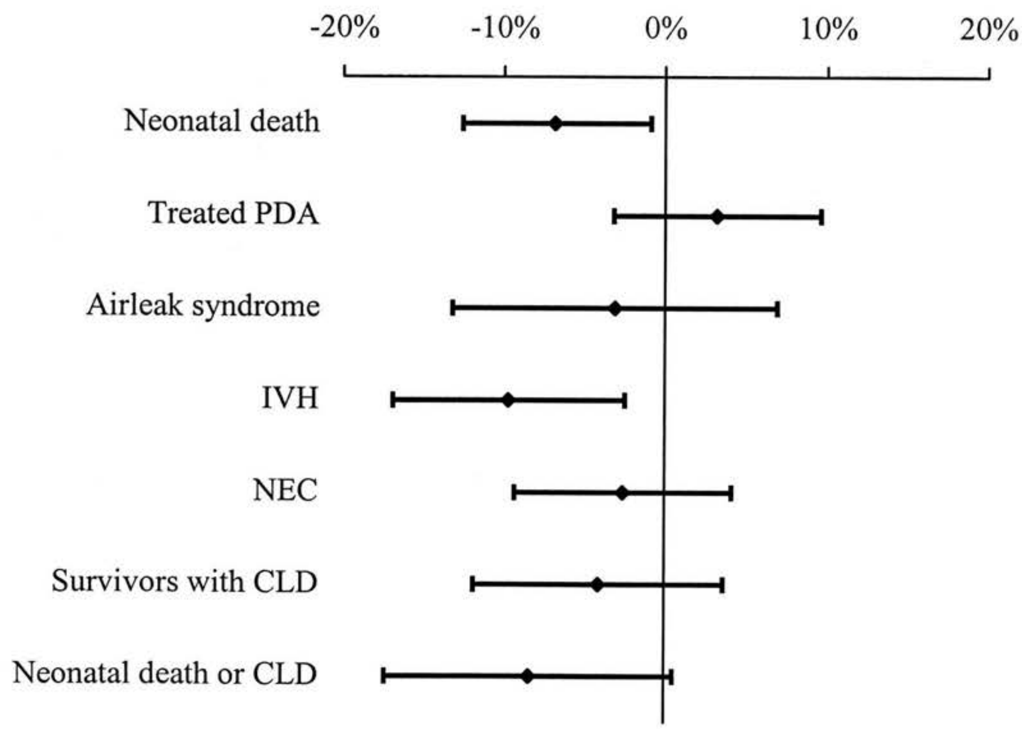
Pulmonary Air Leak: Again both trials report this outcome, but using different forms. The larger Ten Centre Study uses an all-encompassing definition of pulmonary air leak syndrome, whereas the Two Centre Study reports pneumothoraces only. The typical estimate from the Ten Centre Study suggests a trend towards a decrease in the risk of pulmonary air leak associated with ***ALEC*** (typical relative risk 0.89, 95% CI 0.62 to 1.28; typical risk difference –3.1%; 95% CI –13.2 to +6.9%). Similarly a trend towards a decrease in the risk of pneumothorax was reported in infants <30 weeks gestation in the Two Centre Study, but an increase in the risk for infants ≥30 weeks.

Patent Ductus Arteriosus: Both trials reported on the incidence of patent ductus arteriosus. The typical estimate from the Ten Centre Study suggests a trend towards an increase in the risk of patent ductus arteriosus associated with ***ALEC*** (typical relative risk 1.22, 95% CI 0.89 to 1.84; typical risk difference +3.2%; 95% CI –3.2 to +9.6%).

Necrotising Enterocolitis: NEC is given as an outcome in the Ten Centre study but not the Two Centre Study. This reported small non-significant decrease in the risk of necrotising enterocolitis after ***ALEC*** (typical relative risk 0.77, 95% CI 0.39 – 1.51; typical risk difference –2.6%; 95% CI –9.3 to +4.1%).

Figure 2: Meta-view charts of risk difference and relative risk between ***ALEC*** treated infants and controls.





Total Intraventricular Haemorrhage: Total IVH (irrespective of severity) was only reported in the Two Centre Study. This reported a decrease in the risk of IVH after ***ALEC*** (typical relative risk 0.45, 95% CI 0.24 – 0.84; typical risk difference –9.7%; 95% CI –16.9 to –2.5%). This was largely as a result of reductions in total IVH in ***ALEC*** treated infants <30 weeks gestation.

Bronchopulmonary Dysplasia / Chronic Lung Disease: Only the Two Centre Study reported oxygen dependency at 28 days postnatal age, the Ten Centre Study limited itself to persistence of an oxygen requirement beyond the 10th day of life. The Two Centre Study reported a non-significant decrease in the risk of BPD/CLD among surviving infants (of any gestation at birth) who had received ***ALEC*** (typical relative risk 0.73, 95% CI 0.41 - 1.32; typical risk difference –4.1%; 95% CI –11.9 to +3.6%).

Bronchopulmonary Dysplasia / Chronic Lung Disease* OR *Death: Again because the Ten Centre Study did not report the outcome of BPD/CLD at 28 days this outcome is limited to the result published in the Two Centre Study. This reported decrease in the risk of BPD/CLD or neonatal death among all infants (any gestational age) who had received ***ALEC*** (typical relative risk 0.68, 95% CI 0.45 – 1.03; typical risk difference –8.4%; 95% CI –17.4 to +0.5%). However the subgroup analysis of infants of <30 weeks gestation showed a decrease in the risk of BPD/CLD or neonatal death among infants who had received ***ALEC*** (typical relative risk 0.58, 95% CI 0.40 – 0.85; typical risk difference –24.9%; 95% CI –41.2 to –8.7%). This is more significant because it represents those infants more at risk of RDS.

Conclusion

ALEC was shown to be an effective drug for reducing neonatal and pre-discharge mortality. It reduced oxygen and ventilator requirements during the acute phase of RDS. The incidence of intraventricular haemorrhage was also significantly reduced. However other complications of prematurity, including pneumothoraces and pulmonary air leak, showed only trends towards better outcomes after ***ALEC***. There was no reduction in the numbers of survivors of any gestation that required supplemental oxygen at 28 days postnatal age compared to the control arm. However when mortality and CLD is combined as an outcome in the sub-group of infants <30 weeks gestation there were significantly more infants who survived without requiring oxygen.

There are however some unanswered questions regarding ***ALEC***: the published trials only compare ***ALEC*** when used prophylactically in infants at risk of RDS. Whilst prophylactic administration of surfactant is more clinically advantageous than rescue treatment, ***ALEC*** has not been demonstrated to be an effective "rescue" therapy for RDS. It is unlikely that a placebo-controlled trial of "rescue" ***ALEC*** would be considered ethical. The Ten Centre Study (1987) concentrated on infants of 25-29 weeks gestation and the two centre study enrolled few mature infants, therefore the clinical efficacy of ***ALEC*** in larger mature infants has not been demonstrated.

5.2 Curosurf (poractant alfa) Chiesi Farmaceutici S.p.A., Italy

5.2.1 Development and early trials of Curosurf

Curosurf (poractant alfa) is a porcine-derived surfactant developed by Tore Curstedt and Bengt Robertson at the Karolinska Institute of Stockholm, Sweden. It was subsequently licensed to Chiesi Farmaceutici SpA. of Italy. Pursuant to a license agreement in 1991, Ares-Serono became the exclusive European licensee. ***Curosurf*** was a late newcomer on the American market receiving FDA approval in 1999. It is distributed in America by Dey Laboratories, California.

The use of porcine surfactant was first reported by Noack *et al* (1987) in a trial of natural-derived surfactants in 10 infants with severe RDS. The final three infants in the series were treated with porcine lung extract that had been isolated from minced pig lungs by a combination of washing, centrifugation, and extraction with chloroform-methanol and liquid gel chromatography. ***Curosurf*** continues to be manufactured in this manner. The product differs from that obtained from lavage of the lungs in that it contains phospholipids from the cells of the lungs.

The final composition of ***Curosurf*** is phosphatidylcholine 60-80% (of which DPPC at least 40%), acidic phospholipids 10-15% (Phosphatidylserine, phosphatidylinositol, phosphatidylglycerol), lysophosphatidylcholine $\leq$ 4%, other phospholipids < 20% (phosphatidylethanolamine, sphingomyelin), surfactant proteins SP-B and SP-C 1.0 $\pm$ 0.5%, cholesterol and triglycerides $\leq$ 2%. There are in addition trace amounts of ethanol ($\leq$0.5%) and chloroform ($\leq$10 ppm) representing residual manufacturing components.

In the report by Noack *et al* (1987), treatment was a last-ditch effort in infants with severe

RDS but nonetheless improvements in gas exchange and clinical course were seen. The radiological appearances of RDS also improved after treatment (Mortensson *et al* 1987). Two non-randomised studies followed (Speer *et al* 1988, Speer *et al* 1991). A single 200mg/kg dose of ***Curosurf*** produced improvements in gaseous exchange, and in comparison to matched controls the second study showed improved outcomes in neonatal deaths, numbers of pneumothoraces and duration of ventilation. A series of multi-centre trials looking at the effects of ***Curosurf*** on neonatal mortality followed. These trials were the **EURO I** to **EURO VI** trials (Table 9).

Some centres, notably Belfast, published results on the infants they enrolled in the **EURO** trials (McCord *et al* 1988, Halliday *et al* 1989, Walti *et al* 1990). Some **EURO** trials have appeared in the literature but others have only been presented at neonatal meetings. Randomised trials outside the **EURO** series have looked at the timing of Curosurf administration (Egberts *et al* 1993, Walti *et al* 1995, Bevilacqua *et al* 1996). ***Curosurf*** use in infants on nasal CPAP (Verder *et al* 1994, Verder *et al* 1999) and two alternative methods of administration have been reported (Valls-i-Soler *et al* 1997, Valls-i-Soler *et al* 1998).

To some extent the research into other surfactants reduced the need for placebo-controlled trials and thus few trials indicate how ***Curosurf*** compares with no treatment/placebo. The three trials that achieve this (Collaborative European Multicenter Study Group 1988, Walti *et al* 1990, Verder *et al* 1994) all compare 200mg/kg of ***Curosurf*** administered to infants who had established RDS. In the case of the Collaborative European Multicenter Study Group (1988) and Walti *et al* (1990) the infants were ventilated and required an $FiO_2 > 0.6$. In the case of the Verder *et al* (1994) study the infants were in supplemental oxygen and were given ***Curosurf*** if they reached an $FiO_2 > 0.6$ and were then started on nasal CPAP. Statistically significant outcomes from these trials are shown in Table 10.

The trials of Bevilacqua *et al* (1993), Egberts *et al* (1993), Walti *et al* (1995), Bevilacqua *et al* (1996) and Verder *et al* (1999) all compare early versus late administration of ***Curosurf***. Bevilacqua *et al* (1993) and Verder *et al* (1999) use severity of disease to differentiate early versus late, whereas Egberts *et al* (1993), Walti *et al* (1995) and Bevilacqua *et al* (1996) use a temporal criteria to differentiate the concept of early ("prophylaxis") versus late rescue. The importance of these trials is discussed in the next chapter.

Table 9; The ***Curosurf*** EURO trials

Study	Number of centres	Type of trial	Babies enrolled	Reference
EURO I	8	Randomised controlled - rescue therapy	146	Collaborative European Multicenter Study group (1988)
EURO II	8	Open study of rescue therapy	78	Collaborative European Multicentre Study group (1991)
EURO III	26	Randomised comparative; "early" rescue versus "late" rescue	182	Bevilacqua *et al*, (1993)
EURO IV	15	Randomised comparative, single versus multiple doses	343	Speer *et al*, (1992)
EURO V	18	Non- randomised open trial of ***Curosurf*** use in severe RDS	86	Unpublished - manuscript available from Serono Laboratories (UK) Ltd
EURO VI	82	Randomised comparison of high dose (up to 600mg/kg) versus low dose (up to 300mg/kg)	2186	Halliday *et al* (1993)
EURO I and II follow-up	8	1 and 2 year follow-up of survivors from EURO I and II		Robertson *et al* (1992)

Table 10: Significant 28-day outcomes reported in randomised-controlled trials of ***Curosurf***

Study	Outcome	Surfactant treated infants	Placebo	Relative risk	95% CI	Risk difference	95% CI
Collaborative European multicenter Study Group (1988)	Neonatal death	24 / 77 (31.2%)	35 / 69 (50.7%)	**0.61**	0.41 to 0.92	**-19.6%**	-35.2 to -3.9%
	Pneumothorax	14 / 77 (18.2%)	24 / 69 (34.8%)	**0.52**	0.29 to 0.93	**-16.6%**	-30.8 to -2.4%
	PIE	18 / 77 (23.4%)	27 / 69 (39.1%)	**0.60**	0.36 to 0.99	**-15.8%**	-30.7 to -0.9%
	CLD in survivors	11 / 53 (20.8%)	16 / 34 (47.1%)	**0.44**	0.23 to 0.83	**-26.3%**	-46.3 to –6.3%
	Death or CLD	20 / 77 (26.0%)	51 / 69 (73.9%)	**0.35**	0.24 to 0.53	**-47.9%**	-62.2 to -33.7%
Verder *et al* (1994)	Mechanically ventilated	15 / 35 (42.9%)	28 / 33 (84.8%)	**0.51**	0.34 to 0.76	**-42.0%**	-62.4 to -21.5%

The two other areas of ***Curosurf*** research have been; the number and frequency of doses (Speer *et al* 1992, Halliday *et al* 1993) and the method of administration of ***Curosurf*** (Valls-i-Soler *et al* 1997, Valls-i-Soler *et al* 1999).

Speer *et al* (1992) showed that multiple doses of ***Curosurf*** improved early ventilator and oxygen requirements, and had a greater protective effect against pulmonary air leak with a significant reduction in pneumothoraces. Halliday *et al* (1993) found similar early improvements in ventilator and oxygen requirements with their high dose group (up to 600mg/kg) compared to their low dose group (up to 300mg/kg), but could not demonstrate any longer-term differences.

The two studies from Spain (Valls-i-Soler *et al* 1997, Valls-i-Soler *et al* 1999) looked at administration technique. In all previous trials ***Curosurf*** was administered as a bolus via a nasogastric tube passed down the endotracheal tube (ETT), this method had not been altered much since Fujiwara *et al* (1980). In particular the authors were interested in trying to reduce the number of episodes of hypoxia (transcutaneous oxygen saturation less than 80%) and bradycardia (heart rate less than 80/minute) during surfactant administration. These episodes are transient but have been reported frequently in surfactant trials (approximately 28% with ***Survanta***, between 25-39% with ***Exosurf*** and between 17-58% with ***Infasurf***). There were some reductions in the number of hypoxic and bradycardic episodes when ***Curosurf*** was administered via the dual lumen ETT but not the ETT side-port.

Whether these transient hypoxic and bradycardic episodes are significant is unclear. Even when transient cerebrovascular changes have documented during surfactant administration they have not correlated with any longer-term evidence of neurological impairment. Both changes in cerebral haemodynamics (Cowan *et al* 1991, Bell *et al* 1994) and transient depression of brain electrical activity (Hëllstrom-Westas *et al* 1992) have been reported during ***Curosurf*** administration.

Since dual lumen ETT cost more (£2.20 each) compared to a standard soft ETT of the same internal diameter (*source*; Vygon catalogue, Vygon UK Ltd. 1998) and have added dead-space (the ETT cannot be cut to the right length) the authors were cautious regarding the significance of their results and suggested that a larger trial is required before dual lumen ET tubes are routinely used in infants likely to require surfactant.

The studies by Verder and colleagues (Verder *et al* 1994 and Verder *et al* 1999) are worth special mention in that they investigate the use of ***Curosurf*** as a means to preventing the need for long-term ventilation. Nasal CPAP if frequently used in Scandinavian countries to treat RDS (Lundstrom 1996, Jonsson *et al* 1997). A UK based study, the IFDAS trial, looks at the same approach in this country and has recently finished recruiting (source: *The National Research Register*; http://www.update-software.com/nrronline/NRROpen.htm). Verder *et al* (1994) demonstrated that ***Curosurf*** used with routine nasal CPAP can significantly reduce the need for ventilation, and that early rather than late treatment has better results (Verder *et al* 1999). Unfortunately there was no comparison with conventional management of a ventilated group of infants with which to compare longer-term benefits of this mode of therapy.

Although ***Curosurf*** has been compared to controls in only two fully randomised controlled trials, results from these and extrapolation from other surfactant trials mean further placebo-controlled trials can no longer be seen to be ethical. The single versus multiple dose study of Speer *et al* (1992) and the low versus high dose regime study (Halliday *et al* 1993) suggest most infants can be treated with two 100mg/kg doses. The evidence (reviewed in detail in chapter 6) from the "early" versus late trials (Bevilacqua *et al* 1993, Egberts *et al* 1993, Walti *et al* 1995, Bevilacqua *et al* 1996 and Verder *et al* 1999) suggests the first dose is administered as soon as possible.

Only two randomised trials (Speer *et al* 1995, Kukkonen *et al* 2000) have compared ***Curosurf*** with another surfactant in a neonatal population. These reviewed in chapter 8 along with two non-randomised comparisons between ***Curosurf*** and ***Exosurf*** (Rollins *et al* 1993 and Stenson *et al* 1994), and a study of the effects of these two surfactants on cerebral blood flow (Murdoch & Kempley 1998).

5.2.2 Meta-analysis of the randomised controlled trials of Curosurf

Method

The objective of this section was to assess the effect of intra-tracheal administration of ***Curosurf*** administered either prophylactically or in premature infants with established RDS. The search strategy outlined in section 5.1.2 was used to examine outcomes in randomised controlled trials that compared the effect of ***Curosurf*** to controls in preterm infants with

RDS or at risk of RDS. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Studies were considered if they fulfilled the following criteria:

(a) Types of studies - Randomised controlled trials comparing ***Curosurf*** to control treatment whether using placebo or no treatment.

(b) Types of participants – preterm neonates at risk of or with clinical and radiological evidence of RDS requiring assisted ventilation.

(c) Types of intervention - Infants randomised to receive ***Curosurf*** versus control treatment (no treatment or intratracheal administration of air or saline placebo).

(d) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, pulmonary air leak (reported as PIE and pneumothorax), patent ductus arteriosus, intraventricular haemorrhage, bronchopulmonary dysplasia (at 28 days in survivors), bronchopulmonary dysplasia or death (at 28 days). Necrotising enterocolitis, often reported as an outcome in surfactant trials was not reported by any ***Curosurf*** trial suitable for inclusion in the meta-analysis.

Results

Only two studies were identified as suitable for inclusion – the EURO I Study by the Collaborative European Multicenter Study Group (1988) and Verder *et al* (1994). These trials were somewhat different however in that Verder *et al* (1994) used ***Curosurf*** in infants receiving nasal CPAP whereas the EURO I infants were treated with conventional ventilation. Despite the differences in mode of respiratory support, the point at which infants became eligible for randomisation was very similar ($FiO_2 \geq 0.6$).

A third report comparing ***Curosurf*** against saline placebo (Walti *et al* 1990) has been published; however some of the infants in this study were enrolled in the EURO I study (Collaborative European Multicenter Study Group 1988). The report by Svenningsen *et al* (1987) was also excluded as this report concentrated on early outcomes. Summaries for these trials are shown in Table 11. All other publications shown below were excluded from the analysis:

- Collaborative European Multicenter Study Group (1991) – The EURO II study. An open non-randomised study of a single dose of ***Curosurf***.

- Bevilacqua *et al* (1993) – The EURO III study. A comparison of "early" (treatment at a stage of less severe RDS) versus "late" ***Curosurf***.
- Speer *et al* (1992) – A comparison of single versus multiple doses.
- The EURO V study (manuscript available from Serono Laboratories UK. Ltd) – a non-randomised open design study of ***Curosurf*** in severe RDS.
- Halliday *et al* (1993) – High versus low dose regimes of ***Curosurf***.
- Noack *et al* (1987) – non-randomised trial.
- Mortensson *et al* (1987) – report on the radiological outcomes in the above study.
- Speer *et al* (1988) and Speer *et al* (1991) – non-randomised studies.
- McCord *et al* (1988) – report on the prevalence of IVH in Belfast infants enrolled in EURO I study.
- Halliday *et al* (1989) - report on changes in pulmonary blood after surfactant in Belfast infants enrolled in EURO I study.
- Egberts *et al* (1993) – randomised controlled trial of prophylactic versus rescue.
- Walti *et al* (1995) – randomised controlled trial of prophylactic versus rescue.
- Bevilacqua *et al* (1996) – randomised controlled trial of prophylactic versus rescue.
- Valls-i-Soler *et al* (1997) – randomised controlled trial of two methods of administering ***Curosurf***.
- Valls-i-Soler *et al* (1998) – randomised controlled trial of two methods of administering ***Curosurf***.

Table 11: Summaries of the controlled trials involving ***Curosurf***

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Svenningsen *et al* (1987) Rescue trial (8 infants)	Randomised (?method) Single centre study No blinding 200 mg/kg Curosurf or air placebo	Gestation 26-30 weeks Clinical and radiological RDS $FiO_2 \geq 0.6$	Not stated	Survival to discharge Early changes in ventilator and oxygen requirements Complications of prematurity
Collaborative European multicenter Study Group (1988) – The EURO I study Rescue trial (146 infants)	Randomised Eight centre study Sealed envelopes (stratification by weight) Not blinded 200 mg/kg Curosurf or air placebo	Birthweight 700-2000 grams Clinical and/or radiological RDS Age 2-15 hours Ventilated with $FiO_2 \geq 0.6$	Congenital abnormality Prolonged rupture of membranes (≥3 weeks) Grade III or IV IVH Birth asphyxia GBS infection	Ventilator and oxygen requirements Complications of prematurity
Bevilacqua *et al* (1993) – The EURO III study (182 infants) - early versus late Curosurf	Randomised Multicentre study (26 centres) Sealed envelopes Not blinded 200 mg/kg Curosurf	Birthweight 600-2000 grams. Between 2-24 hours old. Clinical and radiological diagnosis of RDS. Ventilated with FiO_2 0.4 – 0.59	Congenital abnormality Prolonged rupture of membranes (≥3 weeks) Grade III or IV IVH Birth asphyxia GBS infection $FiO_2 \geq 0.6$	Ventilator and oxygen requirements Complications of prematurity

Table 11: Summaries of the controlled trials involving ***Curosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Speer *et al* (1992) – The EURO IV Study; single versus multiple doses (343 infants)	Randomised Multicentre study (26 centres) Sealed envelopes (stratified by centre and weight) Not blinded 200 mg/kg Curosurf, with 2^{nd} and 3^{rd} doses of 100 mg/kg at 12 hourly intervals in multiple dose arm	Birthweight 700-2000 grams Clinical and/or radiological RDS Age 2-15 hours Ventilated with $FiO_2 \geq 0.6$	Congenital abnormality Prolonged rupture of membranes (≥3 weeks) Grade III or IV IVH Birth asphyxia (Apgar ≤3 at 5 minutes, cord pH <7.1 or early onset seizures) (14 post allocation exclusions)	BPD or neonatal death Ventilator and oxygen requirements Complications of prematurity
Halliday *et al* (1993) – The EURO VI Study (2186 infants)	Randomised Multicentre study (82 centres) Telephone randomisation (stratified by centre) Not blinded Up to 300 mg/kg Curosurf, versus up to 600 mg/kg in multiple doses	< 72 hours old. Clinical and radiological RDS. $a/APO_2 < 0.22$.	Severe congenital malformations	BPD or neonatal death BPD or death before discharge/EDD Ventilator and oxygen requirements Complications of prematurity

Table 11: Summaries of the controlled trials involving ***Curosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Walti *et al* (1990) - rescue trial of Curosurf (30 infants)	Randomised Single centre report of part of EURO I study with additional patients Sealed envelopes (stratification by weight) Not blinded 200 mg/kg Curosurf or air placebo	Birthweight 700-2000 grams Clinical and/or radiological RDS Age 2-15 hours Ventilated with $FiO_2 \geq 0.6$	Congenital abnormality Prolonged rupture of membranes (≥3 weeks) Grade III or IV IVH Birth asphyxia GBS infection	Ventilator and oxygen requirements Complications of prematurity
Egberts *et al* (1993) - comparison of prophylaxis and rescue Curosurf (147 infants)	Multicentre trial (4 centres) Sealed envelopes (stratification by centre) Not blinded 200 mg/kg Curosurf within 10 minutes of delivery or when $FiO2 \geq 0.6$.	26-30 weeks' gestation	Prolonged rupture of membranes (≥3 weeks) Congenital abnormalities (2 post allocation exclusions)	Reduction in RDS Ventilatory support Complications of prematurity
Verder *et al* (1994) - Nasal CPAP and Curosurf trial (68 infants)	Multicentre trial Sealed envelopes (stratification by centre) All babies receiving CPAP, treatment arm given 200 mg/kg Curosurf	25-35 weeks' gestation Clinical and radiological RDS. Nasal CPAP in use (≥6 cm H_2O $a/APO_2 < 0.22$.	Congenital abnormality Prolonged rupture of membranes (≥2 weeks) Birth asphyxia with Apgar score ≤ 3 at 5 minutes Congenital pneumonia (5 babies withdrawn post-allocation)	Need for mechanical ventilation beyond period of surfactant administration Neonatal mortality Oxygen requirements Complications of prematurity

Table 11: Summaries of the controlled trials involving ***Curosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Walti *et al* (1995) - prophylaxis versus rescue trial of Curosurf (256 infants)	Randomised Multicentre (12 centres) Telephone randomisation (stratification by centre) Not blinded 100 mg/kg Curosurf within 15 minutes of birth or if CXR shows RDS and PaO_2:FiO_2 <20kPa between 3-18 hours of age	Gestation 25-31 weeks In-born in participating centre	Congenital abnormality Prolonged rupture of membranes (≥3 weeks)	Survival without BPD at 28 days Ventilator and oxygen requirements CXR appearances Complications of prematurity
Bevilacqua *et al* (1996) - prophylaxis versus rescue trial of Curosurf (266 infants)	Multicentre trial (18 centres) Sealed envelopes (stratification by centre, and gestation) Not blinded 200 mg/kg Curosurf within 10 minutes of delivery or if ventilated for RDS	24-30 weeks' gestation	Prolonged rupture of membranes (≥3 weeks) Congenital abnormalities Congenital infection (19 post allocation exclusions)	Reduction in RDS Complications of prematurity

Table 11: Summaries of the controlled trials involving ***Curosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Valls-i-Soler *et al* (1997) – Curosurf administration via a side-port or as a bolus (68 infants)	Multicentre trial Sealed envelopes (stratified by centre) 200 mg/kg Curosurf administered via either an ETT side-port or as conventional bolus through NG tube	600 – 2000 grams birthweight Less than 24 hours old Clinical and radiological RDS Ventilated with $FiO_2 \geq 0.4$	Congenital abnormality Pre-existing severe IVH Birth asphyxia (Apgar score <3 at 5 minutes)	Episodes of transient hypoxia and/or bradycardia during Curosurf administration Neonatal mortality Complications of prematurity
Valls-i-Soler *et al* (1998) – Curosurf administration via a dual-lumen ETT or as a bolus (68 infants)	Multicentre trial Sealed envelopes (stratified by centre) 200 mg/kg Curosurf administered via either an ETT side-port or as conventional bolus through NG tube	600 – 2000 grams birthweight Less than 24 hours old Clinical and radiological RDS Ventilated with $FiO_2 \geq 0.4$	Congenital abnormality Pre-existing severe IVH Birth asphyxia (Apgar score <3 at 5 minutes)	Episodes of transient hypoxia and/or bradycardia during Curosurf administration Neonatal mortality Complications of prematurity
Verder *et al* (1999) - Nasal CPAP and early versus late Curosurf (60 infants)	Multicentre trial Sealed envelopes (stratification by centre) All babies receiving CPAP, given 200 mg/kg Curosurf at randomisation in early arm or if $a/APO_2 < 0.22$ in late arm.	<30 weeks' gestation Clinical and radiological RDS. Nasal CPAP in use (≥6 cm H_2O a/APO_2 between 0.35 and 0.22	Congenital abnormality Prolonged rupture of membranes (≥2 weeks) Birth asphyxia with Apgar score ≤ 3 at 5 minutes Congenital pneumonia	Need for mechanical ventilation beyond period of surfactant administration Neonatal mortality Oxygen requirements Complications of prematurity

Treatment of premature infants with ***Curosurf*** leads to an improvement in oxygenation and ventilatory requirement. It has the following clinical impact (Figure 3):

Neonatal Mortality: Both trials report on the risk of neonatal mortality. The typical estimate from the meta-analysis suggests a decrease in the risk of neonatal mortality associated with ***Curosurf*** (typical relative risk 0.59, 95% CI 0.39 to 0.90; typical risk difference –16.0%; 95% CI –28.3 to –3.7%).

Pulmonary Air Leak: Again both trials report this outcome, but using the two forms of PIE (not reported by Verder *et al* 1994) and pneumothorax rather than an all-embracing air leak syndrome. The typical estimate from the meta-analysis of both trials shows a decrease in the risk of pneumothorax associated with ***Curosurf*** use (typical relative risk 0.53, 95% CI 0.30 to 0.93; typical risk difference –12.1%; 95% CI –22.6 to –1.5%). The typical estimate (from the EURO I study only and therefore not included in the meta-view chart) suggests a decrease in the risk of PIE associated with ***Curosurf*** use (typical relative risk 0.27, 95% CI 0.13 to 0.54; typical risk difference –28.7%; 95% CI –42.1 to –15.4%).

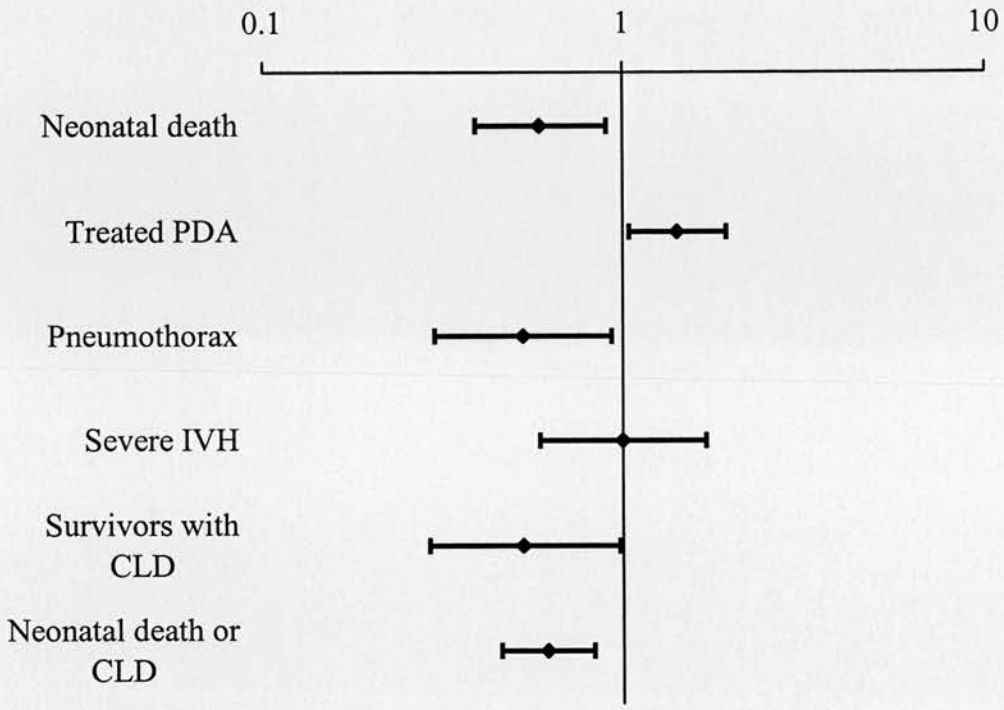
Patent Ductus Arteriosus: Both trials reported on the incidence of PDA. The typical estimate suggests an increase in the risk of significant PDA (requiring treatment) associated with ***Curosurf*** (typical relative risk 1.41, 95% CI 1.04 to 1.92; typical risk difference +15.4%; 95% CI +2.3 to +28.6%).

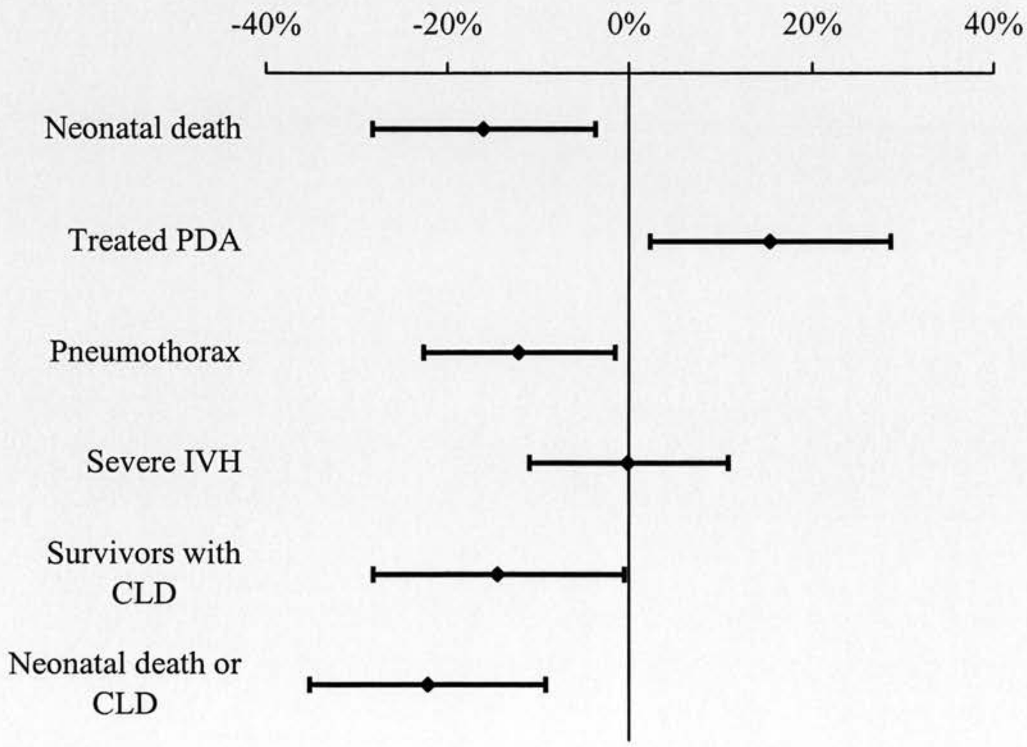
Severe Intraventricular Haemorrhage: Severe IVH (defined as Papile grades III and IV) was reported by both eligible studies. The typical estimate from the meta-analysis suggests a no difference in the risk of severe IVH after ***Curosurf*** (typical relative risk 1.00, 95% CI 0.59 – 1.69; typical risk difference –0.1%; 95% CI –10.9 to +10.8%).

Bronchopulmonary Dysplasia / Chronic Lung Disease: Surviving infants with BPD/CLD at 28 days were reported by both studies. The typical estimate from the meta-analysis of both trials shows a decrease in the risk of BPD/CLD in infants who had received ***Curosurf*** (typical relative risk 0.53, 95% CI 0.29 – 0.98; typical risk difference –14.4%; 95% CI –28.2 to –0.5%).

Bronchopulmonary Dysplasia / Chronic Lung Disease* OR *Death: This reported by both studies. The typical estimate from the meta-analysis of both trials shows a decrease in the risk of BPD/CLD or neonatal death in infants who had received ***Curosurf*** (typical relative risk 0.62, 95% CI 0.46 – 0.83; typical risk difference –22.1%; 95% CI –35.2 to –9.1%).

Figure 3: Meta-view charts of risk difference and relative risk between ***Curosurf*** treated infants and controls.





Conclusion

Curosurf has been shown to be an effective drug for reducing neonatal mortality. It reduces oxygen and ventilator requirements during the acute phases of RDS. The incidences of intraventricular haemorrhage, pneumothoraces and PIE are also significantly reduced. There is also a reduction in surviving infants who required supplemental oxygen at 28 days postnatal age, and either BPD/CLD or death at 28 days.

The main disadvantage of ***Curosurf*** is the relatively high cost of a vial (£400 per 120mg vial. *Source: British National Formulary*). It is currently the most expensive surfactant available in the UK. Whether the additional expense is negated by gains in other areas (reductions high dependency care, other drugs as well as health outcomes) compared to cheaper surfactants is explored in chapters 9 and 10.

5.3 Exosurf Neonatal (Colfosceril palmitate) Burroughs Wellcome Co., California, USA

5.3.1 Development and early trials of Exosurf

Exosurf Neonatal was developed by John Clements and is based on DPPC (colfosceril palmitate). Clements hoped that designing a synthetic surfactant might "*avoid the potential problems of variable composition of material extracted from animals, sensitivity to foreign proteins, and contamination with infectious agents*" (Clements 1997). Although animal-derived surfactants have yet to be shown to transmit prion or other diseases, the recent experience in the United Kingdom with bovine spongiform encephalopathy still causes reluctance in some people's minds when it comes to using these products (Lacey 1999).

To improve the properties of DPPC, hexadecanol was added to aid adsorption in the lung and tyloxapol to facilitate dispersion. Given in a dosage of 67mg/kg of DPPC, ***Exosurf*** is prepared as a lyophilised powder stored under vacuum in individual vials and reconstituted with sterile water prior to use. Animal studies had shown that this surfactant improved lung function in prematurely delivered rabbits (Tooley *et al* 1987) and improved survival among preterm lambs by 50% (Durand *et al* 1985).

The first study in a neonatal population used both "prophylaxis" and "rescue" strategies (see chapter 6 for further discussion regarding strategies of surfactant administration). A single dose of ***Exosurf*** reduced both ventilator and oxygen requirements (Phibbs *et al* 1991), but, apart from fewer respiratory deaths in the "prophylaxis" study, did not appear to improve overall mortality or the complications of prematurity. The authors suggested this was due to the size of the trial; they were however encouraged enough to proceed to larger controlled trials.

The further clinical trials with ***Exosurf*** were conducted in numerous institutions in North America under sponsorship from the manufacturers, Burroughs Wellcome Co., as part of the process of obtaining approval from the Food and Drug Administration. These studies enrolled much larger numbers of infants. The aim was to demonstrate the clinical effectiveness of ***Exosurf*** and to discover the optimum dosing schedule for the treatment of RDS. Some of the trials were long-term follow-up. Table 12 summarises the relationships between the trials and their follow-up studies.

The trials were of similar structure in that all were double blind, randomised, and controlled. Placebo, where used, was air rather than saline. Blinding was achieved through the use of drug administration teams who were responsible for the surfactant/placebo dosing in secret. These teams were not involved in the subsequent management of the infants. Parents and the clinical team responsible for the infants were unaware of the allocation.

There was stratification of infants by birthweight (Figure 4) and gender. In general the weight criteria of the trials were designed to include infants of a specific gestation (the 03 trial looked at very immature infants of 500-699 grams, whereas the 06/09 trial looked at more mature infants of ≥ 1250 grams). Summaries of the trials, their entry and exclusion criteria as well as the primary and secondary outcomes are given in Table 13.

Table 12: The North American ***Exosurf*** trials and their follow-up studies

Study number	Initial study	One year follow-up		Two year follow-up
01 / 02	Bose *et al* (1990)	-	Over-view follow-up in all prophylaxis trials: Corbet *et al* (1995b)	Kraybill *et al* (1995)
03	Stevenson *et al* (1992)	Walther *et al* (1995)		
04	Corbet *et al* (1991a and 1991b)	Sell *et al* (1995)		
05	Long *et al* (1991b)	Gong *et al* (1995)	Over-view of 1 year follow-up in all four rescue trials: Courtney *et al* (1995)	
06/09	Long *et al* (1991a)	Sauve *et al* (1995)		
07	Smyth *et al* (1995)	Casiro *et al* (1995)		
08	McMillan *et al* (1995)	Saigal *et al* (1995)		
12	Berry *et al* (1994)	-		
13	Corbet *et al* (1995a)	Gerdes *et al* (1995)		
17	Pramanik *et al* (1992)	-		
19	Long *et al* (1992)	-		

Figure 4: Birthweight ranges in the North American trials of ***Exosurf***

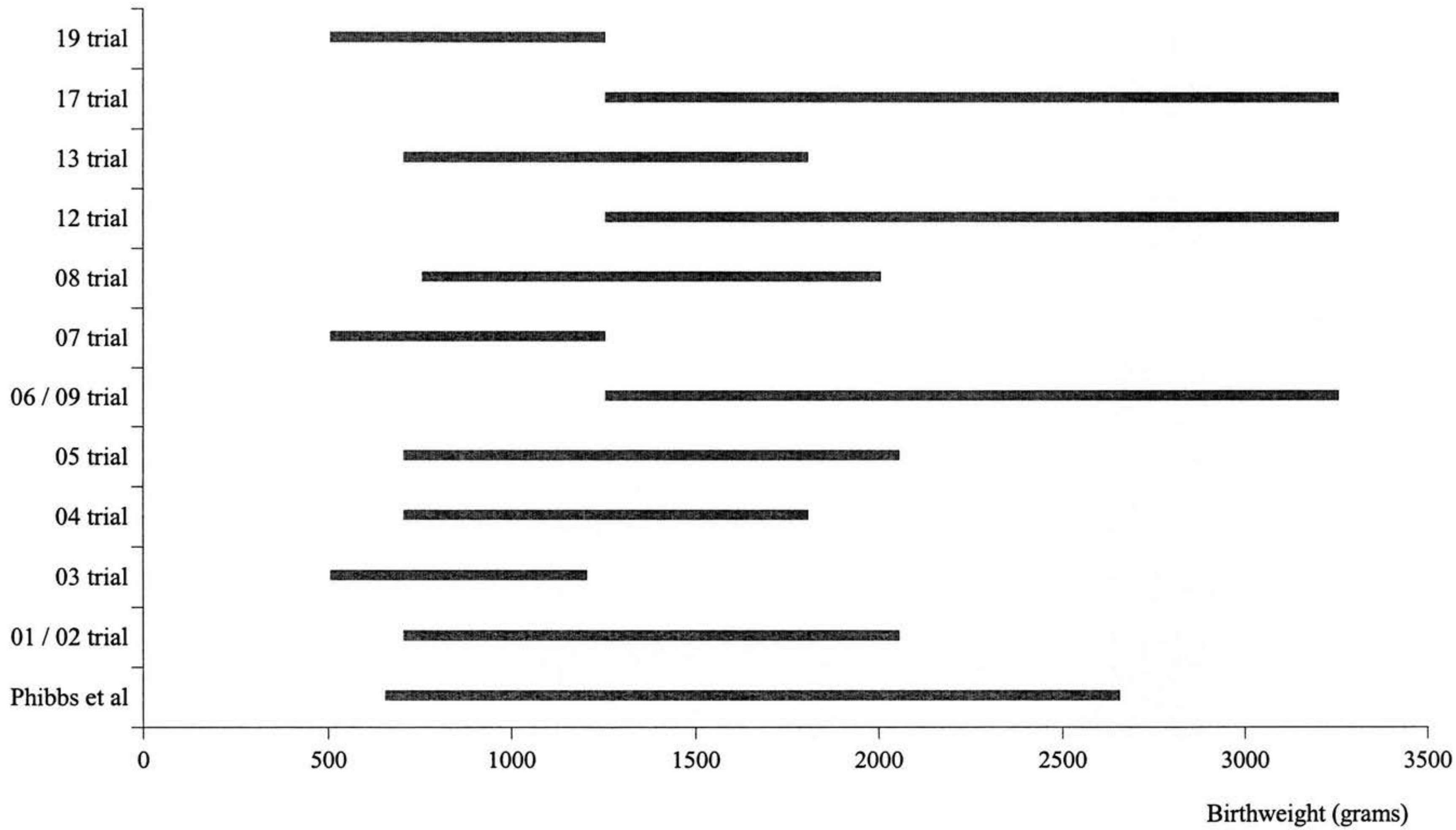


Table 13: Summaries of the randomised trials involving ***Exosurf***

Study	Methods	Participants	Exclusions	Outcomes
Phibbs *et al* (1991) Prophylaxis trial (77 infants)	Randomised Single centre study Sealed envelopes (no stratification) No blinding 5 ml/kg Exosurf or air placebo	In-born infants Gestation <34 weeks Birthweight >650 grams	Congenital abnormality (3 infants excluded from analyses)	Incidence of RDS Ventilatory requirements Complications of prematurity prior to discharge
Phibbs *et al* (1991) Rescue trial (110 infants)	Randomised Single centre study Sealed envelopes (no stratification) No blinding 5 ml/kg Exosurf or air placebo	Birthweight >650 grams Clinical RDS Ventilated (MAP $\geq$ 7cm H_2O, $FiO_2 > 0.4$) Between 4 - 24 hours old	Congenital abnormality (6 infants did not meet all entry criteria – excluded)	Complications of prematurity prior to discharge
Bose *et al* (1990) Prophylaxis trial (385 infants) Exosurf trials 01 / 02	Randomised Two centre study Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or air placebo	In-born infants Birthweight 700-1350 grams	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis (24 post-natal exclusions – malformations or congenital pneumonia)	Survival at 28 days without BPD Ventilatory requirements Complications of prematurity

Table 13: Summaries of the randomised trials involving ***Exosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Stevenson *et al* (1992) Prophylaxis trial (215 infants) Exosurf trial 03	Randomised Multicentre (23 centres) Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or air placebo	In-born infants Birthweight 500-699 grams	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis	Neonatal mortality Ventilatory requirements Death due to RDS BPD and complications of prematurity
Corbet *et al* (1991a and 1991b) Prophylaxis trial (446 infants) Exosurf 04 trial	Randomised Multicentre (19 centres) Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or placebo	In-born infants Birthweight 700-1100 grams	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis	Survival at 28 days without BPD Complications of prematurity
Long *et al* (1991b) Rescue trial (419 infants) Exosurf 05 trial	Randomised Multicentre (21 centres) Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or air placebo with 2nd dose at 12 hours if ventilated	Birthweight 700-1350 grams Clinical RDS $a/APO_2 < 0.22$ Less than 24 hours old	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis $a/APO_2 < 0.22$ for >4 hours Congenital infection	Neonatal death Survival without BPD Respiratory support Complications of prematurity

Table 13: Summaries of the randomised trials involving ***Exosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Long *et al* (1991a) Rescue trial (1237 infants) Exosurf 06 / 09 trials	Randomised Multicentre (36 centres) Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or air placebo with second dose at 12 hours if still ventilated	Birthweight ≥1250 grams (Canadian centres) or >1350 grams (USA centres) Clinical RDS $a/APO_2 < 0.22$ Less than 24 hours old	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis	Neonatal death Survival without BPD Respiratory support Complications of prematurity
Smyth *et al* (1995) Rescue trial (226 infants) Exosurf 07 trial	Randomised Multicentre (12 centres) Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or air placebo with second dose at 12 hours if still ventilated	Birthweight 500-749 grams Clinical RDS $a/APO_2 < 0.22$ 2 - 24 hours old	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis	Neonatal mortality BPD Survival at 28 days without BPD Complications of prematurity

Table 13: Summaries of the randomised trials involving ***Exosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
McMillan *et al* (1995) Rescue trial (344 infants) Exosurf 08 trial	Randomised Multicentre (12 centres) Sealed envelopes (stratification by gender and weight) Blinded (drug administration team) 5 ml/kg Exosurf or air placebo with second dose at 12 hours if still ventilated	Birthweight 750-1249 grams Clinical RDS $a/APO_2 < 0.22$ 2 - 24 hours old	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis	Survival without BPD Respiratory support Complications of prematurity
Berry *et al* (1994) Dose ranging study (263 infants) Exosurf 12 study	Randomised Multicentre (14 centres) Sealed envelopes (stratification by gender, weight and a/APO_2 at entry) Blinded (drug administration team) 2.5 – 7.5 ml/kg Exosurf or air placebo with second dose (same volume) at 12 hours if still ventilated	Birthweight $\geq$1250 grams Clinical RDS $a/APO_2 < 0.22$ Less than 24 hours old	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis	Death by 14 days Death from RDS Duration of ventilatory support Complications of prematurity

Table 13: Summaries of the randomised trials involving ***Exosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Corbet *et al* (1995a) Single versus 3 doses prophylaxis trial (826 infants) Exosurf 13 study	Randomised Multicentre (33 centres) Sealed envelopes (stratification by gender and weight) Blinded for 2nd and 3rd doses, 1st dose given to all babies (drug administration team) 5 ml/kg Exosurf at birth with further doses at 12 and 24 hours if still ventilated	Birthweight 700-1100 grams	Congenital abnormality Proven lung maturity (method of testing not stated) Growth retardation Hydrops fetalis Maternal opiate abuse Maternal chorioamnionitis	Survival at 28 days without BPD Ventilator and oxygen requirements Complications of prematurity
Pramanik *et al* (1992) Two versus four doses rescue trial (522 infants) Exosurf 17 trial	Randomised (method not stated) Multicentre (36 centres) 5 ml/kg Exosurf with subsequent doses at 12 hourly intervals if still ventilated	Birthweight ≥1250grams Clinical RDS $a/APO_2 < 0.22$ 2 - 24 hours old	Not stated	Neonatal death Complications of prematurity (pulmonary airleak, NEC, IVH)
Long *et al* (1992a) Three versus six doses prophylaxis trial (348 infants) Exosurf 19 study	Randomised (method not stated) Multicentre (36 centres) 5 ml/kg Exosurf with subsequent doses at 12 hourly intervals if still ventilated	Birthweight <750 grams	Not stated	Neonatal death Complications of prematurity (pulmonary airleak and IVH) Published data available on only 228 babies.

Table 13: Summaries of the randomised trials involving ***Exosurf*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
OSIRIS study group (1992) Early versus late Exosurf (2690 infants)	Randomised Multicentre Telephone randomisation Not blinded 5 ml/kg Exosurf at randomisation or when a/APO_2 < 0.22 with second dose at 12 hours if still ventilated (and third fourth doses if allocated under the concurrent study)	At risk of RDS Less than 2 hours old Ventilated	Congenital abnormality	Death at any stage Death or oxygen dependency at 28 days Death or oxygen dependency at "EDD" Complications of prematurity
OSIRIS study group (1992) Two versus four doses of Exosurf (6757 infants)	Randomised Multicentre Telephone randomisation Not blinded 5 ml/kg Exosurf at randomisation or when a/APO_2 < 0.22 with further doses at 12 hourly intervals	At risk of RDS Less than 2 hours old Ventilated a/APO_2 < 0.22 or "at risk of RDS"	Congenital abnormality	Death at any stage Death or oxygen dependency at 28 days Death or oxygen dependency at "EDD" Complications of prematurity

Table 13: Summaries of the randomised trials involving ***Exosurf*** (continued)

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
European Exosurf Study (1992) - Early versus late Exosurf (420 infants)	Randomised Multicentre Sealed envelopes, stratified by gestation and sex. Blinded first dose of Exosurf or air placebo with rescue if $a/APO_2 < 0.22$. Second dose at 18 hours	Gestation 26 – 29 weeks Less than 2 hours old	Congenital abnormality Hydrops fetalis Maternal chorioamnionitis	Neonatal survival without cranial USS abnormalities RDS requiring rescue therapy Duration of intensive care, oxygen therapy Complications of prematurity

Outcome measures of the complications of prematurity were pre-defined. The primary outcomes most commonly used were the incidence of bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD), neonatal mortality or neonatal survival without BPD/CLD.

Trials 01 and 02 (Bose *et al* 1990), 03 (Stevenson *et al* 1992) and 04 (Corbet *et al* 1991a and 1991b) were "prophylaxis" trials using a single dose of Exosurf 5ml/kg (67.5mg/kg of DPPC) administered as soon as possible after birth. Trials 05 (Long *et al* 1991b), 06 and 09 (combined and reported as a single study by Long *et al* 1991a), 07 (Smyth *et al* 1995) and 07 (McMillan *et al* 1995) were "rescue" trials whereby ***Exosurf*** was administered to infants who were clinically and radiologically diagnosed as having RDS. To standardise the severity of RDS at which infants became eligible for these trials, a cut-off employing the arterial/alveolar pressure ratio (a/APO_2) of <0.22 was used. This ratio was used because the "normal" range is more stable with changing inspired oxygen concentrations. This stability has allowed a value of 0.75 to be defined as the lower limit of normal in an adult (Gilbert & Keighley 1974).

Trials 12, 13, 17 and 19 looked at different dosing schedules and amounts of phospholipids (Table 14). Trials 10, 11, 14 and 18 were follow-up studies, and 15 and 16 were bridging protocols.

In trials where a single dose of ***Exosurf*** was given prophylactically there were reductions in the ventilator and oxygen requirements. The 03 trial (Stevenson *et al* 1992) did not demonstrate the same benefits for infants treated with ***Exosurf*** that were seen in the other trials. This trial had investigated a less mature population of infants and the only result to reach statistical significance was an increase in CLD among surviving infants in the treated arm. The result was not fully explained, but several ideas were postulated. These include; whether the more immature infants require more than one dose (i.e. the more immature infants have less endogenous surfactant and a single dose of exogenous surfactant might be "used up" or inactivated fairly readily); there was an excess of male infants in the treatment arm – this is one of the risk factors for RDS and also a risk factor for a worse outcome (chapter 1); there is also a co-existing immaturity of non-pulmonary organs that contribute to mortality in this birth weight/gestation group - surfactant therapy has no direct influence on these.

Table 14: Summary of dosing schedules in the North American ***Exosurf*** trials

Study number	No. of centres	Birthweight	Dosing regime*	Infants studied	References
01 / 02	2	700 - 1350 grams	Single dose prophylaxis	385	Bose *et al* (1990)
03	23	500 – 699 grams	Single dose prophylaxis	215	Stevenson *et al* (1992)
04	19	700 - 1100 grams	Single dose prophylaxis	446	Corbet *et al* (1991b)
05	21	700 - 1350 grams	Two dose rescue	419	Long *et al* (1991b)
06 / 09	36	≥ 1250 grams	Two dose rescue	1237	Long *et al* (1991a)
07	12	500 – 749 grams	Two dose rescue	221	Smyth *et al* (1995)
08	12	750 – 1249 grams	Two dose rescue	342	McMillan *et al* (1995)
12	14	≥ 1250 grams	Variable doses of 2.5ml/kg to 7.5 ml/kg	244	Berry *et al* (1994)
13	33	700 – 1100 grams	Single dose vs. three doses prophylaxis	826	Corbet *et al* (1995a)
17	36	≥ 1250 grams	Two vs. four rescue doses	522	Pramanik *et al* (1992)
19	36	500 – 749 grams	Modified prophylaxis of three vs. four - six rescue doses	348	Long *et al* (1992)

*One dose = 5ml/kg ***Exosurf neonatal*** unless stated

Studies 10, 11, 14 and 18 were follow-up studies, 15 and 16 were bridging protocols

It is likely that a number of these different factors played a role in the results from the 03 trial. Increasing immaturity is reported to predict poor response to exogenous surfactant (Skelton & Jeffrey 1996) and infants in whom there is a poor response to surfactant have worse outcomes (Hamvas *et al* 1993, Kuint *et al* 1994).

Whether these infants would have benefited from additional doses of surfactant was not addressed in infants this immature, however the 13 trial (Corbet *et al* 1995a, Gerdes *et al* 1991) examined whether a further two doses after the initial prophylaxis dose was of benefit in slightly more mature infants. Neonatal death and NEC were significantly reduced after multiple doses rather than a single dose. The study also demonstrated better oxygenation and lower mean airway pressures after 24 hours of age for this group.

Another consideration regarding the 03 trial is that outcomes are reported at 28 days. The average gestations at birth were 24.9 weeks (treatment group) and 24.8 weeks (placebo). Thus the 28 day outcome relates to a corrected gestational age of <29 weeks, the clinically more meaningful definition of CLD at 36 weeks corrected age was not used and there may have been differences if this definition had been used.

The 01/02 (Bose *et al* 1990) and 04 (Corbet *et al* 1991a and 1991b) trials both demonstrated significant reductions in pulmonary air leaks, but only in the 04 trial was this accompanied by a reduction in neonatal mortality.

The two dose "rescue" trials – trial 05 (Long *et al* 1991b), trial 07 (Smyth *et al* 1995), trial 08 (McMillan *et al* 1995) and trials 06 / 09 (Long *et al* 1991a) - all used ***Exosurf*** in infants with clinical and radiological RDS, and in whom the a/APO_2 was <0.22. A second dose was given 12 hours later to infants who remained ventilated. In all these "rescue" trials there was improved neonatal mortality (Table 15) but in the 07 trial (looking at the most immature infants of 500-749 grams birth weight) this was a trend only and did not achieve statistical significance. Fewer pulmonary air leaks were reported in "rescue" all the trials except the 07 trial. Again like the prophylaxis (03) trial in very immature infants (Stevenson *et al* 1992) it appears that ***Exosurf*** has a less beneficial effect than in more mature infants.

Table 15: Significant 28-day outcomes reported in controlled trials of ***Exosurf***

Study	Outcome	Surfactant treated infants	Placebo	Relative risk	95% CI	Risk difference	95% CI
Bose *et al* (1990)	Air leak syndrome	15 / 192 (7.8%)	35/ 193 (18.1%)	**0.43**	0.24 to 0.76	**-10.3%**	-17.0 to –3.7
	Death or CLD	42 / 192 (21.9%)	63 / 193 (32.6%)	**0.67**	0.48 to 0.93	**-10.8%**	-19.6 to –1.9
Stevenson *et al* (1992)	CLD in survivors	26 / 51 (51.0%)	17 / 53 (32.1%)	**1.59**	0.99 to 2.56	**+18.9%**	+0.3 to +37.5%
Corbet *et al* (1991b)	Neonatal death	27 (12.1%)	44 (19.8%)	**0.61**	0.39 to 0.95	**-7.8%**	-14.5 to -1.0%
	Air leak syndrome	71 (31.7%)	115 (51.8%)	**0.61**	0.49 to 0.77	**-20.1%**	-29.1 to –11.1%
Long *et al* (1991a)	Neonatal death	23 (11.2%)	50 (23.5%)	**0.48**	0.30 to 0.75	**-12.3%**	-19.4 to -5.2%
	Air leak syndrome	71 (34.5%)	114 (53.5%)	**0.64**	0.51 to 0.81	**-19.1%**	-28.4 to -9.7%
	Death or CLD	57 (27.7%)	80 (37.6%)	**0.74**	0.56 to 0.98	**-9.9%**	-18.8 to -1.0%

Table 15: Significant 28-day outcomes reported in controlled trials of ***Exosurf*** (continued).

Study	Outcome	Surfactant treated infants	Placebo	Relative risk	95% CI	Risk difference	95% CI
Long *et al* (1991b)	Neonatal death	26 / 614 (11.2%)	43 / 622 (6.9%)	**0.61**	0.38 to 0.98	**-2.7%**	-5.2 to -0.1%
	Treated PDA	279 / 614 (45.4%)	334 / 622 (53.6%)	**0.85**	0.76 to 0.95	**-8.2%**	-13.7 to –2.6%
	Air leak syndrome	109/ 614 (17.8%)	187 / 622 (30.0%)	**0.59**	0.48 to 0.73	**-12.3%**	-17.0 to –7.6%
	CLD in survivors	16 / 588 (2.7%)	31 / 580 (5.3%)	**0.51**	0.28 to 0.92	**-5.3%**	-4.9 to –0.4%
	Death or CLD	42 / 614 (6.8%)	74 / 622 (11.9%)	**0.57**	0.40 to 0.83	**-9.9%**	-8.3 to –1.8%
Smyth *et al* (1995)	CLD in survivors	32 / 69 (46.4%)	37 / 55 (67.3%)	**0.69**	0.50 to 0.94	**-20.9%**	-38.0 to -3.8%
	Death or CLD	85 / 115 (72.2%)	91 / 109 (83.5%)	**0.89**	0.77 to 1.02	**-11.3%**	-22.1 to -0.6%

Although the investigators had embarked on these trials of ***Exosurf*** using a dosage of 67.5mg/kg (5ml/kg) of DPPC, there was little evidence to suggest that this was the optimum dosage for a neonate. Work by Jackson *et al* (1986) had suggested the alveolar surfactant pool after adaptation to extra-uterine life was 100mg/kg, this compared with 4-5 mg/kg found in preterm infants with RDS (Adams *et al* 1970, Hallman *et al* 1986). The ***Exosurf*** 12 trial (Berry *et al* 1994) attempted to discover if there was any benefit to using a smaller or larger dose. Recognising that very large numbers of infants would be needed to demonstrate differences in mortality and chronic lung disease, the researchers concentrated on ventilation requirements, duration of ventilation and death from RDS.

Both the 5ml/kg and 7.5ml/kg groups showed improvements over the 2.5ml/kg group but only in terms of ventilatory requirements in the short term. The authors concluded from this that 5ml/kg and 7.5ml/kg were better than 2.5ml/kg but that there was no additional benefit of 7.5ml/kg over 5ml/kg. The findings are very much in keeping with those of the ***Surfactant TA*** trial of Konishi *et al* (1990) looking at doses of 60 mg/kg versus 120 mg/kg of phospholipids.

The question of optimum number of doses raised by the ***Exosurf*** 13 trial was further explored in the 17 (Pramanik *et al* 1992) and 19 (Long *et al* 1992) trials. The results obtained showed that the more doses that were given the more favourable the outcomes. Whereas the 13 trial had shown a reasonably large benefit of three over one dose, there was less benefit to be gained when using four as opposed to two doses (17 trial) or six as opposed to three doses.

The optimum number of doses was also investigated as part of a UK based study – the OSIRIS (Open Study of Infants at high risk of or with Respiratory Insufficiency - the role of Surfactant) trial. This trial (The OSIRIS Collaborative Group 1992) looked at two aspects of drug administration under the auspices of a single trial; the first – whether early or late administration was better is discussed more fully in chapter 6; the second – looking at the optimum number of doses (up to two versus up to four 5ml/kg doses) – suggests that third, and subsequent, doses of surfactant do not significantly improve outcomes. Treatment investigational new drug experience with ***Exosurf*** under the regulations of the Food and Drug Administration (Easa *et al* 1992) agreed with the OSIRIS trial but stated that some infants might benefit from the third dose.

The last large ***Exosurf*** trial to be discussed also came from Europe. This study (The European Exosurf Study Group 1992) examined early versus late treatment using ***Exosurf*** but underwent a change in protocol after publication of the ***Exosurf*** 05 trial (Long *et al* 1991b). It is discussed in chapter 6.

Overall ***Exosurf*** was shown to be both safe and efficacious. Few adverse events were reported in the North American ***Exosurf*** and the two European studies. The 03 trial (Stevenson *et al* 1992) reported what was a worrying adverse event of an increase in pulmonary haemorrhage from 2% to 12%. In other trials there was no difference. A retrospective analysis did not reveal any evidence that ***Exosurf*** affected coagulation (Long *et al* 1992b). Most pulmonary haemorrhages occur as a result of pulmonary oedema and patent ductus (Garland *et al* 1994), and authors of the 03 study suggested that a non-significant excess of treated ducts in the ***Exosurf*** group might have contributed to this. Chatfield *et al* (1994) reported adverse experiences with ***Exosurf*** treated outside the trials, postulating that the relatively large volume (5ml/kg) might be a problem and Saliba *et al* (1994) suggested the large volume may also cause hypercarbia and altered cerebral blood flow during rapid instillation. Longer-term follow-up of ***Exosurf***-treated infants (Table 12) suggested that despite better neonatal survival there was no increase in the numbers of handicapped children.

As with other surfactants further placebo-controlled trials of ***Exosurf*** can no longer be considered to be ethical. ***Exosurf*** is the synthetic surfactant most widely used on a global basis. It is not surprising that most trials between synthetic and animal-derived surfactants use ***Exosurf***. These trials are discussed in chapters 8.

5.3.2 Meta-analysis of the randomised controlled trials of Exosurf

Method

The objective of this section was to assess the effect of intra-tracheal administration of ***Exosurf*** administered either prophylactically or in premature infants with established RDS. The search strategy outlined in section 5.1.2 was used to examine outcomes in randomised controlled trials that compared the effect of ***Exosurf*** to controls in preterm infants with or at risk of RDS. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Studies fulfilling the following criteria were included

(a) Types of studies - Randomised controlled trials comparing ***Exosurf*** to control receiving either placebo or no treatment.

(b) Types of participants – preterm neonates at risk of or with clinical and radiological evidence of RDS requiring assisted ventilation.

(c) Types of intervention - Infants randomised to receive ***Exosurf*** versus control treatment (intratracheal administration of air placebo).

(d) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, pulmonary air leak, patent ductus arteriosus, necrotising enterocolitis, severe intraventricular haemorrhage (Papile Grade III) and/or periventricular echodensities (Papile Grade IV), bronchopulmonary dysplasia (at 28 days in neonatal survivors), bronchopulmonary dysplasia or death (at 28 days). In particular for the North American ***Exosurf*** trials BPD was defined as:

   1). Presence of tachypnoea and retraction

   2). Need for supplemental oxygen

   3). Chest x-ray changes rating a score of ≥ 4 using Edwards' classification (Edwards 1982).

Results

The following studies were identified as suitable for inclusion:

Preliminary trial of Exosurf (Phibbs *et al* 1991)

Exosurf Trial 01 / 02 (Bose *et al* 1990)

Exosurf Trial 03 (Stevenson *et al* 1992)

Exosurf Trial 04 (Corbet *et al* 1991a and 1991b)

Exosurf Trial 05 (Long *et al* 1991b)

Exosurf Trial 06 / 09 (Long *et al* 1991a)

Exosurf Trial 07 (Smyth *et al* 1995)

Exosurf Trial 08 (McMillan *et al* 1995)

The trials that compared different doses, different dosing schedules and early versus late administration were unsuitable for inclusion. All these trials are summarised in Table 13.

Treatment of premature infants with ***Exosurf*** leads to an improvement in oxygenation and ventilatory requirement. It has the following clinical impact (Figure 4):

Neonatal Mortality: All trials report on the risk of neonatal mortality and all trials except the 03 trial (Stevenson *et al* 1992) and 07 trial (Smyth *et al* 1995) reported a decrease in the risk of neonatal mortality associated with ***Exosurf*** use. These two trials examined the use of ***Exosurf*** in the most immature infants where a high mortality from non-respiratory causes would negate some of the benefit gained by improving respiratory disease. However even when the meta-analysis includes the 03 and 07 trials the typical estimate suggests a decrease in the risk of neonatal mortality associated with ***Exosurf*** treatment (typical relative risk 0.74, 95% CI 0.64 to 0.86; typical risk difference –4.9%; 95% CI –7.4 to –2.5%).

Pulmonary Air Leak: Again all trials report this outcome, using an all-encompassing definition of pulmonary air leak syndrome. As such this does not differentiate pneumothoraces from PIE. The typical estimate suggests a decrease in the risk of pulmonary air leak syndrome associated with ***Exosurf*** use (typical relative risk 0.68, 95% CI 0.62 to 0.75; typical risk difference –12.5%; 95% CI –15.6 to –9.3%).

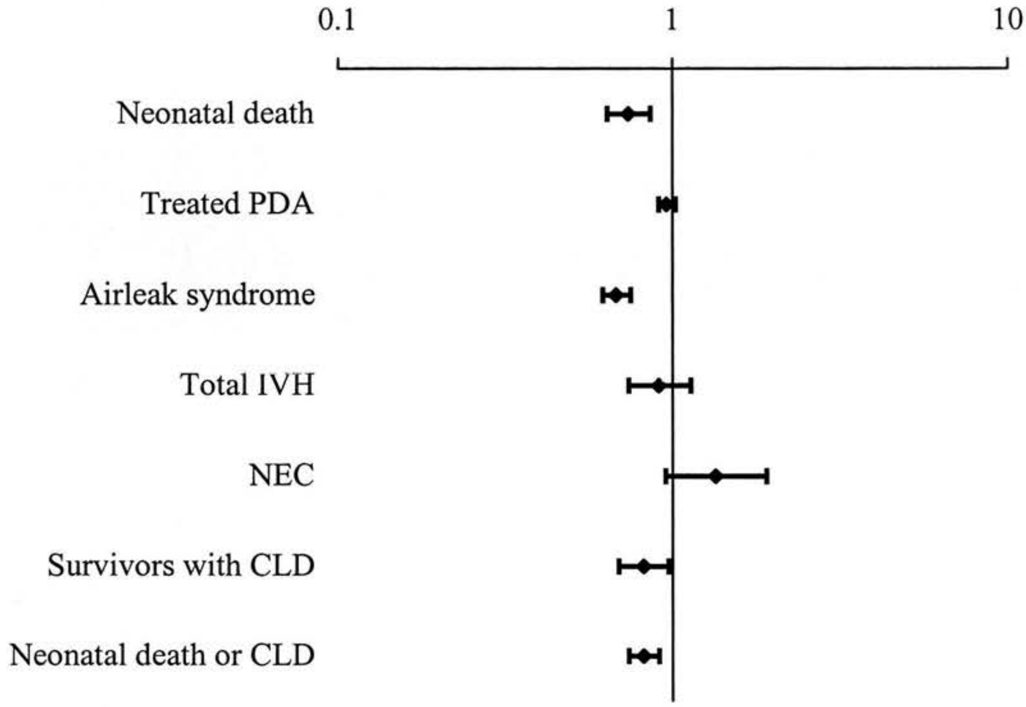
Patent Ductus Arteriosus: All trials reported on the incidence of PDA requiring treatment (indomethacin or surgical ligation). The typical estimate shows no difference in the risk of significant PDA associated with ***Exosurf*** (typical relative risk 0.96, 95% CI 0.91 to 1.02; typical risk difference –2.2%; 95% CI –5.5 to +1.2%).

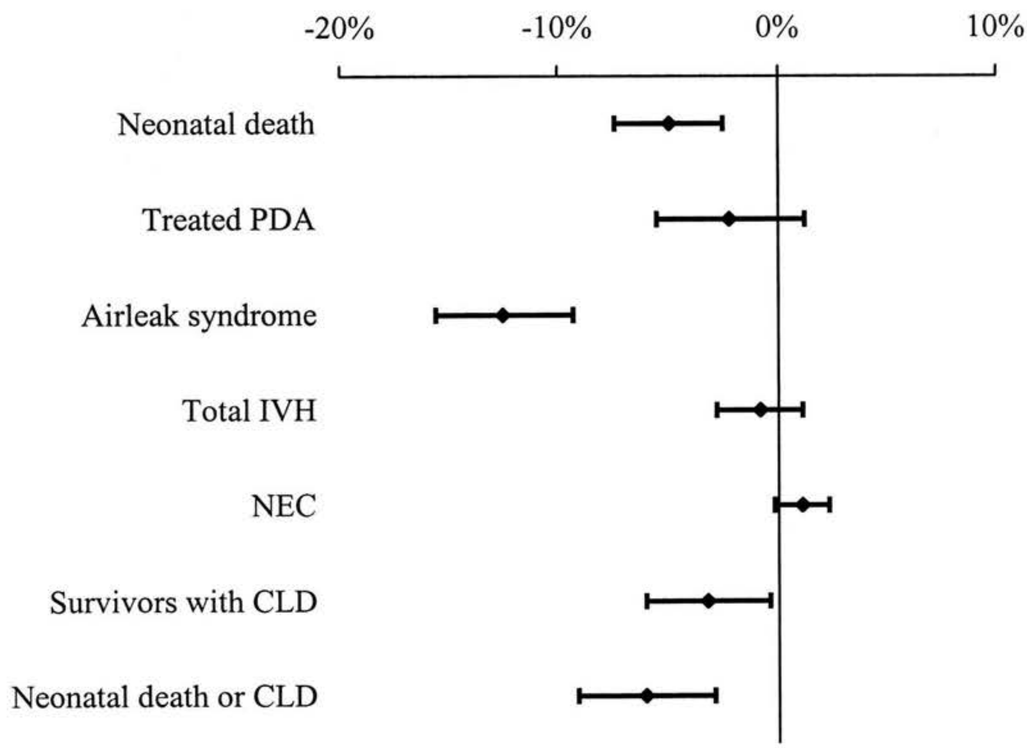
Necrotising Enterocolitis: The typical estimate shows small non-significant increase in the risk of NEC after ***Exosurf*** (typical relative risk 1.34, 95% CI 0.95 – 1.89; typical risk difference +1.1%; 95% CI –0.2 to +2.3%).

Intraventricular Haemorrhage: The ***Exosurf*** trials report the incidence of severe (grade III) IVH and/or periventricular echodensities (periventricular haemorrhage and ischaemia). The typical estimate reported a trend to decreased risk of severe IVH/ periventricular echodensities after ***Exosurf*** (typical relative risk 0.91, 95% CI 0.74 – 1.13; typical risk difference –0.8%; 95% CI –2.8 to +1.1%).

Bronchopulmonary Dysplasia / Chronic Lung Disease: This was one of the primary outcomes of most of the North American ***Exosurf*** trials. There had been a fairly widespread expectation prior to these trials, which were among the first large trials of surfactant in a neonatal population that RDS and all its complications would be reduced. The typical estimate of oxygen dependency at 28 days postnatal age in survivors shows a decrease in the risk of BPD/CLD among surviving infants treated with ***Exosurf*** (typical relative risk 0.82, 95% CI 0.69 – 0.97; typical risk difference –3.2%; 95% CI –6.0 to –0.4%).

Figure 4: Meta-view charts of risk difference and relative risk between ***Exosurf*** treated infants and controls.





Bronchopulmonary Dysplasia / Chronic Lung Disease* OR *Death: The typical estimate of oxygen dependency or death at 28 days postnatal age shows a decrease in the risk of BPD/CLD among surviving infants treated with ***Exosurf*** (typical relative risk 0.82, 95% CI 0.74 – 0.91; typical risk difference –6.0%; 95% CI –9.1 to –2.9%).

Conclusion

Exosurf was shown to be both safe and efficacious It reduces oxygen and ventilator requirements during the acute phases of RDS. It is the only surfactant that has been shown to reduce the incidence of BPD/CLD in surviving infants although the limitations of using a 28 day definition need to be taken into consideration. Incidence of neonatal death and pulmonary air leak were significantly reduced, but other complications of prematurity including PDA and NEC were not.

5.4 Survanta (beractant) Abbott Laboratories, Chicago, Illinois, USA

5.4.1 Development and early trials of Survanta:

Survanta (beractant) is a derivative of the bovine surfactant used by Fujiwara *et al* (1980). This was developed and became commercially available under the name ***Surfactant TA*** (Surfacten, Tokyo Tanabe, Tokyo, Japan). This product was then licensed by Abbott Laboratories and subsequently launched under the Investigational New Drug program in the USA, acquiring the name ***Survanta*** in 1993. Beractant is widely available and is also known as ***Survanta-Vent*** in Sweden, Switzerland and Malaysia. This review considers all the published trials of beractant irrespective of the name and place of manufacture (see Table 16). The only differences between ***Surfactant TA*** and ***Survanta*** relate to phospholipid concentration (30 mg/ml versus 25 mg/ml) and an additional final stage autoclaving of ***Survanta***. These differences are insufficient to consider the surfactants as separate entities.

Table 16: Summaries of the controlled trials involving ***Survanta*** and ***surfactant TA***

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Raju *et al* (1987) - placebo controlled trial of surfactant TA (30 infants)	Randomised Single centre Sealed envelopes (no stratification) Blinded using drug administration teams Saline placebo in control arm	Birthweight 751-1750 grams Clinical and radiological RDS Ventilated with $FiO_2 \geq 0.5$ at a MAP 8 cm H_2O. $a/APO_2 \leq 0.24$ Were less than six hours old.	Chromosomal or congenital abnormalities	Ventilator and oxygen requirements Complications of prematurity
Gitlin *et al* (1987) - placebo controlled trial of surfactant TA (41 infants)	Randomised Multicentre (3 centres) Sealed envelopes Saline placebo in control arm	Birthweight 1000-1500 grams. Less than 8 hours old. Clinical and radiological RDS. Ventilated with $FiO_2 \geq 0.4$	Chromosomal or congenital abnormalities	Ventilator and oxygen requirements Complications of prematurity
Konishi *et al* (1988) – high versus low dose regimen of surfactant TA (46 infants)	Randomised Multicentre (8 centres) Sealed envelopes (stratified by centre) Blinded using drug administrators Low dose of 60 mg/kg versus 120 mg/kg after randomisation	Birthweight 1000-1499 grams Immature microbubble testing of gastric aspirates Ventilated with $FiO_2 \geq 0.4$	Congenital malformation or sepsis	Improvements in FiO_2, a/APO_2 and ventilation in first 3 days Complications of prematurity

Table 16: Summaries of the controlled trials involving ***Survanta*** and ***surfactant TA*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Horbar *et al* (1989) – rescue trial of single dose Survanta (159 infants)	Randomised Multicentre (7 centres) Sealed envelopes (stratified by centre) Blinded using drug administrators 100 mg/kg after randomisation	In-born Birthweight 750-1750 grams Clinical and radiological RDS Clinically stable Post-ductal arterial catheter in situ Ventilated with $FiO_2 \geq 0.4$	Congenital malformation or sepsis	Improvements in FiO_2, a/APO_2 and ventilation in first 3 days Clinical status at 7 and 28 days of age. Complications of prematurity
Horbar *et al* (1990) – rescue trial of single dose Survanta (106 infants)	Randomised Multicentre (8 centres) Sealed envelopes (stratified by centre and birthweight) Blinded using drug administrators 100 mg/kg after randomisation	In-born Birthweight 750-1750 grams Between 3-6 hours old Clinical and radiological RDS Clinically stable Post-ductal arterial catheter in situ Ventilated with $FiO_2 \geq 0.4$	Congenital malformation or sepsis Co-existing diseases Pre-existing pneumothorax or pneumopericardium Maternal opiate abuse	Improvements in FiO_2, a/APO_2 and ventilation in first 3 days Clinical status at 7 and 28 days of age. Complications of prematurity
Soll *et al* (1990) – controlled trial of prophylaxis dose of Survanta (156 infants)	Randomised Multicentre (4 centres) Attempted blinding using drug administrators Sealed envelopes (stratified by centre, antenatal steroids and birthweight) Air placebo or 100 mg/kg of Survanta within 15 minutes of birth	Gestation 24-30 weeks Birthweight 750-1250 grams. Stabilised and intubated within 15 minutes of delivery.	Chromosomal or congenital abnormalities Congenital sepsis Use of intratracheal drugs during resuscitation at birth	Improvements in FiO_2, a/APO_2 and ventilation in first 3 days X-ray appearance at 24 hours. Clinical status at 7 and 28 days of age. Complications of prematurity

Table 16: Summaries of the controlled trials involving ***Survanta*** and ***surfactant TA*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Chen (1990) - single dose of surfactant TA (18 infants)	Randomised (method not stated) Single centre 120 mg/kg of surfactant TA or 4 ml of air placebo Blinding method (not stated)	Clinical and radiological RDS Immature microbubble testing of gastric aspirates	Not stated	Improvements in FiO_2, a/APO_2 and ventilation Clinical status at 28 days Complications of prematurity
Fujiwara *et al* (1990) - single dose rescue trial of surfactant TA (100 infants)	Randomised Multicentre Sealed envelopes (stratified by weight and centre) Blinded using drug administrator	Birthweight 750-1749 grams Appropriate for gestational age). Clinical and radiological RDS. Ventilated with$_2$ $\geq$ 0.4 and MAP $\geq$ 7 cm H_2O. Less than eight hours old. Stable microbubble test on gastric aspirate	No pre-existing grade III or IV IVH Pre-existing PIE/pneumothorax. Any congenital cardiac abnormality Multiple congenital abnormalities Congenital sepsis	Improvements in FiO_2, a/APO_2 and ventilation Clinical status at 28 days Complications of prematurity
Hoekstra et al (1991) - placebo controlled multiple- dose Survanta (430 infants)	Randomised Multicentre (8 centres) Sealed envelopes (stratified by centre, weight and antenatal steroid course) Blinded by dosing investigators	Gestation 23-29 weeks Birthweight 600-1250 grams In-born	Unstable or bradycardic after 15 minutes of age Maternal opiate abuse Congenital abnormality Mature L/S ratio	Mortality and/or chronic lung disease at 28 days Improvements in FiO_2, a/APO_2 and ventilation Cause of death Complications of prematurity

Table 16: Summaries of the controlled trials involving ***Survanta*** and ***surfactant TA*** (continued)

Study	Methods	Participants	Exclusions	Outcomes
Liechty *et al* (1991) - controlled multiple dose Survanta (798 infants)	Randomised Multicentre (8 centres) Sealed envelopes (stratified by centre and weight) Blinded by dosing investigators	Birthweight 600–1750 grams. Were clinically. Clinical and radiological RDS. Ventilated with FiO2 $\geq$ 0.4 Age 1-6 hours. Indwelling arterial catheter.	Congenital malformation Pre-existing pneumopericardium or pneumothorax	Mortality and/or chronic lung disease at 28 days Improvements in FiO_2, a/APO_2 and ventilation Cause of death Complications of prematurity
Konishi *et al* (1992) – early versus late single dose of surfactant TA (32 infants)	Randomised Multicentre Randomisation method not stated Blinding method not stated	Birthweight 500-1500 grams. Intubated. Stable microbubble test on gastric aspirate	Prolonged rupture of membrane ($\geq$ 72 hours). Evidence of infection (maternal fever or gastric aspirate leucocyte count of <10). Congenital malformations Oligo- or polyhydramnios. Apgar score $\leq$ 4 at 5 minutes.	Differences in a/APO_2 at 72 hours Differences in severity of RDS Outcomes at 7 and 28 days

Table 16: Summaries of the controlled trials involving ***Survanta*** and ***surfactant TA*** (continued)

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Zola *et al* (1993a) – 3 dosing methods for Survanta (299 infants)	Randomised Multicentre (6 centres) Method of randomisation not stated but stratified by weight Blinded using dosing administration teams	Birthweight ≥ 600 grams. Age < eight hours. Clincal and radiological RDS. Ventilated with $FiO_2 \geq 0.4$. Clinically stable Arterial catheter and SaO_2 probe in use.	Congenital malformation Pre-existing pneumopericardium, pneumothorax or other form of airleak	Events during surfactant administration. Oxygen and ventilation for the first 72 hours. Complications of prematurity at 28 days

Survanta initially became available in the United States under the name ***Surfactant TA***, thus some early trials use the name ***Surfactant TA***. Following US Food and Drug Administration (FDA) approval, the product that was made by Ross/Abbott Laboratories became known as ***Survanta*** (*personal communication* – RF Soll). It is therefore possible to find an abstract, such as that by Horbar *et al* (1988), using the name ***Surfactant TA*** and the full-published trial using the name ***Survanta*** (Horbar *et al* 1990). In general ***Surfactant TA*** is the name of the product of the Japanese manufacturers, whereas ***Survanta*** is that used by the American Ross/Abbott Laboratories.

Beractant is a modified lung surfactant extract obtained from minced bovine lung by organic solvent extraction. The extract is first sterilised by autoclaving and then modified through the addition of DPPC, tripalmitin and palmitic acid. This is then dispersed in physiological saline to give a phospholipid concentration of 25mg/ml. The final preparation contains approximately 88-90% phospholipids, 3% triglycerides, 6% free fatty acids, 1% protein and 0.2% cholesterol. During the early trials the surfactant preparation (usually ***Surfactant TA***) was frozen and stored as a lyophilised powder at $-20^{o}C$. It was thawed at room temperature for about 20 minutes prior to use and mixed with variable amounts of saline. ***Survanta*** is no longer frozen and is available ready mixed. The *in vitro* properties of ***Surfactant TA*** have been reviewed by Taeusch *et al* (1986).

Survanta is given at a dose of 100mg/kg of phospholipids. The volume (4 ml/kg), therefore, represents a substantial proportion of the infants' tidal volume and to avoid flooding the lungs it is given in aliquots of 2 ml/kg. After each aliquot the infant is reattached to the ventilator or bag and mask and given about one minute of positive pressure ventilation. Thus compared with the two small volume surfactants (***Curosurf*** and ***ALEC***), ***Survanta*** is more difficult to administer.

Fujiwara and colleagues were responsible for the initial development of beractant. It was shown to improve pulmonary mechanics in immature rabbits (Fujiwara *et al* 1979a) and to reduce the lung injury sustained as a result of positive pressure ventilation (Fujiwara *et al* 1979b). It was then tested in an unselected human neonatal population (Fujiwara *et al* 1980). Ten infants of a mean gestation of 30 weeks and severe RDS were treated with a single dose of the surfactant. Within 3 hours of surfactant administration the mean FiO_2 had decreased, and within 6 hours mean airway pressure had decreased.

Eight of the infants survived. The two deaths were unrelated to RDS: one infant died with post-operative complications 36 hours after surgery for tracheo-oesophageal fistula, the other died at 30 days of age with *Serratia* sepsis). All nine infants who survived the first week developed patent ducts – an unexplained finding but one that came to dominate the thinking in some of the later trials. Of the eight long-term survivors, one remained oxygen dependent at several months.

The next published trials of ***Surfactant TA*** appeared in 1987 (Raju *et al* 1987, Gitlin *et al* 1987, and were small trials that compared a single dose of ***Surfactant TA*** against a saline placebo in established RDS. The aim of the trials was to establish the safety and efficacy of the surfactant, and to demonstrate the changes in oxygenation that occurred.

In the meantime work was being undertaken to establish the optimum dosage for ***Surfactant TA*** (Konishi *et al* 1988). Although the early trials had used a dose of approximately 100mg/kg of phospholipids, it was unclear whether this was the best dose for infants with RDS. This trial compared doses of 60mg/kg versus 120mg/kg in infants who were shown to have immature endogenous surfactant (screening their gastric aspirates prior to enrolment). The trial was designed to look at the relatively short-term outcomes of oxygenation in the period after surfactant rather than the neonatal outcomes. It was found that both doses improved oxygenation but that the higher dose produced a more sustained response. The high dose group also had fewer survivors with CLD. It is likely that the comparable initial improvements followed by a later worsening of the RDS was due to exogenous surfactant being effective initially but in the low-dose group the smaller amounts of surfactant were inactivated by proteinaceous leak. In the end a dose of 100mg/kg of phospholipids was recommended for the commercially available product.

The move into the American and world market by ***Survanta*** was preceded by several trials that paralleled the Asian trials of ***Surfactant TA*** and further studies using animal models (Vidyasagar *et al* 1985). The major difference between the two sets of trials is that the Asian investigators screened all infants using a stable microbubble test (Pattle *et al* 1979) on their gastric aspirates. A "less than weak" stable microbubble rating ($\leq$10 bubbles per mm^3) indicated surfactant deficiency. All infants in the Asian studies (Konishi *et al* 1988, Chen *et al* 1990, Fujiwara *et al* 1990, Konishi *et al* 1992) had immature surfactant.

The stable microbubble test had been developed by Pattle *et al* (1979) and was intended for use on samples of amniotic fluid. The investigators in the ***Surfactant TA*** studies reported that it was easy to use and reliable (Chida *et al* 1991) and to be 100% predictive on testing amniotic fluid (Chida & Fujiwara 1993). On tracheal aspirates the sensitivity of the stable microbubble test remained high (>90%) but its specificity was only 52% (Friedrich *et al* 1998). Testing for surfactant maturity using samples other than the amniotic fluid such as gastric aspirates has been found to be even less reliable (Rüdiger *et al* 1998, Teeratakulpisan *et al* 1998).

Two identical studies in North America (Horbar *et al*1989) and Europe (Horbar *et al* 1990) followed looking at a single "rescue" dose of ***Survanta*** in established RDS. They were designed to establish the early (≤72 hours) efficacy of ***Survanta*** compared to air placebo. Despite this simply primary outcome the trials also showed significant reductions in pneumothoraces in treated infants however the FDA halted the European ***Survanta*** trial (Horbar *et al* 1990) after an excess of severe (grades III and IV) IVH was found in the ***Survanta*** arm. No explanation could be offered for this finding. With the exception of a non-significant excess of severe IVH in the ***Survanta*** arm of a multiple dose versus control study (Hoekstra *et al* 1991) this finding was not confirmed elsewhere.

Soll *et al* (1990) used a single dose of ***Survanta*** prophylactically and again both ventilation and oxygen requirements were shown to be better in the treated group. Of the outcomes at 28 days, there were statistically significantly fewer pneumothoraces in the surfactant group but significantly more cases of necrotising enterocolitis.

Larger multicentre placebo controlled studies involving 400 (Hoekstra *et al* 1991) and 800 infants (Liechty *et al* 1991) comparing multiple doses of ***Survanta*** followed. Up to four doses of surfactant were used, with additional doses given to infants who remained ventilated with an $FiO_2 \geq 0.3$. These trials produced similar results that clearly demonstrated the early benefits of ***Survanta*** (oxygen and ventilator requirements), but they also demonstrated that ***Survanta*** treatment reduced both overall neonatal mortality and mortality from RDS.

Overall the placebo-controlled trials of ***Surfactant TA/Survanta*** were fairly consistent in reporting reductions in early oxygen and ventilator requirements. Most studies also reported significant reductions in pulmonary air leaks (reported variably as pulmonary interstitial emphysema, pneumothorax or "air leak"). Only Hoekstra *et al* (1991) and Liechty *et al* (1991) demonstrated a significant reduction in neonatal mortality, most of which arose because of a similarly significant reduction in deaths from RDS. It is perhaps significant that these studies were large multicentre studies recruiting 428 (Hoekstra *et al* 1991) and 798 infants (Liechty *et al* 1991), and therefore statistically powered to do so. Only the study of Fujiwara *et al* (1991) reported a reduction in survivors with CLD at 28 days. However the small numbers mean that one additional infant in the treatment arm requiring oxygen at this stage would prevent the study reaching significance. All statistically significant outcomes in the placebo-controlled trials of beractant, irrespective of commercial source, are shown in Table 17.

The other studies involving one of the beractant preparations that have been reported are:

- Konishi *et al* (1992) – a randomised comparative trial between early and late administration of ***Surfactant TA*** (discussed further in chapter 6).
- Zola *et al* (1993a) a comparison of three methods of administering ***Survanta*** in infants with established RDS.
- Zola *et al* (1993b): Treatment Investigational New Drug (TIND) experience with ***Survanta***.
- Trials that compare ***Survanta*** with another surfactant (versus ***Exosurf***, ***Curosurf*** and ***Infasurf***) are discussed in chapter 8.

The work by Zola *et al* (1993a) arose because of concerns about the administration technique involving disconnecting the infant from the ventilator on 3-4 occasions whilst giving surfactant. This procedure was based on the work of Fujiwara *et al* (1980), and persisted through the subsequent development of beractant. Other surfactants can be administered in a single aliquot that clearly is easier to administer, although some have the advantage in that they were smaller volumes.

Zola *et al* found some minor differences between the groups, for example administering ***Survanta*** in 2ml/kg aliquots produced more reflux up the ET tube, four 1ml/kg aliquots took longer to administer than two aliquots. However there were no differences in the numbers of infants who had bradycardia and/or hypoxia during surfactant administration, nor were there differences in long-term outcomes.

Table 17: Significant outcomes reported in controlled trials of ***Survanta/surfactant TA***

Study	Outcome	Surfactant treated infants	Placebo	Relative risk	95% CI	Risk difference	95% CI
Gitlin *et al* (1987)	Pneumothorax	3 / 18 (16.7%)	13 / 23 (56.5%)	**0.29**	0.18 to 0.88	**-39.9%**	-66.4 to –13.3%
Raju *et al* (1987)	PIE	2 / 17 (11.8%)	7 / 13 (53.8%)	**0.22**	0.05 to 0.88	**-42.1%**	-73.2 to –11.0%
Horbar *et al* (1989)	Pneumothorax	10 / 78 (12.8%)	30 / 81 (37.0%)	**0.35**	0.18 to 0.66	**-24.2%**	-37.1 to –11.3%
Horbar *et al* (1990)	All grades of IVH	31 / 53 (59.6%)	14 / 53 (26.9%)	**2.21**	1.34 to 3.65	**+32.7%**	+14.7 to +50.7%
	Severe IVH (grades III and IV)	20 / 53 (38.5%)	8 / 53 (15.4%)	**2.50**	1.21 to 5.16	**+23.1%**	+6.6 to +39.5%
Fujiwara *et al* (1990)	CLD (survivors)	5 / 46 (10.9%)	11 / 36 (30.6%)	**0.36**	0.14 to 0.93	**-19.7%**	-37.2 to -2.2%
	Death or CLD	13 / 54 (24.1%)	21 / 46 (45.7%)	**0.53**	0.30 to 0.93	**-21.6%**	-39.9 to -3.2%
	PIE	1 / 54 (1.9%)	12 / 46 (26.1%)	**0.07**	0.01 to 0.53	**-24.2%**	-37.4 to –11.0%
	Pneumothorax	4 / 54 (7.4%)	18 / 46 (39.1%)	**0.19**	0.07 to 0.52	**-31.7%**	-47.5 to –16.0%
	All grades of IVH	11 / 54 (20.4%)	25 / 46 (54.3%)	**0.37**	0.21 to 0.68	**-34.0%**	-51.9 to -16.0%

Table 17: Significant outcomes reported in controlled trials of ***Survanta/surfactant TA*** (cont.)

Study	Outcome	Surfactant treated infants	Placebo	Relative risk	95% CI	Risk difference	95% CI
Hoekstra *et al* (1991)	Neonatal death (all causes)	24 / 210 (11.4%)	41 / 218 (18.8%)	**0.61**	0.38 to 0.97	**-7.4%**	-14.1 to –0.6%
	Death due to RDS	4 / 210 (1.9%)	34 / 218 (15.6%)	**0.12**	0.04 to 0.34	**-13.7%**	-18.9 to –8.5%
	PIE	49 / 210 (23.1%)	80 / 218 (36.7%)	**0.63**	0.47 to 0.85	**-13.6%**	-22.1 to –5.0%
	Other air leak	20 / 210 (9.4%)	45 / 218 (20.6%)	**0.46**	0.28 to 0.75	**-11.2%**	-17.9 to –4.5%
Liechty *et al* (1991)	PIE	75 / 403 (18.6%)	155 / 395 (39.2%)	**0.47**	0.37 to 0.60	**-20.6%**	-26.8 to –14.5%
	Other airleak	46 / 403 (11.4%)	102 / 395 (25.8%)	**0.44**	0.32 to 0.61	**-14.4%**	-19.7 to –9.1%
	Neonatal death (all causes)	74 / 403 (18.4%)	108/ 395 (27.3%)	**0.67**	0.52 to 0.88	**-8.9%**	-14.7 to –3.3%
	Death due to RDS	36 / 403 (9.0%)	80 / 395 (20.2%)	**0.44**	0.31 to 0.64	**-11.2%**	-16.1 to –6.4%
	Death or CLD	264 / 403 (65.7%)	288 / 395 (72.7%)	**0.90**	0.82 to 0.99	**-7.1%**	-13.4 to –0.7%

A Treatment Investigational New Drug (TIND) programme under an FDA agreement added to the experience gained through randomised trials (Zola *et al* 1993b), and reflected use of ***Survanta*** outside academic centres. The results in this programme were consistent with those in the controlled trials. No new safety problems were identified and the rate of adverse events was, if anything, lower in the TIND programme than in the trials.

Longer-term follow-up of infants in the above studies is limited to those infants enrolled in the two multiple dose trials. At an adjusted age of 6 months, beractant-treated infants had significantly more wheezing than control infants but had a significantly reduced need for supplemental oxygen and a significantly lower incidence of cerebral palsy (Survanta Multidose Study Group 1994).

Concerns regarding the immunological effects of beractant were also dispelled. Specific immunological responses to the bovine surfactant proteins present in ***Survanta*** could not be detected during the neonatal period (Whitsett *et al* 1991) or at 6 and 12 months of age (Survanta Multidose Study Group 1994).

Further placebo-controlled trials of beractant can no longer be seen to be ethical. However research into beractant has continued in the form of comparative trials (versus synthetic and other animal-derived surfactants). These are discussed in chapter 8.

5.4.2 Meta-analysis of the randomised controlled trials of beractant (Survanta or Surfactant TA).

Method

The objective of this section was to assess the effect of intra-tracheal administration of beractant (either ***Survanta*** or ***Surfactant TA***) administered either prophylactically or in premature infants with established RDS. The search strategy outlined in section 5.1.2 was used to examine outcomes in randomised controlled trials that compared the effect of beractant to controls in preterm infants with or at risk of RDS. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Studies fulfilling the following criteria were included

(a) Types of studies - Randomised controlled trials comparing beractant (as either ***Surfactant TA*** or ***Survanta***) to control receiving either placebo or no treatment.

(b) Types of participants – preterm neonates at risk of or with clinical and radiological evidence of RDS requiring assisted ventilation.

(c) Types of intervention - Infants randomised to receive beractant versus control treatment (intratracheal administration of air or saline placebo).

(d) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, pulmonary air leak syndrome, PIE, pneumothorax, patent ductus arteriosus, necrotising enterocolitis, total and severe intraventricular haemorrhage (Papile Grade III-IV), bronchopulmonary dysplasia (at 28 days in neonatal survivors), bronchopulmonary dysplasia or death (at 28 days).

Results

The following studies were identified as suitable for inclusion:

- Raju *et al* (1987): Randomised controlled, double blind trial of ***Surfactant TA*** in established RDS
- Gitlin *et al* (1987): Randomised controlled trial of single dose ***Surfactant TA*** in established RDS
- Horbar *et al* (1989): Randomised controlled trial of a single dose of ***Survanta*** in established RDS
- Horbar *et al* (1990): European randomised controlled trial of a single dose of ***Survanta*** in established RDS
- Soll *et al* (1990): Randomised controlled trial of single dose ***Survanta*** in prevention of RDS
- Chen (1990): Randomised controlled trial of ***Surfactant TA***
- Fujiwara *et al* (1990): Randomised controlled trial of single dose of Surfactant TA in treatment of RDS
- Hoekstra *et al* (1991): Randomised controlled trial of multiple doses of Survanta in prevention of RDS
- Liechty *et al* (1991): Randomised controlled trial of multiple doses of Survanta in established RDS

The other trials comparing different dosing schedules and early versus late administration were deemed unsuitable for inclusion in this meta-analysis. Details of all these trials are summarised in Table 16. Trials between beractant and different surfactants are reviewed in chapter 8.

Treatment of premature infants with beractant leads to an improvement in oxygenation and ventilatory requirement. It has the following clinical impact (Figure 5):

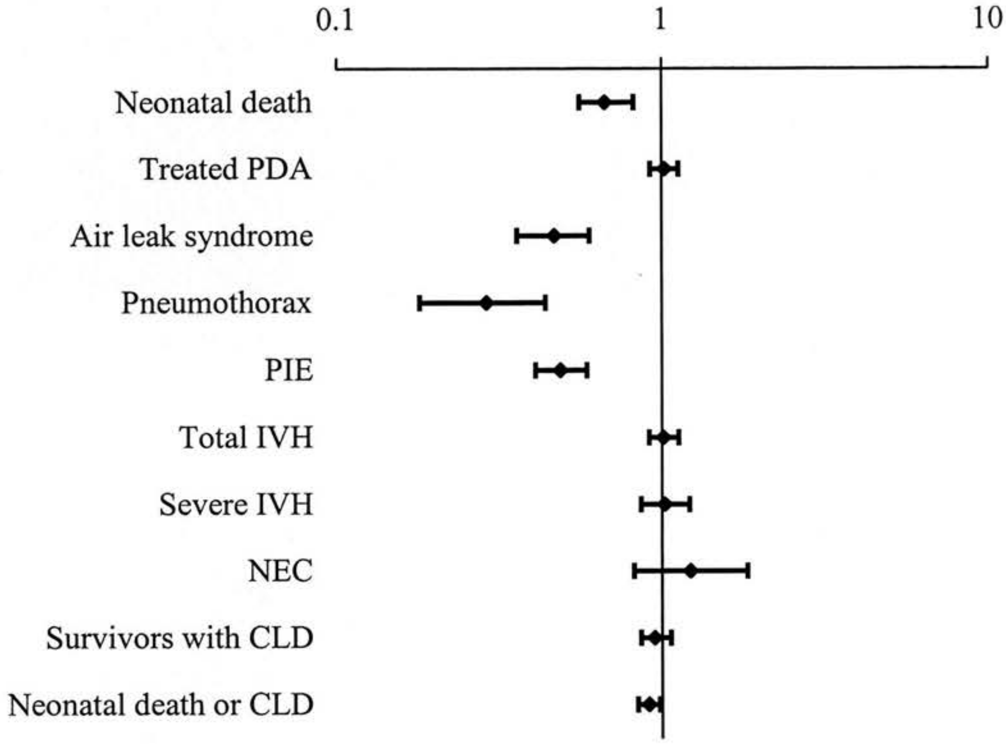
Neonatal Mortality: All trials report on the risk of neonatal mortality. Only the large trials of Hoekstra *et al* (1991) and Liechty *et al* (1991) are able to demonstrate significant reductions in neonatal mortality after beractant. There are trends to reduced neonatal mortality in the beractant group in all other trials except Horbar *et al* (1989) where no difference existed. The typical estimate from the meta-analysis suggests a decrease in the risk of neonatal mortality associated with beractant (typical relative risk 0.67, 95% CI 0.56 to 0.82; typical risk difference –7.4%; 95% CI –11.0 to –3.8%).

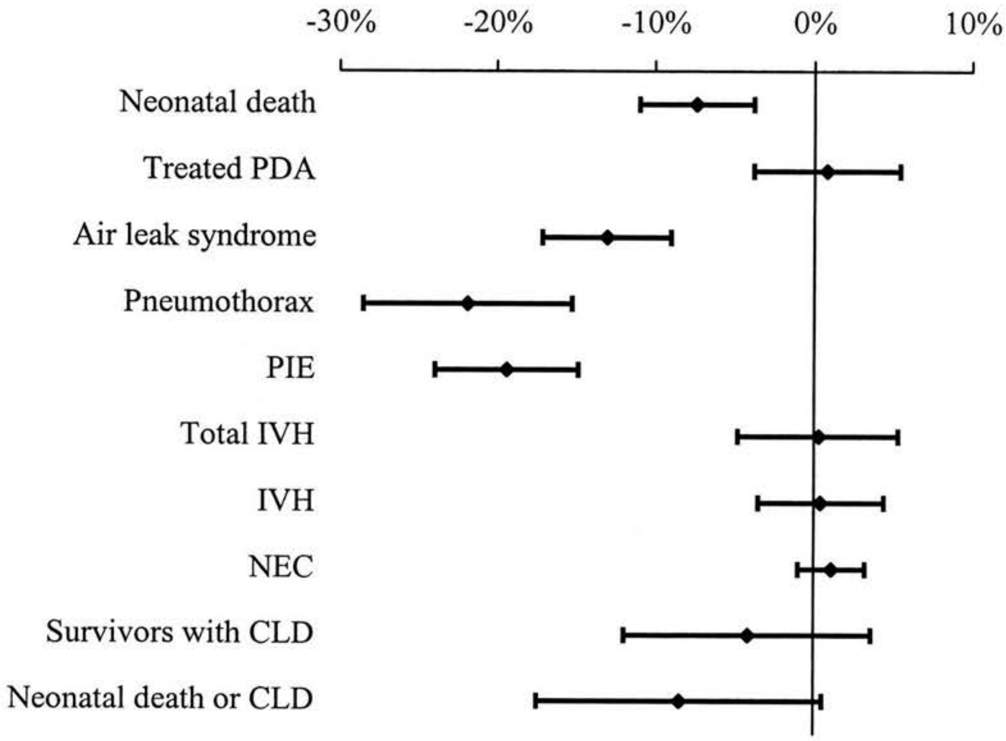
Pulmonary Air Leak: The trials vary in how they report this. Hoekstra *et al* (1991) and Liechty *et al* (1991) report both PIE and other air leak separately. Horbar *et al* (1990) reports other air leak without qualifying this further. All the other trials report both PIE and pneumothorax as separate outcomes. No trials report any trend to fewer air leaks among control infants and most trials report significant reductions in whatever air leak category that they use. The typical estimate suggests a decrease in the risk of PIE associated with beractant use (typical relative risk 0.49, 95% CI 0.41 to 0.59; typical risk difference –19.3%; 95% CI –23.9 to –14.8%). The typical estimate also suggests a decrease in the risk associated with beractant use for pneumothoraces (typical relative risk 0.29, 95% CI 0.18 to 0.44; typical risk difference –21.8%; 95% CI –28.5 to –15.2%). Similarly for air leak syndrome in general (typical relative risk 0.47, 95% CI 0.36 to 0.60; typical risk difference –13.0%; 95% CI –17.1 to –9.0%).

Patent Ductus Arteriosus: All trials reported on the incidence of PDA requiring treatment (indomethacin or surgical ligation). The typical estimate shows no difference in the risk of significant PDA associated with beractant (typical relative risk 1.02, 95% CI 0.92 to 1.12; typical risk difference +0.8%; 95% CI –3.8 to +5.4%).

Necrotising Enterocolitis: All the North American trials and the European trial (Horbar *et al* 1990) report this outcome. The typical estimate shows small non-significant increase in the risk of NEC after beractant (typical relative risk 1.22, 95% CI 0.82 to 1.82; typical risk difference +1.1%; 95% CI –1.0 to +3.2%).

Figure 5: Meta-view charts of risk difference and relative risk between beractant (***Survanta*** and ***Surfactant TA***) treated infants and controls.





Intraventricular Haemorrhage: The beractant trials report the incidence of total and severe (grade III-IV) IVH. One trial of ***Survanta*** (Horbar *et al* 1990) reported a statistically significant increase in both total and severe IVH in treated infants that led to termination of that trial by the FDA. Nonetheless the typical estimate shows no difference in the risk of IVH (any grade) after beractant (typical relative risk 1.01, 95% CI 0.91 to 1.12; typical risk difference +0.3%; 95% CI –4.8 to +5.3%). Similarly there was no difference in the risk of severe IVH (typical relative risk 0.99, 95% CI 0.83 to 1.17; typical risk difference –0.3%; 95% CI –4.1 to +3.5%).

Bronchopulmonary Dysplasia / Chronic Lung Disease: This was reported in all trials of beractant. The typical estimate of oxygen dependency at 28 days postnatal age in survivors shows a no difference in the risk of BPD/CLD among surviving infants treated with beractant (typical relative risk 0.95, 95% CI 0.86 to 1.06; typical risk difference –4.1%; 95% CI –11.9 to +3.6%).

Bronchopulmonary Dysplasia / Chronic Lung Disease* OR *Death: The typical estimate of oxygen dependency or death at 28 days postnatal age shows a decrease in the risk of BPD/CLD among infants treated with beractant (typical relative risk 0.91, 95% CI 0.84 to 0.98; typical risk difference –8.4%; 95% CI –17.4 to –0.5%).

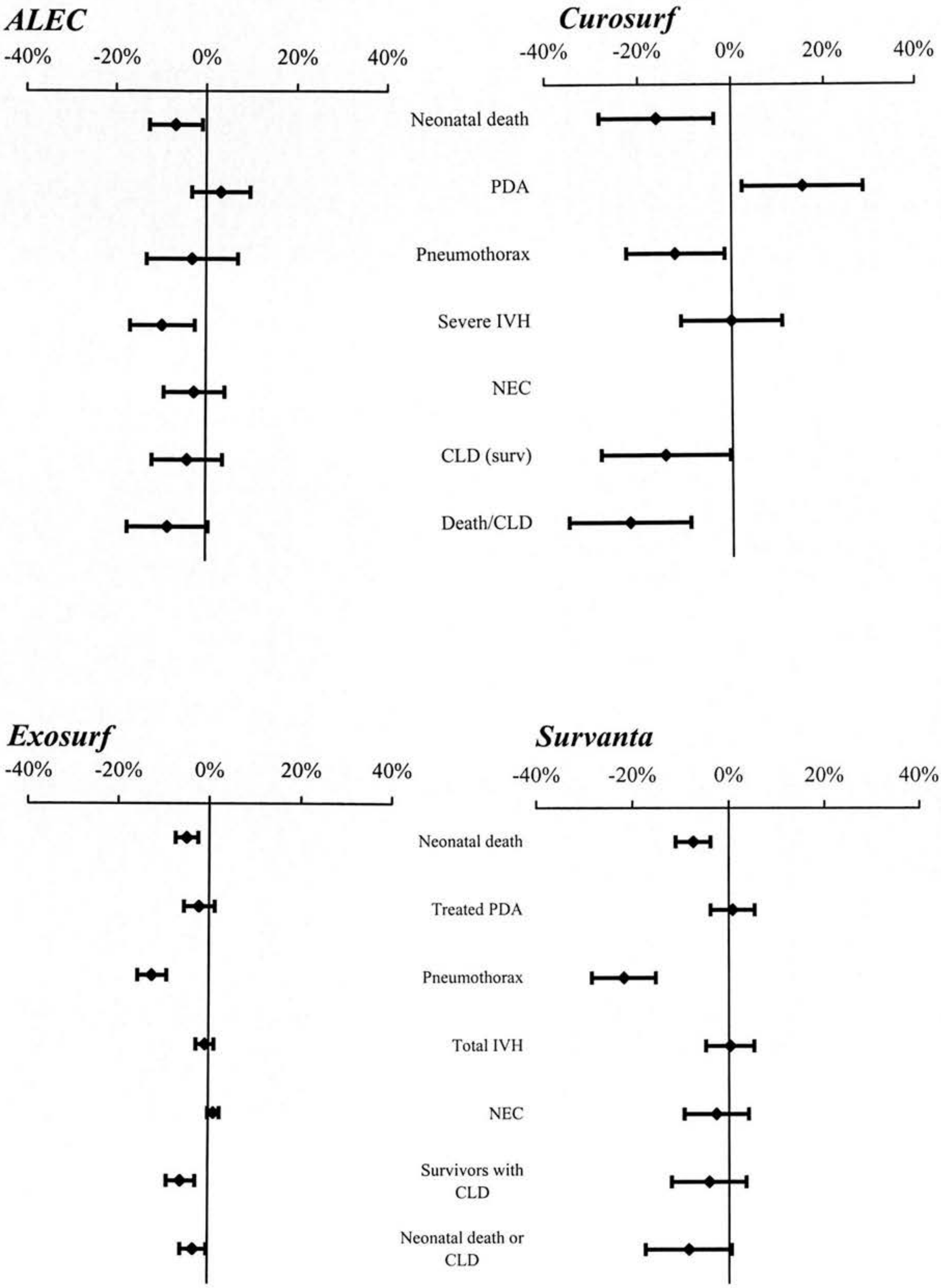
Conclusion

Beractant (as either ***Survanta*** or ***Surfactant TA***) has been shown to be an effective drug for reducing neonatal mortality. It reduces oxygen and ventilator requirements during the acute phases of RDS. Neonatal death and pulmonary air leak (whether this is reported as pneumothorax, PIE or a general air leak syndrome) are significantly reduced. But other complications of prematurity including PDA and NEC are not. Horbar *et al* (1990) reported an increase in total and severe IVH, however the meta-analysis suggests this result is unusual and there is no increased risk.

5.5 Overall conclusion

All four of the surfactant preparations that received licenses in the UK have been shown to be better than placebo for reducing neonatal mortality and early respiratory morbidity. Of the four, ***ALEC*** has been subjected to the fewest number of trials. The only large randomised trials of ***ALEC*** are the Ten Centre Study (Ten Centre Study Group 1987) and the Two Centre Study (Morley *et al* 1988). Whereas ***Curosurf***, ***Exosurf*** and ***Survanta*** have undergone a wider range of trials that not only looked at benefits compared to placebo but also examined other questions regarding timing of the first dose, the quantity of each dose, the number of doses and different methods of administration. A simple comparison of the results of the four meta-analyses (Figure 6) would suggest ***Curosurf*** might be the best of the currently available surfactants, however this method fails to take into account population variables that can influence the incidence and severity of RDS. The only fair methods for comparing different surfactants are direct comparisons. These are discussed in chapters 7 and 8.

Figure 6: Meta-analysis of risk difference between surfactant treated infants and controls for the four surfactants licensed in the UK.



Chapter 6

Dose size, frequency and timing of treatment.

Introduction

There are many questions that remain unanswered from simple placebo controlled trials of exogenous surfactant. Data obtained from studies of any given surfactant may not be applicable to the other preparations, but similarities in the doses and dosing schedules have emerged with all surfactant preparations. This chapter reviews the evidence for the dose, number of doses and timing of administration of surfactant.

6.1 Surfactant dose size

In clinical trials of surfactant the dose of phospholipids used varied from as little as 25 mg irrespective of birth weight (Morley *et al* 1981) to 200mg/kg (Collaborative European Multicenter Study Group 1988, Collaborative European Multicentre Study Group 1991, Bevilacqua *et al* 1993).

Use of these dose sizes had very little scientific basis, although as more became known about surfactant and surfactant deficiency it has become evident that a term infant who has adapted to extra-uterine life has a surfactant pool size of approximately 100mg/kg (Jackson *et al* 1986). By comparison an infant with RDS has a surfactant pool size of 5-10mg/kg (Hallman *et al* 1986).

Three trials have examined the effects of a varying dose of surfactant:

- Halliday *et al* (1993) – The EURO VI Study comparing multiple doses of ***Curosurf*** in high (up to 600mg/kg, initial dose 200mg/kg) and low (up to 300mg/kg, initial dose 100mg/kg) dose regimens.
- Berry *et al* (1994) - ***Exosurf*** 12 study, a dose ranging study comparing 2.5ml/kg (34mg/kg), 5ml/kg (67.5mg/kg) and 7.5ml/kg (101mg/kg) of ***Exosurf***.
- Konishi *et al* (1988) – high (120mg/kg) versus low (60mg/kg) dose regimen of ***Surfactant TA***.

In the EURO VI study, infants treated with an initial dose of 200mg/kg of ***Curosurf*** demonstrated better physiological improvements in ventilator and oxygen requirements in the immediate post surfactant period. The nature of the trial comparing not only the difference between doses but also the different number of doses precluded analysis of the effect of high versus low doses on longer-term outcomes as the number of doses and hence total accumulated surfactant dose can also affect outcome (see section 6.2).

Thus question of whether an initial dose of 200mg/kg produces better longer-term outcomes than 100mg/kg remains unclear. Within the EURO VI study (Halliday *et al* 1993) no statistically significant differences could be found in outcomes at 28 days or at discharge. Where there were differences these were of a small magnitude (the greatest difference was found in a 2.5% reduction in air leak in the high dose regime).

The other two trials compared the effects of a single dose of surfactant but using different amounts. Konishi *et al* (1988) examined the effects of the two dose sizes (60mg/kg and 120 mg/kg) of ***Surfactant TA*** in infants of 1000-1499 grams ventilated for RDS soon after birth. All infants had surfactant deficiency results on testing of their gastric aspirates. Both groups initially showed reductions in FiO_2 values and rises in calculated arterial-alveolar tension ratio (a/APO_2) after treatment, however after 6 hours there were differences with values in the low-dose group showing a worsening of RDS. The high dose group required significantly less oxygen between 6-72 hours after treatment, and had significantly higher a/APO_2 between 6-120 hours. In the longer-term significantly fewer infants in the high dose group were ventilated at 30 days of age. There were no significant differences in neonatal mortality probably due to the small numbers, but incidences of CLD at 28 days and IVH were significantly lower in the high dose (120 mg/kg) group.

In the other study, Berry *et al* 1994 looked at doses of 2.5ml/kg, 5ml/kg and 7.5ml/kg (34mg/kg, 67.5mg/kg and 101mg/kg of phospholipids) of ***Exosurf*** in infants of $\geq$1250 grams. Infants were enrolled and given "rescue" surfactant once the a/APO_2 was <0.22. They could receive up to two doses. Infants in both the 5ml/kg and 7.5ml/kg groups showed greater improvements compared to the 2.5ml/kg group in their short-term ventilatory requirements. There were two extra deaths in the 2.5ml/kg group due to RDS (not statistically significant), but the duration of ventilation was no greater in surviving infants. Outcomes such as pulmonary air leak and the other complications of prematurity were not reported. The authors nevertheless concluded that doses of 5ml/kg and 7.5ml/kg were better than 2.5ml/kg but that there was no additional benefit of 7.5ml/kg over 5ml/kg.

It would seem from the studies of Konishi *et al* (1988) and Berry *at al* (1994) that low doses of surfactant are less effective than ones that give infants approximately 70-100mg/kg of phospholipids. This would support evidence from a rabbit model of RDS with immediate and delayed times of surfactant administration where Seidner *et al* (1995) showed that a higher surfactant dose counteracted some of the surfactant inactivation that occurs with proteinaceous leak. What remains unclear is whether much higher doses such as that used by Halliday *et al* (1993) lead to clinically better outcomes. Neither this study nor the Berry *et al* (1994) study could show any difference at 28 days, although both showed lower oxygen and ventilator requirements in the early course of RDS. Evidence from a porcine model of RDS using the surfactants ***Survanta*** and ***Curosurf*** showed greater changes in systemic and cerebral blood flow after doses of 200mg/kg than after 100mg/kg (Moen *et al* 1998). This could potentially lead to ischaemic or haemorrhagic cerebral damage.

Conclusion

Whilst it appears that phospholipid doses of 70-100mg/kg are better than smaller doses, there is no evidence that more is better and some evidence to suggest that it might be counter-productive causing unwanted effects on systemic and cerebral circulations. Whether by accident or design most surfactants are given in a dose of approximately 70-100mg/kg of phospholipids.

6.2 How many doses are required?

Exogenous surfactant is lost from the alveolus in several ways. Some is incorporated into the metabolic and re-cycling pathways and becomes mixed with endogenous surfactant (Jobe *et al* 1993) and inactivation by serum proteins also plays a role (Ikegami *et al* 1983). The amount of exogenous surfactant lost seems to be about 15-20% of the total (Pettenazzo *et al* 1986), but this does not take into account the inactivated portion. With the incorporation into endogenous surfactant only 20-30% of the dose can be recovered by alveolar lavage in preterm lambs with RDS after 24 hours and turnover of alveolar phosphatidylcholine in this model of RDS was about 13 hours (Jobe *et al* 1989).

Several trials addressed the question of what is the optimum number of doses of surfactant. These are:

- Corbet *et al* (1995a) - the ***Exosurf*** 13 study. A single versus up to three doses of ***Exosurf*** used prophylactically in infants of 700-1100 grams.

- Pramanik *et al* (1992) – the ***Exosurf*** 17 trial. Two versus four doses of ***Exosurf*** used to treat infants ≥1250grams in a "rescue" strategy.
- Long *et al* (1992a) – the ***Exosurf*** 19 study. Three versus six doses of ***Exosurf*** used prophylactically in infants of <750 grams.
- OSIRIS study group (1992) - Two versus four doses of ***Exosurf*** (some given as early treatment, some given as late treatment).
- Speer *et al* (1992) – The EURO IV Study; single versus multiple doses of ***Curosurf***.

The results among the studies were variable, but among the statistically significant results were a reduction in neonatal mortality in a three dose group of ***Exosurf*** (Corbet *et al* 1995a), and fewer pneumothoraces in infants treated with multiple rather than a single dose of ***Curosurf*** (Speer *et al* 1992). There were no significant differences in the neonatal outcomes in the studies that looked at two versus four or three versus six doses. The conclusion of the authors of the largest study (OSIRIS study group 1992) was that third, and subsequent, doses of surfactant do not significantly improve outcomes over two doses.

Conclusion

There is general consensus that most infants with RDS benefit from two doses of surfactant irrespective of the type of surfactant used. Some more mature infants, particularly those that have received antenatal steroids, may manage with only a single dose whereas in a minority of infants more than two doses may be beneficial. In all studies the dosing regime employed was predominantly a 12-hour interval between doses. No study has looked at the effects of a variable dosing regime based on illness severity as determined using oxygenation index, a/PO_2 or other parameter looking at ventilation or oxygenation.

6.3 When should the first dose of surfactant be administered?

6.3.1 Evidence from animal models of RDS

The pathological processes that lead to the formation of the hyaline membrane seen in postmortem histology begin soon after birth and may be exacerbated by factors such as resuscitation manoeuvres, mechanical ventilation and oxygen therapy. Increasing maturity protects against this protein leakage (Ikegami *et al* 1996).

Leak of protein into the alveoli has long been recognised as an inhibitor of surfactant function and contributory to RDS (Tierney & Johnson 1965, Taylor & Abrams 1966). Most protein leak occurs early in the course of RDS, and this diminishes so that by 24 hours of age there is a six-fold reduction in net influx of serum protein to the alveolus (Ikegami *et al* 1992). Protein leak would appear to be related to more than just ventilation and oxygen exposure; Berry *et al* (1991) delivered and ventilated preterm lambs in which segments of lungs were obstructed. There was still evidence of protein leak in the obstructed segments, but not as much as in the ventilated portions of the lungs.

Treatment of RDS using conventional positive pressure ventilation exacerbates the protein leak in RDS. It is thought that the cyclical volume changes that occur with shear forces lead to alveolar disruption allowing protein leak. High frequency oscillatory ventilation (HFOV) uses a higher mean airway pressure but with cycle volumes that are smaller than the tidal volume of the ventilated infant. In comparison to conventional ventilation HFOV has been shown to limit the development of proteinaceous material in animals with RDS (Coalson *et al* 1989, Niblett *et al* 1989). When HFOV is combined with exogenous surfactant there is a greater reduction in lung injury than if surfactant or HFOV had been used alone (Jackson *et al* 1994). In addition reducing the protein leak with early use of HFOV prolongs the effectiveness of exogenous surfactant (Froese *et al* 1993).

Prevention of the protein leak may also be achieved through surfactant administration (Robertson *et al* 1985, Ikegami *et al* 1992, Seidner *et al* 1995). The sooner surfactant is given the more effective it is: Maeta *et al* (1988) showed delaying surfactant for two hours in a baboon model of RDS adversely affected compliance and oxygen requirements; Cummings *et al* (1995) used preterm sheep to show similar differences in those receiving early and late surfactant. Seidner *et al* (1995) showed that the amount of protein leak correlated with the delay in surfactant administration - preterm rabbits treated at 30 minutes of age had more severe RDS than those treated either immediately after delivery or at 15 minutes.

Researchers have questioned whether surfactant should be given before the first breath if it is to be entirely protective. Most preterm neonates receive resuscitation that involves the establishing a resting lung volume through the use of positive airways pressure, either via a pressure limited gas supply or a resuscitation bag. Both of these may give uncontrolled tidal volumes that in turn may contribute to the start of pulmonary inflammation (Spears *et al* 1991, Bjorklund *et al* 1997, Wada *et al* 1997).

Pre-resuscitation treatment with surfactant can be protective against protein leak but whether a clinically apparent advantage can be gained is not clear (Klopping-Ketelars *et al* 1994). Intra-amniotic fluid administration of ***Exosurf*** has been shown to be no better than post-natal administration in preterm rabbits (Galan *et al* 1992). Intra-amniotic surfactant has been reported in 6 neonates who developed only minimal RDS after treatment (Cosmi *et al* 1997). The technical difficulties of administering surfactant intra-amniotically - close to the fetal nostrils under ultrasound guidance and then stimulating respiratory activity using aminophylline administered to the mother - are not inconsiderable. Despite this and the fact that there is a net expulsion of lung fluid both in utero and during parturition the authors of this report proposed that the intra-amniotic route offered a reliable option for antenatal prevention of RDS.

6.3.2 Evidence from trials in neonatal populations

There are several studies that have tried to examine this question in a neonatal population (Table 18). "Prophylactic" surfactant has been advocated as being more beneficial than "rescue" therapy (Morley 1997, Soll & Morley 1998) and early "rescue" is more beneficial pthan late "rescue" (Yost & Soll 1999).

The literature, however, is confusing in the use of terms. This relates largely to the absence of accepted definitions of "prophylactic" and "rescue" treatment. "Rescue" therapy is that which is given when infants have developed respiratory failure due to RDS. A number of different criteria, such as oxygen requirement ≥ 0.4 or a/APO_2 <0.22 have been used to decide when "rescue" surfactant should be given (Table 19). "Prophylaxis" should by definition mean that all "at risk" infants receive surfactant before the onset of symptoms. The issue of "prophylaxis" has been further complicated by the use of tests of surfactant maturity such as the L/S ratio. Morley (1997) suggested that these preclude the trial being from being "prophylaxis" whereas Soll & Halliday (1998) disagreed.

Table 18: Summaries of the trials involving early and late administration of surfactant

Study	Methods	Participants	Exclusions	Outcomes
Dunn *et al* (1991) – trial of bLES in delivery room versus rescue at 6 hours (122 infants with further 60 controls receiving no surfactant)	Randomised Single centre Sealed envelopes (stratified by gestation and antenatal steroids) Not blinded Early arm intubated ASAP and given 3-4ml of surfactant, late arm treated if requiring ventilation with any O_2 at ≥7 cm H_2O	In-born infants < 30 weeks gestation	Chromosomal or congenital abnormality Ruptured membranes > 2 weeks Mature L/S ratio in amniotic fluid	Differences in the a/A ratio Ventilation requirements and duration of support Complications of prematurity
Kendig *et al* (1991) – trial of delivery room versus rescue Infasurf (479 infants)	Randomised Multicentre (3 centres) Sealed envelopes (stratified by centre) Not blinded Early arm given 3ml surfactant bolus prior to respiration, late arm if radiological RDS, ventilated with FiO_2 0.4 at ≥ 7 cm H_2O	In-born infants < 30 weeks gestation	Congenital abnormality considered lethal	Neonatal mortality Severity of RDS (ventilator and oxygen requirements) Complications of prematurity All analysed on "intention to treat basis"

Table 18: Summaries of the trials involving early and late administration of surfactant (continued)

Study	Methods	Participants	Exclusions	Outcomes
Merritt *et al* (1991) – delivery room versus rescue human surfactant (trial of singleton births - 107 infants with a further 50 non-surfactant treated controls)	Randomised Multicentre trial Sealed envelopes (stratified by centre and gestation) Early arm given 3.5 ml/kg after few inflation breaths, late arm if ventilated with $FiO_2 \geq 0.5$	Between 24-29 weeks gestation	Congenital abnormality Chromosomal abnormality Mature L/S ratio Rupture of membranes > 3 weeks	Neonatal death or CLD Ventilatory support Complications of prematurity
Merritt *et al* (1991) – delivery room versus rescue human surfactant (trial of multiple births - 43 infants)	Quasi-randomised (one twin to each arm, for triplets two to "late" and one to "early") Multicentre trial Sealed envelopes (stratified by centre and gestation) Early arm given 3.5 ml/kg after few inflation breaths, late arm if ventilated with $FiO_2 \geq 0.5$	Between 24-29 weeks gestation	Congenital abnormality Chromosomal abnormality Mature L/S ratio Rupture of membranes > 3 weeks	Neonatal death or CLD Ventilatory support Complications of prematurity

Table 18: Summaries of the trials involving early and late administration of surfactant (continued)

Study	Methods	Participants	Exclusions	Outcomes
Konishi *et al* (1992) – early versus late single dose of surfactant TA (32 infants)	Randomised Multicentre Randomisation method not stated Blinding method not stated Early arm given surfactant within 30 minutes, late arm at 6 hours if FiO_2 0.4 at ≥ 7 cm H_2O	Birthweight 500-1500 grams. Intubated. Stable microbubble test on gastric aspirate	Prolonged rupture of membrane (≥ 72 hours). Evidence of infection (maternal fever or gastric aspirate leucocyte count of <10). Congenital malformations Oligo- or polyhydramnios. Apgar score ≤ 4 at 5 minutes.	Differences in a/APO_2 at 72 hours Differences in severity of RDS Outcomes at 7 and 28 days
OSIRIS study group (1992) Early versus late Exosurf (2690 infants)	Randomised Multicentre Telephone randomisation Not blinded 5 ml/kg Exosurf at randomisation or when $a/APO_2 < 0.22$ with second dose at 12 hours if still ventilated (and third fourth doses if allocated under the concurrent study)	At risk of RDS Less than 2 hours old Ventilated	Congenital abnormality	Death at any stage Death or oxygen dependency at 28 days Death or oxygen dependency at "EDD" Complications of prematurity

Table 18: Summaries of the trials involving early and late administration of surfactant (continued)

Study	Methods	Participants	Exclusions	Outcomes
European Exosurf Study (1992) - Early versus late Exosurf (420 infants)	Randomised Multicentre Sealed envelopes, stratified by gestation and sex. Blinded first dose of Exosurf or air placebo with rescue if a/APO$_2$ < 0.22. Second dose at 18 hours	Gestation 26 – 29 weeks Less than 2 hours old	Congenital abnormality Hydrops fetalis Maternal chorioamnionitis	Neonatal survival without cranial USS abnormalities RDS requiring rescue therapy Duration of intensive care, oxygen therapy Complications of prematurity
Egberts *et al* (1993) - comparison of prophylaxis and rescue Curosurf (147 infants)	Multicentre trial (4 centres) Sealed envelopes (stratification by centre) Not blinded 200 mg/kg Curosurf within 10 minutes of delivery or when FiO2 ≥ 0.6.	26-30 weeks gestation	Prolonged rupture of membranes (≥3 weeks) Congenital abnormalities (2 post allocation exclusions)	Reduction in RDS Ventilatory support Complications of prematurity
Bevilacqua *et al* (1993) – The EURO III study (182 infants) - early versus late Curosurf	Randomised Multicentre study (26 centres) Sealed envelopes Not blinded 200 mg/kg Curosurf, early group at randomisation, late group if FiO$_2$ ≥0.6	Birthweight 600-2000 grams. Between 2-24 hours old. Clinical and radiological diagnosis of RDS. Ventilated with FiO$_2$ 0.4 – 0.59	Congenital abnormality Prolonged rupture of membranes (≥3 weeks) Grade III or IV IVH Birth asphyxia GBS infection FiO$_2$ ≥ 0.6 at randomisation	Ventilator and oxygen requirements Complications of prematurity

Table 18: Summaries of the trials involving early and late administration of surfactant (continued)

Study	Methods	Participants	Exclusions	Outcomes
Kattwinkel *et al* (1993) – delivery room versus rescue Infasurf (1246 infants)	Randomised Multicentre (9 centres but data from 8 only because of problems in 1 centre) Sealed envelopes (stratified by centre) Not blinded Early arm given 4.5ml surfactant bolus prior to respiration, late arm if ventilated with $FiO_2 \geq 0.3$	In-born babies Between 29-32 weeks gestation	Congenital malformation Congenital sepsis Perinatal asphyxia (not defined) Too mature	Development of moderately severe RDS Complications of prematurity
Walti *et al* (1995) - prophylaxis versus rescue trial of Curosurf (256 infants)	Randomised Multicentre (12 centres) Telephone randomisation (stratification by centre) Not blinded 100 mg/kg Curosurf within 15 minutes of birth or if CXR shows RDS and PaO_2:FiO_2 <20kPa between 3-18 hours of age	Gestation 25-31 weeks In-born in participating centre	Congenital abnormality Prolonged rupture of membranes (≥3 weeks)	Survival without BPD at 28 days Ventilator and oxygen requirements CXR appearances Complications of prematurity

Table 18: Summaries of the trials involving early and late administration of surfactant (continued)

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Bevilacqua *et al* (1996) - prophylaxis versus rescue trial of Curosurf (266 infants)	Multicentre trial (18 centres) Sealed envelopes (stratification by centre, and gestation) Not blinded 200 mg/kg Curosurf within 10 minutes of delivery or if ventilated for RDS	24-30 weeks gestation	Prolonged rupture of membranes (≥3 weeks) Congenital abnormalities Congenital infection (19 post allocation exclusions)	Reduction in RDS Complications of prematurity
Gortner *et al* (1998) – early versus late Alveofact (317 infants)	Randomised Multicentre (6 centres) Method of randomisation not stated Not clear whether blinding used Early group given surfactant in first ½ hour if $FiO_2 \geq$ 0.5, late group if $FiO_2 \geq$ 0.4 between 2 and 6 hours of age.	In-born infants 27-32 weeks gestation	Congenital malformations affecting cardio-respiratory function Prolonged rupture of membranes >3 weeks	Ventilator and oxygen requirements Complications of prematurity
Kendig *et al* (1998) – trial between two strategies for very early surfactant (Infasurf) administration (651 infants)	Randomised Multicentre Sealed envelopes (stratified by centre and gestation) Not blinded	In-born infants Between 24-28 weeks gestation	Stillbirths	Problems with administration Ventilator and oxygen requirements Complications of prematurity

Table 18: Summaries of the trials involving early and late administration of surfactant (continued)

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Verder *et al* (1999) - Nasal CPAP and early versus late Curosurf (60 infants)	Multicentre trial Sealed envelopes (stratification by centre) All babies receiving CPAP, given 200 mg/kg Curosurf at randomisation in early arm or if a/APO_2 < 0.22 in late arm.	<30 weeks gestation Clinical and radiological RDS. Nasal CPAP in use (≥6 cm H_2O a/APO_2 between 0.35 and 0.22	Congenital abnormality Prolonged rupture of membranes (≥2 weeks) Birth asphyxia with Apgar score ≤ 3 at 5 minutes Congenital pneumonia	Need for mechanical ventilation beyond period of surfactant administration Neonatal mortality Oxygen requirements Complications of prematurity

Table 19: A summary of all published trials comparing two different strategies for surfactant administration

Study	Surfactant	No of babies			Early time	Late time
		Total	Early	Late		
Bevilacqua *et al* 1993	***Curosurf***	182	86	96	FiO_2 between 0.4 - 0.59	If $FiO_2 > 0.6$ in first 48hours
Bevilacqua *et al* 1996	***Curosurf***	285	135	132	Within 10 minutes of delivery	Up to 24 hours if ventilated
Dunn *et al* 1991	***bLES***	122	62	60	As soon as intubated	If ventilated for RDS (FiO_2>0.21 at MAP 7cmH_2O)
Egberts *et al* 1993	***Curosurf***	147	75	72	Within 10 minutes of delivery	Between 2 and 6 hours if $FiO_2 > 0.6$
European Exosurf Study Group 1992	***Exosurf***	420	212	208	If intubated before 2 hours	When $a/APO_2 < 0.22$
Gortner *et al* 1993	***Alveofact***	317	154	163	Within 1 hour if $FiO_2 \geq 0.5$	Between 2 and 6 hours if $FiO_2 \geq 0.4$
Kattwinkel *et al* 1993	***Infasurf***	1248	627	621	As soon as intubated	If ventilated and $FiO_2 \geq 0.3$
Kendig *et al* 1991	***Infasurf***	479	235	244	As soon as intubated (preventilation)	If ventilated with $FiO_2 \geq 0.4$ or MAP ≥ 7 cm H_2O
Kendig *et al* 1998	***Infasurf***	651	323	328	As soon as intubated (preventilation)	After resuscitation and stabilisation (post ventilation)
Konishi *et al* 1992	***Surfactant TA***	32	16	16	Within 30 minutes of delivery	At 6 hours if $FiO_2 \geq 0.4$
Merritt *et al* 1991	***Human***	148	76	72	As soon as intubated	If ventilated with $FiO_2 \geq 0.5$ or MAP ≥ 7 cm H_2O
OSIRIS Collaborative Group 1992	***Exosurf***	2690	1344	1346	Age < 2 hours	When $a/APO_2 < 0.22$
Verder *et al* 1999	***Curosurf***	60	33	27	Age 2-72 hours and a/APO_2 0.35-0.22 and falling	$a/APO_2 < 0.22$
Walti *et al* 1995	***Curosurf***	256	134	122	Within 15 minutes of delivery	If ventilated at 3 - 18 hours

Section 6.3.2 showed that evidence from animal models favoured of administering surfactant as early as possible to obtain the maximum benefit. However preterm infants are a heterogeneous group and some treated prophylactically may not develop RDS, they thus receive unnecessary treatment.

Surfactant therapy is expensive (costs range from £150 per vial of ***ALEC*** to £400 per vial of ***Curosurf*** – source British National Formulary 1999) and although these costs are small compared to the overall cost of neonatal intensive care they may be important to healthcare purchasers. Surfactant can only be administered to an infant that is intubated, and this has been associated with some transient side-effects. To be considered effective an early or prophylactic strategy needs to produce benefits that outweigh these considerations.

Table 18 shows trials that have compared two different strategies for administering surfactant. A number of different outcomes were studied, and not all trials showed a benefit of one strategy over the other. Again, variation in early and late strategies may well play a part when it comes to positive and negative findings in these trials. The following meta-analyses look at:

1. Pre-ventilation (i.e. pre-first breath) versus rescue administration strategies. (Section 6.3.2a)
2. Prophylaxis within 15 minutes of birth versus rescue administration strategies. But excluding studies that screen for surfactant maturity. (Section 6.3.2b)
3. Early administration versus late rescue administration strategies. Including all prophylaxis, early and screened trials. (Section 6.3.2c)

6.3.2a Meta-analysis of pre-ventilation versus rescue surfactant administration strategies

Method

The objective of this section was to assess the effect of intra-tracheal administration of surfactant prior to the first breath versus rescue treatment of established RDS. The search strategy outlined in section 5.1.2 was used to examine outcomes in randomised controlled trials that compared intra-tracheal administration of surfactant given prior to the first breath versus rescue treatment of established RDS. Data were taken from trials involving any surfactant and not just those that have been licensed in the UK. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Studies were considered if they fulfilled the following criteria:

(a) Types of studies - Randomised controlled trials comparing a pre-ventilation strategy of surfactant administration and a late rescue strategy in infants who develop symptoms and signs of RDS.

(d) Types of participants - preterm neonates at risk of RDS.

(e) Types of intervention - Infants randomised to receive surfactant prior to the onset of respiration/respiratory support versus treatment in only those infants who reach criteria (defined before the study) at which treatment is given.

(f) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, chronic lung disease (at 28 days in survivors), chronic lung disease or death (at 28 days), pulmonary air leak (reported as PIE and pneumothorax), patent ductus arteriosus, severe intraventricular haemorrhage (Papile grades III and IV).

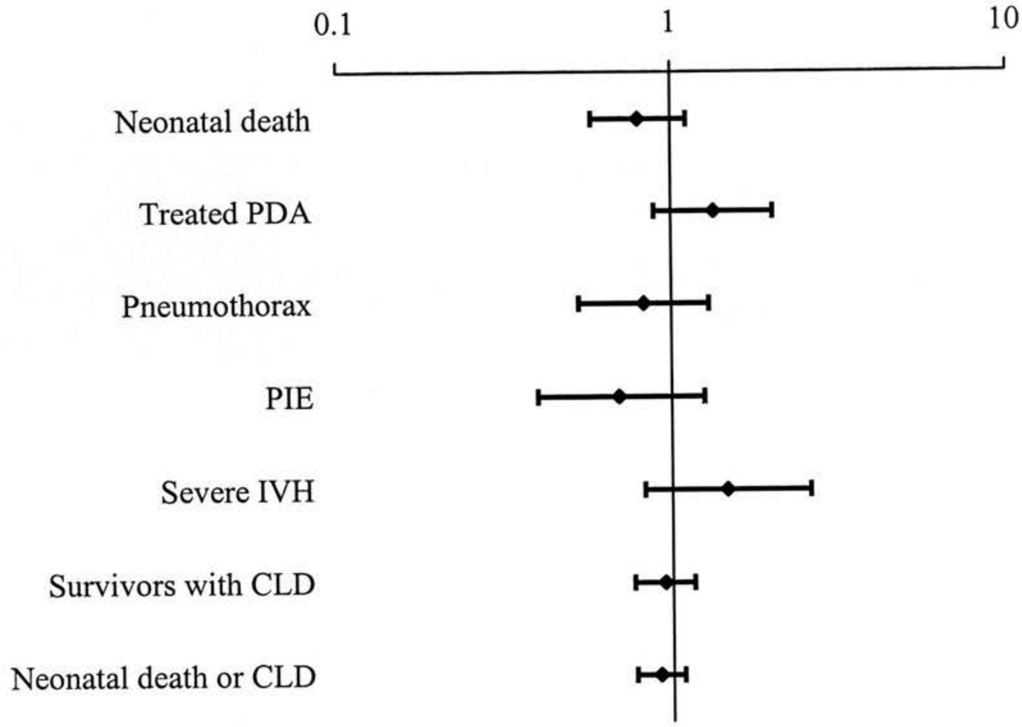
Results

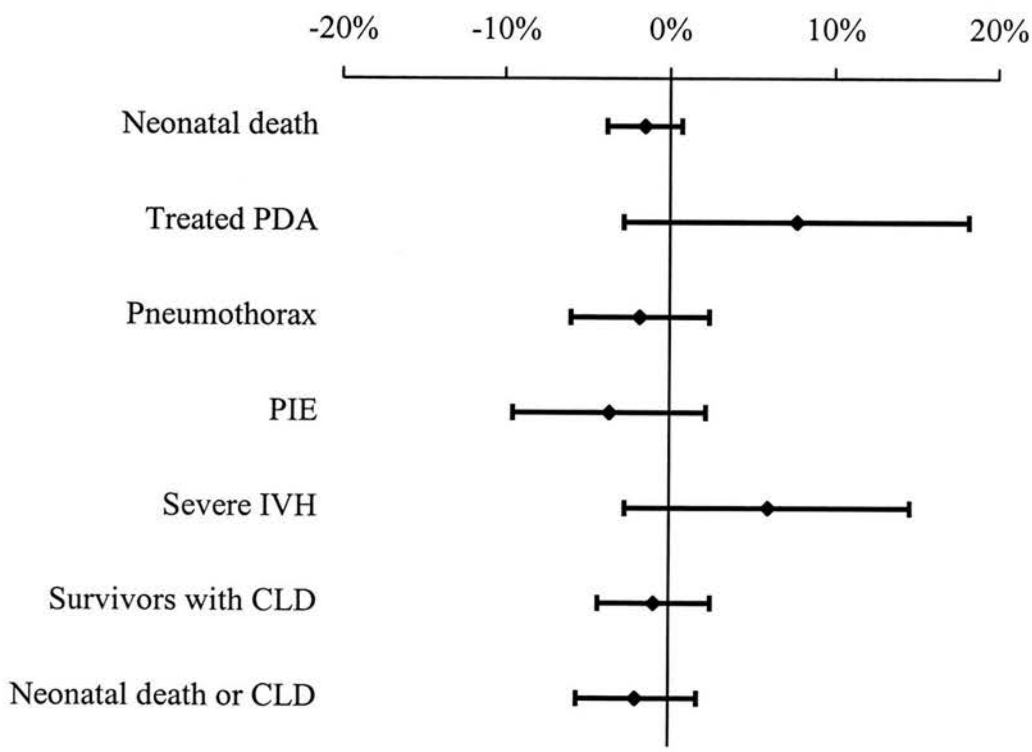
Only four studies were identified as suitable for inclusion in this meta-analysis – Dunn *et al* (1991), Kendig *et al* (1991), Merritt *et al* (1991) and Kattwinkel *et al* (1993). A further study that compared a pre-ventilation strategy versus an immediate post-resuscitation strategy has been reported (Kendig *et al* 1998) but was excluded, as the latter arm was not a "rescue" arm. Other studies in Table 18 were excluded since in all of these the early arm received surfactant after the first breath.

Treatment of premature infants using a pre-ventilation surfactant administration strategy appears to have no clear advantage in outcomes at 28 days. Some trends towards improved outcomes are seen but these do not reach statistical significance (Figure 7).

Neonatal Mortality: All trials report on the risk of neonatal mortality. The typical estimate from the meta-analysis suggests a trend to decreased neonatal mortality associated with pre-ventilation surfactant administration (typical relative risk 0.80, 95% CI 0.58 to 1.11; typical risk difference –1.5%; 95% CI –3.8 to +0.7%).

Figure 7: Meta-view charts of risk difference and relative risk in trials comparing pre-ventilation prophylaxis and post-ventilation rescue strategies





Pulmonary Air Leak: All trials report this outcome, but using the two sub-groups of PIE and pneumothorax, rather than an all-embracing air leak syndrome. The typical estimate suggests a trend to decreased risk of PIE associated with pre-ventilation surfactant administration (typical relative risk 0.70, 95% CI 0.40 to 1.25; typical risk difference –3.6%; 95% CI –9.5 to +2.2%). Similarly, the typical estimate shows a trend to decreased risk of pneumothorax associated with pre-ventilation surfactant administration (typical relative risk 0.83, 95% CI 0.53 to 1.29; typical risk difference –1.8%; 95% CI –6.0 to +2.4%).

Patent Ductus Arteriosus: The typical estimate shows a trend to increased risk of significant PDA (requiring treatment) with pre-ventilation surfactant administration (typical relative risk 1.34, 95% CI 0.89 to 2.00; typical risk difference +7.7%; 95% CI –2.8 to +18.2%).

Severe Intraventricular Haemorrhage: The typical estimate from the meta-analysis suggests a trend to increased risk of severe IVH (defined as Papile grades III and IV) with pre-ventilation surfactant administration (typical relative risk 1.46, 95% CI 0.83 – 2.57; typical risk difference +6.0%; 95% CI –2.7 to +14.6%).

Chronic Lung Disease: Surviving infants with CLD at 28 days were reported by all studies. The typical estimate shows a no difference in the risk of CLD with pre-ventilation surfactant administration (typical relative risk 0.95, 95% CI 0.77 – 1.16; typical risk difference –0.9%; 95% CI –4.3 to +2.5%).

Chronic Lung Disease* OR *Death: This reported by all studies. The typical estimate shows a small trend to decreased risk of CLD or neonatal death with pre-ventilation surfactant administration (typical relative risk 0.92, 95% CI 0.78 – 1.08; typical risk difference –2.0%; 95% CI –5.6 to +1.7%).

The implications of these results are discussed in section 6.3.2d.

6.3.2b Meta-analysis of prophylaxis versus rescue surfactant administration strategies

Method

The objective of this section was to assess the effect of intra-tracheal administration of surfactant administered prophylactically (including those where it was administered pre-ventilation) to infants at risk of RDS versus rescue treatment of established RDS. In particular tests for surfactant maturity were felt to preclude the study being considered as "prophylaxis". The search strategy outlined in section 5.1.2 was used to examine outcomes in randomised controlled trials that compared prophylactic surfactant versus rescue treatment of established RDS. Data were taken from trials involving any surfactant and not just those that have been licensed in the UK. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Studies were considered if they fulfilled the following criteria:

(a) Types of studies - Randomised controlled trials comparing a prophylactic strategy (without screening for surfactant maturity) of surfactant administration and a late rescue strategy in infants who develop symptoms and signs of RDS.

(b) Types of participants - preterm neonates at risk of RDS.

(c) Types of intervention - Infants randomised to receive surfactant prophylactically (first dose within 15 minutes of birth) versus treatment in only those infants who reach criteria (defined before the study) at which treatment is given.

(d) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, chronic lung disease (at 28 days in survivors), chronic lung disease or death (at 28 days), pulmonary air leak (reported as PIE and pneumothorax), patent ductus arteriosus, severe intraventricular haemorrhage (Papile grades III and IV) and necrotising enterocolitis.

Results

Only five studies were identified as suitable for inclusion - Kendig *et al* (1991) and Kattwinkel *et al* (1993) - trials using ***Infasurf***, Egberts *et al* (1993), Walti *et al* (1995) and Bevilacqua *et al* (1996) - trials using ***Curosurf***. Other studies in Table 18 were excluded, either because they did not fit the definition of prophylaxis or the investigators used one of the tests of surfactant maturity.

Treatment of premature infants at risk of RDS using a prophylactic surfactant administration strategy appears to have several clear advantages in outcomes at 28 days with improved outcomes seen in almost all complications of prematurity at 28 days (Figure 8).

Neonatal Mortality: All trials report on the risk of neonatal mortality. The typical estimate suggests decreased neonatal mortality associated with prophylactic surfactant administration (typical relative risk 0.57, 95% CI 0.43 to 0.74; typical risk difference –4.9%; 95% CI –7.1 to –2.6%).

Pulmonary Air Leak: The trials report this outcome, using the two forms of PIE and pneumothorax rather than an all-embracing air leak syndrome. The typical estimate suggests a trend to decreased risk of PIE associated with prophylactic surfactant administration (typical relative risk 0.70, 95% CI 0.40 to 1.25; typical risk difference –3.6%; 95% CI –9.5 to +2.2%). Whereas, the typical estimate shows decreased risk of pneumothorax with prophylactic surfactant administration (typical relative risk 0.59, 95% CI 0.38 to 0.90; typical risk difference –3.8%; 95% CI –6.8 to –0.8%).

Patent Ductus Arteriosus: The typical estimate shows decreased risk of significant PDA (requiring treatment) with prophylactic surfactant administration (typical relative risk 0.72, 95% CI 0.56 to 0.92; typical risk difference –9.0%; 95% CI –15.7 to –2.3%).

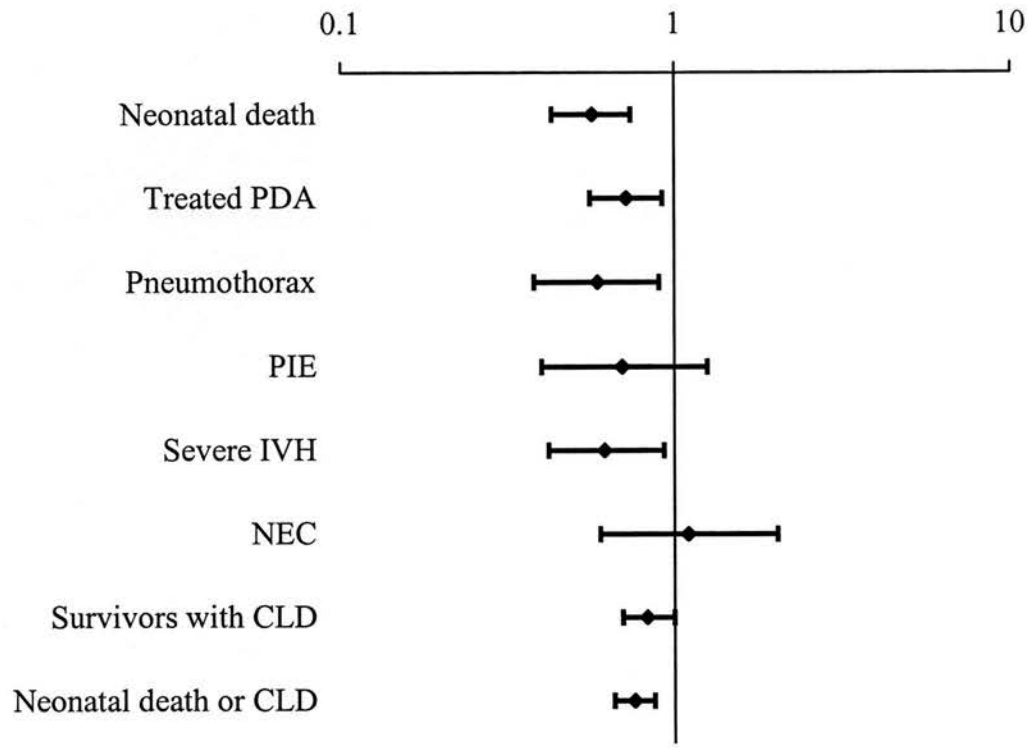
Severe Intraventricular Haemorrhage: The typical estimate from the meta-analysis shows a decreased risk of severe IVH (defined as Papile grades III and IV) with prophylactic surfactant administration (typical relative risk 0.62, 95% CI 0.42 – 0.93; typical risk difference –6.1%; 95% CI –11.2 to –1.0%).

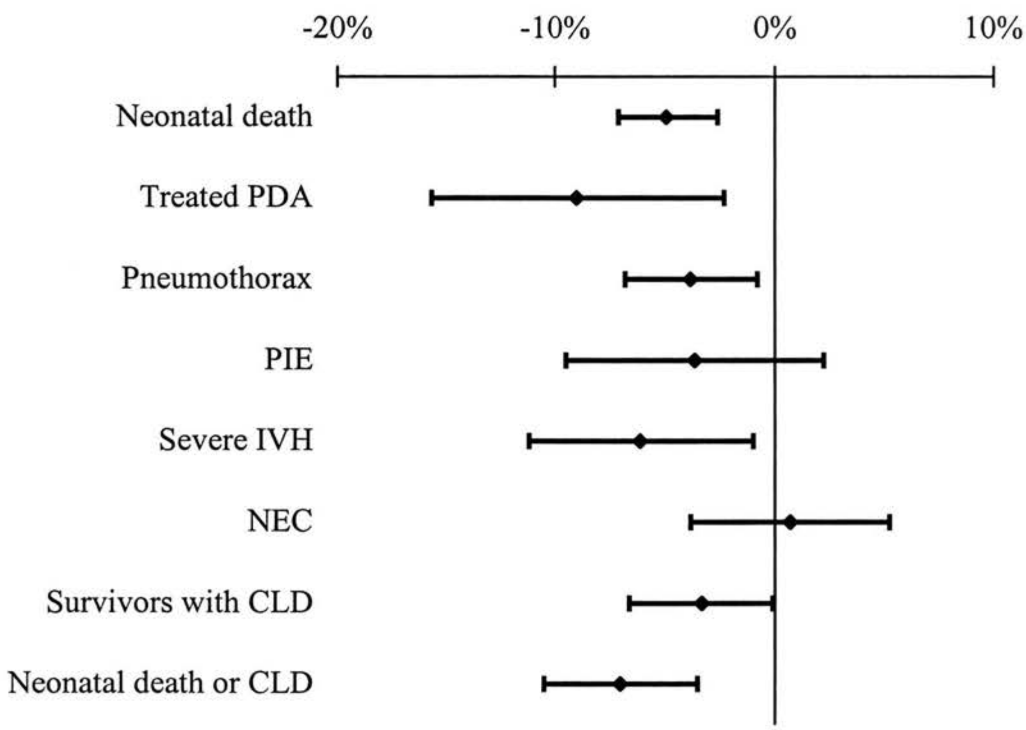
Chronic Lung Disease: Surviving infants with CLD at 28 days were reported by all studies. The typical estimate shows a reduction in the risk of CLD with prophylactic surfactant administration (typical relative risk 0.83, 95% CI 0.70 – 0.99; typical risk difference –3.3%; 95% CI –6.6 to –0.1%).

Chronic Lung Disease* OR *Death: This reported by all studies. The typical estimate shows a decreased risk of CLD or neonatal death with prophylactic surfactant administration (typical relative risk 0.76, 95% CI 0.66 – 0.87; typical risk difference –7.0%; 95% CI –10.5 to –3.5%).

The implications of these results are discussed in section 6.3.2d.

Figure 8: Meta-view charts of risk difference and relative risk in trials comparing prophylaxis and rescue strategies.





6.3.2c Meta-analysis of early versus late rescue surfactant administration strategies

Method

The objective of this section was to assess the effect of early intra-tracheal administration of surfactant in infants at risk of or with existing RDS versus late rescue treatment. The search strategy outlined in section 5.1.2 was used to examine outcomes in those randomised controlled trials that compared early versus late surfactant administration strategies. Data were taken from trials involving any surfactant and not just those that have been licensed in the UK. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Studies were considered if they fulfilled the following criteria:

(a) Types of studies - Randomised controlled trials comparing any different temporal (i.e. early vaersus late, where early could include prophylaxis or pre-first breath) strategies for the prevention of or treatment of RDS.

(b) Types of participants – preterm neonates at risk of or with existing RDS.

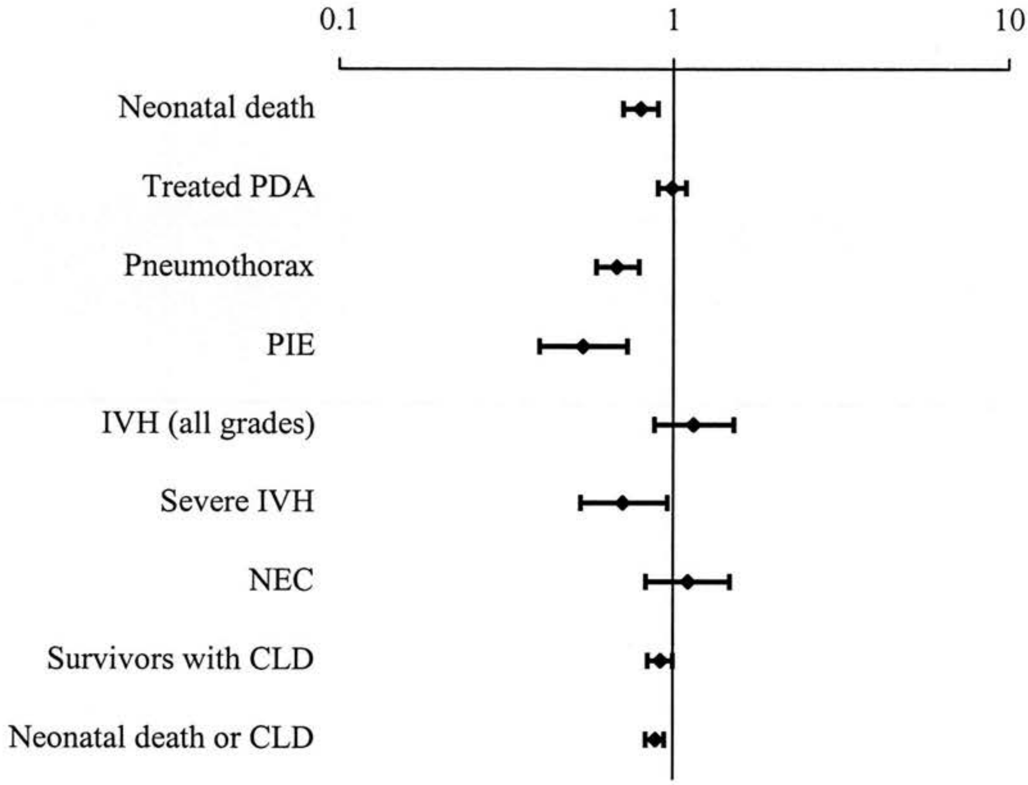
(c) Types of intervention - Infants randomised to receive surfactant either early (prophylactically or as early rescue treatment) versus late rescue treatment.

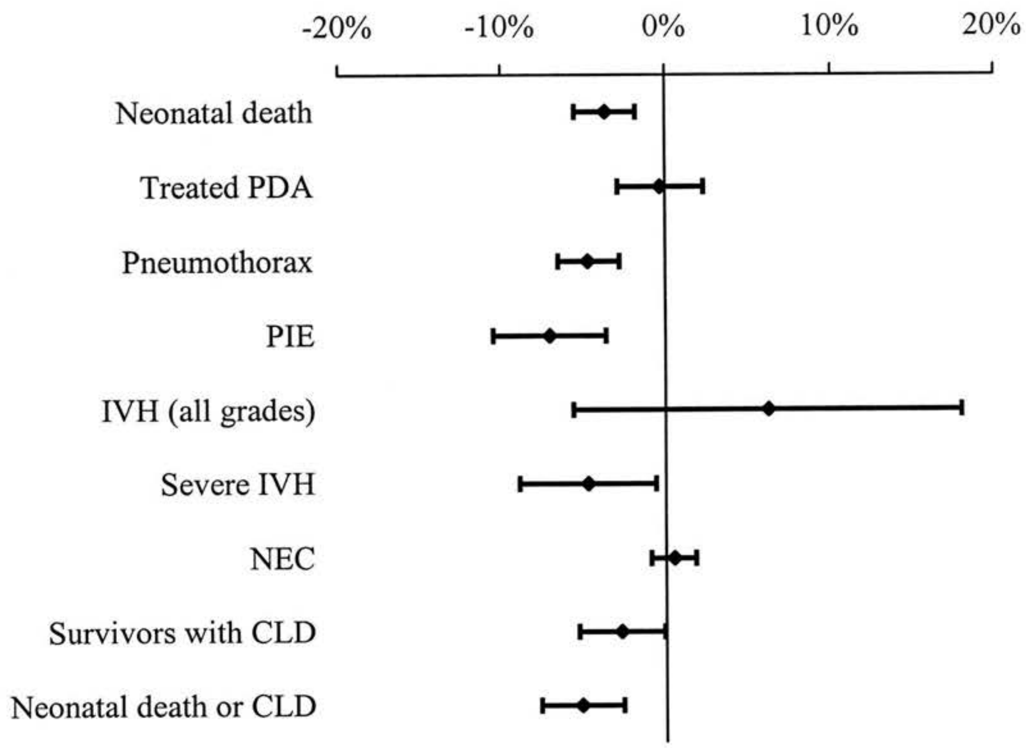
(d) Types of outcome measures - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, chronic lung disease (at 28 days in survivors), chronic lung disease or death (at 28 days), pulmonary air leak (reported as PIE and pneumothorax), patent ductus arteriosus, intraventricular haemorrhage – given as overall and severe (Papile grades III and IV) IVH - and necrotising enterocolitis.

Results

All studies in Table 18 are included with the exception of Kendig *et al* (1998) because this trial compares two different prophylactic strategies. There is some overlap in the timings of surfactant in trials considered in this review because the early treatment arm in some trials may receive their surfactant at a later stage than the so-called late arm in another trial. Treatment of premature infants at risk of RDS using an early surfactant administration strategy appears to have several clear advantages in outcomes at 28 days with improved outcomes seen in almost all complications of prematurity at 28 days (Figure 9).

Figure 9: Meta-view charts of risk difference and relative risk between early and late rescue strategies.





Neonatal Mortality: All trials report on the risk of neonatal mortality. The typical estimate suggests decreased neonatal mortality associated with early surfactant administration (typical relative risk 0.80, 95% CI 0.71 to 0.90; typical risk difference –3.6%; 95% CI –5.5 to –1.8%).

Pulmonary Air Leak: The trials report this outcome, using the two forms of PIE and pneumothorax rather than an all-embracing air leak syndrome. More trials report the rates of pneumothorax than PIE. The typical estimate suggests a decreased risk of PIE associated with early surfactant administration (typical relative risk 0.54, 95% CI 0.40 to 0.73; typical risk difference –7.0%; 95% CI –10.5 to –3.6%). Similarly, the typical estimate shows decreased risk of pneumothorax with early surfactant administration (typical relative risk 0.68, 95% CI 0.59 to 0.73; typical risk difference –4.7%; 95% CI –6.5 to –2.8%).

Patent Ductus Arteriosus: The typical estimate shows no difference in the risk of significant PDA (requiring treatment) with early surfactant administration (typical relative risk 0.99, 95% CI 0.90 to 1.09; typical risk difference –0.3%; 95% CI –2.9 to +2.3%).

Intraventricular Haemorrhage (all grades): While more trials reported just severe IVH (defined as Papile grades III and IV), a few trials also reported overall totals. The typical estimate from the meta-analysis suggests no difference in the risk of IVH with early surfactant administration (typical relative risk 1.15, 95% CI 0.88 – 1.51; typical risk difference +6.2%; 95% CI –8.9 to +18.0%).

Severe Intraventricular Haemorrhage: On the other hand, the typical estimate from the meta-analysis suggests a decreased risk of severe IVH (defined as Papile grades III and IV) with early surfactant administration (typical relative risk 0.71, 95% CI 0.53 – 0.96; typical risk difference –4.7%; 95% CI –8.9 to –0.6%).

Necrotising enterocolitis: The typical estimate shows no difference in the risk of NEC with early surfactant administration (typical relative risk 1.11, 95% CI 0.83 to 1.47; typical isk difference +0.5%; 95% CI –0.9 to +1.8%).

Chronic Lung Disease: Surviving infants with CLD at 28 days were reported by most studies. The typical estimate shows a reduction in the risk of CLD among survivors after early surfactant administration (typical relative risk 0.92, 95% CI 0.84 – 0.99; typical risk difference –2.7 %; 95% CI –5.3 to -0.1%).

Chronic Lung Disease* OR *Death: This outcome was limited to those trials that reported CLD at 28 days. The typical estimate shows a decreased risk of CLD or neonatal death with early surfactant administration (typical relative risk 0.89, 95% CI 0.83 – 0.94; typical risk difference –5.1%; 95% CI –7.6 to –2.6%).

6.3.2d Summary of results

The literature supports the view, both in meta-analysis and the majority of randomised controlled trials that a policy of early surfactant therapy is better than a selective late rescue therapy. This also applies when the surfactant is given prophylactically compared to a rescue therapy. Because of the differences between the various trials and lack of any uniform definition it is not possible to further subdivide the prophylaxis versus rescue trials into those using an "early" rescue" and a "late" rescue. Whether prophylaxis retains its beneficial effects compared to an early rescue strategy (such as administration on delivery suite versus tragetted delivery on admission neonatal unit) cannot be shown.

Using the notion of "number needed to treat" to prevent an adverse event, it can be seen that in order to prevent one additional neonatal death it would be necessary to treat an extra 28 infants using the early strategy. In contrast using a prophylactic strategy only 20 additional infants would need to be treated to save that additional infant. This would suggest that a prophylactic strategy is better.

The disadvantage of a prophylactic strategy is the need to treat infants who do not develop RDS. In the five trials reviewed having a prophylactic strategy an average of 1.195 doses were given to each infant, compared to an average of 0.677 doses per infant in the "late" treatment arm. Translating both "number needed to treat" and number of doses to 100 infants, for every 100 infants treated prophylactically there would be an additional 5 neonatal survivors. They would be treated with 120 doses of surfactant (along with the respiratory support that this entails) whereas a rescue strategy would use only 68 doses (52 doses less). This means that each additional life saved costs around 10 extra vials of surfactant. The extra cost of surfactant for each extra life saved for the currently marketed surfactants in the UK at 1998-99 (source; *British National Formulary*) prices would be:

ALEC £1500 (£150 per dose)
Exosurf and ***Survanta*** £3060 (£306 per dose)
Curosurf £4000 (£400 per dose)

These surfactant costs however may be offset by additional hidden costs in the late arms of treating more infants with pneumothoraces, more severe RDS, and other complications of prematurity.

It is not clear why in the meta-analysis pre-ventilation strategies of surfactant administration were not seen to improve outcomes in a human neonatal population when the evidence from experimental and animal studies is fairly conclusive. Kendig *et al* (1998) has tried to answer this question using two delivery room strategies. The first strategy was used in the majority of pre-ventilation trials and used a pre-first breath bolus of surfactant (of a 3 ml volume of ***Infasurf***), whereas the other strategy employed a series of post-ventilatory aliquots. Immediate outcomes did not show significant differences between groups however the post-ventilatory strategy showed an improved survival rate at 36 weeks without chronic lung disease. The study does not answer why this might be the case, but one possibility may be poorer surfactant distribution after bolus administration of the 4ml volume in an atelectatic lung that contains some fluid. If surfactant did not enter some of the airways they could remain atelectatic and inflammatory processes would begin, leading in turn to chronic lung disease.

Currently the evidence supports "early" surfactant treatment, preferably in a "prophylactic" strategy however the evidence to support a pre-ventilation strategy in a human neonatal population is lacking. Whether using a small volume surfactant (***ALEC*** or ***Curosurf***) in this manner has any beneficial effect has yet to be demonstrated. The optimum choice would seem to be to stabilise the "at risk" infant in the delivery room, and to administer surfactant within 10 to 15 minutes after birth. The disadvantages of this strategy are that it would prolong the duration the infant spent in a cold environment, monitoring would be limited to a pulse oximeter and it relies on being able to rapidly stabilise the airway with the ETT in the correct position.

6.4 Do all "at risk" infants require surfactant therapy?

It is clear from studies in the meta-analysis of prophylaxis versus rescue surfactant strategies that not all "at risk" infants develop RDS that is severe enough to warrant surfactant therapy. The various studies have reported that between 31.9% (Egberts *et al* 1993) and 63.2% (Gortner *et al* 1998) of infants in the rescue arms did not receive surfactant. With an increasing use of antenatal steroids by obstetricians it is more likely that infants born prematurely today would have surfactant that is more mature than their counterparts of the same gestation born some 5-10 years ago when most of the early versus late trials were undertaken.

Screening of infants using tests of surfactant function such as the L/S ratio, stable microbubble test or the click test, prior to administration of surfactant has been advocated. Indeed these tests have been used to varying extents in some of the early versus late trials. In the trial by Konishi *et al* (1992) it was a requirement that infants had immature surfactant on testing using the stable microbubble test; Dunn *et al* (1991) studied only those infants where the amniotic fluid testing indicated immature surfactant. Although surfactant therapy has been shown to be largely safe and efficacious there is no data to support its use in those infants with a mature surfactant profile. These infants are exposed to a therapeutic agent, that, whilst largely agreed to be safe, is nonetheless of animal origin in many cases and is administered in an invasive manner with the incumbent dangers that go along with intubation.

Osborn *et al* (2000) examined the role of the click test not just as a means to reduce the number of unnecessary treatments but also to speed up their administration times that previously were based on a rescue strategy in moderately severe RDS. This strategy depended on radiological and clinical criteria and had led to a median time to first dose of over 4 hours. They used the click test to decide if the infant had immature endogenous surfactant. If this was the case exogenous surfactant was administered prior to chest radiographs and line placement. Using this strategy they were able to demonstrate a statistically significant reduction in the median time to surfactant administration from 2.7 hours to just less than 1 hour.

The problem with this study is that the greater body of evidence to date supports the use of earlier surfactant therapy and that most neonatologists would agree 4 hours was still too long. It is not clear whether a click test (or similar) performed on the amniotic fluid prior to delivery could reduce unnecessary surfactant administration, it would not reduce the time to administration in truly "prophylactic" or early surfactant administration strategies.

6.5 Subsequent doses of surfactant

Although there is strong evidence to support the use of a first dose of surfactant as soon as possible after birth there is considerably less evidence when the second or subsequent doses should be given. A variety of timing intervals have been reported in the medical literature (and adopted by the manufacturers). These vary from the ***ALEC*** regime of a dose at birth, a second at 1 hour and a third at 24 hours, through doses at six hourly intervals (***Survanta***), at 8 hourly intervals (***Infasurf***) and at 12 hourly intervals (***Curosurf***). In most cases the subsequent doses are given to any infant that continues to require positive pressure ventilation and minimal supplemental oxygen.

Kattwinkel *et al* (2000) examined 2484 infants treated either prophylactically or with rescue therapy to establish whether there was any difference between a "high" versus "low" threshold for the re-treatment doses. In this randomised trial "low" corresponded to a threshold widely recommended by manufacturers – namely that of requiring ≥30% oxygen in any ventilated infant. "High" corresponded to ventilation at MAP ≥ 7 cm H_2O and an $FiO_2 \geq 40\%$.

There were fewer infants in the low threshold arm that required supplemental oxygen (≥30%) at 72 hours, although whether this was clinically important is not clear. There were no differences between the two arms in any important long-term outcomes. In a subgroup analysis of infants that had "complicated" RDS (where there was proven or a high risk of sepsis or birth asphyxia) 24% of infants in the low threshold arm versus 34% in the high threshold arm died (typical relative risk 0.71, 95% CI 0.51 – 0.99; risk difference –10%; 95% CI –19.5 to –0.5%).

This outcome relates to the fact that infants in the "complicated" subgroup were more likely to have inactivation of their surfactant, thus those in the high threshold arms were more likely to deplete their surfactant stores and suffer lung damage and it consequences.

6.6 Conclusion

The optimum dosage of surfactant appears to be approximately 100mg/kg of phospholipid per dose. The number of doses seems to be very variable, and is dependent on several factors of which the major one would appear to be degree of immaturity. Most infants manage with two doses, before they produce sufficient endogenous surfactant. The evidence that third and subsequent doses add much to outcomes is sparse, although in individual infants there might be a case if RDS was still considered as the primary reason for an on-going high oxygen and ventilation requirement.

The dosing interval has not been investigated, although nowadays most surfactants are administered at 12-hourly intervals, the question of whether an individualised regime based on indices of ventilation and/or oxygen requirements is any better has not been explored. Evidence from the Kattwinkel *et al* (2000) study suggests that re-treatment at a lower threshold may be important in "complicated" cases of RDS where surfactant may be inactivated, but in "uncomplicated" RDS a higher threshold may suffice.

It appears clear that earlier treatment, whether given prophylactically or as very early rescue (within 15-30 minutes of birth in intubated infants), is preferable to rescue at later stages. Of the two "early" strategies, a prophylactic strategy seems on evidence from animal models of RDS to means of reducing inflammation and complications, but no clinical trials have compared these two strategies.

This chapter has assumed that all surfactants have similar effects in neonates, however as the next two chapters demonstrate this is not the case. Chapter 7 examines differences in composition and the biophysical properties of the different surfactants. It also examines the performance of surfactant in various animal models of RDS. Chapter 8 examines evidence from published clinical trials that look at the use of two different surfactants.

Chapter 7

Evidence of differences between surfactants from *in vitro* studies and animal models of RDS

Introduction

As shown in chapter 5 all four surfactants licensed in the UK were more effective than control treatment in preterm infants with RDS. There are clearly differences, not only in the surfactants, but also in outcomes as judged by the meta-analyses of the relevant placebo-controlled trials in that chapter. Whether the differences in constituents, reflecting the sources of the various products, convey long-term benefits to the infant with any one surfactant being better than the other is less clear.

When considering the question of whether using an animal-derived or a synthetic surfactant offers the neonate the best chance of survival with the minimum of impairment (respiratory or otherwise) - it is necessary to consider evidence from various sources. There are five areas to be considered: composition, *in vitro* or biophysical properties, effects in excised lungs, animal model experiments and the neonatal population. In this chapter the first four of these factors are discussed. Evidence from studies in neonatal populations is discussed in the chapter 8.

7.1 Differences in surfactant composition

There is no evidence to suggest that duplication of mature human surfactant constitutes the optimum or "gold standard" surfactant therapy for preterm infants with RDS. Human surfactant has been harvested from amniotic fluid but as yet has not been a commercially viable source of enough surfactant to treat preterm infants with RDS. There are differences between surfactant produced by a 28 weeks gestation fetus and a term infant (chapter 3), although the reason for this is unclear and there is no published evidence to suggest that surfactant that compositionally resembles that of the less mature fetus/neonate would be any more or any less beneficial than mature surfactant.

Technology to date has limited existing exogenous surfactants either to be synthetic (and compositionally relatively simple) or to be derived from either human amniotic fluid or, more commonly, from the lungs of slaughtered animals. The main difference between these surfactants is that current synthetic surfactants are wholly composed of phospholipids, whereas the animal-derived surfactants contain surfactant-associated proteins SP-B and SP-C. In particular these proteins play an important role in the spreading and adsorption of phospholipids to the air/tissue interface (sections 3.3.3 & 3.3.4).

The phospholipids in synthetic and animal-derived surfactants also differ. DPPC is the most abundant phospholipid in both the synthetic and animal-derived surfactants and is considered to be essential for surface tension reduction. Lavaged human surfactant has a mixture of saturated and unsaturated phosphatidylcholine molecules with DPPC accounting for only 54.7 ± 3.9% (Poets *et al* 1997). By comparison it accounts for 70% of ***ALEC***, 84% of ***Exosurf***, 30-40% of ***Curosurf*** and 57% of ***Survanta / Surfactant TA***. Surfactants that have lower percentage of DPPC appear to be compressed more easily (Holm *et al* 1996) and may be more effective at reducing surface tension especially at lower lung volumes.

Thus in terms of composition, the animal-derived surfactants, with lower ratios of DPPC and particularly the presence of surfactant-associated proteins, would seem to offer advantages over the currently available synthetic surfactants.

7.2 *In vitro* (biophysical) differences between surfactants

It is generally accepted that lowering the surface tension of the air-tissue interface is the major function of surfactant. As a result attention has focused on this property of surfactant preparations *in vitro*. The Wilhelmy-Langmuir balance (Clements 1957) and the Enhörning pulsating bubble surfactometer (Enhörning *et al* 1965) are two commonly used tools for performing measurements of surface tension. Surface spreading properties are best measured using the Wilhelmy-Langmuir balance (or equivalent), whereas dynamic surface tension is best demonstrated using the Enhörning pulsating bubble surfactometer.

Criteria, proposed by King & Clements (1972) and, subsequently modified by Goerke & Clements (1986), suggest that:

1. Surfactant should form a DPPC monolayer in the space of a single breath
2. Surface tension should approach zero as the film is compressed
3. Surface tension should be stable at low (near zero) values
4. Surfactant should have a low compressibility so that low surface tensions can be achieved quickly without surface film collapse

These properties are demonstrable using *in vitro* methods.

Infants with severe RDS have surfactant with an initial surface tension of 30mN/m; this falls to <20mN/m as the infant improves (Griese & Westerburg 1998). In term infants without RDS the surface tension <5mN/m (Poets *et al* 1997). Exogenous surfactant therapy improves the surface tension in tracheal aspirates of affected infants. Tracheal aspirate surface tensions of ***Exosurf***-treated infants fell significantly from 20.9±1.4 to 17.6±1.3mN/m, whereas that from controls (air-treated) infants showed no change (McMillan *et al* 1998).

Animal-derived surfactants lower surface tension more *in vitro* than synthetic surfactants (Scarpelli *et al* 1982, Corcoran *et al* 1994, Takahashi *et al* 1994). However other factors may influence *in vitro* surfactant function: for example, the storage of ***ALEC*** under different conditions affects its properties (Tables 20 and 21). It is interesting to note that none of the surfactants (***Exosurf***, ***Infasurf*** and ***Survanta***) tested by Scarpelli *et al* (1994) met all the criteria stipulated above as being essential for surfactant function.

In vitro studies, nonetheless, would seem to support the view that animal-derived surfactants may offer better surface tension reduction than synthetic surfactants. However caution needs to be exercised in extrapolating *in vitro* properties to animal models or neonates. Tween 20, a synthetic detergent that has little structural resemblance to pulmonary surfactant, reduces surface tension at an air-water interface by only a small amount yet when instilled into the lungs of surfactant-deficient lambs improves lung function (Mercurio *et al* 1989) and gas exchange (Jacobs *et al* 1985). The need for caution is also illustrated by the *in vitro* properties of dry powder ***ALEC*** (section 5.1.1). Dry powder ***ALEC*** has superior *in vitro* properties to ***ALEC*** stored at 4°C or 37°C (Takahashi *et al* 1994), yet dry powder ***ALEC*** was ineffective in neonates (Milner *et al* 1983, Wilkinson *et al* 1985).

Table 20: Surface tension of various surfactant preparations as measured using the Wilhelmy-Langmuir balance (Takahashi *et al* 1994)

Surfactant preparation	**Surface tension**
ALEC (stored at 37°C)	71.0 ± 1.0 mN/m
ALEC (stored at 4°C)	47.2 ± 1.1 mN/m
ALEC with added SP-B and SP-C*	32.6 ± 1.7 mN/m
Dry powder ***ALEC***	58.0 ± 0.5 mN/m
Exosurf	28.0 ± 0.7 mN/m

Table 21: Maximum and minimum surface tensions of various surfactant preparations as measured using the Enhörning pulsating bubble surfactometer (Takahashi *et al* 1994)

Surfactant preparation	**Minimum surface tension**	**Maximum surface tension**
ALEC (stored at 37°C)	35.6 ± 8.8 mN/m	63.2 ± 5.7 mN/m
ALEC (stored at 4°C)	20.8 ± 1.9 mN/m	48.0 ± 4.6 mN/m
ALEC with added SP-B and SP-C*	22.8 ± 1.1 mN/m	38.8 ± 2.3 mN/m
Dry powder ***ALEC***	7.4 ± 1.1 mN/m	35.2 ± 2.4 mN/m
Exosurf	26.8 ± 0.8 mN/m	63.2 ± 1.3 mN/m
Surfactant TA	4.4 ± 0.5 mN/m	26.8 ± 0.4 mN/m

* Surfactant proteins SP-B and SP-C derived from bovine lung surfactant extract and added to *ALEC* to give 7 parts DPPC: 3 parts PG: 1 part protein

7.3 Lavaged excised animal lung models of RDS

Excised animal lungs (typically from small rodents) provide information of short-term nature regarding the effects of surfactant on gas exchange and lung compliance. The lungs are lavaged to remove surfactant producing an RDS-like state (reflecting ARDS rather than neonatal surfactant-deficient RDS) for the experiment and the pre-lavaged state provides a control. Efficacy of surfactant is usually reflected by short-term improvements of lung compliance (Bermel *et al* 1984). There are few comparisons of the commercially available exogenous surfactants using this model, and most of the published work refers to experimental addition of synthetic protein analogues to a phospholipid mixture.

Examining the "distensibility" of the lung (an indirect way of measuring compliance pre-lavage and post-lavage), Obladen *et al* (1983) showed calf lung surfactant extract restored compliance better than a DPPC: PG mixture. However neither surfactant mixture was able to restore "distensibility" to the pre-lavage state.

Similarly, Bruni *et al* (1998) showed addition of synthetic surfactant proteins SP-B and SP-C to a phospholipid mixture to be more effective than pure phospholipid for restoring (again only partially) the lung compliance of the excised rat lung. These proteins were shown to be more effective than a phospholipids mixture with only SP-B or a preparation of ***Surfaxin*** (KL4), however these, in turn, were better than a protein-free preparation of phospholipids (Walther *et al* 1998).

This model of surfactant function supports the view that surfactants with surfactant proteins SP-B and SP-C produce greater improvements in lung compliance, and a combination of the two is better than SP-B alone. SP-A (although not available in any commercially available surfactants) does not enhance surfactant spreading but does appear to be protective against surfactant inactivation by serum proteins.

7.4 Lavaged *in vivo* lung models of RDS

Whilst the excised lung model is adequate for generating initial physiological data of surfactant preparations there is the disadvantage in that they are usually taken from mature animals and the study is usually short-term. A different approach is the *in vivo* lavaged lung reported by Lachmann *et al* (1980). Again these may not be truly relevant to the preterm infant with RDS, where structural immaturity is also a factor. The maturity of the lungs in this model may also mean that they retain the capacity for surfactant production and a shortened duration of surfactant deficiency post-lavage. Similarly the lungs demonstrate an ARDS-like picture rather than RDS due to primary surfactant deficiency.

Several investigators have used this model to show what happens to individual surfactant preparations (Berggren *et al* 1986, Kobayashi *et al* 1984) and to investigate the comparative absence of hyaline membrane formation in high frequency oscillation compared to conventional ventilation (see section 6.3.1).

Using adult New Zealand white rabbits that had been subjected to repeated saline lavage Kelly *et al* (2000) compared partial liquid ventilation (PLV), ***Curosurf***, ***ALEC*** and untreated controls. They assessed gaseous exchange, changes in lung compliance and survival to 12 hours post-lavage. The greatest improvements were seen in those rabbits given PLV or Curosurf, but what was surprising given the results of clinical trials was that results from rabbits treated with ***ALEC*** were no better than from controls.

7.5 *In vivo* physiological effects in preterm animals

These may be the most relevant models for surfactant deficiency in RDS and it may be appropriate to extrapolate experimental findings from them to the preterm neonate. The animal models most commonly used are the preterm rabbit, baboon and lamb.

In rabbits delivery at 27 days gestation (term is 31 days) followed by mechanical ventilation is sufficient to induce bronchiolar lesions similar to those seen in hyaline membrane disease (Nilsson 1982) however rabbits can only be ventilated for short periods allowing only short-term assessment of surfactant function.

The second model that has been used is the baboon. Lungs of fetal (delivered at 75% of normal gestation) and term baboons subjected to ventilation and high oxygen concentrations develop histopathological lesions similar to RDS (Escobedo *et al* 1982, Coalson *et al* 1982). This model has not been used to compare different surfactants.

Lambs are regarded as a useful model for RDS as they are often born as twins and these act as controlled pairs. Whether this is an appropriate way of obtaining controls is not clear, the evidence from humans is that the second twin may be at greater risk of RDS (chapter 1). However compared to rabbits the larger size of the newborn lamb means that improvements in blood gases, lung mechanics and survival are easier to assess (Cumming *et al* 1992).

Cummings *et al* (1992) found that ventilated lambs treated with ***Exosurf*** did as poorly as controls (no treatment). Other surfactants produced better survival rates at 24 hours. Of lambs treated with ***Infasurf*** with 67% were alive at 24 hours as compared to 33% of ***Survanta*** treated lambs and, surprisingly, only 20% of sheep surfactant treated lambs.

The exogenous surfactant extract ***Surfactant TA*** has *in vitro* surface tension lowering properties that were as good as natural sheep, rabbit and human surfactant, and a smaller amount (8μg versus 30μg) was needed to achieve this effect (Ikegami *et al* 1987). However when administered to preterm sheep a hierarchy of dynamic compliance measurements was produced (Table 22) that was different from that achieved *in vitro*. Furthermore although these different surfactants appeared equally effective in preventing alveolar protein leak *in vivo* when they were recovered by lavage the *in vitro* performance showed a greater inactivation by proteins of the human surfactant.

Similar results were obtained with lavaged cow and synthetic (7: 3 ratio of DPPC: PG) surfactants (Egan *et al* 1983). Although *in vitro* the surface tension lowering properties were very similar, the cow surfactant produced greater improvements in both oxygenation and measurements of dynamic compliance. The addition of natural surfactant-associated proteins to phospholipids improved the treatment responses when given to preterm rabbits (Rider *et al* 1993).

Thus extrapolation of the results from comparisons of the *in vitro* properties of surfactant to animal models is not straightforward. *In vitro* studies do not take into account the interactions between the lung environment and the immunological responses of the lungs to oxidative and mechanical stresses from ventilation.

Table 22: Dynamic compliance in preterm lambs 4 hours after treatment with various surfactant preparations (Ikegami *et al* 1987).

	Dynamic compliance (ml/cm H_2O/kg)
Controls	0.18 ± 0.04
Sheep surfactant	0.66 ± 0.16
Rabbit surfactant	0.42 ± 0.05
Surfactant TA	0.53 ± 0.09
Human surfactant	0.24 ± 0.09

7.6 Conclusion

Animal-derived exogenous surfactants bear a closer resemblance to endogenous human surfactant than the currently available synthetic surfactants. This is apparent both in the phospholipid profiles and the presence of the surfactant-associated proteins SP-B and SP-C. Theoretically the animal-derived surfactants should have properties *in vitro* and *in vivo* that more closely match those of human surfactant.

Studies of the *in vitro* properties of animal-derived surfactants suggest that they are better than the synthetic surfactants, ***ALEC*** and ***Exosurf***. However results from *in vitro* (physiological) testing are not good predictors of clinical efficacy either in preterm animals or in humans. Caution needs to be exercised in extrapolating these *in vitro* properties – as demonstrated by dry powder ***ALEC***, which has good *in vitro* properties but a poor clinical effect and Tween 20, which had poor *in vitro* properties but nonetheless allowed good gas exchange in an animal model of RDS.

Overall however animal models of RDS suggest that animal-derived surfactants are more effective than synthetic surfactants. However the various animal models are not comparable with each other, and may not be comparable with surfactant-deficient RDS in premature human neonates (Henry *et al* 1997). The preterm neonate still has some surfactant at even at early gestations, and animal models that remove all pre-existing surfactant by lavage, as in the study by Kelly *et al* (2000) may, therefore, not be representative. If the animal models were to be believed, ***ALEC*** and ***Exosurf*** would work no better than control infants that received saline or no treatment. Therefore only by undertaking a randomised trial in a neonatal population can we truly compare two different surfactants in RDS.

Chapter 8

Comparisons between different surfactants in neonates

Introduction

Although, as the previous chapter reports, studies of the biophysical properties of surfactants and animal models suggest surfactants that contain surfactant-associated proteins may have advantages over protein-free synthetic surfactants, there are limitations to the conclusions that can be drawn with respect to a human neonatal population for example, Scarpelli *et al* (1992) caution that none of the existing exogenous preparations establish full surfactant function.

Preterm neonates are heterogeneous in nature, subject to a variety of environmental and genetic differences that cannot be replicated in the animal and experimental models. Race, gender and antenatal steroids are among the many variables that effect RDS (chapter 1). They also have some endogenous surfactant that can supplement an endogenous surfactant that administered (Ikegami *et al* 1993).

Several investigators have compared different surfactant preparations in preterm neonates. Some groups have compared synthetic and animal-derived surfactants; whereas others compared two different animal-derived surfactants. All published trials of this nature are shown in Table 23. A summary of each trial is given in Table 24.

The focus in these trials varies considerably. Some trials concentrate on the changes in early oxygenation and ventilation that occur after surfactant administration, whereas other trials concentrate on neonatal and longer-term outcomes. Other trials look at the effect of these early changes on cerebral circulation or radiographic changes after two different surfactants.

The following review of these trials therefore concentrates on these areas separately, before examining the whole question of animal-derived versus synthetic surfactants as a meta-analysis and presenting conclusions based on existing evidence.

Table 23: Studies comparing two different surfactant preparations in neonatal populations.

Authors	**Comparison between**	**Type of study**		**Infants**
Alvarado *et al* 1993	Survanta v. Exosurf	Randomised controlled	Abstract	66
Arnold *et al* 1996	Survanta v. Exosurf	Historic cohort	Full report	114
Bassiouny *et al* 1997	Survanta v. Exosurf	Randomised controlled	Full report	27
Bloom *et al* 1994	Survanta v. Infasurf	Randomised controlled	Abstract	609
Bloom *et al* 1997	Survanta v. Infasurf	Randomised controlled	Full report	608
Choukroun *et al* 1994	Curosurf v. Exosurf	Historic cohort	Full report	34
Cotton *et al* 1992	Survanta v. Exosurf	Not randomised	Abstract	7
Cotton *et al* 1993	Survanta v. Exosurf	Not randomised	Full report	17
Da Costa *et al* 1999	Survanta v. Exosurf	Randomised controlled	Full report	89
Graugaug *et al* 1994	Survanta v. Exosurf	Randomised controlled	Abstract	34
Graugaug *et al* 1995	Survanta v. Exosurf	Randomised controlled	Abstract	60
Horbar *et al* 1993	Survanta v. Exosurf	Randomised controlled	Abstract	617
Horbar *et al* 1994	Survanta v. Exosurf	Randomised controlled	Full report	617
Hudak *et al* 1994a	Infasurf v. Exosurf	Randomised controlled	Abstract	854
Hudak *et al* 1994b	Infasurf v. Exosurf	Randomised controlled	Abstract	1126
Hudak *et al* 1996	Infasurf v. Exosurf	Randomised controlled	Full report	1033
Hudak *et al* 1997	Infasurf v. Exosurf	Randomised controlled	Full report	871
Kukkonen *et al* 2000	Curosurf v. Exosurf	Randomised controlled	Full report	228
Levine *et al* 1991	Exosurf v. human surfactant	Historic cohort	Full report	67

Table 23: Studies comparing two different surfactant preparations in neonatal populations (continued).

Authors	Comparison between	Type of study		Infants
Malathi & Ng 1995	Exosurf v. Survanta	Non-randomised	Full report	77
Modanlou *et al* 1994a	Survanta v. Exosurf	Randomised controlled*	Abstract	291
Modanlou *et al* 1994b	Survanta v. Exosurf	Randomised controlled*	Abstract	291
Modanlou *et al* 1997	Survanta v. Exosurf	Randomised controlled*	Full report	203
Murdoch *et al* 1998	Curosurf v. Exosurf	Randomised controlled	Full report	20
Pearlman *et al* 1993	Survanta v. Exosurf	Quasi-randomised	Abstract	121
Peliowski *et al* 1998	bLES v Exosurf	Randomised controlled	Abstract	635
Rollins *et al* 1993	Curosurf v. Exosurf	Not randomised	Full report	66
Sehgal *et al* 1994	Survanta v. Exosurf	Randomised controlled	Full report	41
Schlessel *et al* 1995	Infasurf v Exosurf	Randomised controlled	Abstract	39
Speer *et al* 1995	Curosurf v. Survanta	Randomised controlled	Full report	75
Stenson *et al* 1994	Curosurf v. Exosurf	Not randomised	Full report	73
Szymankiewicz *et al* 1999	Alveofact v. Survanta	Not randomised	Full report	54
van Overmeire *et al* 1999	Alveofact v. Survanta	Randomised controlled	Abstract	131
Vermont Oxford 1994	Survanta v. Exosurf	Randomised controlled	Abstract	1318
Vermont Oxford 1994	Survanta v. Exosurf	Randomised controlled	Full report	1296

* Trials reported by Modanlou *et al* (1994a, 1994b and 1997) are composite of infants randomised to ***Exosurf*** and ***Survanta***, and additional historic ***Exosurf*** controls.

Table 24: Summaries of the clinical trials involving two different surfactants

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Levine *et al* (1991) – comparison of radiological appearances in two cohorts treated with human surfactant or Exosurf (67 infants	Non-randomised comparison of two historic cohorts	25-36 weeks gestation treated with surfactant	Not stated	Chest radiograph disease severity over first 48 hours
Cotton *et al* (1993) – trial between Survanta and Exosurf - (17 infants)	Not randomised Single centre Not blinded	Preterm infants (gestation and birthweight not stated)	Not stated	Early improvements in FRC and oxygenation No long term outcomes reported
Alvarado *et al* (1993) – trial between Survanta and Exosurf (66 infants)	Randomised (method not stated) Single centre Blinded (method not stated)	Preterm infants Less than 24 hours old Birthweight < 1250 grams Radiological RDS Ventilated with $FiO_2 \geq 0.4$	Not stated	Days of ventilation Days of supplementary oxygen Length of hospital stay Mortality
Pearlman *et al* (1993) – trial between Survanta and Exosurf (121 infants)	Quasi-randomised (alternate calendar months) Single centre study Not blinded	Clinical features consistent with RDS	Not stated	Days of ventilation Neonatal mortality Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	Methods	Participants	Exclusions	Outcomes
Rollins *et al* (1993) – comparison between Curosurf and Exosurf (66 infants)	Non-randomised comparison of two historical cohorts Two centres Not blinded	Exosurf infants eligible for OSIRIS trial (a/APO_2 <0.22 or "at risk of RDS", >2 hours old, ventilated), Curosurf infants eligible for EURO VI study (<72 hours old, radiological and clinical RDS, a/APO_2 <0.22)	As for OSIRIS trial (congenital abnormality) and EURO VI (severe congenital malformations)	Early improvements in ventilation and oxygenation Complications of prematurity
Horbar *et al* (1994) – trial between Survanta and Exosurf (614 infants)	Randomised Multicentre (11 centres) Unique randomisation lists held in each centre stratified by birthweight Not blinded	In-born Less than 6 hours old. Ventilated with $FiO_2 \geq 0.3$. Radiological appearance of RDS. Felt "likely to benefit from surfactant".	Mature L/S ratio. Previous treatment with any surfactant. Clinically unstable (hypotensive, hypoglycaemic, fitting) Pre-existing pneumothorax or pneumopericardium Life threatening congenital or chromosomal anomalies	Neonatal death or CLD at 28 days Early improvements in ventilation and oxygenation Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	Methods	Participants	Exclusions	Outcomes
Grauaug *et al* (1994) and Grauaug *et al* (1995) – trial between Survanta and Exosurf (60 babies)	Randomised (method not stated) Single centre Blinded (method not stated)	In-born Less than 33 weeks' gestation Birthweight >600 grams Ventilated with supplemental oxygen	None stated	Differences in dynamic elastance Mortality and CLD Complications of prematurity
Sehgal *et al* (1994) – trial of Survanta and Exosurf (41 infants)	Randomised Single centre Sealed envelopes (not stratified) No blinding	Birthweight 600-1750 grams. Clinically stable (normotensive, normoglycaemic, and no seizures). Clinical and radiological RDS. Ventilated with $FiO_2 \geq 0.4$.	Pre-existing pneumothorax or pneumopericardium Severe congenital anomalies	Early improvements in ventilation and oxygenation Mortality Complications of prematurity
Stenson *et al* (1994) - comparison between Curosurf and Exosurf (88 infants)	Non-randomised comparison of two historical cohorts Two centres Not blinded	Curosurf treated infants eligible for EURO VI study (< 72 hours old, clinical and radiological RDS, $a/APO_2 < 0.22$), Exosurf treated infants if ventilated with oxygen requirement	If apnoea could not be induced or if leak around ETT If initial measured compliance suggested "mature surfactant" present	Differences in static lung compliance Mortality and CLD Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	Methods	Participants	Exclusions	Outcomes
Choukroun *et al* (1994) – comparison between Curosurf and Exosurf (34 infants)	Non-randomised comparison of two historical cohorts Single centre Not blinded	Infants receiving rescue surfactant for RDS ($a/APO_2 < 0.22$)	Congenital malformation	Differences in dynamic and static lung compliance Early improvements in ventilation and oxygenation
Speer *et al* (1995) – trial between Survanta and Curosurf (75 infants)	Randomised Multicentre (5 centres) Sealed envelopes (stratified by centre and birthweight) Not blinded	Birthweight 500-1500 grams. Clinical and radiological RDS. 1-24 hours old. Ventilated with $FiO_2 \geq 40\%$	Prolonged rupture of membranes >3 weeks grade III or grade IV IVH birth asphyxia major congenital anomaly pneumothorax, congenital infection, hypoglycaemia, hypotension, acidosis unless treated	Early improvements in ventilation and oxygenation Mortality Complications of prematurity
Schlessel *et al* (1995) - trial between Infasurf and Exosurf (36 infants).	Randomised (method not stated)	Eligibility criteria not stated	Not stated	Early lung function and oxygenation
Malathi & Ng (1995) – comparison of Survanta and Exosurf (77 infants)	Historic cohorts (not randomised) Single centre	Preterm infant Ventilated with MAP $\geq$ 7 cm H_2O and $FiO_2 \geq 0.4$	Not stated	Early improvements in ventilation and oxygenation Mortality Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Hudak *et al* (1996) – trial between Infasurf and Exosurf used as rescue therapy (1033 infants)	Randomised Multicentre (21 centres) Sealed envelopes Blinded using drug administrators	No specified gestation or birthweight Radiological and clinical RDS. Ventilated with $a/APO_2 \leq 0.22$. Less than 72 hours old.	Previously received surfactant. Lethal congenital or chromosomal anomaly. Clinically unstable (hypotensive, hypoglycaemic, bradycardic) Pre-existing pneumothorax or pneumopericardium	Pulmonary airleak in first seven days. Severity of RDS after surfactant therapy Death due to RDS (death due to respiratory failure during the first 14 days). Neonatal outcomes of death and BPD at 28 days. Cross-over treatment
Vermont-Oxford Neonatal Network (1996) – trial between Survanta and Exosurf (1296 infants)	Randomised Multicentre (38 centres) Randomisation lists held in each centre (stratified by birthweight)	Birthweight 600-1500 grams. Ventilated with $FiO_2 \geq 0.3$. Less than 6 hours old. Clinical and radiological RDS.	Mature L/S ratio Previous surfactant treatment Lethal congenital or chromosomal anomaly. Clinically unstable (hypotensive, hypoglycaemic, bradycardic) Pre-existing pneumothorax or pneumopericardium	Neonatal death and/or CLD Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	**Methods**	**Participants**	**Exclusions**	**Outcomes**
Arnold *et al* (1996) – comparison between Survanta and Exosurf (144 infants)	Retrospective review - non-randomised initially (surfactant according to neonatologists preference), then infants enrolled and randomised as part of larger multicentre trial Two centres Not blinded	Any baby treated with either Survanta or Exosurf	Congenital infection (positive blood cultures within 24 hours of birth) Major congenital malformations.	Duration of ventilation Duration of oxygen therapy
Bloom *et al* (1997) – "rescue" trial of Infasurf versus Survanta (608 infants)	Randomised Multicentre (13 centres) Sequentially numbered masked vials of surfactant (stratified by centre and birthweight) Blinded	Birthweight < 2000 grams. Age < 48 hours. Clinical and radiological RDS. Ventilated with $FiO_2 \geq 0.4$ OR $a/APO_2 \leq 0.22$.	Cardio-respiratory malformation Chromosomal abnormality Errors in surfactant administration (mixed types, wrong dosage) Congenital sepsis or pneumonia	Number of doses Oxygen and ventilator requirements Complications of prematurity
Bloom *et al* (1997) – "prophylaxis" trial of Infasurf versus Survanta (374 infants)	Randomised Multicentre (7 centres) Sequentially numbered masked vials of surfactant (stratified by centre and gestation) Blinded	Gestation <29 weeks In-born	Birthweight >1250 grams Not stabilised by 15 minutes of age Cardio-respiratory malformation Chromosomal abnormality Congenital sepsis	Development of RDS ($FiO_2 \geq 0.4$) Number of doses Oxygen and ventilator requirements Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	Methods	Participants	Exclusions	Outcomes
Hudak *et al* (1997) – trial between prophylactic Infasurf and Exosurf (846 infants)	Randomised Multicentre (10 centres) Sealed envelopes Blinded using drug administrators	In-born Gestation <29 weeks	Pre-viable Not intubated Not stabilised by 15 minutes of age Lethal congenital or chromosomal anomaly.	RDS at 24 hours of age. Death attributable to RDS in the first two weeks of life. Survival without chronic lung disease at 28 days. Air leak syndrome Complications of prematurity
Bassiouny *et al* (1997) – trial between Exosurf and Survanta (27 infants)	Quasi-randomised (alternate days) Single centre Not blinded	Premature infants with RDS Mechanically ventilated with $a/APO_2 < 0.22$ Less than 24 hours old	Not stated	Changes in a/APO_2 ratio after treatment
Modanlou *et al* (1997) – trial of Survanta versus Exosurf (122 infants)	Randomised (with historic cohort for comparison) Single centre Sequentially coded cards (not stratified) Not blinded	In-born. Birthweight 500-1500 grams. Clinical and radiological RDS. Ventilated. Less than 8 hours old. Had an $a/APO_2 < 0.22$ OR an $FiO_2 \geq 0.4$ OR both.	Major congenital anomalies.	Early improvements in ventilation and oxygenation Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	Methods	Participants	Exclusions	Outcomes
Pelioski *et al* (1998) – trial between bLES and Exosurf (635 infants)	Randomised (method not stated but stratified by weight and centre) Multicentre (?Number of centres) Blinding method not stated	Birthweight <1250 grams	Not stated	Survival to 36 weeks' gestation without CLD Early improvements in ventilation and oxygenation Complications of prematurity Duration of oxygen therapy
Murdoch & Kempley (1998) – effects of Exosurf or Curosurf on cerebral circulation (20 infants)	Randomised (method not stated) Not blinded	Gestation 25-36 weeks Ventilated	Sepsis Congenital abnormalities	Changes in cerebral blood flow velocity Cranial ultrasound outcomes
Overmeire *et al* 1999 – randomised trial between Survanta and Alveofact (131 infants)	Randomised (method not stated) No. of centres not stated Blinding method not stated	Less than 33 weeks' gestation	Not stated	Early improvements in ventilation and oxygenation Complications of prematurity

Table 24: Summaries of the clinical trials involving two different surfactants (continued)

Study	Methods	Participants	Exclusions	Outcomes
Da Costa *et al* (1999) – trial of Survanta versus Exosurf (89 infants)	Randomised Single centre Sealed envelopes Not blinded	In-born and out-born infants $\leq$ 8 hours old Ventilated with $FiO_2 \geq 0.4$ Radiological RDS $\geq$1000 grams birthweight <37 weeks gestation	Congenital malformations Congenital infection Persistent pneumothorax Pre-existing grade III or IV IVH	Ventilation and oxygenation at 24 hours of age Incidence of CLD/death at 28 days Complications of prematurity
Szymankiewicz *et al* (1999) - comparison between Survanta and Alveofact (54 infants)	Non-randomised comparison Single centre Not blinded	Infants $\leq$ 32 weeks gestation Ventilated with $FiO_2 \geq 0.4$ Radiological RDS	Ventilated with $FiO_2 \geq 0.4$ Radiological RDS IUGR	Differences in dynamic and static lung compliance Early improvements in ventilation and oxygenation
Kukkonen *et al* (2000) – comparison between Curosurf and Exosurf (224 infants)	Randomised Three centres Not blinded Stratified by centre and birthweight	In-born. Clinical and radiological RDS. Ventilated. Had an $a/APO_2 < 0.22$.	Congenital malformation	Duration of ventilation and O_2 dependency Complications of prematurity Incidence of sepsis

8.1 Early changes in oxygenation, ventilation and respiratory function after surfactant.

Although neonatologists frequently explain to parents that infants with RDS have stiff lungs and that surfactant helps to improve their compliance, this explanation is very much an over-simplification of the actual process. Compliance does improve after surfactant, however this is preceded by improvements in functional residual capacity (FRC) as a result of alveolar recruitment (Edberg *et al* 1990). Hence oxygenation changes are seen more readily than changes in ventilation (carbon dioxide excretion).

Studies specifically of the changes in oxygenation, ventilation and respiratory function are:

- Cotton *et al* (1993) – non-randomised study between two cohorts treated with either ***Survanta*** or ***Exosurf***
- Grauaug *et al* (1994 and 1995) – randomised trial between infants treated with ***Survanta*** or ***Exosurf***, examining effect on lung elastance
- Stenson *et al* (1994) - non-randomised study between two cohorts treated with ***Curosurf*** or ***Exosurf***
- Choukroun *et al* (1994) – non-randomised comparison of effects of ***Exosurf*** and ***Curosurf*** on pulmonary mechanics
- Schlessel *et al* (1995) - randomised trial examining effects of ***Infasurf*** and ***Exosurf*** on pulmonary mechanics
- Bassiouny *et al* (1997) – effects of ***Survanta*** and ***Exosurf*** on early a/APO_2 values

Overall it is apparent that animal-derived surfactants (whatever the origin) have a more rapid onset of action than ***Exosurf*** (the only synthetic surfactant to have been compared in these studies). At its simplest level Bassiouny *et al* (1997) report improvements in early a/APO_2 values that are greater and of earlier onset in ***Survanta***-treated than in ***Exosurf***-treated infants. This finding is reported in the larger randomised controlled trials as improvements in FiO_2 and MAP. Using a multiple-breath nitrogen washout technique, Cotton *et al* (1993), demonstrated that these improvements in oxygenation closely mirrored improved FRC. A greater FRC and improved oxygenation was seen earlier in ***Survanta***-treated than in ***Exosurf***-treated infants.

Compliance may be measured either using a single breath (static technique) or more recently by on-line monitoring on modern ventilators (dynamic technique). The latter is dependent on ventilator rate and other variables that can make it a less reliable technique. Stenson *et al* (1994) examined static respiratory compliance (C_{rs}) in two historic cohorts treated with either ***Curosurf*** or ***Exosurf***. Infants receiving ***Curosurf*** were treated according to the EURO VI study protocol (Halliday *et al* 1993), those receiving ***Exosurf*** according to the manufacturer's instructions.

Significant improvements in C_{rs} were seen in the ***Curosurf*** group at three and twelve hours, in the ***Exosurf*** group C_{rs} fell at 3 hours and exhibited only a small improvement at 12 hours. The ***Curosurf*** group also demonstrated greater and earlier reductions in FiO_2 and changes in ventilator requirements than the ***Exosurf*** group.

These findings were similar to those of Choukroun *et al* (1994) who measured both dynamic (C_{dyn}) and static compliance (C_{rs}) in infants treated with ***Curosurf*** or ***Exosurf***. There were improvements in static compliance measurements after both surfactants, but improvements occurred earlier after ***Curosurf*** (evident at 6 hours) than ***Exosurf*** (evident after 24 hours). Dynamic compliance changed after 6 hours with ***Curosurf*** but changes were not evident until 72 hours after ***Exosurf***.

Schlessel *et al* (1995) also examined dynamic compliance (but used a standardised ventilator rate during measurements) in infants randomised to treatment with ***Infasurf*** or ***Exosurf***. Improvements were seen in measurements of compliance and tidal volumes in all infants irrespective of surfactant allocation, but the ***Infasurf*** group had earlier and greater improvements than the ***Exosurf*** group however differences between the two groups had diminished by 24 hours.

Grauaug and colleagues (Grauaug *et al* 1994 and 1995) report the effects of ***Survanta*** and ***Exosurf*** on lung elastance. Elastance, which is the reciprocal of compliance, is related to the volume of the lung, the resistance to the velocity of airflow and the inertia to the acceleration (inertia in turn is related to the pressure gradient and the cross-sectional area of the airways). Early improvements in elastance (and hence compliance) were noted in the ***Survanta*** group but differences between the two groups did not persist beyond 24 hours.

In essence all studies report that lung function, and its effects on ventilation and oxygenation occur earlier in infants treated with an animal-derived surfactant, however the differences persist for only 24-48 hours. The question then arises whether this brief period of lower ventilator and oxygen requirements seen in animal-derived surfactants is enough to produce longer-term advantages. Longer-term complications are more important both to the family and to providers of neonatal intensive care because of their resource implications. Longer-term outcomes are examined in sections 8.4 and 8.5, and the resource implications are examined in chapters 9 and 10 in relation to a comparison between ***ALEC*** and ***Curosurf***.

8.2 Changes in radiographic appearances after natural and synthetic surfactants

This aspect is examined in one study comparing two historic cohorts: Levine *et al* (1991) used a standardised scoring system to evaluate the severity of RDS from the appearances of the chest radiograph (Edwards *et al* 1985). One cohort had been treated with human amniotic fluid-derived surfactant, and a later cohort with ***Exosurf***. The authors reported no demonstrable differences in the radiological scores after treatment with either surfactant.

The authors reported that ***Exosurf*** treated infants had scores that were slower to improve. However the time scale is recorded as age from birth and these infants had been treated using a rescue strategy, whereas infants in the earlier cohort were treated prophylactically. It would not be unreasonable to expect to find the infants treated prophylactically had lower scores earlier (chapter 6).

It also could be argued that radiological appearances are not as reliable or sensitive in assessing disease severity compared to clinical assessment or pulmonary function testing. Radiographic appearances do not correlate with lung function testing (Dimitriou *et al* 1995), and radiographic clearing of RDS occurs approximately 18-20 hour prior to the improvement in pulmonary compliance (Shimada *et al* 1990). Nonetheless Levine and colleagues concluded, "Exosurf, *by radiologic criteria, is nearly as effective as human surfactant in ameliorating RDS*". No correlation was made in this study to longer-term clinical outcomes in either group of infants.

8.3 The effects of different surfactants on cerebral blood flow.

As stated in section 8.3, animal-derived surfactants act faster than synthetic ones, bringing about changes in arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) that can affect systemic, and, more importantly, cerebral circulations. There had already been concern from placebo-controlled trial of animal-derived surfactants of the effects of this on long-term cerebral outcomes with one trial (Horbar *et al* 1990) being stopped early by the FDA because of a high rate of severe IVH in ***Survanta***-treated infants.

Only one small study (Murdoch & Kempley 1998) specifically examines this aspect of surfactant therapy in small groups of infants treated with either ***Curosurf*** or ***Exosurf***. Anterior cerebral artery blood flow velocity (CBFV) was assessed before surfactant administration and then at 1, 5, 30, 60 and 120 minutes intervals using Doppler ultrasound. Following ***Curosurf*** there was a rapid and sustained decrease (by up to 36% of baseline values) in CBFV. Velocities returned to baseline values after two hours. In the ***Exosurf*** group there was also a significant, albeit smaller, increase in cerebral blood flow velocities (up to 20% of baseline values).

The authors rejected changes in $PaCO_2$ as the reason for the altered CBFV after ***Curosurf*** on the grounds that observed changes were small although others have disagreed (Fenton *et al* 1992a). Small changes in $PaCO_2$ cause alterations in arterial blood pressure and cardiac output that affect the cerebral circulation (Fenton *et al* 1992b). Similar effects on systemic and cerebral blood flow were also reported after treatment with ***Survanta*** in a porcine model of RDS (Moen *et al* 1998).

In contrast to measurements of CBFV near infrared spectrometry has shown that total cerebral blood volume remains relatively unchanged after surfactant therapy (Edwards *et al* 1992, Roll *et al* 1999). It seems likely that changes in venous return match arterial blood flow velocity.

It is not clear whether this means animal-derived surfactants, because of their rapid onset of action and effects on the systemic circulation, have a cost that is reflected in terms of a challenge to the maintenance of the cerebral circulation. Reduced cerebral blood flow may lead to an increase in periventricular ischaemia particularly due to venous stasis/infarction and subsequent development of PVL (Volpe 1997). Low cerebral blood flow has been shown to be associated with an increased risk of intraventricular haemorrhage (Meek *et al* 1999).

The incidence of PVL is not widely reported in animal-derived versus synthetic surfactant trials, nor is it reported in the Cochrane review of these trials (Soll 1999c). Where it is reported (Hudak *et al* 1996, Hudak *et al* 1997) there is a doubling of the numbers of infants with PVL after treatment with the animal-derived surfactant. There were, however, trends to greater mortality in the ***Exosurf***-treated infants and it was not determined whether these had PVL before they died.

8.4 Effects of different surfactants on neonatal mortality and the complications of prematurity

Outcomes at 28 days form the basis for most comparisons between different surfactants, and are also used in the Cochrane review of natural (animal-derived) versus synthetic surfactants (Soll 1999c). Almost all comparisons between any surfactants employ a rescue strategy, the exceptions being Hudak *et al* (1997) and part of the study by Bloom *et al* (1997). The importance of this has been debated in chapter 6.

Most studies have compared an animal-derived and a synthetic surfactant; the exceptions to this were comparisons of ***Survanta*** with ***Curosurf*** (Speer *et al* 1995), with ***Infasurf*** (Bloom *et al* 1997) and with ***Alveofact*** (van Overmeire *et al* 1999 and Symankiewicz *et al* 1999). None of these studies was able to support the use of one animal-derived surfactant over the other, suggesting that if there are differences between animal-derived surfactants they may be insignificant as far as neonatal outcomes are concerned.

In the animal-derived versus synthetic surfactant trials, the synthetic surfactant used is ***Exosurf*** whereas the commonest animal-derived surfactant is ***Survanta***. Other surfactants that have been less extensively compared are ***Curosurf*** (Kukkonen *et al* 2000), ***Infasurf*** (Hudak *et al* 1996 and 1997) and ***bLES*** (Peliowski *et al* 1998). Various entry criteria were utilised (Table 24). Alvarado *et al* (1993), Horbar *et al* (1993), Vermont Oxford Neonatal Network (1996), and Modanlou *et al* (1997) studied infants with birthweight <1500 grams. Seghal *et al* (1994) infants with birthweights 600-1750 grams, and da Costa *et al* (1999) infants of >999 grams. Pearlman *et al* (1993), Hudak *et al* (1996) and Kukkonen *et al* (2000) did not have any birthweight or gestation limits. Hudak *et al* (1997) enrolled infants that were <29 weeks gestation.

Among the rescue trials a variety of criteria for oxygen requirement at entry were used. Alvarado *et al* (1993) required that infants be in supplemental oxygen >40%. The studies of Horbar *et al* (1993) and the Vermont Oxford Neonatal Network (1996) required that infants be in supplemental oxygen >30%. Hudak *et al* (1996), Modanlou *et al* (1997) and Kukkonen *et al* (2000) required that infants had an a/APO_2 ratio ≤ 0.22 (corresponding to approximately 40% oxygen). Investigators set out a variety of age criteria; age at entry varied from 6 hours of age (Horbar *et al* 1993, Vermont Oxford Neonatal Network 1996) to 72 hours of age (Hudak *et al* 1996). Da Costa *et al* (1999) required infants are in supplemental oxygen >40% at a mean airway pressure ≥ 7 cmH_2O at less than 8 hours of age.

All the studies reported earlier and greater improvements in immediate respiratory support associated with treatment with the animal-derived surfactant. Alvarado *et al* (1993) reported fewer days on mechanical ventilation, fewer days on supplemental oxygen, and fewer days of hospitalisation associated with treatment with animal-derived surfactant. Some trials were able to report significant improvements in neonatal outcomes (Table 25). The results from these randomised trials are discussed further in the following meta-analysis.

8.5 Meta-analysis of the randomised trials comparing animal-derived versus synthetic surfactants

Method

The objective of this section was to assess the effect of intra-tracheal administration of animal-derived surfactant versus synthetic surfactant in the treatment of RDS using either prophylaxis (prevention) or rescue treatment. The search strategy outlined in section 5.1.2 was used to examine outcomes in randomised controlled trials that compared one animal-derived surfactant versus a synthetic surfactant. Data were taken from trials involving any surfactant and not just those that have been licensed in the UK. Data regarding clinical outcomes, particularly relating to neonatal mortality and respiratory complications of prematurity were excerpted from published reports of the clinical trials and analysed using the statistics outlined in section 5.1.2.

Table 25: Significant outcomes at 28 days of age and 36 weeks corrected gestation reported in randomised trials comparing animal-derived and synthetic surfactants

Study	Outcome	Animal-derived	Synthetic	Relative risk	95% CI	Risk difference	95% CI
Vermont Oxford Neonatal Network (1996)	Pneumothorax	58 / 651 (8.9%)	96 / 644 (14.9%)	**0.60**	0.44 to 0.81	**-6.0%**	-9.5 to –2.5%
Hudak *et al* (1996)	Pneumothorax	29 / 525 (5.5%)	52 / 508 (10.2%)	**0.54**	0.35 to 0.84	**-4.7%**	-8.7 to –1.4%
	PIE	41 / 525 (7.8%)	90 / 508 (17.7%)	**0.44**	0.31 to 0.62	**-9.9%**	-13.9 to –5.9%
	Any air leak	61 / 525 (11.6%)	114 / 508 (22.4%)	**0.52**	0.39 to 0.69	**-10.8%**	-15.4 to –6.3%
Hudak *et al* (1997)	PIE before 7 days	20 / 431 (4.7%)	48 / 422 (11.3%)	**0.42**	0.25 to 0.69	**-6.6%**	-10.3 to –3.0%
	Any air leak before 7 days	34 / 431 (8.0%)	60 / 422 (14.2%)	**0.57**	0.38 to 0.84	**-6.1%**	-10.4 to –1.9%
	Total IVH	168 / 431 (39.0%)	126 / 422 (29.9%)	**1.31**	1.08 to 1.58	**+9.1%**	+2.8 to +15.5%
	Cystic PVL	28 / 431 (6.5%)	14 / 422 (3.3%)	**1.96**	1.05 to 3.67	**+3.2%**	+0.3 to +6.1%

Studies were considered if they fulfilled the following criteria:

(a) ***Types of studies*** – Randomised or quasi-randomised trials comparing any animal-derived surfactant with any synthetic surfactant in the prevention or treatment of RDS.

(g) ***Types of participants*** – preterm neonates at risk of or with clinical and radiological evidence of RDS requiring assisted ventilation.

(h) ***Types of intervention*** - Infants randomised to receive intratracheal administration of either an animal-derived or synthetic surfactant preparation to prevent or treat RDS.

(i) ***Types of outcome measures*** - Data for the following clinical outcomes are included in the meta-analysis: neonatal mortality, pulmonary air leak (reported as pneumothorax and all forms of air leak), patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, chronic lung disease (at 28 days and 36 weeks corrected gestational age in survivors), chronic lung disease or death (at 28 days and 36 weeks corrected gestational age).

Results

Several studies from Table 23 were identified as suitable for inclusion. These are listed below:

- Alvarado *et al* (1993) – trial between ***Survanta*** and ***Exosurf***
- Pearlman *et al* (1993) - quasi-randomised trial between ***Exosurf*** and ***Survanta***.
- Horbar *et al* (1994) - randomised trial between ***Exosurf*** and ***Survanta***
- Grauaug *et al* (1995) – randomised trial between ***Exosurf*** and ***Survanta***
- Vermont Oxford Neonatal Network (1996) - randomised trial between ***Exosurf*** and ***Survanta***.
- Hudak *et al* (1996) - randomised trial between ***Exosurf*** and ***Infasurf*** in established RDS.
- Hudak *et al* (1997) - randomised trial between ***Exosurf*** and ***Infasurf*** in prevention (prophylaxis) of RDS
- Modanlou *et al* (1997) – randomised trial between ***Exosurf*** and ***Survanta***. With some historical cohorts receiving ***Exosurf*** (data excluded from this analysis).
- Murdoch & Kempley (1998) - randomised trial of cerebral haemodynamics after ***Curosurf*** or ***Exosurf***.
- Da Costa *et al* (1999) - randomised trial between ***Exosurf*** and ***Survanta*** in a developing country.

- Kukkonen *et al* (2000) - randomised trial between ***Exosurf*** and ***Curosurf.***

The following trials from Table 23 were excluded for reasons stated;

(a) Comparisons of two animal-derived surfactants:

- Speer *et al* (1995) – randomised trial between ***Survanta*** and ***Curosurf***
- Bloom *et al* (1997) – randomised trial between ***Infasurf*** versus ***Survanta***
- Van Overmeire *et al* (1999) – randomised trial between ***Survanta*** and ***Alveofact***

(b) Non-randomised studies of animal-derived (or human) versus synthetic surfactants:

- Levine *et al* (1991) – comparison of radiological appearances in two cohorts treated with human surfactant or ***Exosurf***
- Cotton *et al* (1993) – trial between ***Survanta*** and ***Exosurf***
- Rollins *et al* (1993) – comparison between ***Curosurf*** and ***Exosurf***
- Stenson *et al* (1994) - comparison between ***Curosurf*** and ***Exosurf***
- Choukroun *et al* (1994) – comparison between ***Curosurf*** and ***Exosurf***
- Malathi & Ng (1995) – comparison of ***Survanta*** and ***Exosurf***
- Arnold *et al* (1996) – comparison between ***Survanta*** and ***Exosurf***

(c) Randomised trials between animal-derived (or human) and synthetic surfactants but in which published reported outcomes were not suitable for inclusion in this meta-analysis:

- Sehgal *et al* (1994) – trial between ***Survanta*** and ***Exosurf***
- Schlessel *et al* (1995) – trial between ***Infasurf*** and ***Exosurf***
- Bassiouny *et al* (1997) – trial between ***Survanta*** and ***Exosurf***
- Pelioski *et al* (1998) – trial between ***bLES*** and ***Exosurf***

Treatment of preterm infants with an animal-derived surfactant led to improvements in oxygenation and ventilatory requirement that occur more rapidly than in those infants treated with synthetic surfactant. It has the following impact on outcomes at 28 days (Figure 10):

Neonatal Mortality: All included trials except Grauaug *et al* (1995) report on the risk of mortality, in most studies this is restricted to neonatal (28 day) mortality rather than overall predischarge mortality. The typical estimate from the meta-analysis suggests a decrease in the risk of neonatal mortality associated with animal-derived surfactants (typical relative risk 0.85, 95% CI 0.74 to 0.98; typical risk difference –2.5%; 95% CI –4.6 to –0.5%).

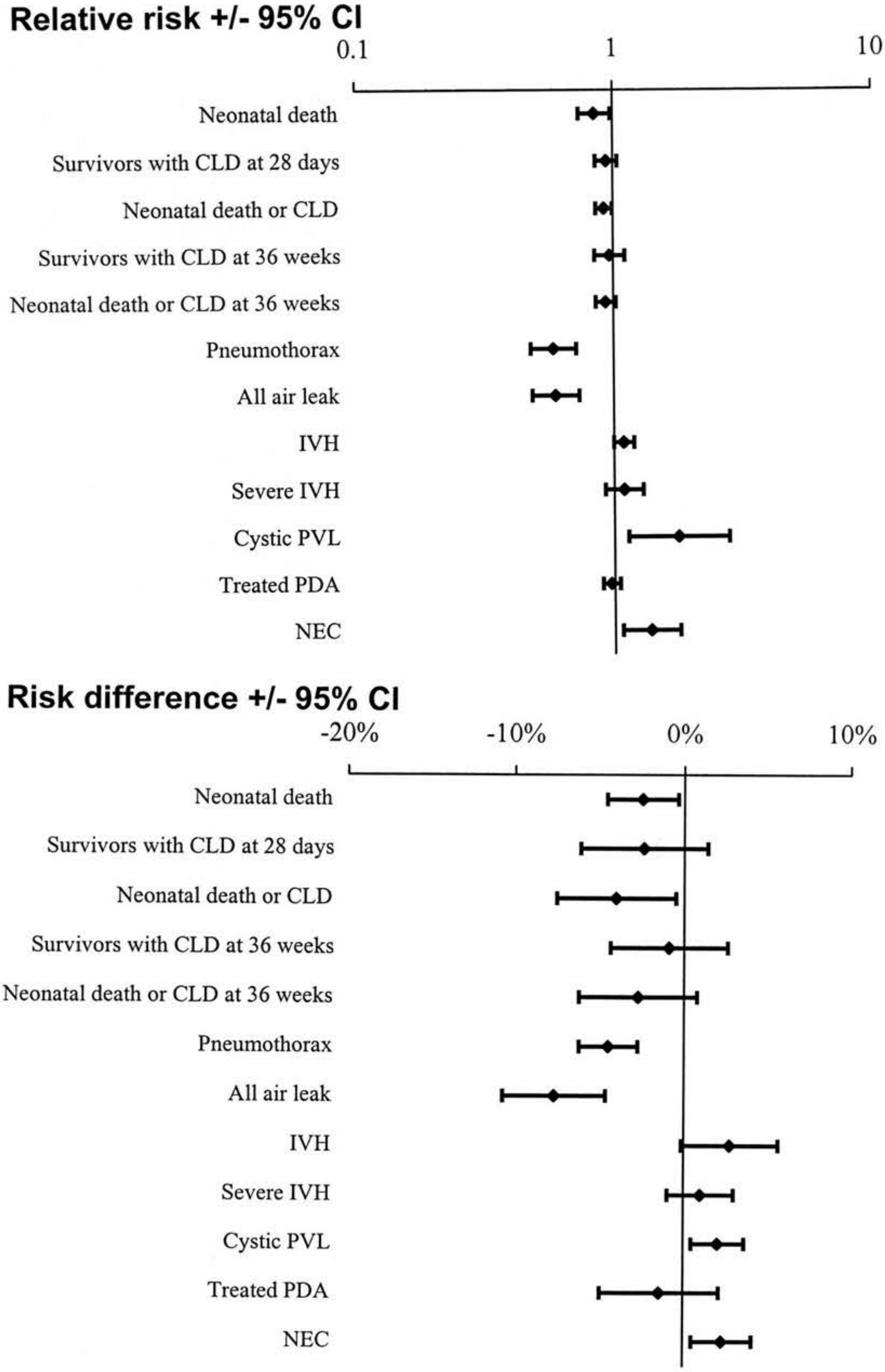
Bronchopulmonary Dysplasia / Chronic Lung Disease (at 28 days postnatal age): Surviving infants with BPD/CLD at 28 days were reported by all studies except Alvardao *et al* (1993), Grauaug *et al* (1995), Hudak *et al* 1996), Murdoch & Kempley (1998) and Kukkonen *et al* (2000). The latter reports CLD at 36 weeks corrected gestational age. The typical estimate shows no difference in the risk of BPD/CLD at 28 days (typical relative risk 0.94, 95% CI 0.85 – 1.04; typical risk difference –2.4%; 95% CI –6.1 to +1.4%).

Bronchopulmonary Dysplasia / Chronic Lung Disease at 28 days* OR *Neonatal Death: Again the studies of Alvardao *et al* (1993), Grauaug *et al* (1995), Hudak *et al* 1996), Murdoch & Kempley (1998) and Kukkonen *et al* (2000) did not report thios outcome. The typical estimate from the meta-analysis of the other studies shows a decrease in the risk of BPD/CLD at 28 days or neonatal death in infants who had received an animal-derived surfactant (typical relative risk 0.92, 95% CI 0.86 – 0.99; typical risk difference –4.0%; 95% CI –7.5 to –0.5%).

Chronic Lung Disease (surviving infants at 36 weeks corrected gestational age): This clinically more useful predictor of long-term respiratory morbidity (Shennan *et al* 1988) was only reported in trials that have been published in full in peer-reviewed literature. Nonetheless sufficient numbers have been reported in the trials of Horbar *et al* (1994), Vermont Oxford Neonatal Network (1996), Hudak *et al* (1997) and Kukkonen *et al* (2000) to allow meaningful analysis. The typical estimate shows no difference in the risk of CLD at 36 weeks post-conception in surviving infants who had received an animal-derived surfactant (typical relative risk 0.97, 95% CI 0.86 – 1.11; typical risk difference –0.9%; 95% CI –4.4 to +2.6%).

Chronic Lung Disease (in surviving infants at 36 weeks corrected gestational age)* OR *death before discharge: This is similar to the CLD/neonatal death category, this analysis makes the assumption that most infants are discharged at around 36 weeks post-conceptual age, and the numbers of infants who stay longer and who subsequently die are very small. The typical estimate shows a trend to reduced risk of CLD at 36 weeks post-conception or death before discharge in infants who had received an animal-derived surfactant (typical relative risk 0.93, 95% CI 0.85 – 1.02; typical risk difference –2.7%; 95% CI –6.2 to +0.8%).

Figure 10: Meta-view charts of trials comparing animal-derived and synthetic surfactants.



Pulmonary Air Leak: Reported using the two forms of pneumothorax or all forms of air leak (which includes pneumothorax). The typical estimate suggests a decrease in the risk of pneumothorax associated with animal-derived surfactant use (typical relative risk 0.58, 95% CI 0.48 to 0.71; typical risk difference –4.7%; 95% CI –6.4 to –3.0%). Similarly, the typical estimate also shows a decrease in the risk of all forms of air leak associated with animal-derived surfactant use (typical relative risk 0.60, 95% CI 0.48 to 0.71; typical risk difference –7.7%; 95% CI –10.7 to –4.6%).

Patent Ductus Arteriosus: The typical estimate suggests no difference in the risk of significant PDA (requiring either medical or surgical treatment) with either surfactant (typical relative risk 0.97, 95% CI 0.90 to 1.05; typical risk difference –1.4%; 95% CI –4.9 to +2.1%).

Intraventricular Haemorrhage: The typical estimate from the meta-analysis suggests a trend (that almost reaches statistical significance) to increased risk of IVH (of any grade) after animal-derived surfactant (typical relative risk 1.09, 95% CI 1.00 – 1.19; typical risk difference +2.7%; 95% CI -0.1 to +5.6%). However when looking specifically at Papile grades III and IV of IVH, the typical estimate from the meta-analysis suggests a lesser trend to increased risk of severe IVH after animal-derived surfactant (typical relative risk 1.09, 95% CI 0.92 – 1.29; typical risk difference +1.0%; 95% CI –1.0 to +3.0%).

Periventricular leukomalacia: This is reported only in the two ***Infasurf*** versus ***Exosurf*** trials (Hudak *et al* 1996 and Hudak *et al* 1997), a small ***Survanta*** versus ***Exosurf*** trial (da Costa *et al* 1999) and the ***Curosurf*** versus ***Exosurf*** trial (Kukkonen *et al* 2000). Nonetheless the typical estimate suggests an increase in the risk of PVL associated with animal-derived surfactant (typical relative risk 1.76, 95% CI 1.13 to 2.76; typical risk difference +2.0%; 95% CI +0.5 to +3.6%).

Necrotising enterocolitis: The typical estimate suggests an increase in the risk of NEC associated with animal-derived surfactant (typical relative risk 1.38, 95% CI 1.07 to 1.78; typical risk difference +2.3%; 95% CI +0.5 to +4.1%).

The implications of this meta-analysis are discussed in section 8.7.

8.6 Differences between animal-derived surfactants

Just as there are compositional and *in vitro* differences between animal-derived and synthetic surfactants, there are differences between the various animal-derived surfactants. These may account for differences seen with speed of onset action but reported neonatal outcomes in trials undertaken to date show great similarity irrespective of the source of the animal-derived surfactant.

The most obvious difference between the animal-derived surfactants is that of composition and the manufacturing process. ***Survanta*** and ***Curosurf*** are both obtained through extraction of minced lung whereas ***Infasurf***, ***Alveofact*** and ***bLES*** are all obtained through lavage of intact lungs. This means that ***Survanta*** and ***Curosurf*** may contain phospholipids that do not originate within the surfactant system, which might make them more susceptible to inactivation by serum proteins compared to lavaged surfactants (Seeger *et al* 1993). In addition ***Survanta*** is manufactured by adding synthetic phospholipids, to the minced lung extract.

There are few trials that compared two animal-derived surfactants (Table 23), of these only Speer *et al* (1995), Bloom *et al* (1997) and van Overmeire *et al* (1999) look at neonatal or longer-term outcomes. Speer *et al* (1995) found a significantly increased risk of PDA requiring treatment in infants treated with ***Curosurf*** compared to ***Survanta***, but no other advantage of either surfactant over the other. Bloom *et al* (1997) could not find any advantage to using ***Infasurf*** over ***Survanta***. Van Overmeire *et al* (1999) and Symankiewicz *et al* (1999) and disagreed whether ***Alveofact*** or ***Survanta*** worked fastest, but van Overmeire *et al* (1999) reports there were no differences in the neonatal and longer-term outcomes.

8.7 Conclusion

The results of the meta-analysis between animal-derived and synthetic surfactants support the view that the former would be the more desirable choice for treatment of infants with or at risk of RDS. There are earlier improvements in the ventilator and oxygen requirements and of mortality. In addition, where it was reported, animal-derived surfactants decreased the both duration ventilation and oxygen therapy, and there was a clear advantage for the use of animal-derived surfactants where reduction of air leaks and pneumothoraces are concerned.

However there may be a price to pay in terms of adverse neurological outcomes for using an animal-derived surfactant. There were trends to a higher incidence of all grades of IVH (almost but not quite reaching statistical significance), a trend to increased severe IVH and a significant increase of PVL after animal-derived surfactant. However these outcomes were restricted to the survivors and it cannot be determined whether infants who died in either group had any of these outcomes. Nonetheless evidence from the studies of cerebral blood flow suggests the need to exercise caution, particularly with responses to rapid changes in blood gases following administration of animal-derived surfactants.

The paper by Arnold *et al* (1996) appears to put the differences of effects of the two types of surfactant into perspective. The authors suggest that the differences in neonatal outcomes as analysed using a proportional-hazards (Cox) regression analysis – a multivariate form of survival analysis that allows for differences in baseline characteristics – for the two different types of surfactant is less than that seen when comparing groups of male infants and female infants, or Caucasian and non-Caucasian infants. In other words, the effect of choosing one surfactant type over the other is small, and that population demographics such as gender and race are more important in determining outcome from RDS.

Whether the results of comparisons between the large volume surfactants (all those compared are given in volume of 3-5 ml/kg) can be extrapolated to the two small volume surfactants (***ALEC*** and ***Curosurf***) is not clear. Only three randomised trials and three non-randomised studies between two surfactants have used either ***Curosurf*** or ***ALEC***, and none compare these directly, yet they are the most widely used animal-derived and synthetic surfactants in the UK.

The published meta-analyses (Halliday 1996, Soll 1999c) and that in section 8.5 have concentrated on clinical outcomes at 28 days. Apart from significant reductions in pulmonary air leaks, which were evident in individual trials, after using animal-derived surfactants, it is only by including the most recent trials that any difference in mortality could be demonstrated. None of the meta-analyses have examined the question of pharmacoeconomics or whether one type of surfactant offers a reduction in costs of neonatal care compared to another?

Thus in terms of UK-based neonatal practice several questions remained. For these reasons it was decided to perform a randomised comparative trial between ***ALEC*** and ***Curosurf*** that was large enough to answer the following questions:

- Firstly, were there any cost benefits to using one surfactant over the other?

(The primary outcome)

- Secondly, were there any differences in clinical outcomes (mortality and the complications of prematurity)?

This study is discussed in chapter 9 and the implications of its results on the provision of neonatal intensive care within one health authority in chapter 10.

Chapter 9

A randomised comparison between *Curosurf* (poractant alfa) and *ALEC* (pumactant)

9.1 Introduction

Although the evidence presented in chapters 7 and 8 suggests that animal-derived surfactants have better *in vitro* properties, produce better outcomes in animal models and would appear to be clinically more efficacious than synthetic surfactant there remain unanswered questions, particularly with respect to ***ALEC*** and ***Curosurf***, which are the most widely used animal-derived and synthetic surfactants in the United Kingdom.

Published meta-analyses (Halliday 1996 and Soll 1999c) both used data from trials that compared either ***Survanta*** or ***Infasurf*** against ***Exosurf***. All these surfactants have a large volume (3-5 ml/kg) compared to ***ALEC*** and ***Curosurf*** and when compared to the infant's tidal volumes (5-8 ml/kg). Differences in the *in vitro* properties of ***ALEC***, ***Curosurf***, ***Exosurf*** and ***Survanta*** have been discussed in chapter 7 and extrapolation of clinical outcomes from studies comparing bovine surfactants and ***Exosurf*** may not reflect clinical differences between ***ALEC*** and ***Curosurf***.

Comparisons involving either ***ALEC*** or ***Curosurf*** with any other surfactants are limited. Speer *et al* (1995) have compared ***Survanta*** and ***Curosurf*** and found no differences in long-term outcomes, but the trial enrolled small numbers of infants and had insufficient power to demonstrate these. Rollins *et al* (1993) and Stenson *et al* (1994) both compared ***Curosurf*** with ***Exosurf*** using historic cohorts. Despite the limitations imposed by the use of historic cohorts Stenson *et al* (1994) showed that ***Curosurf*** had a more rapid effect on static lung compliance as well as oxygenation. Rollins *et al* (1993) showed a reduction in several clinical outcomes (IVH, PIE, PDA and NEC) with ***Curosurf*** use, but antenatal steroid use was 37% higher than in the ***Exosurf*** cohort.

There are two randomised comparisons between ***Curosurf*** and ***Exosurf***. Murdoch & Kempley (1998) showed more rapid changes in cerebral blood flow after ***Curosurf***, but not longer-term differences in neurological outcomes in a very small study. More recently Kukkonen *et al* (2000) compared neonatal outcomes after treatment with ***Curosurf*** or ***Exosurf***. Whilst there were no significant differences in the long-term outcomes, a secondary finding was that of a possible increase in sepsis after ***Curosurf*** use. Interpreting this secondary outcome is difficult because there were several ***Exosurf***-treated infants who received rescue therapy with ***Curosurf*** due to a perceived superiority of that surfactant by the attending clinicians. There are no previously published trials comparing ***ALEC*** against any other surfactant in a neonatal population.

Importantly at the time of initiating the trial comparing ***Curosurf*** and ***ALEC*** there was still some equipoise in whether animal-derived or synthetic surfactants were equally efficacious. The Halliday (1996) meta-analysis had demonstrated a reduction in neonatal mortality with animal-derived surfactants but the conclusions were reached after including data from several abstracts. Two of these abstracts, notably the trials involving ***Infasurf*** (Hudak *et al* 1994a and 1994b) were later published in full (Hudak *et al* 1996 and 1997) with outcomes that were reported on 100 fewer infants than in the abstracts.

The only way to resolve the issue was to undertake a randomised comparison that compared the two surfactants in a neonatal population. However, despite the reservations of extrapolating from the Halliday (1996) meta-analysis with its dependence on bovine-derived surfactants and ***Exosurf***, it seemed unlikely a single randomised controlled trial would carry sufficient statistical power to unequivocally show whether one surfactant was clinically more efficacious. With this in mind the primary aim of this study was to examine the differences in the cost of management of RDS between groups of infants treated with either ***Curosurf*** or ***ALEC***. Mortality was expected to be equal in the two groups, or at worst not significantly different.

The argument for using an economic as opposed to clinical outcome was strengthened by the price differential between the two surfactants. ***ALEC*** cost £150 per vial during 1997-8 (although this was later reduced to £105 per vial in October 1999), whereas ***Curosurf*** cost £400 per 1.25ml vial (source: British National Formulary). If the manufacturers' recommended regimes were followed the surfactant costs for a 1 kg infant would be £450 for ***ALEC*** (3 dose regime) and £1200 for ***Curosurf*** (200 mg/kg initial dose followed by 100 mg/kg).

The healthcare costs levied by preterm infants with lung disease relate primarily to the length of time for which they require intensive or high dependency nursing and medical care. These costs can be divided into marginal costs and fixed/semi-fixed costs. The workload, the cost of drugs and other expendables affect marginal costs whereas fixed and semi-fixed costs relate to building maintenance, power supply, staff and equipment. Fixed and semi-fixed costs alter in steps that vary according to the size of the annual workload of the individual unit, smaller units having a relatively larger initial step than larger units, whereas marginal costs bear an almost linear relationship to the time an infant spends in intensive care. In a large unit fixed and semi-fixed costs contribute approximately 80% of the total cost, and marginal costs around 20%.

In 1994-95 high dependency cot usage in the former Northern region totalled 5679 days by 1314 infants (data from *Northern Neonatal Consortium annual reports*). Infants therefore spent an average of 4.5 days in high dependency care at a daily cost of £912 per day (1999-2000 costing in the Northern Neonatal Consortium). Fixed and semi-fixed costs account for £800 and marginal costs for the remainder.

The biggest single factor that determines whether an infant receives high or low dependency care is respiratory support. Thus small improvements in respiratory morbidity, for example no longer requiring respiratory support, can give rise to marginal cost savings that could offset the initial cost of the surfactant. Whilst fixed and semi-fixed costs would not be influenced by improvements in respiratory morbidity, marginal costs relating to drugs and disposables might. A reduction of 10% (0.5 high dependency days per infant) would theoretically save £70,000 at marginal rates within the former Northern region.

Reducing high dependency workload may also be achieved by exchanging longer-term morbidity for short-term mortality; in other wotrds those infants that die early receive less intensive care. Thus preventing death from an otherwise fatal disease can actually increase healthcare costs (Bonneux *et al* 1998). However a therapeutic intervention that has a worse mortality rate is not clinically or ethically acceptable and ideally both respiratory morbidity and mortality need to be reduced. If there is no significant difference in neonatal mortality between the animal-derived and synthetic surfactants, the level of respiratory morbidity should therefore be the major determining factor for any difference in the amount of high dependency care.

Economic analyses have previously shown that surfactant therapy reduced the cost of neonatal care compared to controls (Tubman *et al* 1990, Diwaker *et al* 1993, Phibbs *et al* 1993, The Victorian Infant Collaborative Study Group 1997), but no analysis of the costs of care between two different surfactants has been published.

The question then arose as to how to measure the healthcare costs from the infants in a robust manner. One possibility was to adopt one of the classifications of care as a proxy for healthcare costs. Several classifications of care are used in the UK. In 1984 the then British Paediatric Association (BPA) and the British Association for Perinatal Paediatrics (BAPP) recommended a simple classification to audit workload. In 1992 a more comprehensive system was recommended (British Association of Perinatal Medicine and Neonatal Nurses Association 1992). In 1993 simpler dependency scales were published, supported by detailed observations of nursing activity in the Merseyside regional neonatal intensive care unit (Williams *et al* 1993) and the Northern Region (Northern Neonatal Network 1993a).

The latter classification is used in all units in the former Northern region. Infants are classified into one of four groups (A to D) according to the amount of care they require (Table 26). Most of the intensive care is "respiratory" and includes all forms of ventilation and continuous positive airways pressure (CPAP), and is thus directly relevant to a study comparing two surfactants. Categories A and B care are designated as "high dependency" care, whereas C and D are "low dependency". The original study (Northern Neonatal Network 1993a) showed that the length of nursing time high dependency infants receive is twice that of the low dependency infants, thus they consume 2-3 times the marginal costs in a neonatal intensive care unit. In turn this allows costing of the care that infants receive.

The primary outcome measure in the proposed comparison of ***Curosurf*** and ***ALEC*** was the number of high dependency days as measured by the Northern region categories of care. This method for measuring levels of care had been used routinely in the neonatal units of the former Northern region of England and has been shown to be a robust tool for healthcare purchasing and planning. Other clinical outcome data, including mortality, were collected as secondary endpoints.

The protocol, study design and consent forms for the trial were reviewed by consultant neonatologists in the former Northern region and Liverpool Women's Hospital. Ethical approval was sought and obtained from the Northern and Yorkshire Multi-centre Research Ethics Committee, and from the Local Research Ethics Committees of all participating centres.

Table 26: The Northern region categories of care (Northern Neonatal Network 1993a).

Category	Qualifying criteria
Category A*	Any infant that requires respiratory support (including high frequency oscillation, conventional ventilation, CPAP).
Category B*	Infants not in category A who: • Require more than 40% oxygen to maintain adequate arterial oxygenation • Have received all their fluids parenterally in the previous 24 hours • Have a drain, stoma or catheter in situ • Are less than 1000 grams • Have had surgery in the preceding 24 hours
Category C **	Infants not in categories A or B who: • Are receiving supplemental oxygen but require ≤ 40% • Are less than 1750 grams • Have some parenteral fluids • Have had a seizure or apnoeic episode in the preceding 24 hours • Have received some of their feeds via oro- or naso-gastric tubes
Category D **	Infants that are fully bottle or breast fed and weigh ≥ 1750 grams

* Categories A and B are "high dependency" days

** Categories C and D are "low dependency" days

9.2 Methods

Newborn infants treated in participating centres in the former Northern region, Liverpool Women's Hospital, Merseyside, St James University Hospital, Leeds and Leicester Royal Infirmary were enrolled. Four units in the former Northern region (the Royal Victoria Infirmary in Newcastle upon Tyne, North Tees General Hospital in Stockton on Tees, South Cleveland Hospital in Middlesbrough and Sunderland) offer level III neonatal intensive care. These and the other hospitals mentioned above were defined as major centres.

Ten other hospitals ("non-provider units") in the former Northern region with maternity units but not the facilities for long-term neonatal intensive care were also approached and asked to recruit infants for the trial. Historic data from 1996-97 suggested that approximately one third of infants born in the Northern region of an eligible gestation were born in these "non-provider" units. Inborn infants are those born in one of the major centres (whether transferred antenatally or originally booked at those centres), outborn infants are those born elsewhere and transferred postnatally to a major centre.

Infants were enrolled if they were between 25 and 29^{+6} weeks gestation by best obstetric estimate. These gestations were chosen as they corresponded to those for which ***ALEC*** received its market licence, in contrast there are no gestation criteria for the use of ***Curosurf***. In most cases gestation was calculated from an early (first trimester) obstetric ultrasound, but it could also be estimated from the last day of the mother's menstruation if this was corroborated by a later ultrasound scan.

Women who were admitted to the maternity units were approached to inform them about the trial and invite them to participate. Written and verbal information was given, but written consent was required in accordance with the ethical committee guidelines. In most cases this was attempted antenatally, but occasionally a postnatal consent was obtained. In all cases consent was obtained before administration of surfactant. Where parents declined to enter their infant(s) in the trial, surfactant treatment was given according to the preferences of the neonatologists in that centre. Reasons for non-enrolment, particularly where parental consent was withheld was recorded. This latter aspect was deemed important in view of perceived concerns regarding the use of animal products by the general public in the wake of the BSE "crisis" (Lacey 1999).

Only those infants that were intubated for respiratory care were enrolled. This meant that different centres enrolled slightly different populations because of the practices within those units. Three centres (Liverpool Women's, South Cleveland and Sunderland Royal Hospitals) have adopted a policy of giving surfactant in the delivery room. The other centres transfer the infant to the intensive care area before administering surfactant.

Where possible infants were excluded if they were known to have a severe congenital malformation likely to affect cardio-respiratory outcome or overall mortality. This was not possible in all cases and when a significant malformation was later discovered, data collection continued but outcome data from these infants were excluded from subsequent analyses.

Infants were randomised to receive either ***ALEC*** or ***Curosurf*** using a central telephone randomisation point on the neonatal unit at the Royal Victoria Infirmary (RVI). They were randomised either immediately before delivery, in the case of Liverpool Women's Hospital, Sunderland and South Cleveland Hospitals, or as soon as possible after delivery in the other units. The timing of surfactant administration and the need for some units to undertake this antenatally was one reason for stratification by centres. All enrolled infants were allocated a unique trial number.

Within the former Northern region infants who were enrolled by a non-provider unit (minor centre) were randomised according to the major centre where the infant would receive its intensive care after transfer. Thus, for example, if an infant was born at Ashington General Hospital and was to be transferred postnatally to the RVI that infant would be randomised using the envelopes for the RVI. Rarely, a major centre may have been unable to accept referral after the infant has been born if it became full in the intervening period. In these cases the surfactant allocation and trial number remained the same but results were analysed according to the major centre to which the infant was transferred.

No attempt was made to blind the participating clinicians with regards to surfactant allocation. The slight differences in reconstitution (powdered ***ALEC*** is reconstituted prior to use with saline, whereas ***Curosurf*** is available ready to use), dosing (a weight-related dose for ***Curosurf***), administration techniques (***ALEC*** is administered whilst still cold and ***Curosurf*** requires warming prior to use) and the known differences in the speed of onset of action were thought to make blinding difficult without employing surfactant administration teams. Surfactant administration teams, which have been used in a number of other surfactant trials, were not used because of the number of centres involved in the study and it was impractical and too costly to provide 24 hour cover for all these centres.

The immediate aim after stabilisation of the infant was administration of the first dose of surfactant. The study protocol specified that the first dose should be administered within 30 minutes, if at all possible, to try and encourage the use of prophylactic surfactant. ***ALEC*** was given at a dose of 100mg (1.2 ml) of phospholipids irrespective of birthweight; ***Curosurf*** was administered at a dose of 100mg/kg (1.25 ml/kg). Both surfactants were stored and administered according to the manufacturers' guidelines. ***ALEC*** was stored at 4^{o}C. The cold powder was mixed with the supplied dilutant (0.9% saline) prior to use, and the resulting mixture administered via a feeding tube cut to the length of the endotracheal tube. ***Curosurf*** was warmed to 37^{o}C prior to administration, and the calculated dose administered via a cut feeding tube pass though the ET tube. In the case of the hospitals where surfactant was administered in delivery suite the dose was based on the expected weight for the infant's gestation similar to the strategy employed in the trial by Bevilacqua *et al* (1996) for prophylactic ***Curosurf***.

In both arms a second dose of the allocated surfactant was administered twelve hours after the first if the oxygenation index was calculated to be 5 or greater. Oxygenation index was calculated using the formula:

OXYGENATION INDEX = (FiO_2 x MAP) / (PaO_2 x 7.5)

Where: FiO_2 is the percentage of inspired oxygen

MAP is the mean airway pressure (in cm H_2O)

PaO_2 is the partial pressure of arterial oxygen (in kPa)

No cross-over was allowed unless the supervising consultant felt that a faster acting animal-derived surfactant was warranted (for example in a severely ill infant on maximal conventional or high frequency oscillatory ventilation). In these cases it was felt unethical to deny treatment that was known to act rapidly; where this was administered the surfactant used was ***Survanta***. Similarly, third and fourth doses of the allocated surfactant could also be given at the discretion of the consultant supervising the infant's care at the time.

To avoid over- and under-ventilation of the infants, enrolling clinicians were asked to maintain PaO_2 between 6.5-10.5 kPa and $PaCO_2$ between 4.5-7.0 kPa. All other aspects of the infants' care, including ventilation strategies, were determined by local guidelines.

Data were collected prospectively for all enrolled infants and included demographic data and complications of prematurity. High and low dependency scoring, using the Northern region categories of care, was collected separately by nursing staff within the units and two research fellows. Scores for the high dependency days collected by the latter were disaggregated so that reasons for allocating the category could retrospectively be analysed should the qualifying criteria for each category change in future. This was performed because some of the reasons for allocating a "B" category day do not relate to respiratory care (Table 26) and the study was comparing two products that exerted their primary influence on the respiratory system.

To try and ensure the two arms were composed of infants with a similar disease spectrum, critical risk index for infants (CRIB) scores (International Neonatal Network 1993) were collected prospectively. These scores are derived from maximum oxygen, minimum oxygen and worst base deficit during the first 12 hours after birth, gestation at birth, birthweight and the presence of congenital malformations.

9.3 Outcome Definitions

High dependency days were defined as category A and B days according to the Northern region categories of care (Northern Neonatal Network 1993a). Data collection was performed at the same time every day on a daily basis.

Neonatal mortality was defined as death within the first 28 postnatal days. Death prior to discharge was when the infant died in either the unit where he/she received intensive care, or the unit where they received low dependency care before their discharge home.

Chronic lung disease (CLD) was defined in two ways: dependency upon supplemental oxygen at 28 postnatal days (Heneghan *et al* 1986) and dependency upon supplemental oxygen at 36 postmenstrual weeks (Shennan *et al* 1988).

Pneumothorax was defined as intrathoracic, extra-pulmonary air leak necessitating the insertion of a chest drain. Lesser degrees of pulmonary air leak such as PIE were not recorded because of the variation in its reporting by different clinicians and radiologists.

Cerebral ultrasound scans were performed on day 3 and at 6 weeks postnatal age (or as near to these as possible). Radiologists not involved in the trial reported scans. Using their reports the scans were scored separately for each hemisphere. Haemorrhage was scored using the staging proposed by Papile *et al* (1978): Stage 0 - no haemorrhage; stage I - localised sub-ependymal haemorrhage; stage II - intraventicular haemorrhage, stage III - intraventricular haemorrhage with ventricular enlargement, stage IV - parenchymal haemorrhagic lesions. Ventricular size was scored using ventricular index (Levine 1981): stage 0 - no dilatation, stage I - dilatation <4mm above 97^{th} centile corrected for gestation, stage II - dilatation >4mm above 97^{th} centile). Parenchymal lesions were staged simply as stage 0 - no cyst; stage I - porencephalic cyst; stage II - cystic leukomalacia.

Significant patent ductus arteriosus (PDA) was defined as a murmur associated with clinical signs of a left to right shunt clinically requiring medical or surgical closure. The diagnosis was confirmed by echocardiography where possible.

Necrotising enterocolitis (NEC) was defined according to a simplified version of the clinical staging system proposed by Bell *et al* (1978). Only Bell stage 2 or worse (typical radiological appearance) was recorded and analysed.

Pulmonary haemorrhage was defined as the spontaneous appearance of blood or bloodstained fluid in the endotracheal tube. The presence of blood following endotracheal toilet was ignored.

Significant retinopathy of prematurity (ROP) was defined as "threshold disease" (Report of a Joint Working Party 1996). That is stage III ROP present in eight cumulative "clock hours" or five contiguous "clock hours" with "plus" disease (the presence of tortuous vessels) in zone I or II (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988). Eye examinations were performed by ophthalmologists according to accepted international guidelines (Report of a Joint Working Party 1996).

9.4 Early Changes in Oxygen and Ventilator Requirements

Data regarding early oxygenation and ventilation requirements were obtained retrospectively from the intensive care charts of all enrolled infants where these were available. The measurements that were recorded included fraction of inspired oxygen concentration (% FiO_2), mean airway pressure (MAP) in cm H_2O and arterial oxygen concentration (PaO_2) in kPa. These were recorded at admission to the neonatal unit (t=0), two hours after birth (t=2), at six hours of age (t=6) and every six hours thereafter until 72 hours of age (t=72).

Data for FiO_2 were recorded on an hourly basis by nursing staff throughout the duration of respiratory support. From these data were extracted FiO_2 for the first 72 hours or the infant died, whichever occurred first. MAP was recorded (or calculated from the ventilator settings) for as long as the infant required respiratory support. The measurements therefore include MAP whilst on conventional ventilation, high frequency oscillation and CPAP. When the infant was breathing spontaneously the measurements stopped.

9.5 Statistics and sample size calculations

Sample size calculations were made to enable important differences in time in high dependency care to be identified in surviving infants. Historic data from 236 ventilated infants of 25-29 weeks gestation in Newcastle and Liverpool during 1996-97 demonstrated a median duration of 6 days in high dependency care. The distribution of these data followed an exponential decay distribution with large numbers of infants requiring a short duration of intensive care and small numbers of infants requiring a longer duration. This was then used for the calculation of sample size.

It was calculated that to detect a 25% difference in median time in high dependency care with 80% power at the 5% significance level 241 infants would need to be randomised to each arm of the study. This was intended to give samples of adequate size amongst survivors and assumed a predischarge mortality of 20% in each group with no significant difference in mortality rates between the two groups. The study protocol also stipulated that a Data and Safety Monitoring Committee (DSMC) would meet after recruiting approximately half the required numbers. No formal rules for stopping the trial were drawn up because the decision to recommend early cessation would depend on outcomes relating to safety and mortality as well as clinical efficacy.

The null hypothesis for this trial assumed that there would be no difference in the cost of caring for infants treated with either ***Curosurf*** or ***ALEC***. All analyses were performed on an "intention to treat" basis.

The differences between measurements of oxygen and ventilator requirements during the first 72 hours of life were analysed using summary measures as suggested by Matthews *et al* (1990). The reason for using this method of analysis is that measurements in an individual infant are usually correlated to those obtained before and after the current measurement. These then reflect the progression of the clinical condition, for example an infant may begin life with an oxygen requirement of 40% which falls rapidly to 21% after surfactant and stays there, whereas the next infant in that group might require 100% and only slowly begin to improve. A mean FiO_2 value for these infants would not be representative of either. In both cases the second FiO_2 is related to the first.

Similarly graphical representation of values at time points with "error bars" and an indicator of the statistical difference at each time point, whilst commonly used in medical literature and visually understandable to the clinician, are also statistically inappropriate and wrong (Matthews *et al* 1990).

The response following surfactant in each individual infant was calculated and summarised using a geometric mean of the area under a graph plot of time versus the measurement in question. For example, the area (AUC) under the graph of an FiO_2 plot would be calculated for each infant as:

$$AUC = \tfrac{1}{2}\Sigma\,(t_2 - t_1) \times (y_2 - y_1)$$

Where t_1 = time and y_1 = FiO_2 (%) value at time t_1

and t_2 = time and y_2 = FiO_2 (%) value at time t_2.

If measurement were performed for a total duration of n hours, then AUC/n gives the geometric mean FiO_2, this also allowed for deaths and missing measurements (for example if the charts were destroyed or measurements not recorded). The differences between summary data from the two groups of infants can then be analysed using the Mann Whitney

U test for non-parametric data.

9.6 Results

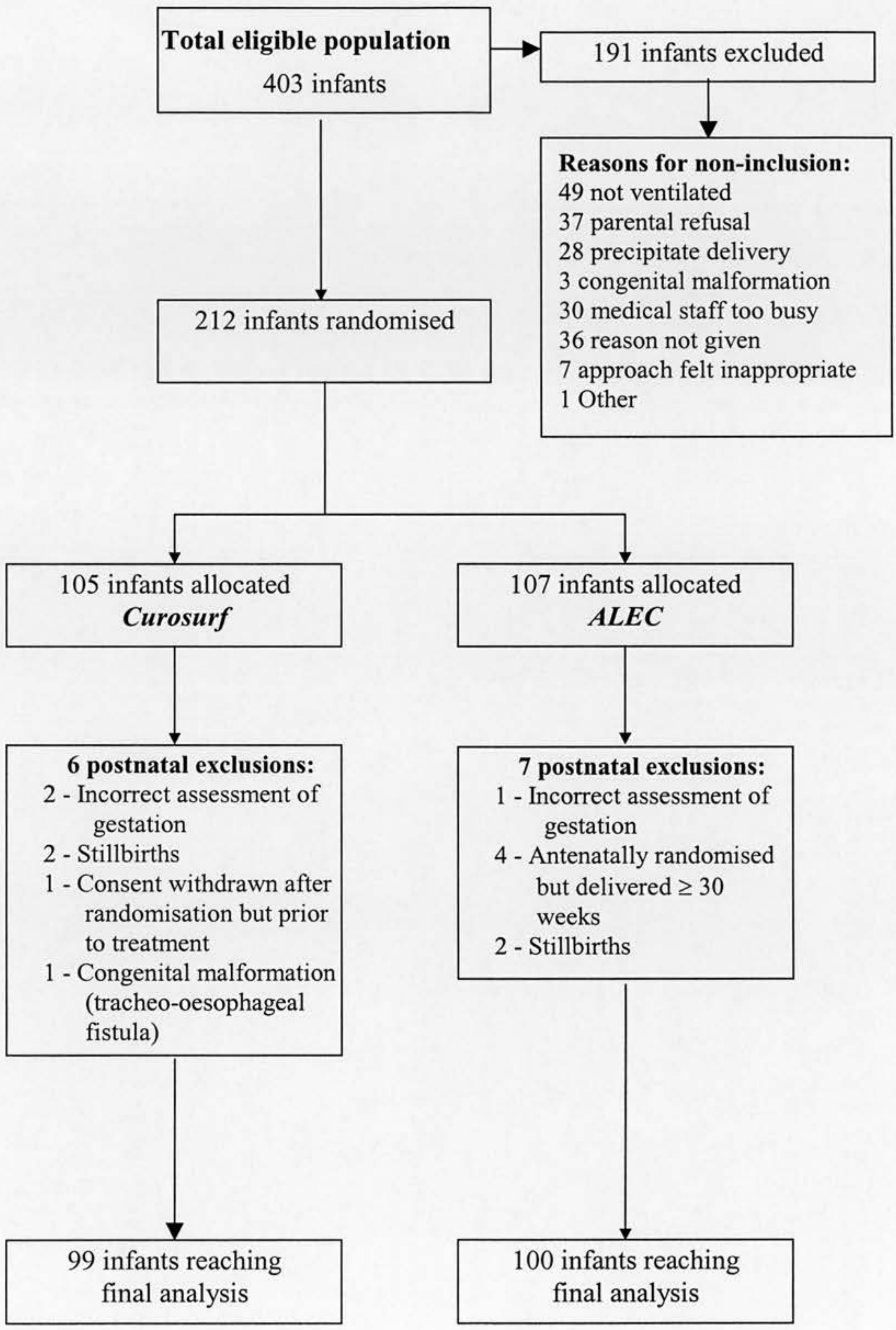
The DSMC met in December 1999, nineteen months after the trial commenced. Data on trial recruitment (207 infants as of December 1st), post-randomisation exclusions (16 for suspected violation of study protocol) and available outcome data in 189 infants were presented (data on 2 infants recruited in South Cleveland and Sunderland Royal Hospitals respectively on November 30th were unavailable at the time). The investigators later revised the postnatal exclusions and the final figure (13) is lower than that presented to the DSMC, but did not affect the outcome.

The DSMC, blinded to treatment allocation, noted an unexpected and highly significant difference in pre-discharge mortality that could not explained by differences in gestational age or gender. They recommended that the trial be stopped. Following this advice the trial co-ordinators terminated recruitment on 14th December 1999 by which time five more infants had been recruited. The DSMC recommendation can be found in Appendix 1.

9.6.1 Enrolment

The total eligible birth cohort from all centres was 403 (Figure 11). Data on the total eligible population were derived from several sources: computerised databases held in each of the four neonatal provider units in the former Northern region, a regional survey of all infants <32 weeks gestation (chapter 10), admission records in Liverpool, Leeds and Leicester neonatal intensive care units. Reasons for non-enrolment were determined from maternal and infant notes, retrospective review of the staff involved in the infant's care after delivery and prospective collection of responses from parental refusals.

Figure 11: The consort diagram for the trial between ***Curosurf*** and ***ALEC***



Two hundred and twelve infants (198 born in the level III units and 14 transferred to these centres postnatally) had been randomised to the trial. Thirteen infants were excluded post-randomisation. Reasons for excluding these infants were:

- Incorrect assessment of gestation (3 infants – 2 ***Curosurf*** and 1 ***ALEC***. These were triplets that were retrospectively recognised to have been assessed to be 24 weeks and 5 days at randomisation).
- Stillbirths (2 infants in each arm who were randomised antenatally and died either in-utero or never responded to resuscitation).
- Congenital malformation (1 infant in the ***Curosurf*** arm was recognised to have a tracheo-oesophageal fistula – confirmed on post-mortem examination).
- Problems with randomisation in one infant allocated to ***Curosurf*** (parents withdrew consent after randomisation but before treatment – this infant received ***Survanta*** outside the study).

There were minor deviations from the trial protocol in several randomised infants: one infant randomised to receive ***Curosurf*** received ***Survanta***, as the ***Curosurf*** had become out-dated, another infant allocated to receive ***Curosurf*** received ***ALEC***. Three infants (all randomised antenatally) in each arm were not ventilated after delivery and received no surfactant. Data from the two infants who received the wrong surfactant type and the six who received no surfactant are included in the outcomes and were analysed by intention to treat.

9.6.2 Demographics of enrolled infants

Demographic data is shown in Table 27. There were more males and twins in the ***Curosurf*** arm and slightly less mature infants in the ***ALEC*** arm, all factors that increase the likelihood of and severity of RDS (chapter 2), but otherwise the two arms were well matched.

Enrolment by centre is demonstrated in Table 28. Although there were some variations between centres regarding birthweights and gestational ages this was felt to probably reflect the role of the centres such as Liverpool and Newcastle being fetal and surgical, as well as neonatal, tertiary referral centres. Within centres the infants were well matched.

Table 27: Summary of demographic data for infants in the trial between ***ALEC*** and ***Curosurf***

	Curosurf n=99	***ALEC*** n=100
Gestation in weeks (median, IQR)	28.3 (26.4 – 29.1)	27.8 (26.3 – 28.9)
Birthweight in grams (median, IQR)	1026 (514 – 1680)	948 (448 – 1750)
Birthweight z-scores (mean, SD)	-0.57 (1.2)	-0.65 (1.2)
Males	64	53
Multiple births		
No. of twins	30	21
No. of triplets	1	2
Antenatal steroids		
Any	93	93
2 or more doses	69	78
Method of delivery		
Vaginal delivery (including breech)	48	50
Caesarean section	51	50

Table 28: Demographics of enrolled infants by centre.

Centre & allocation	Total	PN exclusions	Analysed Inborn	Analysed Out-born	Gestation/weeks (median, IQR)	BWt/grams (median, IQR)
Liverpool						
ALEC	44	2 (stillbirths)	42	0	27.7 (26.4 – 29.1)	935 (720 – 1150)
Curosurf	43	2 (stillbirths)	41	0	28.4 (26.9 – 29.9)	910 (695 – 1126)
Newcastle (RVI)						
ALEC	26	2 (23 weeks; not born)	21	3	27.5 (26.2 – 28.9)	870 (668 – 1073)
Curosurf	25	2 (23 weeks)	19	4	27.3 (25.8 – 28.8)	1055 (781 – 1330)
Sunderland						
ALEC	16	1 (not born)	15	0	28.3 (26.5 – 30.1)	910 (654 – 1166)
Curosurf	14	1 (TOF*)	13	0	28.4 (27.3 – 29.5)	1090 (902 – 1278)
North Tees						
ALEC	9	0	7	2	28.6 (27.7 – 29.5)	1040 (862 – 1219)
Curosurf	10	0	9	1	28.7 (28.1 – 29.4)	1055 (885 – 1305)
S Cleveland (M'boro)						
ALEC	11	2 (not born)	9	0	27.6 (27.0 – 28.3)	1090 (897 – 1283)
Curosurf	10	1 (consent withdrawn)	7	2	28.6 (27.9 – 29.3)	1165 (1005 – 1325)
Leicester						
ALEC	1	0	1	0	27.9	1230
Curosurf	1	0	1	0	27.4	1300
St James (Leeds)						
Curosurf	2	0	2	0	28.3	1100

* TOF = tracheo-oesophageal fistula

9.6.3 Time to first dose of surfactant and total number of doses

The time to first dose of surfactant was similar in both groups. The median times of administration were 16 minutes (interquartile range [IQR] 7 – 41 minutes) in the ***Curosurf*** arm, and 13 minutes (IQR 7 – 34 minutes) in the ***ALEC*** arm. The distribution of these times is shown in Figure 12.

The number of doses required by the infants in the two arms did not differ (Table 29). Infants required a mean 1.7 doses in the ***ALEC*** arm and 1.6 doses in the ***Curosurf*** arm. Five infants treated with ***ALEC*** compared to two infants treated with ***Curosurf*** received more than two doses of surfactant, and more infants in the ***ALEC*** arm received a second dose. Neither of these results reached statistical significance.

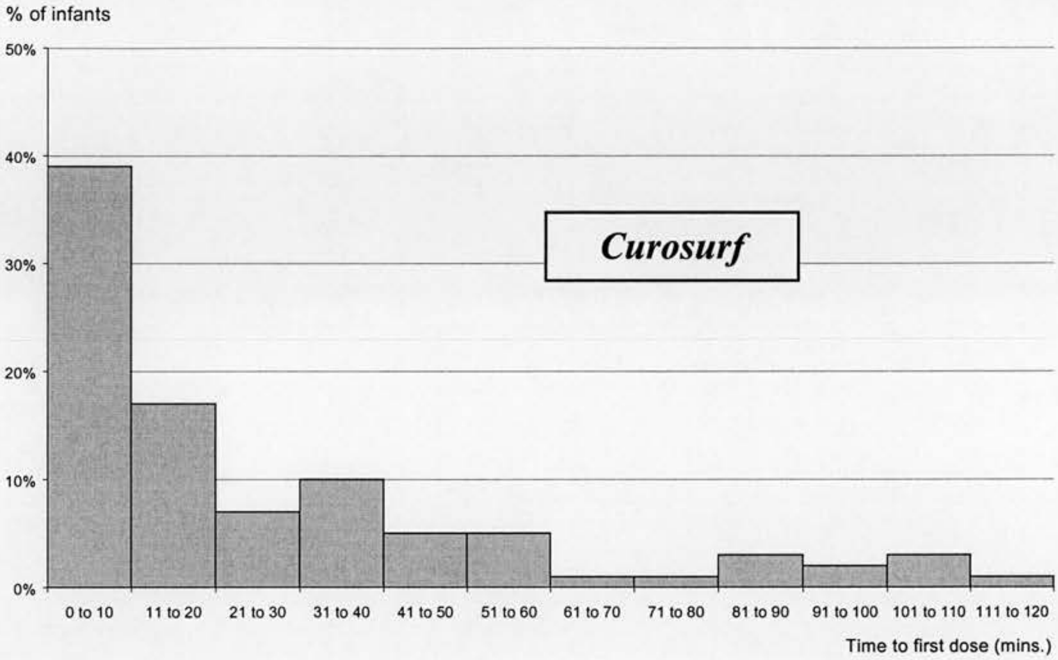
9.6.4 Early changes in ventilator and oxygen requirements

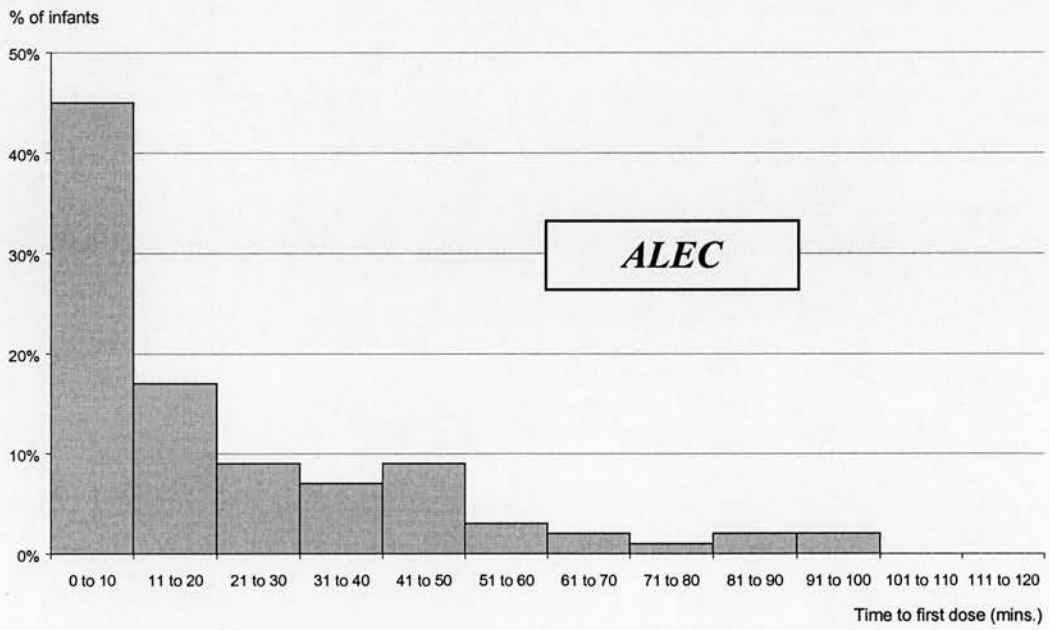
Blood gas data, oxygen requirements and ventilator settings during the first 72 hours were available in 187 infants (93 / 100 in the ***ALEC*** group and 94 / 99 in the ***Curosurf*** group). In particular the availability of arterial blood gases was very variable because some units preferred to use non-invasive means of monitoring arterial oxygen.

There were early, and expected, improvements in oxygen requirements in the ***Curosurf*** arm compared to the ***ALEC*** arm. There was a small reduction in FiO_2 at t=0 in the ***Curosurf*** arm compared to ***ALEC***, reflecting surfactant administration in the delivery room in some units and the onset of monitoring later in the neonatal unit. Differences in oxygen requirements were apparent between the two groups of infants at two hours of age and remained significantly lower throughout the whole period of 72 hours (Figure 13). When analysed as summary data for serial measurements using the method suggested by Matthews *et al* (1990), the differences in geometric means during the whole of the first 72 hours were statistically highly significant ($p<0.0001$).

Similarly there were lower median values for MAP in the infants that received ***Curosurf***. Differences became statistically significant by 2 hours of age and remained lower until 36 hours, after which the values were similar (Figure 14). Again when analysed as summary data the difference in geometric means was also highly statistically significant ($p=0.0049$).

Figure 12: Time to first dose of allocated surfactant.





Histograms of time to first dose of allocated surfactant (for times less then 2 hours). Three patients were given a first dose of ***ALEC*** after 2 hours (at 121, 143, 162 minutes) and five patients were given a first dose of ***Curosurf*** after 2 hours (at 135, 164, 169, 695, 840 minutes).

Table 29: Number of doses of surfactant given.

No. of doses	***Curosurf*** (n = 99)	***ALEC*** (n = 100)
0	3	4
1	35	27
2	59	64
3	2	5
Total number of doses (all infants)	159	170

Figure 13; Mean (+/- SEM) appropriate FiO_2 during the first 72 hours of life

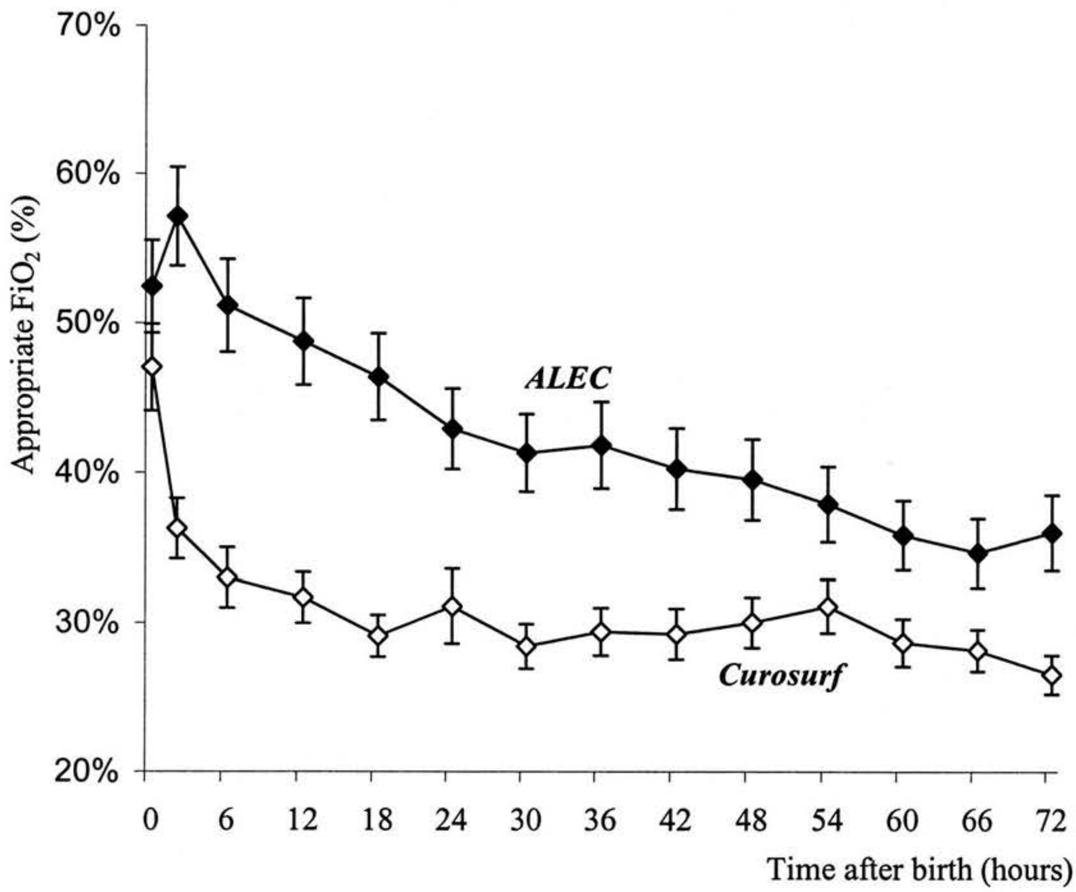
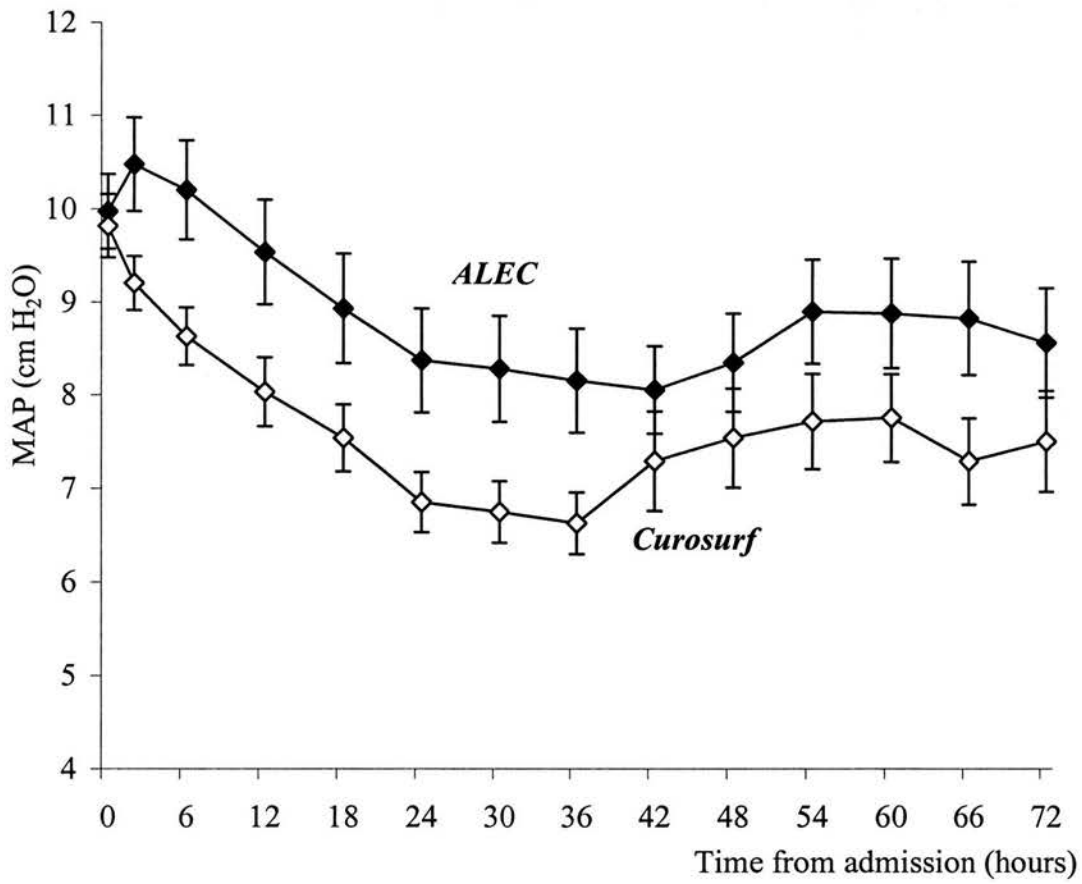


Figure 14: Changes in mean airways pressure (mean +/- SEM) between Curosurf and ALEC arms during the first 72 hours



The mean oxygenation index (OI) was lower in the ***Curosurf*** arm on admission to NICU than in the ***ALEC*** arm (mean [SEM] of 8.7 [0.6] versus 11.2 [0.9], p = 0.06), however the difference may reflect the fact surfactant was administered in the delivery room in approximately 50% of infants – it was not possible due to limitations in monitoring in the delivery suites to collect data earlier These early values are therefore a mixture of pre- and post-surfactant values. At 6 hours of age the OI was significantly lower in the ***Curosurf*** group (5.6 [0.5] versus 11.3 [1.1], p < 0.0001). The OI of infants who died were significantly higher than infants who survived (Figure 15). However in the ***Curosurf*** infants who died the OI fell whereas in the ***ALEC*** infants who died the OI rose, this is most likely a reflection of the number of respiratory-related deaths in the ***ALEC*** arm (section 9.6.5).

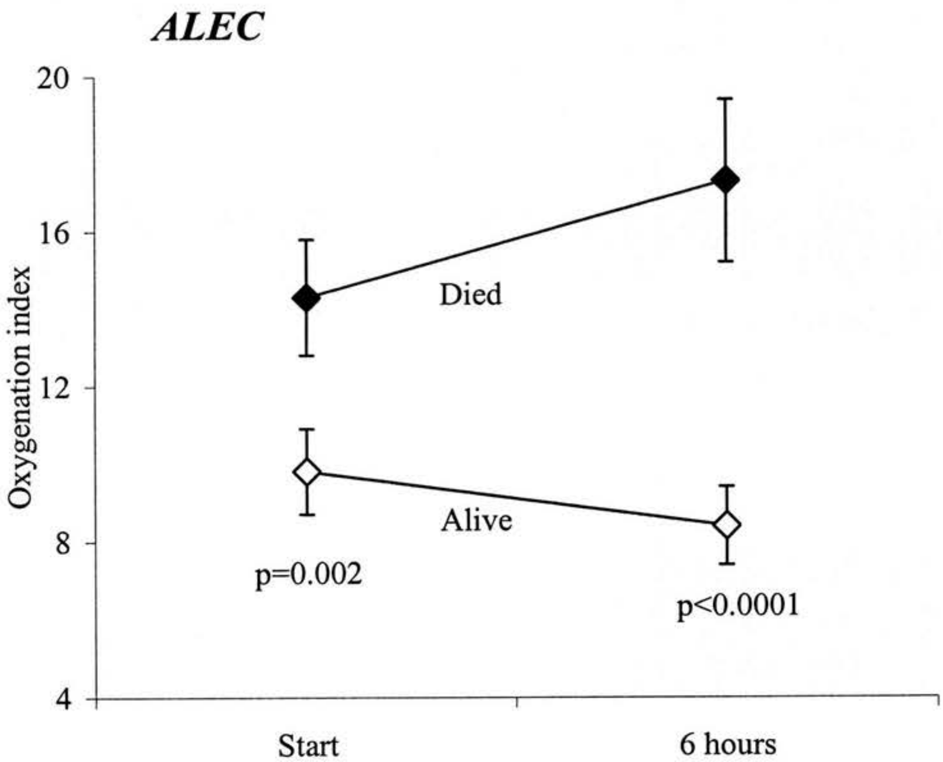
9.6.5 Mortality

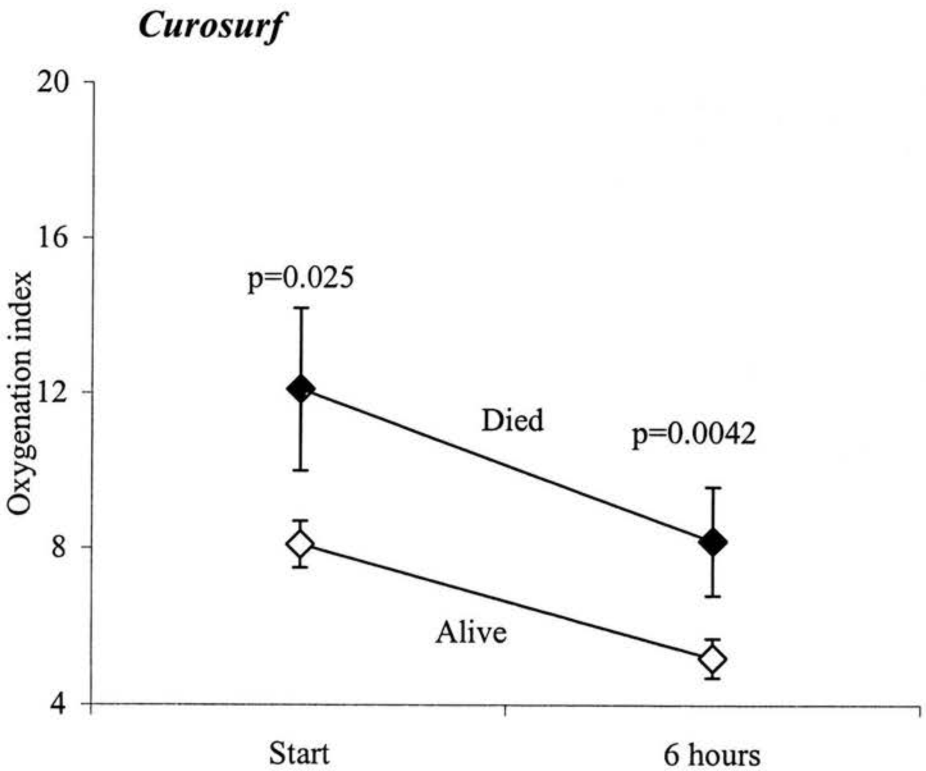
This is considered next as this was the outcome on which the Data & Safety Monitoring Committee had based its decision to recommend early termination of the trial. There were 31 deaths prior to discharge in the ***ALEC*** arm, and 14 deaths prior to discharge in the ***Curosurf*** arm (Odds ratio 0.37; 95% CI 0.18 – 0.74; p = 0.004). Of these 25 and 11 respectively were during the neonatal period (OR 0.38; 95% CI 0.71 – 0.81; p = 0.011).

Because there were imbalances in the two groups particularly with respect to gender and gestation logistic regression was performed. This took also into account effects of treatment centre, gender, use of antenatal steroids, birthweight and whether the infant was a singleton or not. Following this odds ratio for predischarge death was 0.31 (95% CI 0.14 – 0.72, p = 0.006) and for neonatal mortality was 0.36 (95% CI 0.15 – 0.84, p = 0.019).

The cause of death was determined independently by two consultant neonatologists who, blinded to surfactant administration reviewed the clinical notes and post-mortem reports. Each reviewer, who had not been one of the study organisers, was asked to state the cause of death, or where the death was multifactorial, the disease or event that led to the cascade leading to events. For example an infant might have moderately severe RDS that was improving, had they developed symptoms and signs of patent ductus arteriosus and a pulmonary haemorrhage occurred, the clinicians might have increased ventilator pressures which could have led to a pneumothorax; this would have been classified as being death due to pulmonary haemorrhage secondary to PDA, even if RDS and pneumothorax were co-factors.

Figure 15: Changes in Oxygenation Index (mean +/- SEM) during the first 6 hours and mortality





Causes and age of death are shown in Table 30. Three quarters of the deaths in both arms were during the neonatal period. The deaths were also classified as being due to either respiratory or non-respiratory causes by the neonatal consultants that determined the cause of death. More pre-discharge deaths in the ***ALEC*** arm (21%) were attributed to a respiratory cause than in the ***Curosurf*** arm (5%), this result was highly statistically significant (OR 0.20, 95% CI 0.07 – 0.56, $p = 0.001$).

The difference between surfactants in neonatal and pre-discharge mortality rates was maintained across the spread of gestational ages (Table 31), and across the centres (Table 32). At all gestations and in all centres the results favoured ***Curosurf***, but the differences within centres and at given gestations were not significantly different. Timings of the deaths are shown in the Kaplan-Meier plot (Figure 16).

9.6.6 Other complications of prematurity

None of the complications of prematurity that were actively sought as part of the secondary outcomes were significantly different between the ***ALEC*** and ***Curosurf*** groups (Table 33). ***Curosurf*** reduced pneumothoraces whereas there were more clinically significant PDAs requiring treatment in that group. The proportion of infants surviving with CLD at 28 days and at 36 weeks corrected post-menstrual age were similar, as was the proportion of infants discharged home on oxygen.

There were differences between centres in the rates of pneumothoraces. Newcastle had the greatest proportion of pneumothoraces overall (table 34), and unlike other centres there was no appreciable difference between pneumothorax rates in the ***Curosurf*** and ***ALEC*** arms. The reason why there was so is unclear.

The duration of positive pressure ventilation in surviving infants (either conventional ventilation or HFOV) was similar in the two arms. Infants in the ***Curosurf*** arm required a median of 3 days ventilation whereas those in the ***ALEC*** arm required a median of 5 days (Mann Whitney U test; $p = 0.45$).

Table 30: Cause of death of infants

Age (days)	Surfactant	M/F	BWt (gram)	Gest. (week)	Cause of death
Early neonatal deaths					
1	ALEC	F	910	25	Severe RDS and air leak
1	ALEC	F	690	25	Infection (suspected GBS)
1	ALEC	F	728	26	Severe RDS, air leak
1	ALEC	M	880	26	Severe RDS and air leak with PPHN
1	ALEC	M	910	26	Severe RDS and PPHN
1	ALEC	M	1126	27	Severe RDS, air leak
1	ALEC	M	1310	27	RDS with air leak
1	ALEC	F	930	29	Severe RDS / pulmonary hypoplasia
2	ALEC	M	917	26	Severe RDS, air leak, air embolus
2	ALEC	M	1370	28	Severe RDS
2	ALEC	F	1040	28	RDS with air leak
3	Curosurf	M	530	26	Severe RDS, pulm. haem.
3	Curosurf	F	620	26	Intrapartum asphyxia/multi-organ failure
3	ALEC	M	734	27	Severe RDS, air leak
3	ALEC	F	825	28	Severe RDS
3	Curosurf	M	514	29	Acute renal failure, twin-to-twin transfusion, pulm. haem.
4	Curosurf	M	840	28	Severe RDS
5	Curosurf	M	580	25	Severe RDS + infection
5	Curosurf	M	1100	29	Severe RDS with air leak
7	Curosurf	F	585	25	Perforated NEC
7	ALEC	M	735	26	Pulm. haem. 2^{o}ry to PDA.
7	ALEC	F	865	29	Hydrops
Late neonatal deaths					
8	ALEC	M	859	25	Acute renal failure ?Sepsis
8	ALEC	M	750	25	Severe RDS leading to NEC
8	ALEC	M	1378	28	Severe RDS with air leak
8	ALEC	M	1220	28	Antenatal myocardial ischaemia and hydrops
8	ALEC	M	1049	29	Pulm. haem. 2^{o}ry to PDA
10	Curosurf	M	965	25	Intrapartum asphyxia and multi-organ failure
10	ALEC	F	690	25	Staph. epidermidis septicaemia
10	ALEC	M	692	28	Severe RDS
10	ALEC	M	720	28	Air leak
11	ALEC	F	762	25	Fungal septicaemia
11	Curosurf	M	958	26	Enterobacter / candida septicaemia
11	ALEC	F	760	26	NEC
11	Curosurf	M	1220	28	TPN hydrothorax (longline complication)
28	Curosurf	M	570	25	Pulm. haem. 2^{o}ry to PDA
Post-neonatal deaths					
30	Curosurf	M	685	28	NEC
59	Curosurf	M	765	26	Widespread cerebral ischaemia and PVL
110	ALEC	M	550	25	CLD
123	ALEC	F	548	27	CLD
133	ALEC	M	734	29	CLD
143	ALEC	M	600	26	CLD
147	ALEC	M	780	25	CLD
217	ALEC	M	700	28	Hypovolaemia 2^{o}ry to incarcerated hernia
372	Curosurf	M	558	26	CLD

Table 31: Neonatal and pre-discharge deaths according to gestation

Neonatal mortality		
	Curosurf	***ALEC***
Overall	11 / 99 (11.1%)	25 / 100 (25.0%)
25 weeks	4 / 12 (33.3%)	6 / 13 (46.2%)
26 weeks	3 / 17 (17.6%)	6 / 22 (27.3%)
27 weeks	0 / 14 (0%)	4 / 17 (23.5%)
28 weeks	2 / 24 (8.3%)	6 / 24 (25.0%)
29 weeks	2 / 32 (6.3%)	3 / 24 (12.5%)

Pre-discharge mortality		
	Curosurf	***ALEC***
Overall	14 / 99 (14.1%)	31 / 100 (31.0%)
25 weeks	4 / 12 (33.3%)	8 / 13 (61.5%)
26 weeks	5 / 17 (29.4%)	7 / 22 (31.8%)
27 weeks	0 / 14 (0%)	5 / 17 (29.4%)
28 weeks	3 / 24 (12.5%)	7 / 24 (29.2%)
29 weeks	2 / 32 (6.3%)	4 / 24 (16.7%)

Table 32: Neonatal and predischarge deaths according to centre and surfactant allocation

Centre & allocation	Neonatal deaths	Predischarge deaths
Liverpool		
ALEC	9 / 42 (21.4%)	12 / 42 (28.6%)
Curosurf	3 / 41 (7.3%)	5 / 41 (12.2%)
Newcastle (RVI)		
ALEC	6 / 24 (25.0%)	9 / 24 (37.5%)
Curosurf	5 / 23 (21.7%)	5 / 23 (21.7%)
Sunderland		
ALEC	6 / 15 (40.0%)	6 / 15 (40.0%)
Curosurf	2 / 13 (15.4%)	3 / 13 (23.1%)
North Tees		
ALEC	3 / 9 (33.3%)	3 / 9 (33.3%)
Curosurf	1 / 10 (10.0%)	1 / 10 (10.0%)
S Cleveland (M'boro)		
ALEC	1 / 9 (11.1%)	1 / 9 (11.1%)
Curosurf	0 / 9	0 / 9
Leicester		
ALEC	0 / 1	0 / 1
Curosurf	0 / 1	0 / 1
St James (Leeds)		
Curosurf	0 / 2	0 / 2

Figure 16: Kaplan-Meier plot of deaths in the ***ALEC*** and ***Curosurf*** arms

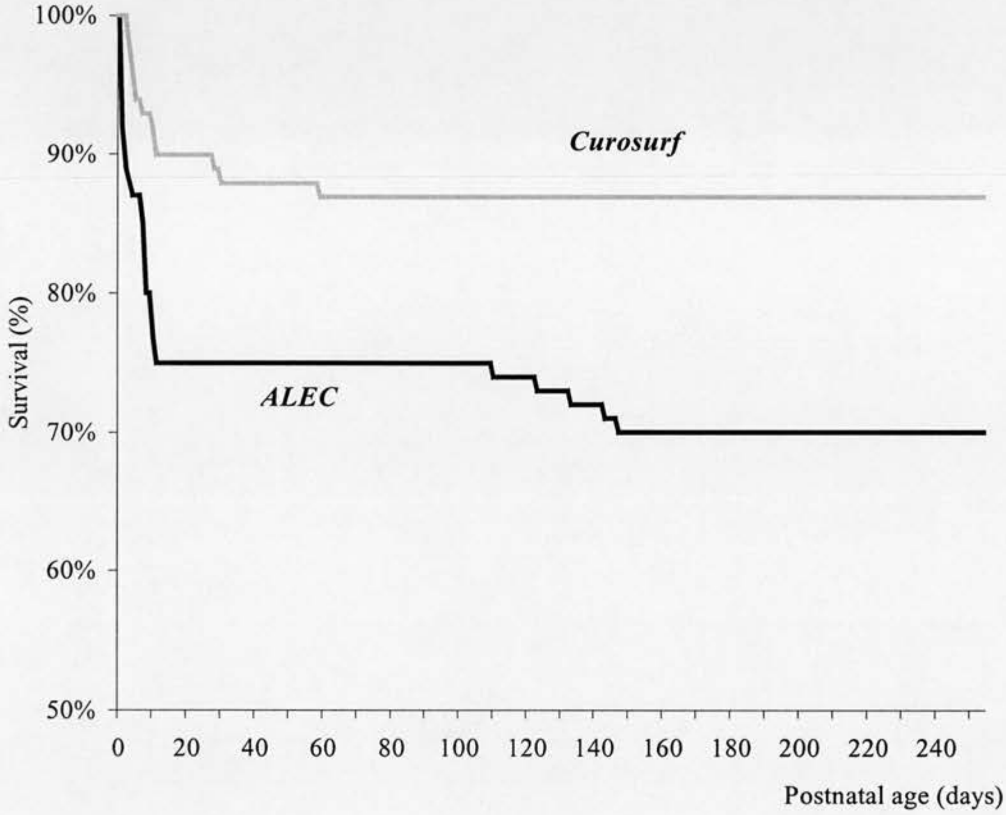


Table 33: Complications of prematurity

Outcome	Curosurf	ALEC	Rel. risk	95% CI	Risk diff.	95% CI
Pneumothorax	11 / 99 (11%)	22 / 100 (22%)	**0.51**	0.26 – 0.99	**-10.9%**	-21.1 to –0.7%
Treated PDA	20 / 99 (20%)	10 / 100 (10%)	2.02	1.00 – 4.09	**+10.2%**	+0.3 to +20.1%
IVH any grade †	42 / 96 (44%)	37 / 93 (40%)	1.10	0.78 – 1.54	+4.0%	-10.1 to +18.0%
Severe IVH †	7 / 96 (7%)	7 / 93 (8%)	0.97	0.35 – 2.65	-0.2%	-7.7 to +7.2%
Cystic PVL †	12 / 96 (13%)	16 / 93 (17%)	0.76	0.38 – 1.52	-4.7%	-14.8 to +5.4%
NEC (≥Bell stage II)	4 / 99 (4%)	3 / 100 (3%)	1.36	0.22 – 9.53	-3.9%	-13.5 to +5.8%
Treated ROP	3 / 85 (4%)	5 / 69 (7%)	0.47	0.07 – 2.52	-4.7%	-14.8 to +5.4%
Pulmonary haemorrhage	9 / 99 (9%)	5 / 100 (5%)	1.90	0.55 – 7.48	-3.9%	-13.5 to +5.8%
CLD (28 days)*	55 / 88 (63%)	44 / 75 (59%)	1.17	0.60 – 2.31	-4.7%	-14.8 to +5.4%
CLD (36 weeks)*	46 / 86 (53%)	42 / 75 (56%)	0.90	0.46 – 1.76	-4.7%	-14.8 to +5.4%
Home oxygen	31 / 85 (36%)	28 / 69 (41%)	0.82	0.41 – 1.66	-3.9%	-13.5 to +5.8%

† Scanned infants only. * Infants surviving to 28 days or 36 weeks post-conception only.

Table 34: Pneumothorax rate according to centre and surfactant allocation

Centre & allocation	Pneumothorax rates
Liverpool	
ALEC	7 / 42 (16.7%)
Curosurf	3 / 41 (7.3%)
Newcastle (RVI)	
ALEC	7 / 24 (29.2%)
Curosurf	6 / 23 (26.1%)
Sunderland	
ALEC	5 / 15 (33.3%)
Curosurf	2 / 13 (15.4%)
North Tees	
ALEC	2 / 9 (22.2%)
Curosurf	0 / 10
S Cleveland (M'boro)	
ALEC	1 / 9 (11.1%)
Curosurf	0 / 9
Leicester	
ALEC	0 / 1
Curosurf	0 / 1
St James (Leeds)	
Curosurf	0 / 2

9.6.7 Disease severity

It has been shown that oxygenation and mean airway pressure were reduced sooner in infants treated with ***Curosurf*** (section 9.6.4). More infants in the ***ALEC*** arm required rescue modalities of respiratory support (HFOV and inhaled nitric oxide) in those centres that offered them. For HFOV the proportions were 22% in the ***ALEC*** arm and 13% in the ***Curosurf*** arm, for inhaled NO the proportions were 5% and 2% respectively. Most of the infants that required rescue treatment died (60% of those that received HFOV and 57% of those that received inhaled NO) although this probably reflects the disease severity at the time of initiating rescue treatment.

The critical risk index in infants (CRIB) score was significantly lower in the ***Curosurf*** arm than the ***ALEC*** arm (3.0 [IQR 0.1-5.9] versus median 6.0 [IQR 3.0-10.0]; Mann Whitney U test $p = 0.0002$). When broken down into the component parts of CRIB (maximum oxygen, minimum oxygen, worst base deficit, gestation, birthweight and congenital malformations) the differences were found to be entirely due to higher values for the maximum and minimum appropriate oxygen concentrations in the ***ALEC*** arm (Table 35). CRIB scores of infants who died (8.3 in the ***Curosurf*** arm and 9.9 in the ***ALEC*** arm) were nonetheless statistically significantly higher than in infants who survived (3.5 in the ***Curosurf*** arm and 4.7 in the ***ALEC*** arm).

The original intention of collecting CRIB data had been to ensure that infants recruited to both arms of the trial were equally sick prior to surfactant administration. However it has become clear during analysis of these data that CRIB was inappropriate for this purpose as it was severely affected by the differential effect the two surfactants had on minimum and maximum oxygen requirements after they were given.

9.6.8 Days of high dependency care

With the difference in mortality this outcome became of secondary importance, particularly with the trial terminating early. There was no statistically significant difference between surviving infants in the two groups for the median number of high dependency (HD) days (22 days [IQR 5-52] in the ***ALEC*** group and 18 days [IQR 6-39] in the ***Curosurf*** group). The median duration of low dependency (LD) care was also similar (47 days [IQR 37-57] in the ***ALEC*** group and 51 days [IQR 39-63] in the ***Curosurf*** group).

Table 35: Median values of the components in CRIB scores between the ***ALEC*** and ***Curosurf*** arms

	Curosurf	***ALEC***	p value*
Gestation (weeks)	28.3	27. 8	NS
Birthweight (grams)	1026	949	NS
Maximum oxygen	50%	77%	0.001
Minimum oxygen	21%	28%	<0.0001
Worst base excess	-5.0	-5.5	NS

* Fishers Exact test

The overall median duration of neonatal care in surviving infants (high and low dependency) was 69 days [IQR 49-87] in the ***Curosurf*** arm and 75 days [IQR 50-100] in the ***ALEC*** arm with infants in both arms being discharge at a median gestation of 38 weeks post-conception.

Among infants that died the duration of HD care was similar in the two arms (median of 8 days [IQR 3.3-12.8] in the ***ALEC*** arm with median of 8.5 days [IQR 0-20.5days] in the ***Curosurf*** arm). The late deaths affected these results so that the mean duration of HD care in the two arms were 31 days in the ***ALEC*** arm and 37 days in the ***Curosurf*** arm.

The differential mortality rates and the late deaths in the ***ALEC*** arm made the primary outcome (cost of care in surviving infants) difficult to assess. Not least because the median duration of HD care in both surviving and non-surviving infants was calculated to be 11.0 days [IQR 0.0-31.0] in the ***ALEC*** arm and 16.0 days [IQR 0-32.0days] in the ***Curosurf*** arm, yet the mean (±1 St. Dev) was 30.9 (±40.0) and 27.0 (±40.0) days respectively.

Using HD care RVI costs quoted earlier (i.e. HD days cost £912 each, of which £800 is at fixed/semi-fixed rate and £112 at marginal rates, LD days cost 20% of HD days) applied to the means of HD and LD days the pre-discharge costs can then be calculated. Thus the mean cost of treating an infant with ***ALEC*** was £34,565 (£28,181 at HD rates and £6,384 at LD rates) and for ***Curosurf*** this was £32,941 (£24,624 at HD rates and £8,317 at LD rates). More importantly mean marginal costs were £3,461 and £3,024 respectively, a slight advantage for ***Curosurf*** but one that disappears when taking into account the costs of 2 vials of ***ALEC*** (£300) versus 2 vials of ***Curosurf*** (£800) as the more expensive ***Curosurf*** would add to these marginal costs by £500 per infant.

However when the costs of producing one survivor are examined the difference becomes larger because of the differential in mortality. The overall cost (at RVI rates) of treating the 100 infants with ***ALEC*** was £3,456,500, this resulted in 69 survivors. The cost per survivor was therefore £50,094 (of this £5,016 was marginal HD cost). For ***Curosurf*** the cost of treating the 99 infants in that arm of the trial was £3,261,159 with a resulting 85 survivors. The cost per survivor was therefore £38,366 (of which £3,522 was at marginal HD rates). This means that ***Curosurf*** use resulted in a saving (per survivor) of £11,728 (£1,408 at marginal rates).

Thus despite being the more expensive surfactant preparation, ***Curosurf*** actually saved £1,408 per surviving infant in marginal costs. The effects of this saving on a regional basis within the former Northern region are explored in chapter 10.

9.7 Discussion

The result of this study with respect to mortality was unexpected and led to the recommendation from the DSMC to terminate the trial prematurely. That mortality was collected as a secondary outcome measure shows how unexpected this result was. Meta-analysis had suggested that there might be a slight advantage for animal-derived surfactants, but this only approached statistical significance with the inclusion of results from 3300 infants (Soll 1999c). None of the previous individual trials between animal-derived and synthetic surfactants had shown such a clear difference despite larger numbers of infants recruited. The following discussion first concentrates on the mortality rates and the decision to terminate the trial prematurely, before comparing this trial with existing data from other trials and meta-analyses, and ending with a discussion of the implications.

The decision of the DSMC to recommend termination was not reached lightly particularly as mortality was not the primary outcome of the trial. Nonetheless it was regarded by the committee as an important outcome in itself. The main purpose of a DSMC is to protect patients - primarily those included in the trial but also other patients with the disease in question (Hampton 2000). Either there was something intrinsically wrong with the trial design or there was a difference in treatment effect that had not been appreciated prior to the trial. In either case the correct ethical decision was termination of the trial.

Some of the deaths reported cannot be attributed to treatment effect; for example a death at over 200 days of age due to hypovolaemia secondary to incarcerated inguinal hernia. However it was decided to include all deaths prior to discharge irrespective of cause. This has been done in other neonatal surfactant trials, particularly the Ten Centre Study (1987) and Two Centre Study (Morley *et al* 1988).

The neonatologists that reviewed the notes to determine the cause of death were blinded to surfactant allocation, although they were aware that ***ALEC*** had a higher mortality rate than ***Curosurf***. They were also asked to differentiate those deaths that were primarily respiratory and whether these could be attributed to RDS and either its short-term or long-term complications. More infants in the ***ALEC*** arm died from a respiratory cause, whereas non-respiratory death rates were similar. Whilst ***Curosurf*** may not have prevented all the excess respiratory deaths in the ***ALEC*** arm, in two groups of infants that were randomised and that had similar pre-treatment profiles, the assumption has to be that it is the better surfactant of the two for treating RDS. ***Curosurf*** reduces oxygen and ventilator requirements more rapidly, and because both oxygen and barotrauma (or volutrauma) are thought to be important in the pathogenesis of CLD it can be reasonably argued that ***Curosurf*** may influence this late outcome as well as RDS.

A statistical difference in mortality rates between the two surfactants had not been expected prior to the trial, and whilst it is possible that this was a true treatment effect, other pre-existing variables that are discussed in chapter 1 may have influenced severity of RDS. One notable difference between the two arms was gestational age breakdown, favouring treatment with ***Curosurf***, whereas there was an excess of male infants in the ***Curosurf*** arm, which favoured the ***ALEC*** group. The imbalances that did happen were within the bounds of chance variation. The use of analysis of covariance methods to allow for the imbalance is a widely accepted and effective statistical tool. Indeed, if stratification had taken gestation and gender into account then they would have to have been included as covariates in the analysis.

In retrospect these imbalances could have been avoided by further stratification (for example using two groups of 25-27 weeks and 28-29 weeks gestation, and by gender). But the introduction of additional strata into the randomisation process would have made it more complicated and time consuming. Owing to the demands on medical and nursing time after the delivery of a preterm infant, the randomisation process was designed to be simple and as quick as possible so that staff could concentrate on the patient.

Whether prior knowledge of surfactant type may have influenced the decision to intubate the infant for respiratory support is difficult to assess. This bias can only affect those patients that are randomised and the randomisation process was through a single centre using sealed opaque envelopes. Only thirteen patients were withdrawn post-randomisation and all of these were for legitimate reasons that could not be influenced by the trial investigators. It is believed their withdrawal did not bias the treatment comparison.

The four infants that were randomised antenatally (all to ***ALEC***) and subsequently had their delivery postponed (because the indication for preterm delivery disappeared or settled) are the only instance where a reasonable argument for bias can be mounted. The decision for postponing the delivery, however, was not made by the investigators and the obstetricians making the decision would have been unaware of the allocation. It should also be noted that as only four potential patients are being discussed there is, in any case, the potential for only a small bias. In the event that the infants were not intubated, they were treated according to their clinical condition at the time, which is an unavoidable risk of the antenatal randomisation process. Similarly infants that died in-utero (stillborn) or that could not be resuscitated were enrolled unavoidably.

The question then arose as to whether the results obtained in this trial were consistent with those seen in earlier trials of the same surfactants. Evidence from the placebo controlled trial of ***Curosurf*** when treatment had been administered at a median of 9 hours of age and infants had established RDS (they required an $FiO_2 \geq 0.6$ for enrolment) suggested a reduction in mortality from 51% in the control arm to 31% in the treatment arm (Collaborative European Multicenter Study Group 1988). The trials of Egberts *et al* (1993), Walti *et al* (1995) and Bevilacqua *et al* (1996) used cohorts that more closely resembled our trial population with their timings of surfactant administration. In the "prophylaxis" arms of these three trials, the neonatal mortality rates were 10.7%, 11.2% and 20.6% respectively.

With ***ALEC*** the evidence from previous trials was limited. Only five trials have been published with this surfactant (Morley *et al* 1981, Milner *et al* 1983, Wilkinson *et al* 1985, Ten Centre Study 1987, Morley *et al* 1988) and only the last two used a preparation similar to that currently available commercially. As the infants <30 weeks gestation from the Two Centre trial (Morley *et al* 1988) were included in the Ten Centre Study, that left only the one trial with which to compare mortality rates. Neonatal mortality in the Ten Centre treatment arm was 14.5%, much lower than 31% despite a higher rate of use of antenatal steroids in our trial.

This difference between mortality rates in ***ALEC*** treated arms of the Ten Centre and the current trial could not be explained by comparison of the population characteristics (median gestation and birthweight, proportion of males were similar, but the antenatal steroid use favoured infants in our trial. Further details about the Ten Centre Study were sought and kindly supplied by Professor Colin Morley.

Differences in disease severity, changes in patterns of care or demographic variables of the populations in studies carried out more than a decade apart may explain some of the differences. 10.7% of infants in the treatment arm of the Ten Centre Study were not ventilated (and received only a pharyngeal dose of pumactant), whereas it was a condition that infants in our trial were eligible only if intubated and ventilated. This may be reflected in the fact that gestation-specific mortality in the more immature (25–26 weeks gestation) ***ALEC***-treated infants in our study was similar to that in the Ten Centre study, but was higher in the more mature infants (27–29 weeks). The differences in mortality between the studies at each gestational week did not reach statistical significance (test for interaction $p = 0.08$).

The only other trial comparing ***Curosurf*** and a synthetic surfactant (***Exosurf***) did not show any difference in longer-term outcomes (Kukkonen *et al* 2000) but this had used a late "rescue" strategy trial whereas the comparison between ***ALEC*** and ***Curosurf*** was, at worst, early treatment, with "prophylaxis" in some centres.

Both the published meta-analyses (Halliday 1996 and Soll 1999c), and the one presented in chapter 8, had suggested that there would be fewer deaths in the animal-derived arm of the study but that within a single trial this would not achieve statistical significance. It may be that the use of different surfactants than in the meta-analyses has contributed to the finding of a much greater mortality after synthetic surfactant in this study. *In vitro* properties were different for all four of the currently available surfactants in the United Kingdom, but extrapolation of these differences to clinical studies is unreliable. There was a significant reduction in the number of pneumothoraces in the ***Curosurf*** group, which agrees with the meta-analyses, however clinically significant PDAs were higher in the ***Curosurf*** group, the meta-analyses had suggested this would be lower.

An important difference between this and other trials of ***ALEC*** was the dosing schedule. In the Ten Centre Study, ***ALEC*** was given up to four times; the first dose was a pharyngeal deposit prior to intubation, the second was immediately after intubation, the third one hour later and a fourth dose at 24 hours. For commercial development the pharyngeal dose had been dropped but the manufacturer's data sheet still recommended the use of the other three doses.

The evidence supporting the second dose of ***ALEC*** at one hour was not very strong but reasons quoted by Professor Morley (personal communication) were:

- If a infant <30 weeks gestation was still ventilated and in oxygen at one hour there was a high probability that severe RDS was developing
- Procedures during the first hour after birth may have removed some of the surfactant
- Further doses may help to overcome the protein inhibition
- There is a slow loss of molecules from the surface and the surface tension properties deteriorate which can be restored with a further dose of surfactant

All of these are equally applicable to any surfactant irrespective of source or type, but the main reason specifically for the time schedule for ***ALEC*** seemed to be procedures such as endotracheal suction that can remove surfactant.

Prior to the trial both Liverpool Women's Hospital and the Royal Victoria Infirmary in Newcastle had used ***ALEC***. Liverpool administered a dose in delivery suite followed by a second dose 12 hours later, the RVI administered the first dose as soon as possible on the neonatal unit and the second dose 24 hours later. Historic data in the two years prior to the trial had shown pre-discharge mortality rates of 26.5% (Liverpool) and 25.4% (Newcastle) in infants of 25-29 weeks gestation that had been ventilated. This historic data also suggested there was no difference between a 12 or 24 hour schedule, although theoretically an earlier dose (of any surfactant) at 12 hours might replenish phospholipids that had been lost through inactivation, endotracheal suction and recycling and prevent periods of low surfactant activity and hence RDS. These mortality rates were thus comparable with the trial ***ALEC*** arm, but much higher than the Ten Centre Study data.

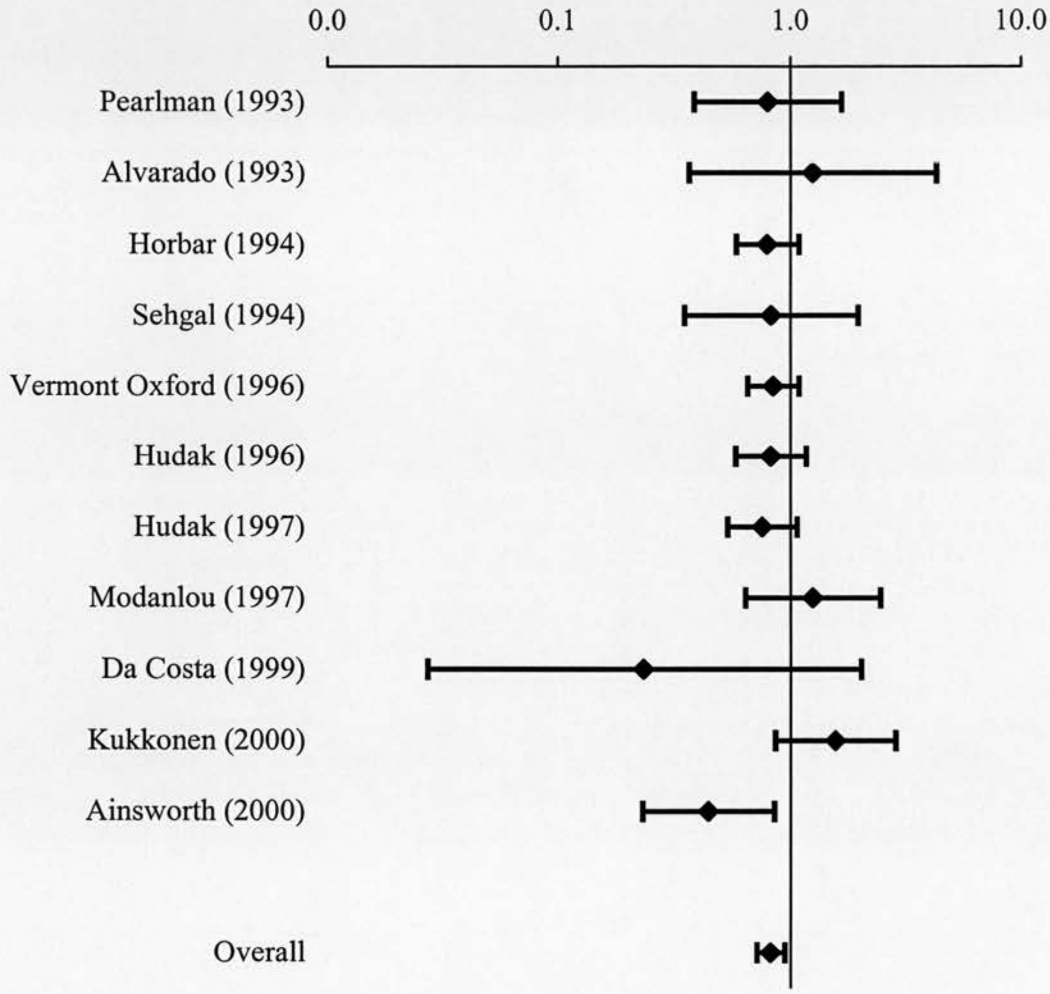
The implication of mortality rate differences between the ***ALEC*** arms of the Ten Centre Study and the current trial is that either the 1-hour dose of ***ALEC*** did matter or the populations of the two trials were inherently different. There is no doubt that neonatal populations have changed, obstetricians are presenting neonatologists with infants that previously would have died in-utero and the trend is towards a sicker and more immature population (Olsen *et al* 1995). There are also inherent differences between the geographic populations of the two trials. The Ten Centre Study reported a control group mortality of 29.5% whereas at the time of this study the mortality in Newcastle General Hospital (the predecessor of the RVI) was close to 36.9% in the 25-29 week gestation band (*data from the NGH neonatal unit annual reports 1989-90*). These infants were not receiving surfactant and represent the closest that we can get to a "control" (non-surfactant treated) group for our population. If this 8% differential in mortality rate were to continue after surfactant was introduced in Newcastle then mortality rates of 26-28% might be expected.

As explained earlier in chapter 6 most commercially available surfactants are administered based on a dose of 100 mg/kg of phospholipids and are given at intervals that range from 1 hour to 24 hours, although the commonest interval is 12 hours. The evidence that 100 mg/kg is the "correct" dose and that any dosing schedule is correct is, at best, limited. Whilst we cannot ignore the fact that ***ALEC*** was not used according to the manufacturer's guidelines, the fact remains that development of the schedule was largely empirical and there is no published evidence that this is better than the dosing schedule used in our trial.

There is no doubt that ***Curosurf*** reduced both ventilation and oxygen more rapidly than ***ALEC***. ***Curosurf*** was able to reduce the mean OI in even this sicker group of infants whereas in the ***ALEC*** group the OI was higher at 6 hours than on admission. Kuint *et al* (1994) suggest that the immediate response to surfactant has prognostic value in predicting outcome, although they were not comparing two different surfactants with differing speeds of onset. However they admit that factors other than speed of onset of action have an influence on mortality – the most important being birthweight and gestation.

This is the only study that has shown a significant advantage in mortality for an animal-derived over a synthetic surfactant (Figure 17). The reason why this is the case when meta-analyses (Soll 1999c and that in chapter 8) only approach statistical significance with many more infants is unclear but this is the only study to have compared ***ALEC*** with any other surfactant.

Figure 17: Relative risk of mortality reported in trials comparing synthetic and animal-derived surfactants



The excess numbers of deaths in the ***ALEC*** arm were attributable to RDS and its complications. In randomised trials ***Curosurf*** has been compared to one other animal-derived surfactant, ***Survanta*** (Speer *et al* 1995) and one synthetic surfactant, ***Exosurf*** (Murdoch & Kempley 1998, Kukkonen *et al* 2000). In none of these trials was there a statistically significant difference in mortality rates. The other advantages for animal-derived over synthetic surfactants – those of speed of action and reducing the numbers of pulmonary air leaks – were also evident for infants treated with ***Curosurf***.

Although the study did not demonstrate significantly reduced costs after treatment with ***Curosurf***, there were some reductions in marginal costs for high dependency care. However these would be offset by the higher costs of ***Curosurf*** itself and by the greater numbers of survivors requiring low dependency care.

9.8 Conclusion

Of the two surfactants ***Curosurf*** reduces predischarge and neonatal mortality compared to ***ALEC***. There were significant reductions in the oxygen and ventilator requirements of infants who received ***Curosurf*** and these changes presumably were responsible for the significantly lower rates of pneumothoraces and respiratory related deaths seen in this arm.

The primary outcome of the study became of a secondary importance after the differential in mortality was seen nonetheless it still remains an important consideration in the provision of neonatal care. There are other ways in which the reduced mortality might impact on care; an increasing number of survivors mean greater competition for the available neonatal intensive care cots. With increasing competition for cots there would have to be a greater number of perinatal transfers.

How the perinatal services in the former Northern health region of England are organised is discussed in the next chapter. This chapter also shows the influence of place of maternal booking and birth on mortality in the "at risk" infants born at <32 weeks gestation and explores the implications of the ***Curosurf*** versus ***ALEC*** trial on the region should all the hospitals use ***Curosurf***.

Chapter 10

Surfactant deficient lung disease in the former Northern health region of England

10.1 Introduction

As the last chapter has shown using ***Curosurf*** instead of ***ALEC*** can have clear implications for the funding and provision of neonatal intensive care. Just as with the SHPIC report (1996) that used data from hospitals in Dundee and Glasgow to illustrate the cost-effectiveness of surfactant versus no treatment, it is possible to use data from infants born in the former Northern region to estimate the impact a change from one surfactant to another.

This chapter begins by tracing the development of a collaborative neonatal service in the region and explains how this currently provides neonatal intensive care for the 33,000 livebirths annually. Data on all infants <32 weeks gestation (i.e. those most at risk from RDS) admitted to the region's neonatal units are discussed in relation to the hospital of booking and of birth and access to neonatal intensive care facilities.

The chapter finishes by looking at a hypothetical situation whereby all infants <32 weeks gestation who require surfactant are treated with ***Curosurf*** and discusses the changes in mortality that might be seen if the results of the ***Curosurf*** versus ***ALEC*** trial were duplicated in this unselected population.

10.2 The development of a collaborative neonatal service in the former Northern health region

The neonatal services in the North East of England have developed from predominantly obstetric-orientated domiciliary service in the 18th century to a collaborative consortium of four level III neonatal intensive care units. These units now perform most of the neonatal intensive care that is required by a proportion of the region's 33,000 annual livebirths.

The first maternity hospital in Newcastle upon Tyne – a Lying-in Hospital in 1760 – was founded at a time when most births occurred at home and maternal, let alone infant, mortality was as high as 6 per 1000. Reductions were not seen in this figure until the 20th century. By this time obstetrics was beginning to move from a domiciliary to a hospital-based service, not only in Newcastle but also elsewhere in the UK.

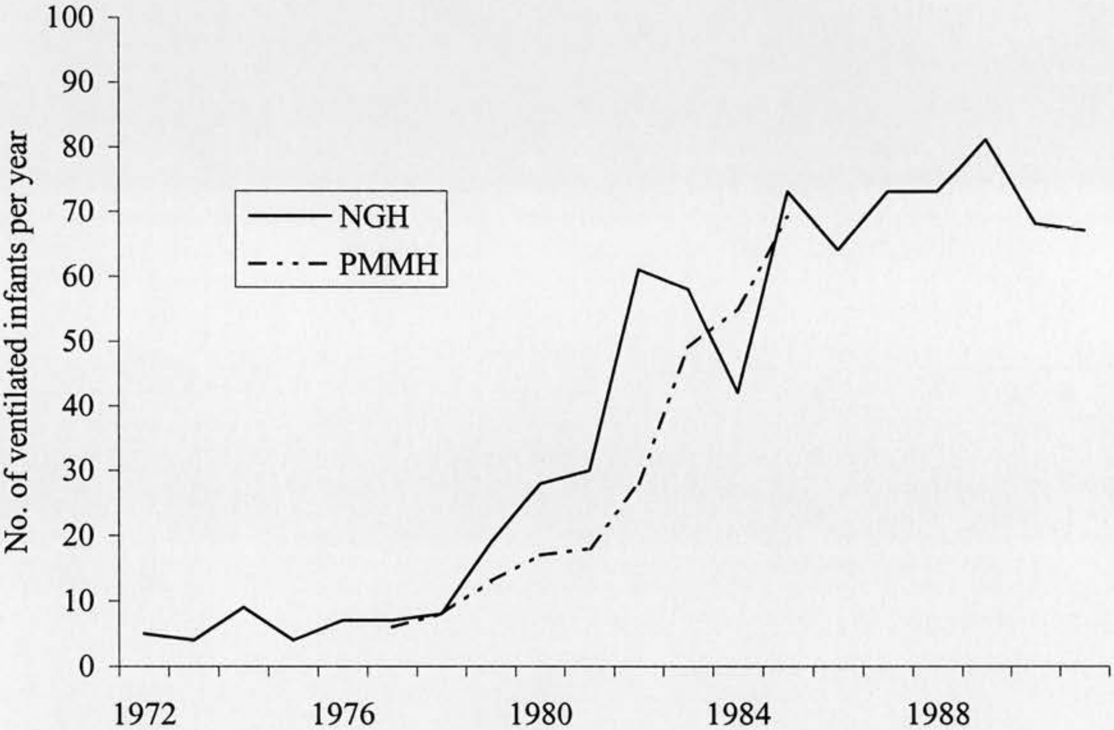
The Princess Mary Maternity Hospital (PMMH) and the building of a maternity ward at the Newcastle General Hospital (NGH) in 1903 were seen as significant steps in the development of a modern obstetrical service in Newcastle. But it was not until 1939 that a spacious and well-equipped nursery that was to function as the premature infant unit was added to the NGH. Following this with the appointment of Dr James Spence as honorary paediatrician to the PMMH care of the newborn infant began to receive the same emphasis as the care of the mother. Spence is reported to have made the first paediatric ward round in an English maternity hospital. In 1942 he was appointed Professor of Paediatrics in overall charge of the RVI, the Infants' Hospital and the University Clinic of Child Health.

With the advent of successful neonatal ventilation in the 1960s (reported first by Delivoria-Papadopoulos & Swyer 1964) many infants that would otherwise have died from respiratory failure could now be offered a chance of survival. In the late 1960's there was an increasing number of reports of infants being successfully ventilated (Tunstall *et al* 1968, Reynolds 1970, Llewellyn *et al* 1970, Strang 1970, Raiha & Vapaavouri 1970). Both Newcastle neonatal units continued to develop separately and began to ventilate increasing numbers of infants (Figure 18). However, North Tees General Hospital in Stockton on Tees lays claim to being the first hospital in the region to ventilate a neonatal patient (*Personal communication* – Dr Myint Oo).

In the 1970's and 1980's neonatal intensive care was beginning to become the low-volume high-intensity specialty that it is today. As in the rest of the United Kingdom, neonatal care in the former Northern region grew on an ad hoc basis according to the perceived need at the time. This was despite calls for a more centralised service based on special care facilities within local hospitals and specialised intensive care unit in regional centres (Department of Health and Social Security 1971).

Nonetheless it was recognised that with developments in ventilator technology and innovations in neonatal care it was becoming increasingly difficult for smaller hospitals to continue to offer neonatal care for infants in whom outcome depended on respiratory support. This led to the development of a "Paediatric Flying Squad" to transfer affected infants. This service was initially based at NGH but duties were later shared on an informal basis with the PMMH. This arrangement was later formalised by the use of a single telephone "hotline" switched between the units on a weekly basis (Tacchi 1994).

Figure 18: The trends of ventilation workload in the two Newcastle neonatal units 1972-92



Data obtained from the annual reports of PMMH and NGH
(no data available from PMMH 1986-91)

This arrangement coped with most of the region's infants who required intensive care during the next five years, by which time rising demand led to some overflow to three other neonatal units in Sunderland, Middlesbrough and Stockton on Tees. This pattern of service provision developed in part as a result of the scattered nature of the region's population. The service provided by the five units then evolved into an informal collaborative between the units providing neonatal intensive care.

The NHS underwent significant changes with the introduction of the internal market, outlined in the 1989 White Paper "*Working for Patients*" and which passed into law as the NHS and Community Care Act 1990. The advent of the internal market threatened the existing clinical collaborative network by devolving neonatal intensive care services to local units (Pope & Wild 1992). The clinicians were faced with the choice of continuing to collaborate, entering into open competition or amalgamating into a centralised service. Collaboration was felt to be the most attractive option, not only to those involved but also to the population the service provided for. In addition mathematical modelling suggested that collaboration would be more efficient in using the available resources (Northern Neonatal Network 1993b). As a result the arrangement was formalised into the Northern Neonatal Network in 1993, beginning to contract their services to the healthcare purchasers in the 1993/94 financial year.

The telephone "hotline" has remained pivotal to the success of this clinical collaboration. A single call via the "hotline" initiates referral and subsequent transfer, freeing the referring clinician to give optimum care and attention to the infant.

10.3 The current status of neonatal services in the former Northern region

With the amalgamation of the PMMH and NGH in Newcastle to a single unit at the Royal Victoria Infirmary (RVI) in 1993 the neonatal intensive care services in the former Northern region currently comprise four level III units - North Tees General Hospital in Stockton on Tees, South Cleveland Hospital in Middlesbrough and Sunderland Royal Hospital and the RVI. Between them these units provide almost all of the region's long-term neonatal intensive care. The RVI also has neonatal and paediatric surgical facilities and a regional fetal medicine service. Cardiac services are based at the Freeman Hospital in Newcastle upon Tyne.

This "centralisation" through collaboration has meant that transfers have become an inevitable component of the region's perinatal service. There are eleven level I neonatal (special care baby) units scattered around the region (Figure 19). These units have neither the facilities nor the staff to undertake long-term neonatal ventilation. Instead infants who are preterm or sick are stabilised in these units and transferred postnatally. Transfers within the region are coordinated through the RVI. Postnatal transfers are undertaken by one of two transfer teams, one based in Newcastle, the other in Middlesbrough. These teams perform all acute neonatal transfers in the region, as well as transfers for other specialties such as paediatric surgery, paediatric intensive care and the ECMO service. Non-acute transfers, such as the return of an infant to a local hospital after intensive care, are the responsibility of the local units.

There is close collaboration between the neonatal provider units, the obstetricians serving these hospitals and regionally-based survey offices. Data collected by the survey offices has resulted in a number of population-based outcomes studies in preterm infants (Wariyar *et al* 1989a, Wariyar *et al* 1989b, Tin *et al* 1997).

There are currently around 33,000 total births in the region annually and in keeping with national trends there has been a reduction in the annual number of births in the region in the past 5 years (Figure 20). The regional perinatal mortality has improved gradually over the past 16 years and currently stands at 8.3 per 1000 total births (Figure 21).

Although most of the neonatal intensive care is undertaken in the four level III units the nature of premature labour and the geography of the region means that there still significant numbers of births that occur in units that do not provide long-term neonatal intensive care. To examine the workload that neonatal respiratory care places on these units a prospective survey was designed. The next section reports on the results of this survey over a 24 month period.

Figure 19: Neonatal units in the former Northern region

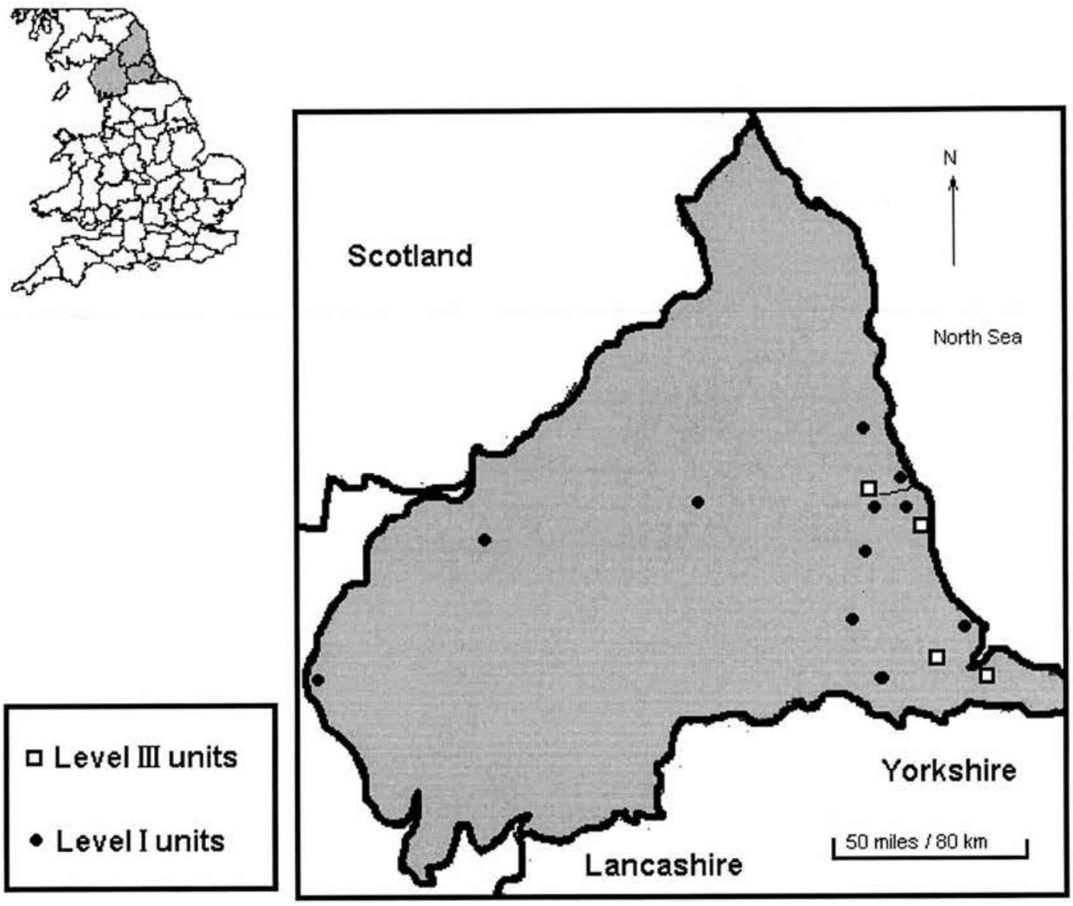
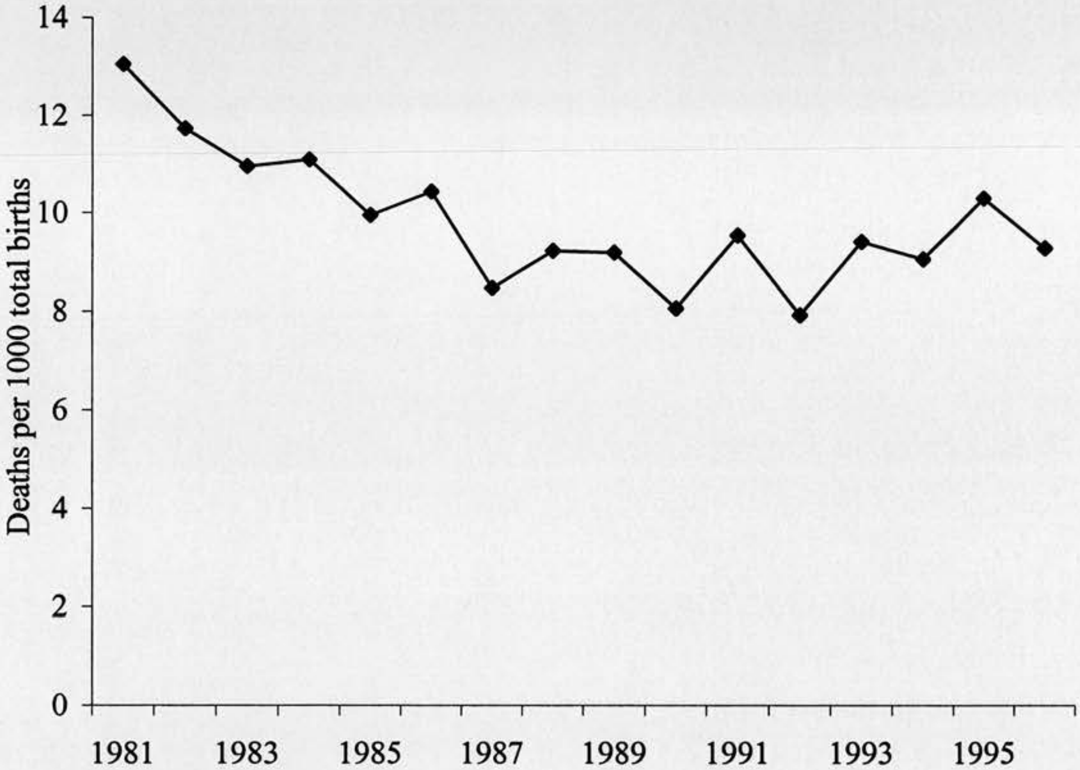


Figure 20: Birthrate in the former Northern region 1981 - 1999

Data obtained from annual reports issued by the
Northern Region Maternity Survey Office

Figure 21: Perinatal mortality in the former Northern region 1981 - 1999



Data obtained from annual reports issued by the
Northern Region Maternity Survey Office

10.4 Survey of outcomes of infants born at <32 weeks gestation in the former Northern region 1998-99.

Introduction

Most of population of the former Northern region is located in the former mining and industrial communities in the east. This is mirrored by the distribution of the level III NICUs. Nonetheless pockets of population served by smaller maternity units can be found throughout the whole of the region. Eleven of these have special care infant units (level I NICUs) that can undertake short-term intensive care prior to the arrival of the neonatal transport team. Once an infant has completed his/her intensive care these units then take over the latter stages of that infants care prior to discharge.

Staff in the level I units resuscitate and stabilise any preterm infants that are born in their hospital. The process of stabilisation might include intubation and ventilation, administration of surfactant and the siting of venous and/or arterial lines. In other words they provide full intensive until the arrival of the transfer team. In a smaller proportion of the more mature infants who develop mild respiratory distress they might institute nasal CPAP.

The aim of this survey was to examine the workload that this group of hospitals undertakes relative to their own delivery rates and to the work undertaken in the four neonatal provider units.

Methods

All infants born between 1st January 1998 and 31st December 1999 and who were admitted to any of 10 of the 11 the level I SCBUs and who fulfilled the following criteria were notified centrally by a nominated nurse using a simple form. The hospitals involved were Ashington, Bishop Auckland, Carlisle, Darlington, Durham (Dryburn), Queen Elizabeth Hospital (Gateshead), Hartlepool, North Shields, South Shields and Whitehaven (West Cumberland Infirmary). Each admission of an eligible infant generated a new form and thus it was possible for some infants to be notified on several occasions depending on their clinical course.

Infants were notified if they:

- Were <32 weeks gestation and/or
- Were ≤1500grams at birth and/or
- Required any form of respiratory support (either continuous positive airways pressure or mechanical ventilation) irrespective of gestation at birth

This section concentrated on the infants who fulfilled the first criterion.

Data from the level I units were supplemented by information retrieved from the four databases held in the four level III units in the region. These are common to all four units and completed by the consultant neonatologists and have been described elsewhere (Fenton AC, Milligan DWA, Ward Platt MP for the Northern Neonatal Network. *A Networked Regional Database – making it work*. Presented at the 2nd Annual RCPCH meeting, York 1998). Data from eligible infants born in the 11th hospital (Hexham) with a level I SCBU were retrieved by hand from admission books. Data were further checked against a transport database profiling all postnatal transfers in the region.

Data on the delivery rates in the hospitals were obtained by contacting the delivery suites in all the hospitals. The regional birthrate was obtained from the Maternity Survey Offices, which collects demographic data on all births, whether in hospital or at home, in the region. The same survey office also receives notifications of all the deaths of infants <1 year of age throughout the region. This also served as a cross-validation of the mortality data as well as providing data concerning deaths after discharge from the neonatal unit.

Infants were divided into three groups. Group A were infants that were booked and born in one of the four level III units. Group B were those infants booked in a level I unit but who were transferred antenatally to a level III unit. Approximately 120 antenatal transfers are undertaken annually in the region and approximately two-thirds deliver in the tertiary centres (Fenton *et al* 2000). Group C were those that were booked and born in the level I units. Some, but not all of these infants were transferred postnatally.

Data were analysed using non-parametric statistical tests (Mann Whitney U test, Fisher's exact test and ANOVA as appropriate).

Results

(a) Demographics of the regional population of infants <32 weeks gestation.

Seven hundred and seventy one infants less than 32 completed weeks post-conception were alive at admission to any one of the four level III or eleven level I neonatal units in the region between 1st January 1998 and 31st December 1999. An additional 18 infants ≥23 weeks gestation were notified to the regional Maternity Survey Office as showing signs of life after birth but who were not admitted to a neonatal unit.

The hospital of booking is shown in Figure 22 and hospital of delivery in Figure 23. For comparison the annual delivery rates in the hospitals are shown in Figure 24. The collaborative nature and the requirement for both antenatal and postnatal transfers are shown in Figure 25. The largest groups were those infants booked and born in hospitals with level III neonatal units, or those booked in level I units and transferred either antenatally or postnatally. 48.4% of infants were booked for delivery in hospitals with level I units compared to 44.6% booking in hospitals with level III units. At delivery these proportions had changed to 26.3% and 70.4% respectively. In addition to the number of in-utero transfers 56.7% of those infants born in the hospitals with level I neonatal care facilities were transferred postnatally. This reflects the nature of provision of neonatal intensive care within the region.

The small number of transfers out of the region demonstrates the efficiency of the collaboration. In a survey of in-utero transfers during 1999 there were only 3 transfers out of the region with two infants delivered in the hospitals receiving the transfer (Fenton *et al* 2000). In contrast there were 48 infants transferred into the region either antenatally or postnatally. These were predominantly from units in Scarborough and Northallerton just south of the region, but which fall within the former Yorkshire region.

Gestation at birth of these infants is shown in Figure 26. The overall mean (± 1SD) gestation was 28.6 (± 2.2) weeks, and the birthweight was 1235 (± 378) grams. Infants transferred antenatally were statistically significantly more immature and smaller than in the infants that were born in level I units. Mean gestations were respectively 28.4 (±2.3) and 29.0 (±2.0) weeks ($p=0.012$) and mean birthweights were 1167 (±357) and 1330 (±361) grams ($p<0.0001$). Reflecting a predominance of intrauterine growth retardation in this group.

Figure 22: Hospital of booking for infants <32 weeks admitted to special care baby units in the former Northern region 1998-9

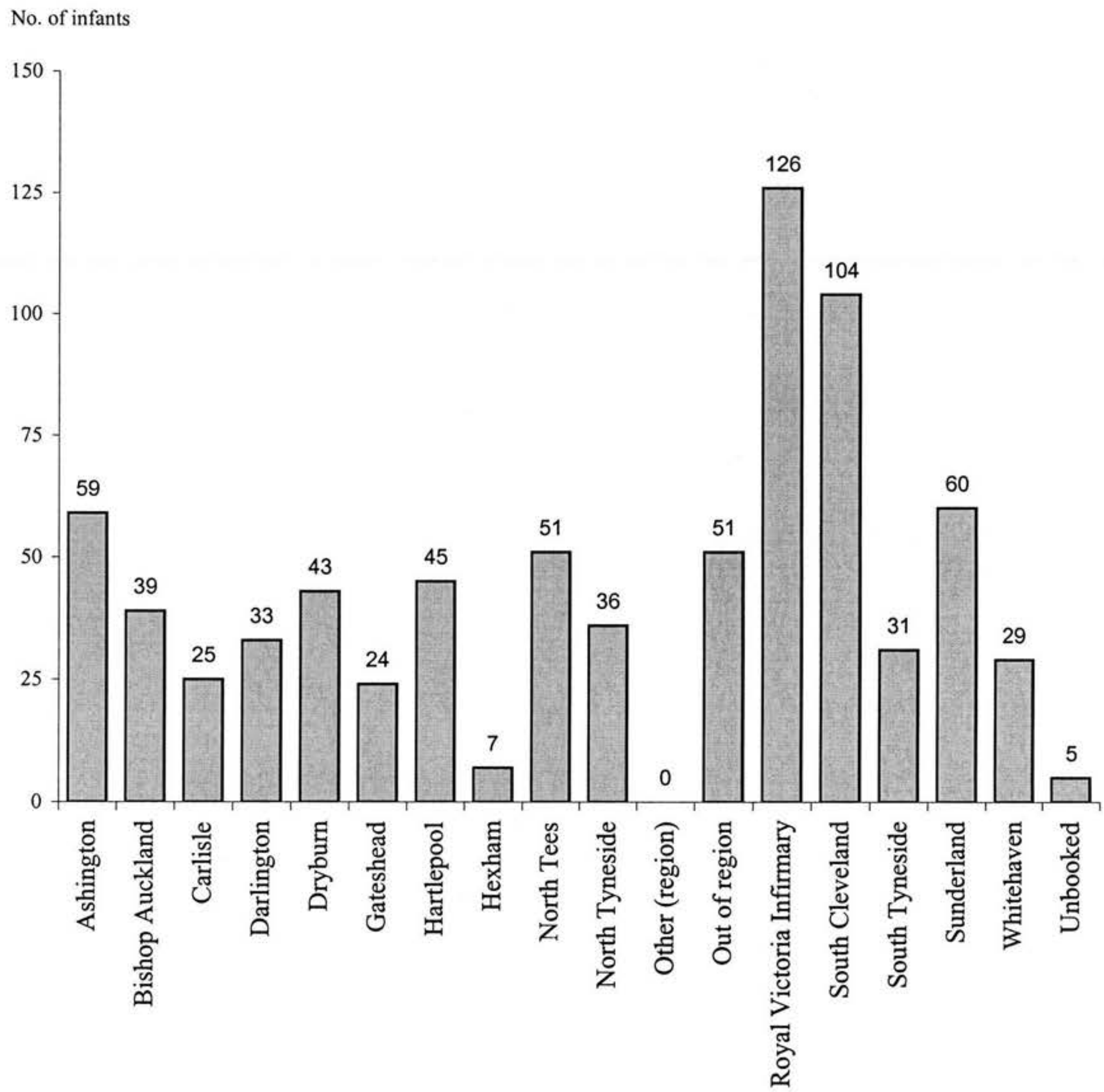
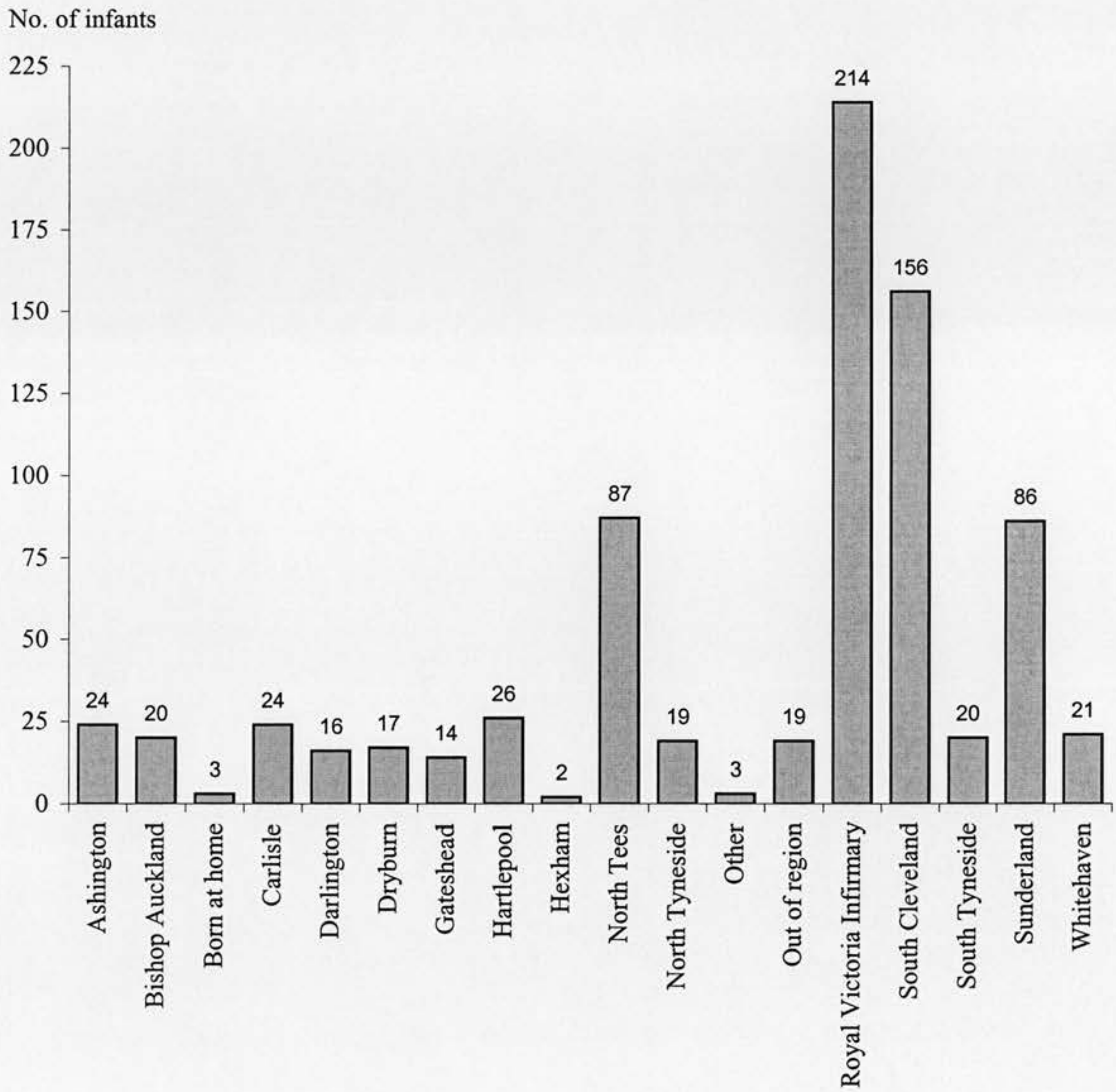


Figure 23: Place of birth of infants <32 weeks admitted to special care baby units in the former Northern region 1998-9



"Other" are 3 infants, two were booked at hospitals in the region and born abroad when their mothers were on holiday, the other was born in an ambulance enroute from Whitehaven to the RVI

Figure 24: Livebirths rates in 1999 in hospitals
in the former Northern region with special care baby units

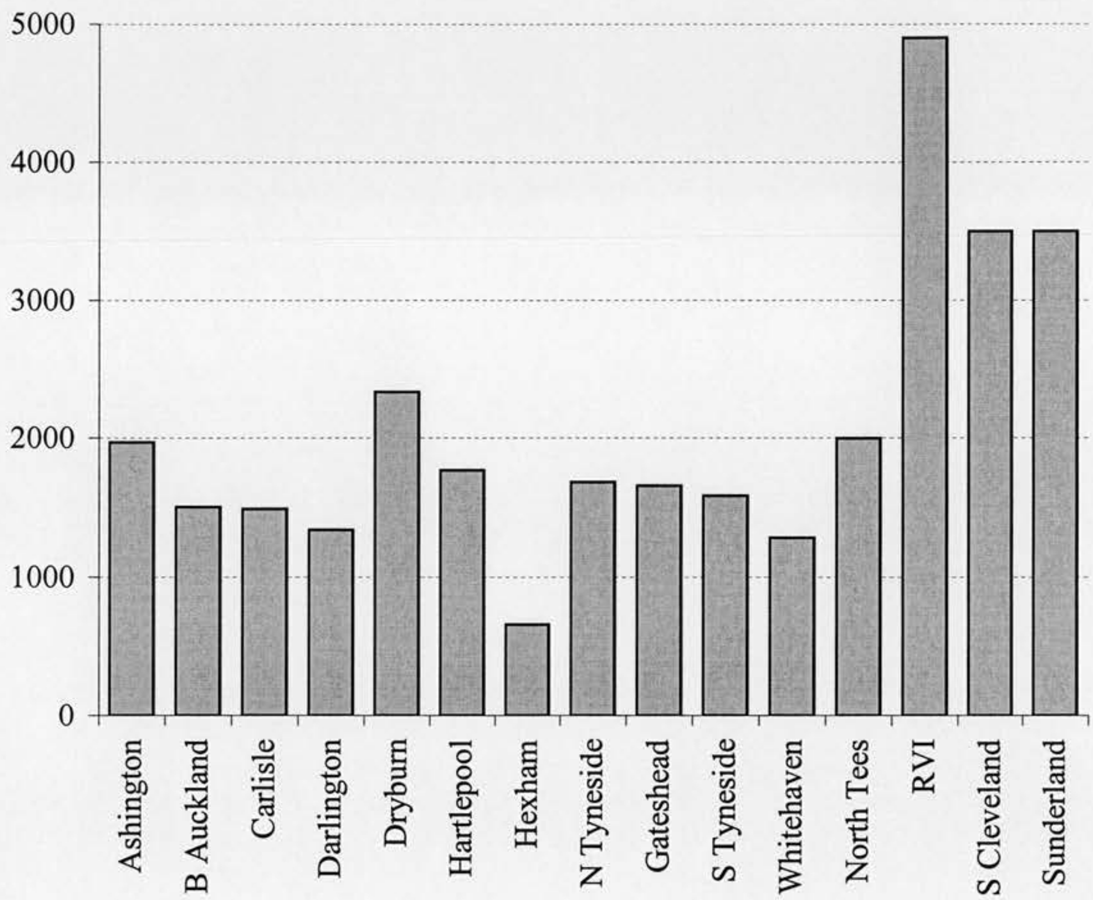


Figure 25: Early neonatal course in relation to place of birth and transfer status

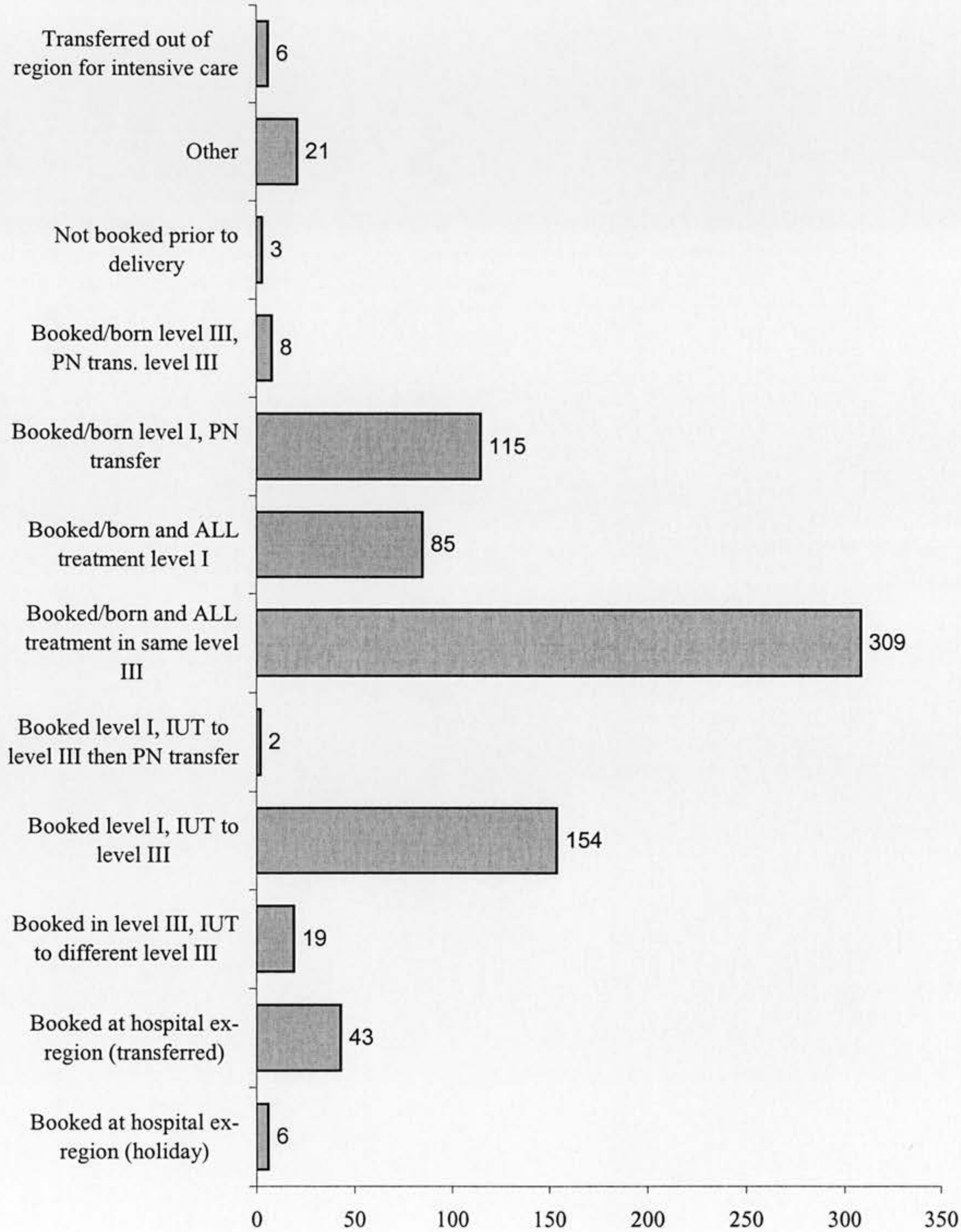
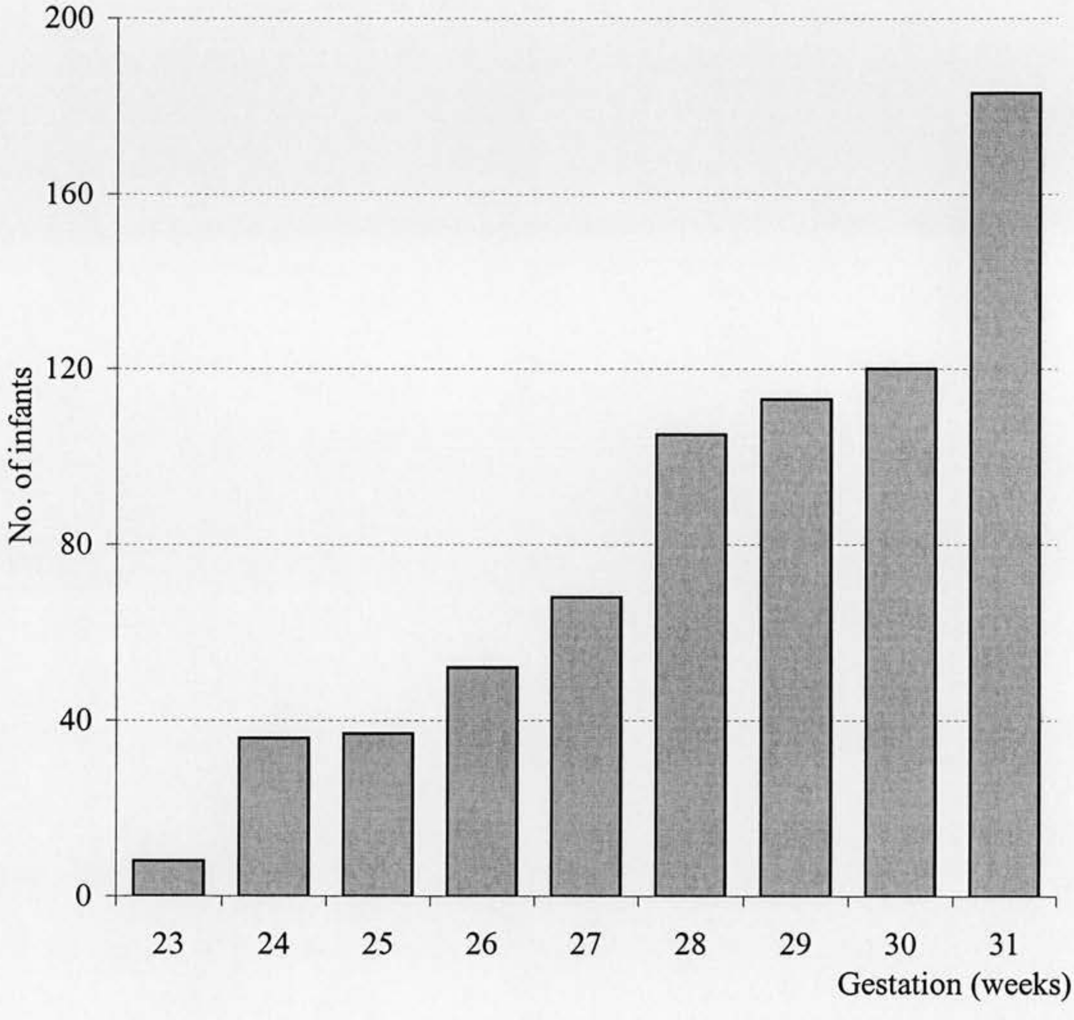


Figure 26: No. of infants (<32 weeks) treated within the special care baby units of the former Northern region 1998-99



(b) Outcomes after admission to the neonatal units

Pre-discharge mortality for the whole group of infants <32 weeks admitted to SCBU was 17.6%. Gestation-specific mortality is shown in Figure 27. Most of the deaths occurred early: 20.6% in the first 24 hours after birth, 39.0% by 48 hours and 56.6% by the end of the first week (Figure 28). Four infants died after discharge (only one of these deaths could be attributed to complications of prematurity). 77.2% of infants were discharged home and 5.1% transferred to a hospital outside the region. The latter were predominantly those infants from mothers that had booked elsewhere and who were either transferred or who were born whilst staying in the region on holiday.

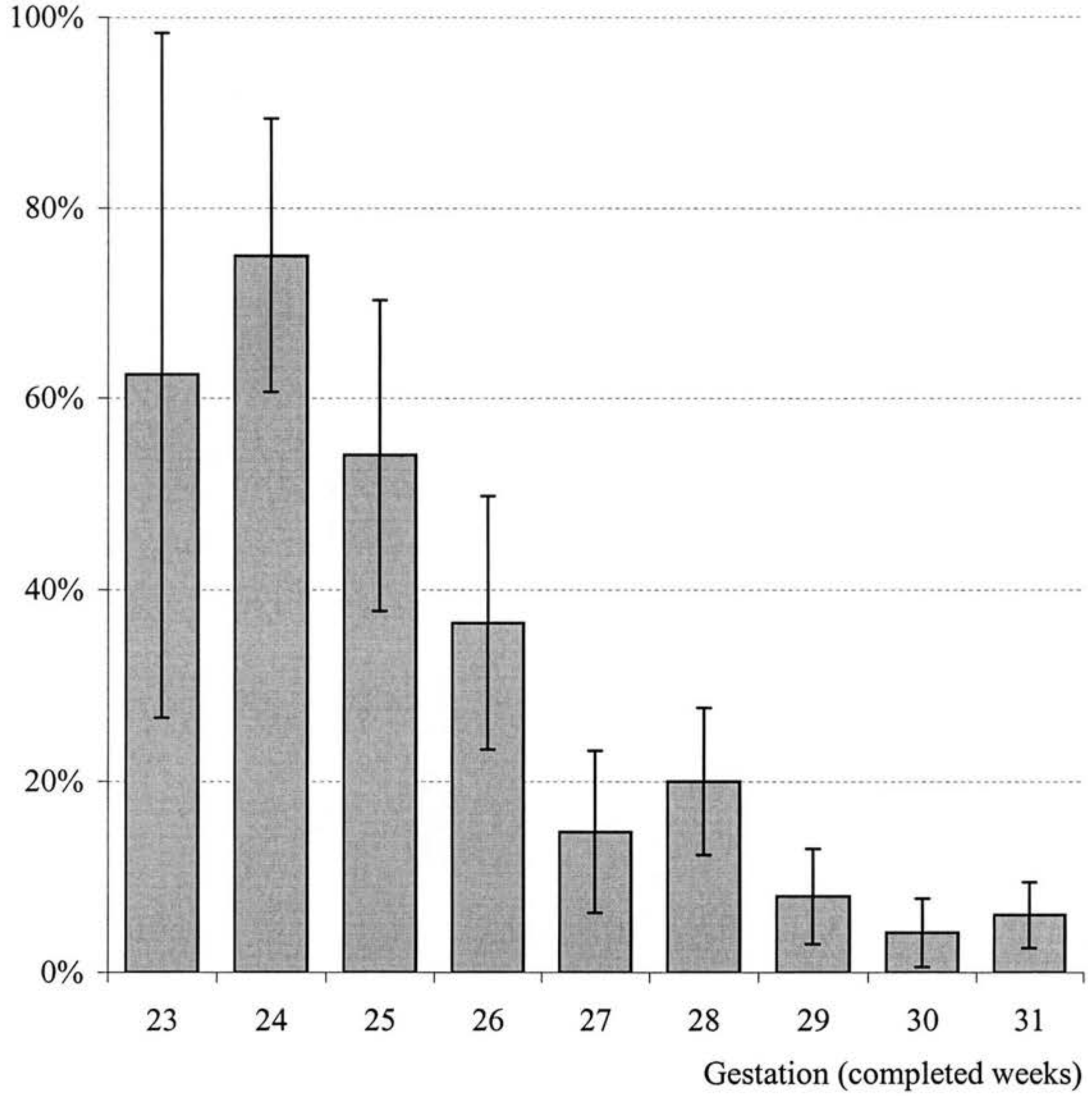
(c) Resource usage in SCBU – ventilation and high dependency days

The "centralised" provision of neonatal intensive care is also reflected by the distribution of respiratory support. During the two year period a total of 615 (79.8%) infants received some respiratory support (either positive pressure ventilation or CPAP). Overall in the period there were 5785 ventilator days and 4292 CPAP days, an average of 7.5 ventilator days and 5.6 CPAP days per infant (Table 36). Of the CPAP days 377 were from infants who were not ventilated. Only 25 ventilator days and 74 CPAP days were received by infants that remained in the level I neonatal units from birth until discharge (7 of the ventilator days were in infants that died before transfer could be effected). Further short-term respiratory support was also provided by level I units for the 115 infants transferred postnatally. These figures reflect only the days of respiratory support received on one of the special baby care units (level I and level III units). Some of the infants that were transferred to the surgical unit at the RVI or to the cardiac unit at the Freeman Hospital were also ventilated but data from the duration of stay in these units was unavailable.

(d) Does the hospital of booking or of birth influence mortality?

The former Northern region has a population of nearly 3 million people and whilst most people live in the industrial cities in the east there are pockets of populations throughout. In the case of preterm or sick infants born in West Cumberland Hospital in Whitehaven where there are only level I neonatal facilities the closest level III unit is nearly 100 miles away. One of the major concerns expressed by people unfamiliar with a collaborative approach to perinatal care was whether outcomes would vary according to the distance from centres of perinatal expertise. In particular would outcomes be worse in hospital that did not offer long-term intensive care.

Figure 27: Mortality rates of infants <32 weeks gestation booked for delivery and admitted to special care baby units in the former Northern region 1998-99



Error bars represent 95% confidence intervals

Figure 28: Kaplan-Meier plot of survival among infants <32 weeks gestation admitted to special care baby units in the former Northern region 1998-99.

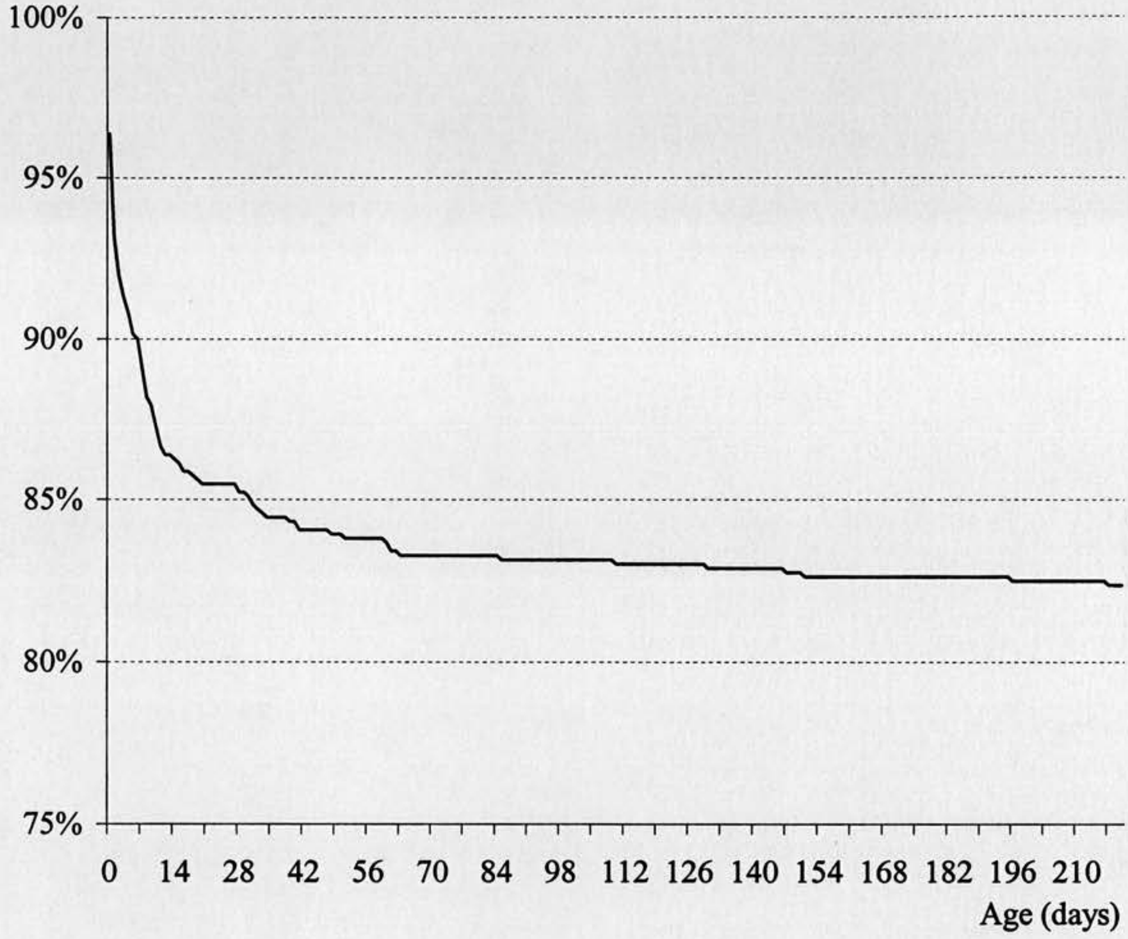


Table 36: Respiratory support in infants <32 weeks gestation admitted to the special care baby units in the former Northern region 1998-99.

No. of infants with:	
Any respiratory support	615 (79.8%)
Period of positive ventilation	506 (65.6%)
Period of CPAP	433 (56.2%)
No respiratory support	156 (20.2%)

No. of infants:	
Both positive pressure ventilation and CPAP	324 (42.0%)
Positive pressure ventilation only:	182 (23.6%)
CPAP only	109 (14.1%)

Total number days of:	
Positive pressure ventilation	5785
CPAP	4292
Either mode of respiratory support	10077

Average number days (per infant) of:	
Positive pressure ventilation	7.5
CPAP	5.6
Either mode of respiratory support	13.1

The biggest problem in trying to determine whether place of birth affects mortality is that case selection greatly affects the results. This can be seen in a simple comparison between a group of infants booked and born in hospitals offering level III neonatal intensive care compared to those booked in a hospital with level I facilities and undergoing postnatal transfer. Using the data from 1998-99 it would appear that mortality is greater in the postnatally transferred group of infants (20.7% versus 17.9%). The significance of case-selection is highlighted by the differences in gestation and illness severity between the two groups. Postnatally transferred infants are more immature (28.1 weeks versus 28.5 weeks, $p<0.05$) and have higher CRIB scores (mean score 6.1 versus 3.6, $p<0.0001$).

To overcome selection bias it is necessary to consider the whole population. Only infants booked for antenatal care and delivered in one of the region's hospitals were included in this analysis. To begin with the infants were divided firstly by level of care offered in their booking hospital (level I or level III). This population is still subject to selection bias to some extent in that the women booking in the west of the region would not reasonably be able to attend perinatal services in any of the four level III units.

The gestation (28.7 ± 2.1 weeks in level I versus 28.5 ± 2.2 weeks in level III), birthweights (1253 ± 368grams versus 1228 ± 381grams) and CRIB scores (4.2 ± 4.7 versus 3.6 ± 4.5) of infants were similar irrespective of the place of booking. Pre-discharge mortality by gestation and by level of care offered at the booking hospital is shown in Figure 29. There is no statistical difference between the two groups at any gestation.

To look more closely at immediate perinatal care infants were also subdivided to three groups according to place of delivery and immediate postnatal course;

- Booked and born in hospital with level III neonatal facilities
- Booked hospital with level I facilities but transferred antenatally to level III
- Booked and born in a unit with level I facilities, the sickest of these infants were transferred postnatally

Although the infants transferred antenatally were smaller at birth reflecting antenatal detection of growth retardation (1167g versus 1331g in the level I infants and 1227g in the level III infants); gestation and CRIB scores were similar in the three groups. Additionally there was no difference in pre-discharge mortality at any gestation (Figure 30).

Figure 29: Mortality (+/- 95% CI) by gestation according to place of booking within the former Northern region 1998-99

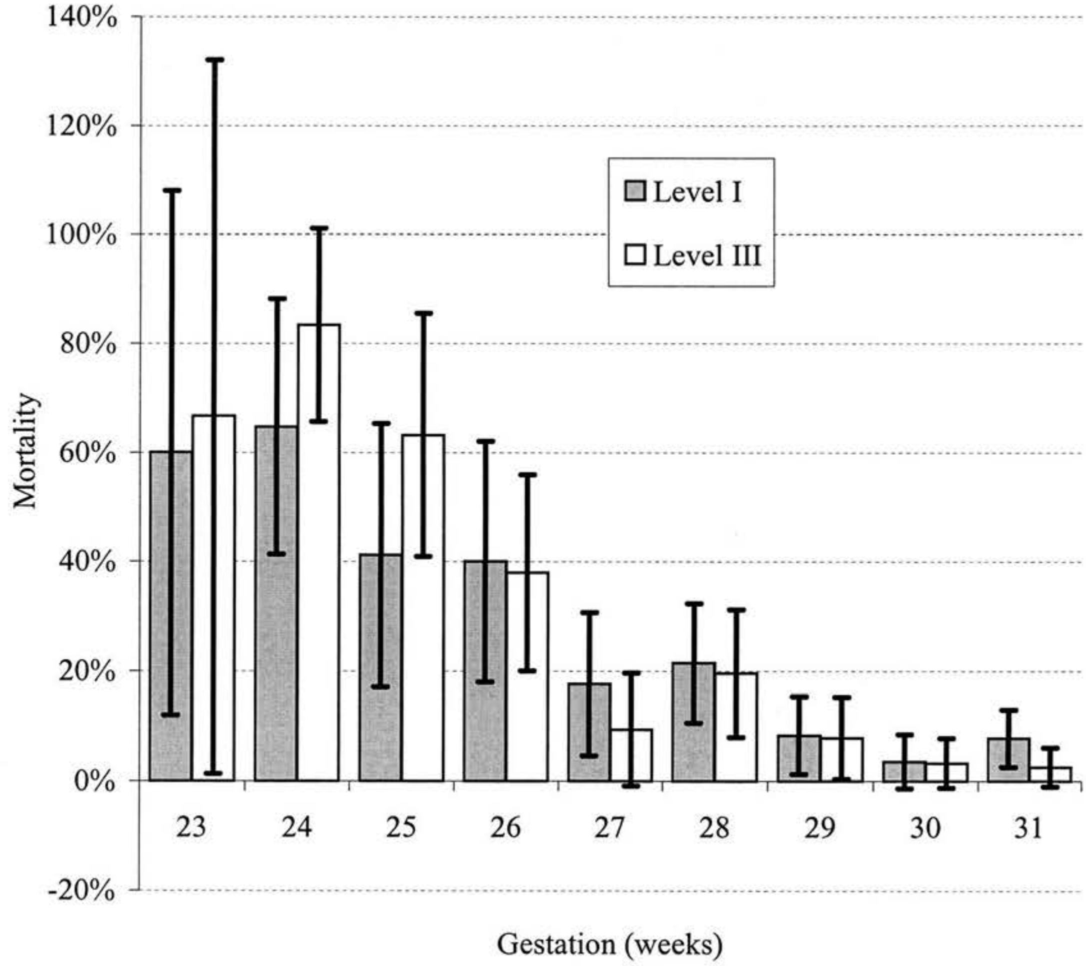
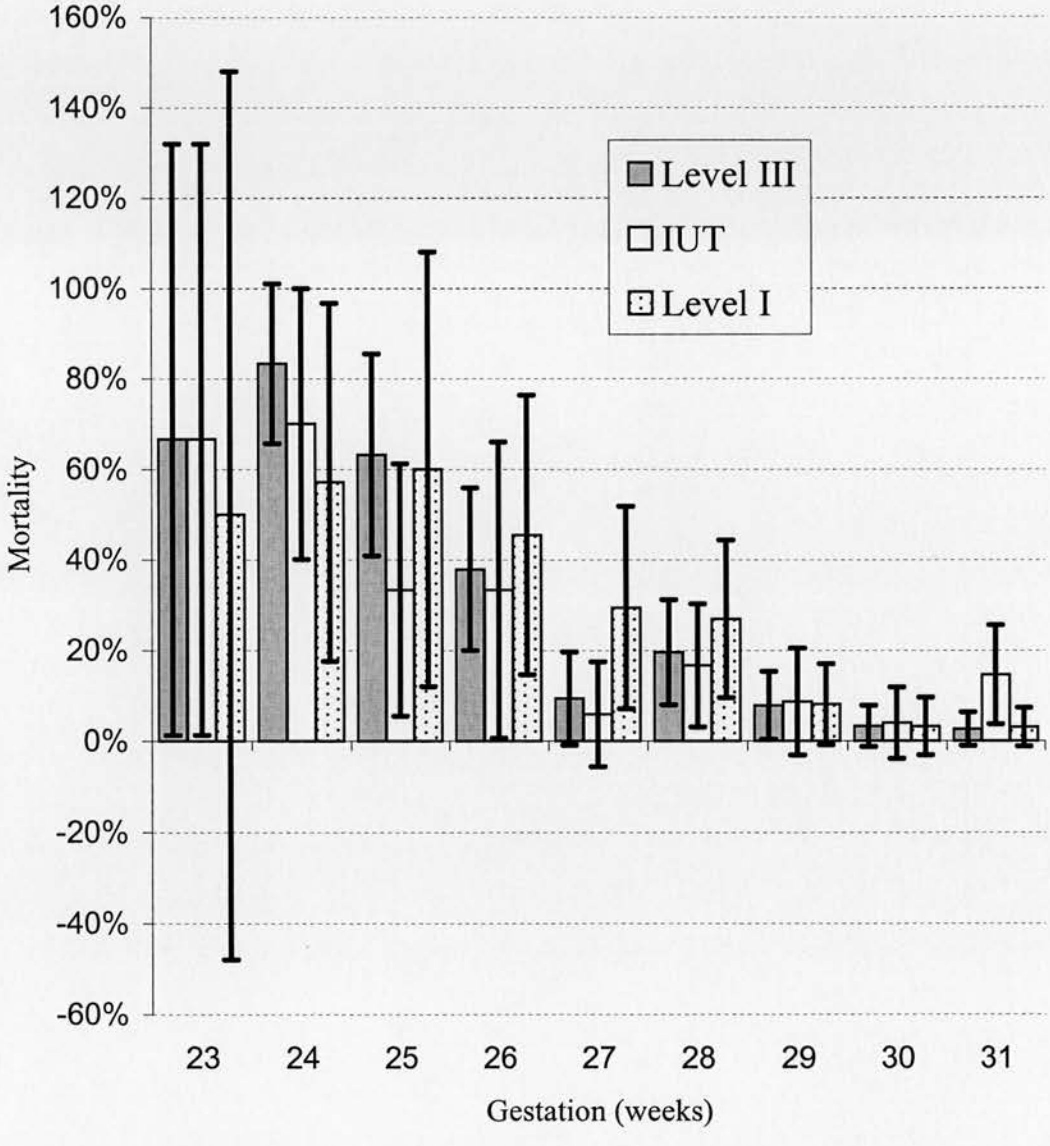


Figure 30: Mortality (+/- 95% CI) by gestation according to transfer and place of birth within the former Northern region 1998-99

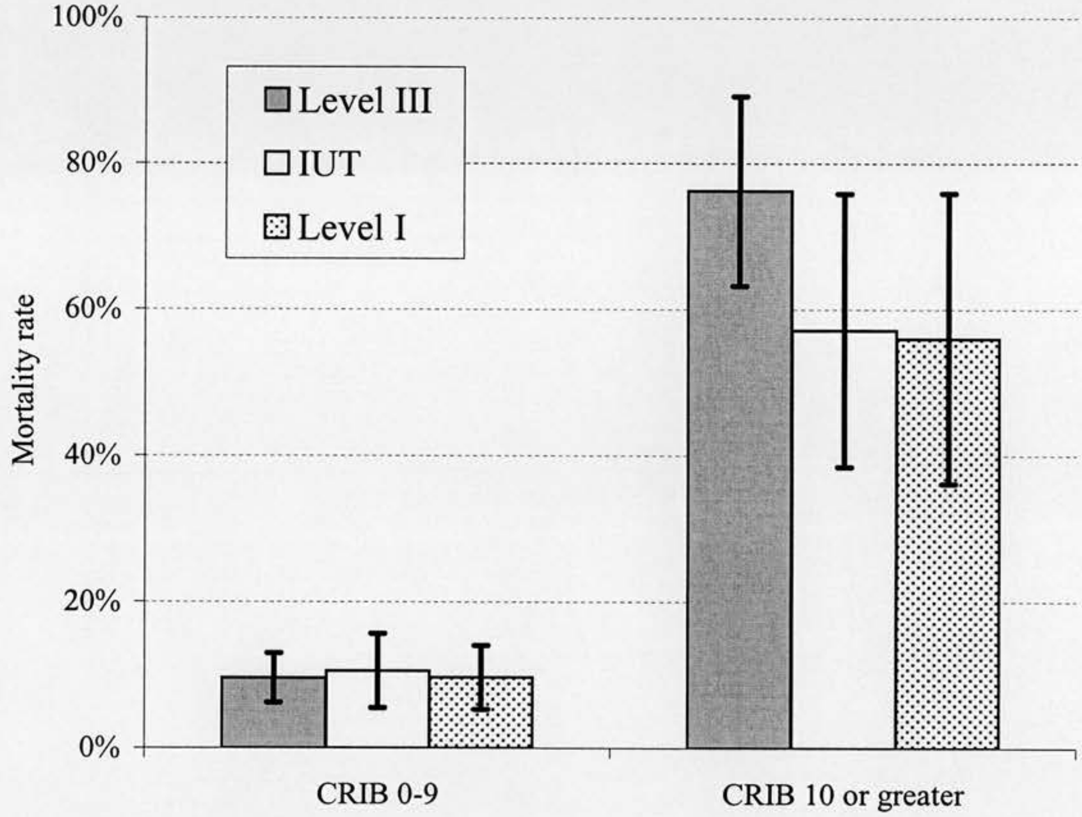


One argument against centralised provision of neonatal care is that sicker infants born in units without long-term neonatal intensive care might have a higher mortality than if they had been born in a unit with these facilities. Evidence suggests that in order to maintain their skills medical and nursing staff require a minimum amount of exposure to sick preterm infants and that the number of deliveries in the smaller level I units are insufficient to allow this.

To examine this argument all the infants in the three groups previous analysis were further subdivided into those with a CRIB score ≤ 10, and those with a CRIB score >10. This cut-off was selected because data (The International Neonatal Network 1993) suggests that infants with CRIB scores >10 have mortality in excess of 50%. There were no differences between the mortality rates of the three groups in infants with low CRIB scores, but there was an apparent increase in mortality in the mortality of infants booked and born in level III hospitals when they have the higher CRIB scores (Figure 31).

This result does not achieve statistical significance, and the apparent difference may be due to the small numbers of infants in these groups. However another reason may be that the provision of perinatal care in the Northern region with collaboration between units, an integrated perinatal transfer service and a high standard of short term intensive care in the level I units ensures that all infants receive the optimum management irrespective of their hospital of booking or birth.

Figure 31: Mortality by CRIB score and place of birth:
all infants <32 weeks gestation in the Northern region 1998-99



10.5 The implications of the Curosurf and ALEC trial for the neonatal services in the former Northern region

Using data from the survey outlined above and data from the study comparing ***Curosurf*** and ***ALEC*** it is possible to estimate the impact of a wholesale change from one surfactant to the other might have. Prior to the study between ***Curosurf*** and ***ALEC*** in the previous chapter the type of surfactant used was determined largely by cost and unit choice. The RVI and all the level I units used ***ALEC*** almost exclusively, Sunderland used ***Survanta*** in infants <29 weeks and North Tees and South Cleveland used ***Curosurf***.

If we restrict the analysis to those gestations in the study (25–29 weeks) and only those infants both booked and born in the region we can assess what might happen if either only ***ALEC*** or only ***Curosurf*** were used exclusively.

During the two year period there were a total of 371 infants of 25-29 weeks gestation born and admitted to one of the neonatal units, of which 317 were ventilated and received a variety of surfactants. Demographics of these groups, with the ***Curosurf*** and ***ALEC*** arms for comparison, are shown in Table 37. Mortality among ventilated infants of 25-29 weeks gestation in the region with a variety of surfactants was 24.0%.

As shown in the last chapter, ***Curosurf*** significantly reduced pre-discharge mortality compared to ***ALEC***. Thus if the trial results were reproduced among a region-wide cohort of infants of 25-29 weeks gestation then among the 158 ventilated infants per year there would be 109 survivors if ***ALEC*** was used as the sole surfactant in the region (i.e mortality would increase by a factor of 1.3 [= mortality rate in ***ALEC*** arm of trial / region mortality]) or 136 if was ***Curosurf*** (similarly mortality is altered by a factor of 0.6 [= mortality rate in ***Curosurf*** arm of trial / region mortality]).

Thus if ***Curosurf*** was exclusively used the patterns of care and the costs would change because most deaths occur early; although ***Curosurf***-treated infants on average spend less time in high dependency care, the additional survivors would spend longer in low dependency care thus consuming more resources. These additional costs would have to be met by the healthcare providers and purchasers.

Table 37: Demographics of the regional cohort of infants of 25-29 weeks gestation. Demographics of infants enrolled in the ***Curosurf*** and ***ALEC*** trial presented for comparison.

	All infants (n = 371)	Ventilated infants (n=317)	Curosurf group (n=99)	ALEC group (n=100)
Gestation (mean ± 1SD)	27.5 ± 1.3 weeks	27.4 ± 1.3 weeks	27.5 ± 1.4 weeks	27.3 ± 1.4 weeks
Birth weight (mean ± 1SD)	1085 ± 261 grams	1058 ± 254 grams	1027 ± 273 grams	989 ± 286 grams
No. ventilated (%)	317 (85.4%)	100%	96 (96.7%)	94 (94%)
Mortality (%)	78 (21.0%)	76 (24.0%)	14 (14.1%)	31 (31.0%)
Respiratory support				
Duration of positive pressure ventilation	9.8 ± 14.6 days	11.4 ± 15.2 days	12.3 ± 18.4 days	15.3 ± 22.8 days
No. days of CPAP	8.9 ± 13.4 days	9.9 ± 14.1 days	6.2 ± 11.7 days	6.6 ± 15.0 days

Extrapolating to include the whole cohort of infants <32 weeks gestation and if the differential in survival rates between the two surfactants was sustained outside the gestation range in the study: We would only be able to affect mortality in those infants who were intubated, ventilated and received surfactant. There were 468 infants booked, born and admitted within the region that required ventilation during the 2 years studied. The mortality rate in these infants was 26.1%. With the inclusion of more immature infants, mortality in an ***ALEC*** treated arm might be expected to increase to 33.9% (= 26.1% x factor of 1.3 as above), and if ***Curosurf*** was used the mortality rate might be 15.7% (= 26.1% x factor of 0.6 as above). This makes the assumption that the differential in mortality seen in the 25-29 week gestation infants is maintained in the more immature 23-24 week infants and the more mature 30-31 week infants.

Annually this equates to 234 ventilated infants with a projected 155 survivors if ***ALEC*** were used or 197 survivors if ***Curosurf*** were used. Therefore if ***Curosurf*** were used in preference to ***ALEC*** there would be an additional 42 infants surviving to discharge. Compared to the present cohort when a mixture of surfactant types were used and mortality in the ventilated infants was 26.1% (no. of surviving infants = 173), if there was a wholesale region-wide change to ***Curosurf***, an additional 24 infants might theoretically survive to discharge annually.

Assuming there is the additional capacity within the region's neonatal intensive care units to absorb these extra survivors, there are also the additional (marginal) costs to be found. Using data from the trial where average duration of low dependency days was 45.6 days for ***Curosurf***-treated infants (chapter 9), these additional survivors would theoretically cost the region an extra £122,573 in low depencency care. The increase in the low dependency costs would be offset by a slight reduction in high dependency costs but another problem would be extra capacity to cope with these survivors.

This does not take into account the additional burden of morbidity from chronic lung disease. There were no differences in the rates of CLD at 36 weeks in the study comparing ***Curosurf*** and ***ALEC*** and with the higher proportion of survivors after treatment with ***Curosurf*** there would be an increase in the absolute numbers of infants with CLD.

10.6 Conclusion

This survey has concentrated on a group of infants that consume a large proportion of the resources of the perinatal services in the former Northern region. This is also the group of infants that are at greatest risk of surfactant deficient lung disease (that is RDS) and its complications. Previous data from the former Northern region has shown that RDS does occur in more mature infants but that it is much less common and less severe as the infant approached term gestation (Madar *et al* 1999).

Current provision of neonatal intensive care within the region appears to be efficient. The "centralised" provision does however mean that transfers within the region are inevitable. Some would argue that any perinatal transfers between units offering level III units are inappropriate (Parnamum *et al* 2000). In our region these account for 25% of in utero transfers (Fenton *et al* 2000), and 6.4% of the postnatal transfers in the <32 week group. Mortality in the years 1998-99 in our region was not different from other studies that have looked either at mortality in an earlier cohort (Tin *et al* 1997) or in other healthcare regions (Draper *et al* 1999, Costeloe *et al* 2000).

Despite the geographical distances involved, infants born at gestations <32 weeks do not have a higher mortality rate than if they had been booked at level III units. Some of this is due to the anticipation of obstetricians in transferring "at risk" pregnancies antenatally, but importantly even those infants that are born in the hospitals with level I facilities only do not have a higher mortality than those booked and born in hospitals with level III facilities. Moreover even when these infants are sick (CRIB scores >10), there is no significant difference in mortality. Clearly mortality is not the only outcome and this does not take into account morbidity, which others have found to be increased in postnatally transferred infants (Halliday *et al* 1986). But these data do answer one of the criticisms levelled at the ***Curosurf*** and ***ALEC*** trial that infants recruited from level I units might affect overall outcomes (Morley 2000).

Infants born at gestations <32 weeks consume a large amount of resources, and 98% of the respiratory intensive care in this group is carried out in one of the level III units. Therapies that influence respiratory outcomes could greatly affect the workload in these units.

The final section of the results postulates how a region-wide change to ***Curosurf*** would affect resources. Up until the time of the trial the type of surfactant used was determined largely by cost, but was also influenced by the choices of clinicians in these units. If the projections of an additional 25 surviving infants per year are accurate, the region would have the capacity to absorb the extra workload but at the cost of reducing extra-regional intake. The additional survivors would therefore have a double impact – costing an additional £122,573 in low dependency care per year and reducing the monies earned from extra-contractual referrals. This clearly illustrates the impact that surfactant therapy has on health service resources even though surfactant treatment itself is only administered on a limited number of occasions.

Chapter 11

Summary

Respiratory distress syndrome (RDS) affects a large number of infants annually. Whilst understanding of the disease and its sequelae has improved over the years it is clear that many questions remain unanswered. Management of infants "at risk" of RDS is resource intensive and costly but nonetheless compared to treatments for other life-threatening diseases is cost-effective (Walti & Monset-Couchard 1998).

Firstly positive pressure ventilation, then antenatal steroids and more recently postnatal surfactant have greatly improved mortality in preterm infants. However these therapies should not be viewed in isolation but rather as part of the whole "package" of improving perinatal care.

This thesis has concentrated on exogenous surfactant therapy and looked at its development as a therapeutic agent. Since the first report of successful exogenous surfactant therapy (Fujiwara *et al* 1980) there has been a large amount of evidence from controlled trials showed that administration of surfactants is effective, such that further placebo-controlled trials of surfactant would be considered unethical. There remain unanswered questions; in particular how much, when and how surfactant should be administered, whether synthetic surfactants that were compositionally very simple could be as effective as surfactants of natural origin.

Evidence from the medical literature and reviewed in this thesis suggests that surfactant should be given as early as possible, that multiple rather than single doses should be used and that currently bolus intra-tracheal administration is the only effective method of administration. Evidence from *in vitro* studies and now studies in neonatal populations support the use of the animal-derived products over the currently available synthetic protein-free surfactants. The surfactant proteins SP-B and SP-C that are retained in the manufacturing processes of most animal-derived exogenous surfactants would appear to be the main reason for the difference in clinical efficacy between synthetic and animal-derived surfactants, although differences in phospholipids may also be important. Synthetic surfactants are currently being developed that contain synthetic analogues of both SP-B and SP-C but they are not widely available as yet.

Neonatal medicine is a low-volume high-cost specialty. A large proportion of the resources of any neonatal unit are directed to caring for infants born <32 weeks gestation who have surfactant deficiency lung disease. The final part of this thesis looked at the organisation of perinatal care in the former Northern health region of England which operates a centralised system of specialised services (fetal medicine, neonatal intensive care, neonatal and paediatric surgery and cardiology) in four large hospitals, but with district general hospitals delivering non-specialised management.

Despite the centralisation of specialist care in the region, mortality among infants born before 32 weeks gestation is the same whether the mother booked at a hospital with level I or level III neonatal intensive care facilities. This has been achieved through collaboration between the units and a well-organised transfer service.

The study of the two surfactants that was central to this thesis has resulted in a region-wide (and arguably a national) change in practice. The effects of this change in practice have yet to become evident, but evidence put forward in the final chapter suggests that this change could have important implications for the provision of neonatal intensive care in the region both financially and in terms of workload.

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APPENDIX 1

Report of the Data and Safety Monitoring Committee

The following is the report of the findings of the Data & Safety Monitoring Committee for the randomised trial between ***Curosurf*** and ***ALEC*** (CandA trial). Permission to include this was given by Dr Janet Rennie, Chair of the Committee.

Data & Safety Monitoring Committee, CandA trial
Royal Society of Medicine, Wimpole Street, London
Tuesday December 14th 1999 15.00 to 16.30

Present:

Dr Janet Rennie	Chairman, Senior Lecturer in Neonatal Medicine, King's College Hospital, London
Professor Neil Marlow	Professor of Neonatal Medicine, Nottingham
Professor Tim Cole	Professor of Medical Statistics, Institute of Child Health, London
Dr Heather Glen	Fellow of New Hall College, Cambridge, Faculty of English, University of Cambridge Mother with experience of premature babies

Advice by telephone from:

Professor Henry Halliday	Professor of Neonatal Medicine, Belfast
Professor John Matthews	Statistician to CandA, Professor of Medical Statistics, Newcastle

Meeting note:

Dr Rennie reminded the group of the aim of the trial, which was to compare two surfactants, one natural and one artificial.

The primary aim of the study was to compare the number of days spent in high dependency care, with 482 infants required to demonstrate a 25% difference in the expected median of 6 days of high dependency care.

No difference in mortality was expected, although a meta-analysis of Survanta v Exosurf had shown an odds ratio for mortality of 0.8 in favour of natural surfactant, so mortality was a secondary outcome measure in the CandA trial.

Other secondary outcomes were: chronic lung disease; number of ventilator days; pulmonary haemorrhage; pneumothorax; seizures; retinopathy of prematurity; patent ductus arteriosus; abnormal cranial ultrasound; necrotising enterocolitis.

There were no stopping rules but an interim analysis at the half-way point had always been planned. The DSMC was asked to meet at 6 monthly intervals, but recruitment was slow. The slow recruitment led to the date for the interim analysis being set for December. Although rather less than half the total number was reached by then it was decided to go ahead because the trial had been running for 20 months.

The results of an interim analysis prepared by Professor Matthews were presented and discussed by Professor Cole.

The following centres had participated in the trial, which began in April 1998:

Liverpool (Women's and Fazakerley)

Newcastle

Middlesbrough (S Cleveland hospital)

Stockton-on-Tees

Sunderland

Leicester and Leeds (2 babies each, late entrants)

In total 337 babies had been eligible; 207 had been randomised. The reasons for non-enrolment included lack of time to gain consent, a request for consent felt to be inappropriate, parental refusal, no need for ventilation after prenatal consent had been obtained. Recruitment was better in Liverpool than in the other centres but there was no major difference between centres in the reasons given, so the enrolment process appeared valid. S Cleveland had randomised only 16 of 51 eligible babies with 3 post-enrolment exclusions which gave rise to some discussion but was not felt to invalidate the results.

207 babies of 25-29 weeks gestation were randomised.

16 were withdrawn;

randomised before birth but not born, or born stillborn;	7
randomised before birth not intubated,	2
wrong gestation	4
malformation detected postnatally (TOF)	1
problems with randomisation	1
other	1

Again the trial committee felt that this was an acceptable number of post-randomisation exclusions considering the difficult nature of neonatal trials, and that the analysis and randomisation process remained valid.

The group decided to tackle mortality first; although this was a secondary endpoint clearly this was the major outcome of interest in any trial. The Committee considered the results without knowledge of the randomisation code. The expected mortality was about 20%.

	Surfactant 1	Surfactant 2
Number enrolled	96	93
Discharged alive	74	51
Dead	13	30
Still in hospital	9	12

Hazard ratio 2.66 with 95% confidence interval 1.36 to 5.22 ($P < 0.004$)

Everyone on the committee expressed surprise and disquiet about this unexpected result. Clearly a difference in mortality had not been expected, and those enrolling babies had been in equipoise about the outcome. We all felt that if there were any possibility that this was a genuine result then it would be difficult, if not impossible, for the trial to continue. Even if the mortality was equal in the two arms for the remaining half of the trial, with no "extra" deaths on surfactant 2, then the outcome would still be worse for this group overall, and time would be lost in drawing the attention of other clinicians to the result.

We discussed the degree of excess mortality that we considered clinically important, and certainly a difference of 10% was felt by us all to be important. A smaller difference would have been considered important had we been asked to state our prior prejudice.

The Kaplan-Meier survival "life table" curves were also strikingly different, with a cluster of deaths on surfactant 2 between 100 and 150 days.

The clinicians in the group wondered if the babies randomised to group 2 had done badly because of an excess of very small babies, or male babies, or multiples. We felt, in view of the importance of the question, that it was reasonable to telephone Professor Matthews and ask him to help with this. At this stage we did not know the code.

Professor Matthews reported back the following additional information:

	Surfactant 1 n=96	Surfactant 2 n=93
	33 girls: 64 boys	44 girls: 49 boys
Mean gestational age	27.4 weeks	27.2 weeks
25 weeks (number)	12	13
26 weeks	17	21
27 weeks	14	15
28 weeks	24	24
29 weeks	30	20

Information about singleton/multiple deliveries was not available.

The group remained concerned; there was no obvious excess in the number of very tiny babies allocated to surfactant 2 that could account for the excess mortality. Correcting the hazard ratio for sex resulted in an increased hazard ratio of 2.93 with 95% confidence interval 1.49 to 5.76 ($P < 0.002$).

On the primary outcome of time spent in high dependency care, there was no difference between the two groups of surviving babies.

Professor Matthews had provided the randomisation code in a sealed envelope. We decided to open it in order to consider the results together with the meta-analysis that showed that there was a disadvantage for artificial surfactant. The meta-analysis suggested that surfactant 2 would be ALEC but we recognised that an excess of pulmonary haemorrhages in the babies treated with Curosurf or some other unexpected complication might have equally severe effects.

The code showed that surfactant 2, the surfactant with excess mortality, was ALEC.

The committee was unanimous in deciding that our recommendation should be to stop the trial. This decision was not taken lightly, the committee were all aware of the serious implications of curtailing a scientific trial early. We were aware that further analysis may reveal the reason for the difference to be other than the trial treatment. However, having found such an important difference in the number of deaths between the groups, and having failed to explain it by any of the more usual and obvious confounders, we all felt that it was unethical to ask clinicians in contributing centres to continue to randomise babies. Randomising clinicians could no longer remain in equipoise regarding the two treatments on offer.

Dr Rennie conveyed the decision by telephone urgently to the two main centre co-ordinators, Dr Ben Shaw and Dr David Milligan. Dr Milligan offered to inform the other centres.

Janet M Rennie MA MD FRCP FRCPCH DCH

Consultant and Senior Lecturer in Neonatal Medicine

On behalf of the CandA DSMC, 14th December 1999

APPENDIX 2

Statement issued by Britannia Pharmaceuticals Ltd.

The following is the statement issued by Britannia Pharmaceuticals following publication of the results of the randomised trial between ***Curosurf*** and ***ALEC*** (CandA trial). Permission to include this was given by Mr Derek Woodcock, Technical Director, Britannia Pharmaceuticals Ltd.

19 April 2000

Voluntary Suspension of Marketing and Use of ALEC™ (pumactant)

A UK trial comparing the lung surfactant ALEC™ (pumactant) with another lung surfactant in Neonatal Respiratory Distress Syndrome (NRDS), has been prematurely terminated because of a higher observed mortality in the ALEC™ treated babies. The results of the study will be published in the Lancet this week.

The finding is unexpected in light of the previously published clinical trials and UK clinical experience with the product over the last eight years. When Britannia first became aware of these findings, the Medicines Control Agency (MCA) were immediately informed and close discussions followed.

Britannia consider that the results of the study need detailed consideration together with all other relevant data on the safety and efficacy of ALEC™. The company is continuing to work closely with all parties to clarify the situation as soon as possible.

While a detailed assessment is considered, Britannia has decided voluntarily to suspend the marketing and distribution of ALEC™ immediately, and to recommend that the product is not used until the implications of the trial are fully understood. All relevant healthcare personnel are being informed and stock can be returned for a refund.

Following a detailed review by the MCA and UK Committee on Safety of Medicines, Britannia will update relevant healthcare professionals on the place of ALEC™ in the treatment of NRDS.

For Further Information

Phone:	01737 773741
Fax:	01737 762672
E-mail:	alec.pumactant@forumgroup.co.uk
Website:	http://www.britannia-pharm.co.uk
Contacts:	Maxwell Noble (Deputy Managing Director), Derek Woodcock (Technical Director), Keith Davies (Technical Director)

APPENDIX 3

Data from the randomised comparative trial between poractant alfa (Curosurf) and pumactant (ALEC).

No	Centre	Surfact	Sex	Gest	BWt	Place of birth	Fetuses	Delivery	Reason delivery	Age 1st dose	AN steroids	Full course	Age at dicharge/death	Out to
1	Liverpool	Curosurf	F	29.1	1386	Liverpool	1	SVD	Spont. labour	Not treated	Yes	Yes	37	Home
2	Liverpool	Curosurf	M	25.6	718	Liverpool	1	SVD	Spont. labour	2	Yes	No	167	Home
3	Liverpool	ALEC	M	28.9	1378	Liverpool	1	Breech	Spont. labour	15	Yes	Yes	8	Died
4	Liverpool	ALEC	F	29.0	1020	Liverpool	1	Prelabour CS	Other	10	Yes	Yes	51	Home
5	Liverpool	Curosurf	F	25.3	724	Liverpool	1	SVD	Spont. labour	25	Yes	No	92	Home
6	Liverpool	Curosurf	F	25.9	664	Liverpool	1	Prelabour CS	Other	15	Yes	Yes	133	Home
7	Liverpool	ALEC	F	26.0	786	Liverpool	1	Prelabour CS	Other	11	Yes	Yes	80	Home
8	Liverpool	Curosurf	M	25.0	820	Liverpool	1	Breech	APH	2	Yes	No	123	Home
9	Liverpool	ALEC	M	29.4	1628	Liverpool	1	SVD	Spont. labour	25	No	No	39	Home
10	Liverpool	ALEC	F	26.0	718	Liverpool	1	Prelabour CS	Other	4	Yes	No	103	Home
11	Liverpool	Curosurf	M	26.0	530	Liverpool	1	Prelabour CS	PIH	5	Yes	Yes	3	Died
12	Liverpool	ALEC	F	28.4	1035	Liverpool	1	Prelabour CS	PIH	4	Yes	Yes	81	Home
13	Liverpool	Curosurf	M	29.0	1406	Liverpool	1	SVD	Spont. labour	10	Yes	Yes	45	Home
14	Liverpool	ALEC	F	29.0	1302	Liverpool	1	SVD	Spont. labour	Not treated	Yes	Yes	44	Home
15	Liverpool	ALEC	M	29.0	708	Liverpool	1	Prelabour CS	APH	17	Yes	Yes	113	Home
16	Liverpool	ALEC	F	27.4	1158	Liverpool	1	Breech	PROM	13	Yes	Yes	90	Home
17	Liverpool	ALEC	F	26.1	842	Liverpool	1	SVD	PROM	8	Yes	Yes	161	Home
18	Liverpool	Curosurf	M	28.6	685	Liverpool	2	Prelabour CS	IUGR	5	Yes	Yes	30	Died
19	Liverpool	Curosurf	M	28.6	1406	Liverpool	2	Prelabour CS	Other	100	Yes	Yes	48	Home
20	Liverpool	Curosurf	F	28.6	1152	Liverpool	1	SVD	PROM	5	Yes	No	79	Home
21	Liverpool	ALEC	F	27.0	548	Liverpool	1	Prelabour CS	PIH	35	Yes	Yes	123	Died
22	Liverpool	ALEC	F	28.4	825	Liverpool	1	Prelabour CS	IUGR	5	Yes	Yes	3	Died
23	Liverpool	Curosurf	M	28.6	842	Liverpool	1	Prelabour CS	PIH	12	Yes	Yes	81	Home
24	Liverpool	Curosurf	M	28.0	904	Liverpool	1	Prelabour CS	PIH	4	Yes	Yes	66	Home
25	Liverpool	ALEC	M	26.3	1070	Liverpool	2	SVD	Spont. labour	4	Yes	Yes	86	Home
26	Liverpool	ALEC	M	26.3	917	Liverpool	2	SVD	Spont. labour	6	Yes	Yes	2	Died
27	Liverpool	Curosurf	M	29.0	1390	Liverpool	1	SVD	Spont. labour	3	Yes	Yes	68	Home
28	Liverpool	Curosurf	M	29.4	635	Liverpool	1	Breech	Other	20	Yes	Yes	111	Home
29	Liverpool	ALEC	F	25.0	762	Liverpool	1	SVD	PROM	16	Yes	Yes	11	Died
30	Liverpool	ALEC	M	27.4	1126	Liverpool	2	SVD	Spont. labour	4	Yes	Yes	1	Died
31	Liverpool	Curosurf	M	27.0	1258	Liverpool	2	Breech	Spont. labour	3	Yes	Yes	57	Home
32	Liverpool	Curosurf	M	26.0	860	Liverpool	1	Prelabour CS	IUGR	12	Yes	Yes	129	Home
33	Liverpool	Curosurf	F	28.9	832	Liverpool	1	Prelabour CS	APH	7	Yes	No	52	Home
34	Liverpool	Curosurf	M	26.9	558	Liverpool	1	Prelabour CS	Other	7	Yes	Yes	372	Died

No	Centre	Surfact	Sex	Gest	BWt	Place of birth	Fetuses	Delivery	Reason delivery	Age 1st dose	AN steroids	Full course	Age at dicharge/death	Out to
35	Liverpool	ALEC	M	28.9	1470	Liverpool	1	Prelabour CS	PIH	6	Yes	Yes	44	Home
36	Liverpool	ALEC	M	27.7	952	Liverpool	1	SVD	PROM	10	Yes	Yes	69	Home
37	Liverpool	ALEC	F	28.7	1180	Liverpool	1	SVD	Spont. labour	30	Yes	Yes	67	Home
38	Liverpool	ALEC	M	26.0	704	Liverpool	1	Prelabour CS	PIH	6	Yes	Yes	107	Home
39	Liverpool	ALEC	F	29.6	1070	Liverpool	1	Prelabour CS	Other	7	Yes	Yes	47	Home
40	Liverpool	Curosurf	M	28.7	895	Liverpool	1	Prelabour CS	Other	46	Yes	Yes	101	Home
41	Liverpool	ALEC	M	29.6	734	Liverpool	2	Prelabour CS	Other	7	Yes	Yes	133	Died
42	Liverpool	Curosurf	M	29.6	910	Liverpool	2	Prelabour CS	Other	7	Yes	Yes	94	Home
43	Liverpool	Curosurf	M	29.0	865	Liverpool	1	Prelabour CS	PIH	3	Yes	Yes	48	Home
44	Liverpool	Curosurf	M	29.0	996	Liverpool	2	Prelabour CS	Other	9	Yes	Yes	50	Home
45	Liverpool	Curosurf	M	29.0	1490	Liverpool	2	Prelabour CS	Other	12	Yes	Yes	44	Home
46	Liverpool	ALEC	F	26.6	448	Liverpool	1	Prelabour CS	PIH	7	Yes	Yes	236	Home
47	Liverpool	ALEC	M	26.7	600	Liverpool	1	Prelabour CS	Other	5	Yes	Yes	143	Died
48	Liverpool	ALEC	F	29.9	1729	Liverpool	2	Prelabour CS	PIH	15	Yes	Yes	31	Home
49	Liverpool	ALEC	F	29.9	1116	Liverpool	2	Prelabour CS	PIH	15	Yes	Yes	59	Home
50	Liverpool	Curosurf	M	26.1	958	Liverpool	1	SVD	Spont. labour	5	Yes	No	11	Died
51	Liverpool	Curosurf	F	29.7	920	Liverpool	2	Prelabour CS	PIH	5	Yes	Yes	54	Home
52	Liverpool	ALEC	M	29.7	1750	Liverpool	2	Prelabour CS	PIH	8	Yes	Yes	39	Home
53	Liverpool	ALEC	M	25.1	859	Liverpool	1	SVD	PROM	3	Yes	Yes	8	Died
54	Liverpool	Curosurf	M	25.7	765	Liverpool	1	SVD	PROM	20	Yes	Yes	101	Home
55	Liverpool	Curosurf	F	26.9	911	Liverpool	1	SVD	APH	5	Yes	Yes	63	Home
56	Liverpool	Curosurf	M	26.0	982	Liverpool	2	SVD	Spont. labour	28	Yes	Yes	107	Home
57	Liverpool	Curosurf	M	26.0	1005	Liverpool	2	Breech	Spont. labour	7	Yes	Yes	107	Home
58	Liverpool	ALEC	M	28.3	692	Liverpool	1	Prelabour CS	Other	7	Yes	Yes	10	Died
59	Liverpool	Curosurf	M	28.4	990	Liverpool	1	Prelabour CS	PIH	10	Yes	Yes	46	Home
60	Liverpool	ALEC	M	27.3	734	Liverpool	1	Prelabour CS	PIH	5	Yes	Yes	3	Died
61	Liverpool	Curosurf	M	25.3	642	Liverpool	2	Prelabour CS	Other	25	Yes	Yes	120	Home
62	Liverpool	ALEC	F	26.4	728	Liverpool	1	SVD	PROM	10	Yes	Yes	1	Died
63	Liverpool	ALEC	M	27.0	722	Liverpool	1	Prelabour CS	PIH	5	Yes	Yes	125	Home
64	Liverpool	ALEC	M	29.7	1228	Liverpool	2	Prelabour CS	Other	6	Yes	Yes	71	Home
65	Liverpool	Curosurf	M	29.7	514	Liverpool	2	Prelabour CS	Other	5	Yes	Yes	3	Died
66	Liverpool	Curosurf	M	26.3	675	Liverpool	2	Prelabour CS	APH	8	Yes	Yes	108	Home
67	Liverpool	ALEC	F	26.3	845	Liverpool	2	Prelabour CS	APH	15	Yes	Yes	108	Home
68	Liverpool	Curosurf	F	26.1	850	Liverpool	1	Prelabour CS	APH	5	Yes	Yes	86	Home
69	Liverpool	ALEC	F	26.6	1115	Liverpool	1	SVD	PROM	10	Yes	Yes	92	Home
70	Liverpool	ALEC	M	29.3	674	Liverpool	1	Prelabour CS	IUGR	7	Yes	Yes	87	Home

No	Centre	Surfact	Sex	Gest	BWt	Place of birth	Fetuses	Delivery	Reason delivery	Age 1st dose	AN steroids	Full course	Age at dicharge/death	Out to
71	Liverpool	Curosurf	M	28.0	1158	Liverpool	1	SVD	Spont. labour	12	Yes	Yes	47	Home
72	Liverpool	ALEC	M	25.1	742	Liverpool	1	SVD	PROM	8	Yes	Yes	99	Home
73	Liverpool	Curosurf	M	29.7	1026	Liverpool	2	SVD	Spont. labour	12	Yes	Yes	92	Home
74	Liverpool	Curosurf	M	29.7	1260	Liverpool	2	SVD	Spont. labour	11	Yes	Yes	70	Home
75	Liverpool	ALEC	F	28.6	966	Liverpool	2	SVD	Spont. labour	12	Yes	No	77	Home
76	Liverpool	Curosurf	M	28.6	1130	Liverpool	2	SVD	Spont. labour	5	Yes	No	77	Home
77	Liverpool	Curosurf	F	28.3	1304	Liverpool	1	SVD	PROM	14	Yes	Yes	57	Home
78	Liverpool	ALEC	F	27.7	962	Liverpool	1	SVD	PROM	55	Yes	Yes	96	Home
79	Liverpool	ALEC	M	28.6	1278	Liverpool	1	SVD	Spont. labour	15	Yes	Yes	68	Home
80	Liverpool	Curosurf	F	26.7	718	Liverpool	1	Prelabour CS	PIH	10	Yes	Yes	73	Home
81	Liverpool	Curosurf	F	29.3	1200	Liverpool	1	CS in labour	Other	10	Yes	Yes	38	Home
82	Liverpool	ALEC	F	29.7	1414	Liverpool	1	Prelabour CS	Other	10	Yes	Yes	64	Home
83	Liverpool	ALEC	F	25.3	454	Liverpool	1	Prelabour CS	PIH	10	Yes	No	101	Home
84	Newcastle	Curosurf	F	25.3	750	Newcastle	1	Prelabour CS	APH	30	Yes	Yes	94	Home
85	Newcastle	ALEC	M	25.6	550	Newcastle	3	SVD	Spont. labour	64	Yes	Yes	110	Died
86	Newcastle	Curosurf	M	25.6	570	Newcastle	3	Instrumental	Spont. labour	32	Yes	Yes	28	Died
87	Newcastle	ALEC	M	25.6	750	Newcastle	3	SVD	Spont. labour	44	Yes	Yes	8	Died
88	Newcastle	Curosurf	M	29.9	1340	Newcastle	1	SVD	PROM	40	Yes	Yes	53	Home
89	Newcastle	ALEC	M	26.3	505	Newcastle	1	Prelabour CS	PIH	29	Yes	Yes	106	Home
90	Newcastle	ALEC	F	28.3	1180	Newcastle	1	SVD	PROM	143	Yes	Yes	52	Home
91	Newcastle	Curosurf	M	27.9	1235	Newcastle	1	SVD	PROM	34	Yes	Yes	69	Home
92	Newcastle	ALEC	M	28.1	1150	Newcastle	1	Instrumental	Spont. labour	21	Yes	No	48	Home
93	Newcastle	Curosurf	M	27.1	1070	Newcastle	1	Breech	Spont. labour	28	No	No	118	Home
94	Newcastle	ALEC	M	28.7	700	Newcastle	1	Breech	PROM	100	Yes	Yes	217	Died
95	Newcastle	Curosurf	M	27.1	900	Newcastle	1	Prelabour CS	APH	17	Yes	No	86	Home
96	Newcastle	ALEC	F	25.3	700	Newcastle	1	SVD	PROM	50	Yes	No	204	Home
97	Newcastle	ALEC	M	26.3	805	Newcastle	1	SVD	PROM	35	Yes	Yes	92	Home
98	Newcastle	Curosurf	M	29.9	1680	Newcastle	1	SVD	Spont. labour	169	No	No	41	Home
99	Newcastle	Curosurf	M	25.6	580	Ashington	1	Breech	Spont. labour	25	Yes	No	5	Died
100	Newcastle	ALEC	M	25.6	780	Newcastle	1	Breech	Spont. labour	25	Yes	No	147	Died
101	Newcastle	Curosurf	F	27.1	1155	Newcastle	1	SVD	Spont. labour	40	Yes	Yes	79	Home
102	Newcastle	ALEC	F	28.9	1050	Newcastle	2	SVD	PROM	45	Yes	Yes	74	Home
103	Newcastle	Curosurf	F	26.1	800	Newcastle	2	SVD	Other	17	Yes	Yes	91	Home
104	Newcastle	ALEC	M	26.1	880	Newcastle	2	SVD	Other	20	Yes	Yes	1	Died
105	Newcastle	Curosurf	F	27.4	1055	Newcastle	1	SVD	PROM	62	Yes	Yes	75	Home
106	Newcastle	ALEC	F	28.1	1195	Dryburn	1	SVD	Spont. labour	18	Yes	No	52	Home

No	Centre	Surfact	Sex	Gest	BWt	Place of birth	Fetuses	Delivery	Reason delivery	Age 1st dose	AN steroids	Full course	Age at dicharge/death	Out to
107	Newcastle	Curosurf	F	26.0	620	Newcastle	1	Prelabour CS	PIH	55	Yes	Yes	3	Died
108	Newcastle	ALEC	M	26.0	1110	Newcastle	1	SVD	PROM	35	Yes	Yes	76	Home
109	Newcastle	Curosurf	F	26.0	700	Newcastle	1	CS in labour	PROM	38	Yes	Yes	152	Home
110	Newcastle	Curosurf	M	27.3	1040	Newcastle	2	CS in labour	Spont. labour	36	Yes	Yes	83	Home
111	Newcastle	ALEC	M	27.3	960	Newcastle	2	CS in labour	Spont. labour	49	Yes	Yes	83	Home
112	Newcastle	ALEC	F	29.4	1485	Newcastle	1	SVD	PROM	56	Yes	Yes	45	Home
113	Newcastle	Curosurf	M	27.9	1255	Newcastle	1	SVD	PROM	57	Yes	No	57	Home
114	Newcastle	Curosurf	M	25.4	965	Newcastle	1	Breech	Spont. labour	41	Yes	Yes	10	Died
115	Newcastle	ALEC	M	26.4	870	Newcastle	1	SVD	Spont. labour	28	Yes	Yes	168	Home
116	Newcastle	Curosurf	M	29.1	1330	Ashington	2	SVD	Spont. labour	84	Yes	No	69	Home
117	Newcastle	Curosurf	F	29.1	1495	Ashington	2	SVD	Spont. labour	117	Yes	No	69	Home
118	Newcastle	ALEC	M	28.7	1370	Newcastle	2	CS in labour	PROM	43	Yes	Yes	2	Died
119	Newcastle	Curosurf	M	29.6	630	Newcastle	1	Prelabour CS	Other	18	Yes	Yes	176	Home
120	Newcastle	ALEC	F	29.7	865	Newcastle	1	Prelabour CS	Other	23	Yes	Yes	7	Died
121	Newcastle	ALEC	F	25.6	670	Newcastle	1	SVD	PROM	31	Yes	Yes	89	Home
122	Newcastle	Curosurf	M	29.0	990	Newcastle	1	Prelabour CS	PIH	44	Yes	Yes	72	Home
123	Newcastle	ALEC	M	28.6	1220	Newcastle	2	Breech	PROM	8	Yes	Yes	8	Died
124	Newcastle	Curosurf	F	26.9	1340	Newcastle	1	Breech	Spont. labour	23	Yes	Yes	80	Home
125	Newcastle	ALEC	F	27.6	870	Newcastle	1	Prelabour CS	APH	47	Yes	No	100	Home
126	Newcastle	ALEC	M	26.0	780	Newcastle	1	Prelabour CS	PROM	89	Yes	Yes	136	Home
127	Newcastle	ALEC	F	29.3	680	Dryburn	1	Prelabour CS	IUGR	65	No	No	69	Home
128	Newcastle	Curosurf	M	27.3	1360	Newcastle	1	Prelabour CS	APH	20	Yes	No	67	Home
129	Newcastle	ALEC	M	29.1	1049	Whitehaven	2	SVD	Spont. labour	162	No	No	8	Died
130	Newcastle	Curosurf	M	29.1	1100	Whitehaven	2	Breech	Spont. labour	60	No	No	5	Died
131	Sunderland	ALEC	F	28.4	1020	Sunderland	1	Prelabour CS	PROM	4	Yes	Yes	65	Home
132	Sunderland	Curosurf	M	28.4	995	Sunderland	1	Prelabour CS	PIH	3	Yes	No	73	Home
133	Sunderland	ALEC	F	25.1	910	Sunderland	1	Breech	PROM	7	No	No	1	Died
134	Sunderland	Curosurf	M	28.4	1220	Sunderland	2	CS in labour	PROM	13	Yes	No	11	Died
135	Sunderland	Curosurf	M	28.4	1135	Sunderland	2	CS in labour	PROM	1	Yes	No	73	Home
136	Sunderland	ALEC	F	29.9	1385	Sunderland	2	CS in labour	Spont. labour	20	Yes	No	43	Home
137	Sunderland	ALEC	F	29.9	1280	Sunderland	2	CS in labour	Spont. labour	19	Yes	No	43	Home
138	Sunderland	Curosurf	F	28.9	1185	Sunderland	1	SVD	Spont. labour	55	Yes	Yes	54	Home
139	Sunderland	Curosurf	F	29.4	1320	Sunderland	1	Prelabour CS	PROM	20	Yes	Yes	62	Home
140	Sunderland	Curosurf	F	27.7	890	Sunderland	1	SVD	IUGR	40	Yes	Yes	86	Home
141	Sunderland	ALEC	M	28.4	1355	Sunderland	1	Instrumental	PROM	5	Yes	Yes	52	Home
142	Sunderland	Curosurf	F	25.1	585	Sunderland	1	Prelabour CS	Other	3	No	No	7	Died

No	Centre	Surfact	Sex	Gest	BWt	Place of birth	Fetuses	Delivery	Reason delivery	Age 1st dose	AN steroids	Full course	Age at dicharge/death	Out to
143	Sunderland	Curosurf	M	25.9	765	Sunderland	1	SVD	APH	104	Yes	Yes	172	Home
144	Sunderland	ALEC	M	28.3	775	Sunderland	1	Prelabour CS	APH	4	No	No	85	Home
145	Sunderland	ALEC	M	29.9	820	Sunderland	1	Prelabour CS	PIH	12	Yes	No	47	Home
146	Sunderland	Curosurf	M	26.0	765	Sunderland	2	Prelabour CS	PROM	8	Yes	Yes	59	Died
147	Sunderland	ALEC	M	26.0	910	Sunderland	2	Prelabour CS	PROM	2	Yes	Yes	1	Died
148	Sunderland	ALEC	F	25.3	690	Sunderland	1	SVD	PROM	7	Yes	Yes	0	Died
149	Sunderland	ALEC	M	28.9	720	Sunderland	1	Prelabour CS	PIH	4	Yes	Yes	10	Died
150	Sunderland	ALEC	M	27.3	895	Sunderland	2	CS in labour	Spont. labour	12	Yes	No	103	Home
151	Sunderland	Curosurf	F	29.4	1280	Sunderland	2	Prelabour CS	APH	49	No	No	48	Home
152	Sunderland	Curosurf	F	29.4	1090	Sunderland	2	Prelabour CS	APH	107	No	No	48	Home
153	Sunderland	Curosurf	M	28.0	920	Sunderland	1	Prelabour CS	PIH	10	Yes	No	91	Home
154	Sunderland	ALEC	F	25.6	690	Sunderland	1	CS in labour	PROM	5	Yes	Yes	10	Died
155	Sunderland	Curosurf	M	29.4	1515	Sunderland	1	Prelabour CS	APH	840	Yes	Yes	50	Home
156	Sunderland	ALEC	M	29.9	1385	Sunderland	1	Prelabour CS	PIH	Not treated	Yes	Yes	30	Home
157	Sunderland	ALEC	M	27.9	1190	Sunderland	1	Instrumental	Spont. labour	Not treated	Yes	No	50	Home
158	Sunderland	ALEC	M	26.1	735	Sunderland	1	Prelabour CS	APH	90	Yes	Yes	7	Died
159	North Tees	Curosurf	F	29.9	820	North Tees	1	CS in labour	PIH	35	Yes	No	69	Home
160	North Tees	ALEC	M	27.6	1070	North Tees	1	Prelabour CS	APH	10	Yes	No	81	Home
161	North Tees	Curosurf	F	28.6	1310	North Tees	2	SVD	Spont. labour	Not treated	Yes	Yes	56	Home
162	North Tees	Curosurf	F	28.6	1410	North Tees	2	Breech	Spont. labour	695	Yes	Yes	56	Home
163	North Tees	Curosurf	M	29.3	1180	North Tees	1	SVD	Spont. labour	56	Yes	Yes	63	Home
164	North Tees	ALEC	F	29.6	1390	North Tees	1	Prelabour CS	PIH	31	Yes	Yes	37	Home
165	North Tees	ALEC	M	28.6	790	North Tees	1	Prelabour CS	PIH	19	Yes	Yes	161	Home
166	North Tees	Curosurf	M	28.0	840	North Tees	1	Prelabour CS	PIH	35	Yes	Yes	4	Died
167	North Tees	Curosurf	M	26.4	1020	North Tees	1	CS in labour	Other	41	Yes	No	95	Home
168	North Tees	ALEC	F	28.7	1140	North Tees	1	Prelabour CS	PIH	73	Yes	Yes	50	Home
169	North Tees	Curosurf	F	29.3	1100	North Tees	1	Prelabour CS	PROM	90	Yes	No	60	Home
170	North Tees	Curosurf	F	29.6	1090	North Tees	2	SVD	PROM	16	Yes	Yes	49	Home
171	North Tees	ALEC	F	29.6	930	North Tees	2	Breech	PROM	6	Yes	Yes	0	Died
172	North Tees	ALEC	M	25.4	850	Hartlepool	1	SVD	Spont. labour	22	Yes	Yes	147	Home
173	North Tees	Curosurf	M	26.3	890	Hartlepool	1	Breech	PROM	75	Yes	Yes	113	Home
174	North Tees	ALEC	F	27.3	1040	Hartlepool	1	Breech	Spont. labour	50	No	No	2	Died
175	North Tees	Curosurf	M	28.7	1340	North Tees	1	CS in labour	PROM	8	Yes	Yes	56	Home
176	North Tees	ALEC	F	26.6	760	North Tees	1	Prelabour CS	APH	121	Yes	Yes	11	Died
177	North Tees	ALEC	M	28.6	1350	North Tees	1	SVD	Spont. labour	92	Yes	Yes	54	Home
178	S Cleveland	Curosurf	M	27.9	1210	S Cleveland	1	SVD	Spont. labour	Not treated	Yes	No	52	Home

No	Centre	Surfact	Sex	Gest	BWt	Place of birth	Fetuses	Delivery	Reason delivery	Age 1st dose	AN steroids	Full course	Age at dicharge/death	Out to
179	S Cleveland	ALEC	F	28.3	1250	S Cleveland	1	SVD	PROM	33	Yes	Yes	57	Home
180	S Cleveland	Curosurf	M	29.1	1400	S Cleveland	1	Breech	Spont. labour	91	Yes	No	29	Home
181	S Cleveland	ALEC	F	27.6	855	S Cleveland	1	Prelabour CS	Other	44	Yes	Yes	70	Home
182	S Cleveland	ALEC	M	27.3	1310	S Cleveland	1	Breech	APH	50	No	No	1	Died
183	S Cleveland	Curosurf	M	29.7	670	S Cleveland	1	Prelabour CS	Other	10	Yes	Yes	66	Home
184	S Cleveland	Curosurf	F	28.0	1060	B Auckland	1	CS in labour	Spont. labour	35	Yes	No	74	Home
185	S Cleveland	ALEC	M	29.1	1490	S Cleveland	1	SVD	PROM	10	Yes	Yes	39	Home
186	S Cleveland	Curosurf	M	29.3	1440	Whitehaven	1	Prelabour CS	PROM	5	Yes	Yes	210	Home
187	S Cleveland	ALEC	F	28.0	945	S Cleveland	1	SVD	PROM	Not treated	Yes	Yes	43	Home
188	S Cleveland	Curosurf	F	28.6	1165	S Cleveland	1	CS in labour	Spont. labour	8	Yes	Yes	32	Home
189	S Cleveland	ALEC	F	26.9	960	S Cleveland	1	Prelabour CS	PROM	7	Yes	Yes	133	Home
190	S Cleveland	Curosurf	M	29.3	1490	S Cleveland	1	SVD	Spont. labour	8	Yes	Yes	34	Home
191	S Cleveland	Curosurf	M	27.0	1100	S Cleveland	1	CS in labour	PROM	6	Yes	No	66	Home
192	S Cleveland	ALEC	M	29.7	1440	S Cleveland	1	Prelabour CS	PROM	8	Yes	Yes	30	Home
193	S Cleveland	Curosurf	F	27.6	1100	S Cleveland	1	SVD	Spont. labour	164	Yes	Yes	61	Home
194	S Cleveland	ALEC	M	27.4	1090	S Cleveland	1	SVD	Spont. labour	25	Yes	Yes	75	Home
195	S Cleveland	ALEC	M	26.6	1070	Newcastle	1	SVD	Spont. labour	40	Yes	Yes	87	Home
196	Leicester	ALEC	F	27.9	1230	Leicester	1	SVD	Spont. labour	60	Yes	No	82	Home
197	Leicester	Curosurf	M	27.4	1300	Leicester	1	Prelabour CS	PROM	83	Yes	Yes	108	Home
198	Leeds	Curosurf	F	28.3	1100	Leeds	2	SVD	Spont. labour	135	Yes	Yes	64	Home
199	Leeds	Curosurf	F	28.3	1100	Leeds	2	Breech	Spont. labour	105	Yes	Yes	64	Home

No	A days	B days	C days	D days	Days IPPV	Days HFOV	Days CPAP	Ptx	PDA	IVH	Severe IVH	PVL	Home O2	CLD (28d)	CLD (36w)	ROP stage	ROP treatment
1	0	1	34	2	0	0	0	No	No	Yes	No	No	No	No	No	0	No
2	88	14	55	10	88	0	0	No	No	Yes	Yes	Yes	No	Yes	Yes	II	No
3	8	0	0	0	8	0	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
4	2	6	36	7	2	0	0	No	No	Yes	No	No	No	No	No	III	No
5	26	19	42	5	16	0	10	No	No	Yes	Yes	Yes	No	No	Yes	II	No
6	50	11	72	0	50	0	0	No	No	No	No	No	Yes	Yes	Yes	I	No
7	19	7	41	13	11	0	8	No	No	Yes	Yes	Yes	No	No	No	II	No
8	79	9	35	0	79	0	0	No	No	Yes	Yes	No	Yes	Yes	Yes	III	Yes
9	3	0	32	4	3	0	0	No	No	No	No	No	No	No	No	0	No
10	50	12	41	0	50	0	0	No	No	No	No	No	Yes	Yes	Yes	I	No
11	3	0	0	0	3	0	0	No	No	No scan	No scan	No scan	N/A	N/A	N/A	Not examined	Not examined
12	6	9	59	7	6	0	0	No	No	No	No	No	No	Yes	Yes	III	No
13	3	5	27	10	3	0	0	No	Yes	Yes	No	No	No	No	No	0	No
14	0	1	39	4	0	0	0	No	No	No	No	No	No	No	No	0	No
15	8	22	83	0	8	0	0	No	No	Yes	No	Yes	Yes	Yes	No	0	No
16	43	12	35	0	43	0	0	Yes	No	Yes	No	Yes	Yes	Yes	Yes	0	No
17	13	23	125	0	9	0	4	No	No	No	No	No	Yes	Yes	Yes	IV	Yes
18	18	12	0	0	18	0	0	Yes	No	Yes	No	No	N/A	Yes	N/A	0	NO
19	3	4	36	5	3	0	0	No	No	Yes	No	No	No	No	No	0	No
20	6	4	64	5	6	0	0	No	No	Yes	Yes	Yes	No	Yes	Yes	0	No
21	113	10	0	0	106	0	7	No	Yes	Yes	No	No	N/A	Yes	Yes	II	NO
22	4	0	0	0	4	0	0	No	Yes	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
23	6	15	53	7	6	0	0	No	No	Yes	No	No	No	Yes	No	0	No
24	3	12	39	12	3	0	0	No	No	No	No	No	No	No	No	0	No
25	14	7	55	10	14	0	0	No	No	No	No	No	No	Yes	Yes	0	No
26	2	0	0	0	2	0	0	Yes	Yes	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
27	3	0	59	6	3	0	0	No	Yes	No	No	No	No	No	No	0	No
28	2	38	65	6	2	0	0	No	No	No	No	No	No	Yes	Yes	0	No
29	11	0	0	0	11	0	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
30	1	0	0	0	1	0	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
31	2	2	47	6	2	0	0	No	No	Yes	No	No	No	No	No	0	No
32	54	27	48	0	54	0	0	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	II	No
33	1	20	28	3	1	0	0	No	No	No	No	No	No	No	No	I	No
34	76	279	17	0	76	0	0	No	No	Yes	No	Yes	N/A	Yes	Yes	II	NO
35	10	0	33	1	8	0	2	No	No	Yes	No	No	Yes	Yes	Yes	0	No
36	2	13	54	0	1	0	1	No	No	No	No	No	Yes	Yes	Yes	0	No
37	3	1	58	5	3	0	0	No	No	No	No	No	No	No	No	I	No
38	8	25	74	0	7	0	1	No	No	No	No	No	Yes	No	Yes	I	No
39	2	1	42	2	2	0	0	No	No	Yes	No	No	No	No	No	0	No
40	15	31	55	0	15	0	0	No	No	No	No	No	Yes	Yes	Yes	0	No
41	46	85	2	0	46	0	0	No	No	No	No	No	N/A	Yes	Yes	0	NO
42	5	12	76	1	5	0	0	No	No	No	No	No	Yes	Yes	Yes	0	No

No	A days	B days	C days	D days	Days IPPV	Days HFOV	Days CPAP	Ptx	PDA	IVH	Severe IVH	PVL	Home O2	CLD (28d)	CLD (36w)	ROP stage	ROP treatment
43	2	16	28	2	2	0	0	No	No	No	No	No	No	No	No	0	No
44	2	5	43	0	2	0	0	No	No	No	No	No	Yes	Yes	Yes	0	No
45	1	2	35	6	1	0	0	No	No	No	No	No	No	Yes	No	0	No
46	46	123	66	1	46	0	0	No	No	Yes	No	Yes	Yes	Yes	Yes	IV	Yes
47	46	77	20	0	46	0	0	No	No	No	No	No	N/A	Yes	Yes	I	NO
48	1	2	25	3	1	0	0	No	No	No	No	No	No	No	No	0	No
49	1	8	47	3	1	0	0	No	No	No	No	No	No	No	No	0	No
50	6	5	0	0	6	0	0	No	No	Yes	No	Yes	N/A	N/A	N/A	Not examined	Not examined
51	3	17	34	0	3	0	0	No	No	Yes	No	No	No	No	No	0	No
52	4	1	29	5	4	0	0	No	No	Yes	No	Yes	No	No	No	0	No
53	8	0	0	0	8	0	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
54	37	0	64	0	37	0	0	No	No	Yes	No	No	Yes	Yes	Yes	0	No
55	5	13	43	2	3	0	2	No	No	No	No	No	No	No	No	II	No
56	18	14	75	0	18	0	0	No	Yes	No	No	No	Yes	Yes	Yes	0	No
57	15	21	71	0	15	0	0	No	Yes	No	No	No	Yes	Yes	Yes	0	No
58	10	0	0	0	10	0	0	No	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
59	5	2	37	2	5	0	0	Yes	No	No	No	No	No	No	No	0	No
60	3	0	0	0	3	0	0	Yes	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
61	35	24	61	0	34	0	1	No	No	No	No	No	Yes	Yes	Yes	II	No
62	1	0	0	0	1	0	0	Yes	No	No scan	No scan	No scan	N/A	N/A	N/A	Not examined	Not examined
63	43	51	31	0	43	0	0	No	No	Yes	No	Yes	Yes	Yes	Yes	III	No
64	6	6	51	8	6	0	0	No	No	Yes	Yes	Yes	No	No	No	0	No
65	4	0	0	0	4	0	0	No	No	Yes	Yes	No	N/A	N/A	N/A	Not examined	Not examined
66	7	35	58	8	7	0	0	No	No	No	No	No	No	Yes	Yes	0	No
67	7	25	57	19	7	0	0	No	No	Yes	No	No	No	Yes	Yes	I	No
68	1	30	55	0	1	0	0	No	No	Yes	No	No	Yes	Yes	Yes	0	No
69	20	39	26	7	20	0	0	No	No	No	No	No	No	No	No	II	No
70	24	28	35	0	16	0	8	No	No	Yes	Yes	No	Yes	Yes	Yes	0	No
71	2	6	34	5	1	0	1	No	No	No	No	No	No	No	No	0	No
72	29	32	38	0	29	0	0	No	No	No	No	No	Yes	Yes	Yes	II	No
73	3	25	64	0	2	0	1	No	No	Yes	No	No	Yes	Yes	Yes	0	No
74	3	0	62	5	3	0	0	No	No	No	No	No	No	No	No	0	No
75	9	23	45	0	1	0	8	No	No	Yes	No	No	Yes	Yes	Yes	I	No
76	4	11	62	0	2	0	2	No	Yes	Yes	No	No	Yes	Yes	Yes	I	No
77	2	0	55	0	2	0	0	No	No	No	No	No	Yes	Yes	Yes	I	No
78	2	20	74	0	2	0	0	No	No	Yes	No	No	Yes	Yes	Yes	0	No
79	2	1	64	1	2	0	0	No	No	No	No	No	Yes	Yes	Yes	I	No
80	7	30	32	4	7	0	0	No	No	No	No	No	No	No	No	0	No
81	1	4	33	0	1	0	0	No	No	No	No	No	No	No	No	I	No
82	2	0	57	5	2	0	0	No	No	No	No	No	No	No	No	I	No
83	20	33	41	7	20	0	0	Yes	No	No	No	No	Not avai	Yes	Yes	II	No
84	68	0	26	0	63	0	5	No	Yes	No	No	No	Yes	Yes	Yes	0	No

No	A_days	B_days	C_days	D_days	Days IPPV	Days HFOV	Days CPAP	Ptx	PDA	IVH	Severe IVH	PVL	Home O2	CLD (28d)	CLD (36w)	ROP stage	ROP treatment
85	70	27	13	0	47	16	7	No	Yes	Yes	Yes	Yes	N/A	No	No	I	NO
86	28	0	0	0	23	5	0	Yes	Yes	No	No	No	N/A	No	N/A	Not examined	Not examined
87	8	0	0	0	3	5	0	No	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
88	1	1	50	1	0	0	1	No	No	No	No	No	No	No	No	0	No
89	60	3	43	0	26	18	16	Yes	Yes	No	No	No	Yes	Yes	Yes	0	No
90	4	0	42	6	1	0	3	No	No	No	No	No	No	No	No	0	No
91	7	0	54	8	3	0	4	No	No	No	No	No	No	Yes	Yes	0	No
92	3	1	39	5	2	0	1	No	No	No	No	No	No	No	No	0	No
93	81	1	36	0	39	0	42	Yes	Yes	Yes	No	No	Yes	Yes	Yes	0	No
94	188	29	0	0	73	6	109	No	No	No	No	No	N/A	No	No	I	NO
95	49	0	34	3	6	0	43	No	Yes	No	No	No	No	Yes	Yes	0	No
96	87	3	114	0	32	0	55	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	0	No
97	41	0	51	0	7	0	34	No	No	Yes	No	Yes	Yes	Yes	Yes	0	No
98	1	1	35	4	1	0	0	No	No	No	No	No	No	No	No	0	No
99	5	0	0	0	3	2	0	Yes	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
100	121	22	4	0	96	14	11	Yes	No	Yes	No	No	N/A	Yes	Yes	I	NO
101	32	0	46	1	8	0	24	No	Yes	Yes	No	No	Yes	Yes	Yes	0	No
102	19	8	47	0	1	0	18	No	No	No	No	No	Yes	Yes	Yes	0	No
103	30	3	58	0	2	0	28	No	Yes	Yes	No	Yes	Yes	Yes	Yes	0	No
104	1	0	0	0	0	1	0	No	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
105	3	4	68	0	1	0	2	No	No	No	No	No	Yes	Yes	Yes	0	No
106	4	0	47	1	0	0	4	No	No	No	No	No	No	No	No	0	No
107	3	0	0	0	1	2	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
108	46	0	30	0	2	0	44	No	No	No	No	Yes	Yes	Yes	Yes	0	No
109	60	0	92	0	55	1	4	Yes	No	No	No	No	Yes	Yes	Yes	0	No
110	36	0	47	0	2	0	34	No	No	No	No	No	Yes	Yes	Yes	0	No
111	33	4	46	0	7	0	26	No	No	No	No	No	Yes	Yes	Yes	0	No
112	2	0	42	1	1	0	1	No	No	No	No	No	No	Yes	No	0	No
113	5	0	50	2	3	0	2	No	No	Yes	No	No	No	No	No	0	No
114	10	0	0	0	1	9	0	Yes	No	Yes	Yes	Yes	N/A	N/A	N/A	Not examined	Not examined
115	66	8	94	0	42	5	19	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	0	No
116	23	0	41	5	3	0	20	No	No	No	No	No	No	Yes	Yes	0	No
117	18	0	38	13	2	0	16	No	No	No	No	No	No	Yes	Yes	0	No
118	2	0	0	0	0	2	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
119	75	0	101	0	43	0	32	No	Yes	No	No	No	Yes	Yes	Yes	0	No
120	7	0	0	0	6	1	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
121	42	0	47	0	3	0	39	No	No	No	No	Yes	No	Yes	Yes	0	No
122	19	0	46	7	11	0	8	No	No	No	No	No	No	Yes	Yes	0	No
123	8	0	0	0	0	8	0	Yes	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
124	42	0	38	0	1	0	41	No	No	No	No	No	Yes	Yes	Yes	0	No
125	75	0	25	0	54	1	20	No	Yes	No	No	No	Yes	Yes	Yes	0	No
126	61	0	75	0	47	0	14	No	No	Yes	No	Yes	No	Yes	Yes	0	No

No	A_days	B_days	C_days	D_days	Days IPPV	Days HFOV	Days CPAP	Ptx	PDA	IVH	Severe IVH	PVL	Home C2	CLD (28d)	CLD (36w)	ROP stage	ROP treatment
127	1	32	36	0	1	0	0	No	No	No	No	No	No	No	No	0	No
128	41	0	26	0	16	0	25	No	No	Yes	No	No	No	Yes	No	0	No
129	8	0	0	0	4	4	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
130	5	0	0	0	0	5	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
131	0	17	45	3	0	0	0	No	No	No	No	No	No	Yes	Yes	0	No
132	39	0	34	0	21	0	18	No	No	Yes	No	No	No	Yes	Yes	0	No
133	1	0	0	0	1	0	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
134	11	0	0	0	11	0	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
135	10	0	63	0	10	0	0	No	No	No	No	No	Yes	Yes	Yes	0	No
136	2	0	35	6	0	0	2	No	No	No scan	No scan	No scan	No	No	No	0	No
137	5	0	29	9	5	0	0	No	No	No scan	No scan	No scan	No	No	No	0	No
138	9	1	43	1	1	0	8	No	No	No scan	No scan	No scan	No	No	No	0	No
139	11	0	51	0	9	2	0	No	No	Yes	No	No	Yes	Yes	Yes	0	No
140	58	0	28	0	35	0	23	No	Yes	No	No	No	Yes	Yes	Yes	0	No
141	5	0	34	13	4	1	0	No	No	Yes	No	No	No	No	No	0	No
142	7	0	0	0	6	1	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
143	74	0	98	0	36	0	38	Yes	Yes	Yes	No	No	Yes	Yes	Yes	0	No
144	46	7	32	0	23	0	23	No	Yes	No	No	No	Yes	Yes	Yes	0	No
145	3	16	21	7	3	0	0	No	No	No scan	No scan	No scan	No	No	No	0	No
146	41	0	18	0	38	0	3	No	Yes	No	No	Yes	N/A	No	N/A	Not examined	Not examined
147	1	0	0	0	0	1	0	Yes	No	No scan	No scan	No scan	N/A	N/A	N/A	Not examined	Not examined
148	1	0	0	0	1	0	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
149	10	0	0	0	4	6	0	Yes	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
150	57	0	46	0	43	0	14	Yes	No	Yes	No	Yes	Yes	Yes	Yes	0	No
151	1	1	37	9	1	0	0	No	No	No	No	No	No	No	No	0	No
152	2	7	30	9	2	0	0	No	No	No	No	No	No	No	No	0	No
153	18	6	67	0	12	0	6	No	No	Yes	No	No	Yes	Yes	Yes	0	No
154	10	0	0	0	10	0	0	No	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
155	10	0	33	7	1	7	2	Yes	No	Yes	No	No	No	No	No	0	No
156	4	2	24	0	3	0	1	No	No	No	No	No	No	No	No	0	No
157	1	1	40	8	0	0	1	No	No	No	No	No	No	No	No	0	No
158	7	0	0	0	5	2	0	No	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
159	25	0	44	0	16	0	9	No	Yes	Yes	No	No	Yes	Yes	Yes	0	No
160	37	0	44	0	27	0	10	Yes	Yes	Yes	No	No	Yes	Yes	Yes	0	No
161	1	0	43	12	1	0	0	No	No	Yes	No	Yes	No	Yes	No	0	No
162	1	1	42	12	1	0	0	No	No	Yes	No	No	No	Yes	No	0	No
163	16	0	42	5	1	0	15	No	Yes	No	No	No	No	Yes	No	0	No
164	5	0	31	1	4	0	1	No	No	No	No	No	No	No	No	0	No
165	84	0	77	0	39	13	32	No	No	No	No	No	Yes	Yes	Yes	0	No
166	4	0	0	0	3	1	0	No	No	No	No	No	N/A	N/A	N/A	Not examined	Not examined
167	45	0	50	0	3	3	39	No	No	No	No	Yes	Yes	Yes	Yes	0	No
168	6	0	38	6	4	0	2	No	No	No	No	No	No	Yes	No	0	No

No	A_days	B_days	C_days	D_days	Days IPPV	Days HFOV	Days CPAP	Ptx	PDA	IVH	Severe IVH	PVL	Home O2	CLD (28d)	CLD (36w)	ROP stage	ROP treatment
169	5	0	43	12	3	0	2	No	No	No	No	No	No	No	No	0	No
170	3	0	41	5	3	0	0	No	No	No	No	No	No	Yes	No	0	No
171	1	0	0	0	1	0	0	No	No	No scan	No scan	No scan	N/A	N/A	N/A	Not examined	Not examined
172	91	0	56	0	83	1	7	No	No	No	No	No	Yes	Yes	Yes	0	No
173	47	0	57	9	5	0	42	No	No	Yes	No	No	No	Yes	Yes	0	No
174	2	0	0	0	1	1	0	Yes	No	No scan	No scan	No scan	N/A	N/A	N/A	Not examined	Not examined
175	4	1	45	6	4	0	0	No	Yes	No	No	Yes	No	Yes	No	0	No
176	11	0	0	0	2	0	9	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
177	2	0	38	14	2	0	0	No	No	Yes	No	Yes	No	No	No	0	No
178	4	1	44	3	3	0	1	No	No	No	No	No	No	No	No	0	No
179	3	0	51	3	3	0	0	No	No	No	No	No	No	No	No	0	No
180	2	2	25	0	2	0	0	No	No	Yes	No	No	No	No	No	0	No
181	15	10	44	1	4	0	11	No	No	No	No	No	No	Yes	Yes	0	No
182	1	0	0	0	0	1	0	No	No	Yes	No	No	N/A	N/A	N/A	Not examined	Not examined
183	2	24	32	8	1	0	1	No	No	No	No	No	No	No	No	0	No
184	24	0	37	13	14	0	10	No	Yes	Yes	No	No	No	Yes	Yes	0	No
185	2	0	36	1	2	0	0	No	No	No	No	Yes	No	No	No	0	No
186	52	2	156	0	29	5	18	No	No	Yes	No	No	Yes	Yes	Yes	0	No
187	0	20	22	1	0	0	0	No	No	Yes	No	No	No	No	No	0	No
188	0	1	29	2	0	0	0	No	No	No	No	No	No	No	No	0	No
189	68	1	64	0	31	0	37	No	Yes	No	No	No	Yes	Yes	Yes	0	No
190	2	0	32	0	2	0	0	No	No	Yes	Yes	Yes	No	No	No	0	No
191	6	0	56	4	4	0	2	No	No	No	No	Yes	No	Yes	No	0	No
192	11	0	19	0	3	5	3	Yes	No	Yes	No	No	No	No	No	0	No
193	5	9	39	8	5	0	0	No	Yes	No	No	No	No	No	No	0	No
194	14	0	54	7	7	0	7	No	No	No	No	No	No	Yes	Yes	0	No
195	32	0	50	5	23	0	9	No	No	No	No	No	No	Yes	Yes	0	No
196	28	0	40	14	9	4	15	No	No	Yes	No	No	No	Yes	Yes	0	No
197	32	0	76	0	10	0	22	No	No	No	No	No	No	Yes	Yes	0	No
198	6	0	58	0	3	1	2	No	No	Yes	No	No	No	No	No	0	No
199	5	0	59	0	2	0	3	No	No	Yes	No	No	No	No	No	0	No

No	Oxygen requirements t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
1	21	21	21	21	21	21	21	21	21	21	21	21	21	21
2		36	87	48	40	52	27	41	27	27	45	21	21	21
3	50	74	85	86	82	100	100	100	90	70	60	80	86	90
4	24	100	97	45	32	27	21	21	21	21	21	21	21	21
5		21	21	32	45	40	23	28	25	37	45	33	32	32
6		80	21	21	21	24	29	21	34	34	32	32	32	32
7	65	24	21	21	21	21	21	21	21	21	21	21	21	21
8		33	30	30	48	35	25	25	40	42	22	30	30	30
9			65	41	60	42	25	23	23	23	40	23	23	21
10	68	85	88	67	65	45	67	70	61	70	57	72	55	45
11	80	70	80	80	36	41	49	50	50	100	100	100		
12	50	100	60	68	66	66	58	62	59	63	70	40	40	40
13														
14	38	34	32	33	21	21	21	21	21	21	21	21	21	21
15	21	28	48	24	34	46	27	25	27	30	25	27	34	77
16	100	100	88	100	100	100	100	98	100	98	99	99	99	99
17	21	45	21	22	21	25	22	22	40	29	22	40	25	34
18	37	75	40	60	41	40	28	29	29	100	73	31	36	38
19	47	25	26	21	32	23	25	26	26	26	55	25	22	25
20	69	53	54	60	30	40	30	28	27	30	29	22	22	21
21			100	59	59	60	62	67	60	60	37	41	25	28
22	42	100	50	56	80	100	100	100	100	100	100	70	100	100
23		65	22	22	25	23	21	22	50	50	51	25	27	29
24	50	60	22	22	23	28	33	32	30	21	21	31	39	21
25	50	80	22	30	22	22	22	21	22	34	35	34	31	31
26	100	100	100	100	83	83	100	100	100	100				
27	21	28	29	29	21	30	23	27	24	21	21	21	21	21
28	100	45	25	21	21	21	21	21	21	21	21	21	21	21
29		77	41	45	40	26	40	40	42	40	41	42	35	48
30	60	82	100	100										
31	22	21	27	47	35	22	21	35	22	21	21	21	21	21
32		58	40	40	31	21	31	34	31	40	39	42	42	35
33		22	50	21	21	21	21	21	21	21	21	21	21	21
34	92	100	75	45	80	100	30	24	21	21	32	27	21	21
35		100	70	80	70	60	61	83	100	80	78	78	53	78
36	21	30	21	21	22	22	30	30	30	30	24	29	35	35
37	22	22	22	22	29	30	28	21	22	21	22	21	21	21
38			24	40	21	21	24	21	21	21	21	22	25	26
39		28	28	65	27	22	21	22	21	21	21	21	21	21
40	35	21	21	22	21	21	21	21	21	21	50	22	37	21
41	65	95	74	74	70	80	82	70	74	50	67	33	31	40
42	64	48	36	51	45	30	30	36	40	41	55	32	62	45
43		21	21	21	21	21	21	21	21	21	21	21	21	21
44	62	50	21	21	21	21	21	22	22	21	21	21	21	21
45		63	56	50	33	27	21	31	27	24	23	21	21	27
46		21	68	59	50	42	64	71	70	80	49	34	40	80

No	Mean airways pressure t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
1														
2		6.9	8.2	14.8	13.6	8.5	7.8	7.3	8.7	8.5	8.8	9.2	7.8	7.8
3	8.3	9.6	9.9	10.0	9.6	12.4	12.0	14.0	12.4	14.8	14.7	17.0	18.0	14.4
4	7.8	7.2	13.0	9.4	8.5	7.8	5.2	4.7	4.4	6.7				
5		9.6	7.6	6.2	6.5	5.6	5.8	5.4	4.8	6.1	7.2	6.8	6.8	5.8
6		10.6	10.6	4.3	5.9	5.8	6.3	6.0	6.0	4.8	4.4	4.4	3.9	3.9
7	12.7	12.6	11.0	8.9	5.5	4.7	3.8	4.4	3.6	3.6	3.6	3.6	3.6	3.6
8		6.6	7.6	7.6	8.2	7.6	6.3	6.5	5.8	5.8	6.9	5.5	5.5	5.8
9			14.8	13.6	12.8	8.9	8.2	7.5	6.1	5.8	4.1	5.0	4.5	
10	11.0	11.0	10.3	10.7	13.5	11.7	10.8	10.3	10.3	11.2	11.2	12.1	12.1	10.3
11	9.0	7.6	7.6	9.6	9.6	7.6	8.2	7.3	7.0	14.1	20.3	18.0		
12	9.8	9.0	8.8	8.8	9.6	8.9	12.8	9.4	13.0	13.4	12.0	10.4	9.0	8.8
13											6.4	8.8	8.1	10.9
14														
15	12.8	7.5	5.8	4.8	3.5	3.2								
16		26.0	23.7	26.3	26.0	30.0	30.0	30.0	22.7	21.3	21.3	19.3	20.4	24.0
17	10.1	7.5	8.2	7.6	6.3	6.0	5.4	4.5	4.5	4.5	4.3	2.7	3.3	6.0
18	7.6	7.6	8.2	8.8	8.2	5.5	4.7	4.7	4.7	14.0	13.2	11.0	9.7	10.2
19		8.9	8.9	7.0	6.5	5.7	4.7	5.0	4.8	4.5				
20	11.7	9.4	9.0	8.2	8.2									
21			9.8	12.0	11.0	9.5	8.0	8.0	7.4	8.0	9.8	11.2	10.7	10.7
22	9.6	8.9	8.9	8.9	8.9	8.9	8.9	8.9	11.7	13.6	17.2	23.5	22.0	17.5
23		8.8	8.9	5.3	4.6	3.5								
24	8.3	8.3	7.5	7.2	5.3									
25	9.0	9.0	7.5	7.6	6.4	4.5	3.5	2.3	4.2					
26	12.2	17.0	17.0	14.4	12.4	12.5	13.6	14.0	15.2	16.5	19.1			
27	9.0	7.5	7.0	6.5	4.8	4.8	4.8	4.6	4.2					
28	7.6	7.5	5.7	6.0	5.2	3.9	3.5	3.2						
29		11.6	9.8	7.4	6.3	5.6	4.7	4.1	4.3	4.9	4.0	3.5	3.6	5.1
30	6.8	8.9	15.2	10.0										
31	8.8	6.5	7.0	5.3	4.8	4.4	3.9	3.5						
32		9.6	9.7	9.3	7.0	5.5	5.1	3.8	3.5	3.5	6.0	6.0	6.0	7.3
33														
34	15.0	20.0	12.6	10.5	8.9	10.8	8.4	7.5	6.0	5.8	5.0	4.5	4.4	4.4
35		10.3	9.4	9.4	10.8	8.3	8.8	9.4	11.2	10.6	11.2	9.8	10.8	10.2
36	7.5	7.5	6.9	5.5	4.4	3.7								
37	9.6	9.6	8.9	7.6	5.0	5.2	4.4	4.1	3.7	3.5				
38			7.6	6.0	6.2	5.7	5.3	5.0	4.1	3.6	3.6	3.6	4.5	5.5
39		8.8	8.8	7.5	6.0	6.3	5.8	3.6	5.0					
40		5.2	5.5	3.5										
41	9.8	12.8	12.0	10.4	8.7	7.5	9.6	10.3	13.6	12.4	15.0	15.8	13.6	12.8
42	9.6	10.4	12.0	10.4	7.6	7.6	6.8	7.0	6.5	7.0	7.5	7.6	7.6	7.0
43		4.5	4.1	4.5										
44	10.4	10.4	9.6	6.8	5.4	5.3	4.8	3.2						
45		7.9	8.6	7.9	7.3	5.2	5.2	4.4	3.5					
46		10.3	6.9	6.9	6.3	5.8	5.2	4.7	4.4	5.0	12.7	10.1	9.3	8.0

No	Oxygen requirements t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
47	37	60	40	36	27	32	32	41	35	27	27	22	22	22
48	21	30	30	25	25	23	33	32	31	29	27	25	22	21
49	21	21	21	21	21	21	21	21	21	21	21	21	21	21
50	40	50	40	21	27	21	28	21	21	40	29	29	29	27
51														
52														
53														
54			47	37	28	35	28	26	43	37	36	42	42	26
55	40	40	21	21	27	25	21	29	21	21	21	30	25	26
56		21	21	21	21	30	26	36	45	21	25	21	31	29
57			50	35	37	37	46	46	22	22	21	21	22	28
58		100	100	55	96	96	97	100	100	100	90	75	75	99
59		60	100	62	70	80	81	73	54	69	66	66	50	41
60	60	45	41	50	60	60	62	100	100	100	100	100	100	100
61	21	21	21	27	35	33	33	25	35	32	42	25	24	24
62														
63		50	62	70	44	40	69	65	51	50	58	54	53	50
64	60	31	45	100	100	58	27	45	35	42	22	25	27	21
65	70	40	40	60	78	58	65	65	46	60	49	45	68	68
66	21	21	21	21	21	21	21	21	21	21	21	21	21	21
67		89	44	45	40	45	26	45	26	43	42	25	31	29
68	21	21	21	32	35	221	31	22	21	21	21	21	21	21
69	49	78	89	100	45	48	49	49	38	38	38	55	43	44
70	31	100	100	100	70	46	35	32	30	30	44	31	27	25
71	34	24	31	24	33	30	27	28	24	23	21	22	21	21
72	50	40	22	21	21	22	21	21	21	21	52	25	27	22
73		21	35	29	27	25	22	45	38	38	30	26	26	30
74	84	85	31	21	30	30	21	21	21	21	21	21	21	21
75	21	21	21	40	21	22	21	21	21	21	21	21	21	21
76	21	23	21	31	21	21	21	21	21	21	21	21	21	21
77	21	35	21	21	44	30	24	21	21	21	27	21	21	21
78		70	22	27	21	21	21	21	21	21	21	21	21	21
79			23	21	22	21	21	21	21	21	21	21	21	21
80	44	44	44	21	21	28	32	30	80	39	35	36	26	21
81		25	32	29	21	21	21	21	21	21	21	21	21	21
82														
83	100	90	100	76	70	66	65	62	44	40	30	30	29	35
84	50	30	24	23	21	21	21	21	21	25	21	21	21	21
85	21	26	43	100	72	80	54	50	50	45	50	40	40	26
86	100	21	30	45	40	48	50	56	100	56	62	54	56	46
87	65	76	85	100	72	80	54	50	50	45	50	40	40	26
88	21	21	21	21	21	21	21	21	21	21	21	21	21	21
89	25	25	35	45	32	29	40	45	45	69	84	74	80	66
90	21	30	24	24	21	21	21	21	21	21	21	21	21	21
91	40	24	21	21	24	21	21	21	21	21	21	21	21	21
92	26	21	21	21	21	21	21	21	21	21	21	21	21	21

No	Mean airways pressure t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
47	9.8	8.9	8.3	7.3	5.5	5.6	5.2	5.5	5.0	8.8	8.8	8.2	7.6	7.0
48	9.6	9.6	7.9	7.3	5.8	4.3								
49	7.6	9.6	7.0	4.9										
50	9.6	9.6	10.0	11.0	9.5	8.9	6.9	4.2	4.5	7.0	5.4	4.8	4.7	
51														
52														
53														
54			12.2	6.6	6.2	5.1	5.3	5.5	5.3	3.6	5.2	6.3	4.4	3.6
55	7.6	5.6	6.4	5.2	7.3	5.2	4.0	4.5	4.3	4.2	3.3	3.3	3.5	
56		6.3	4.7	5.0	3.5									
57														
58		13.8	13.8	13.8	13.8	11.7	11.7	15.7	22.0	20.5	18.4	19.7	15.0	14.1
59	9.6	10.5	11.7	19.4	14.2	12.0	12.0	11.8	11.0	9.6	8.9	9.6	7.5	6.3
60	8.1	8.1	9.0	8.2	6.6	7.9	7.2	6.5	11.2	13.4	15.0	21.5	21.5	
61	10.4	10.4	8.8	6.3	6.9	6.3	6.4	6.3	7.2	7.9	7.6	7.0	5.7	4.3
62														
63		12.1	8.5	7.2	6.8	6.4	6.7	8.1	10.8	10.3	10.0	9.3	10.0	9.4
64	8.8	10.4	9.6	12.8	8.0	6.1	5.7	5.3	6.4	6.0	5.6	5.6	5.2	
65	8.1	8.2	7.8	6.4	6.0	6.3	6.3	7.6	7.6	8.1	10.9	20.0	10.7	9.8
66		9.6	7.2	5.8	5.4	4.2								
67		10.4	10.8	9.6	8.3	7.2	6.5	5.3	7.5	6.8	6.4	6.8	6.5	5.8
68	9.6	7.3	6.5	6.3	5.4	4.2								
69	9.6	9.0	13.0	12.4	10.7	9.1	9.1	9.4	8.8	8.2	8.4	8.8	8.8	
70														
71	10.9	9.1	6.5	4.1	3.9	3.7	2.5							
72	10.5	11.3	8.2	7.6	6.8	6.2	5.6	5.2	4.8	4.6				
73		11.8	10.4	10.4	8.2	7.6	7.0	6.4	5.0	4.2				
74	8.9	9.6	9.2	8.2	8.2	7.6	7.0	6.5	6.9	5.0	5.0	4.4		
75	7.2	7.2	4.8	4.8	4.4									
76	8.8	6.4	6.4	5.2	3.9	4.8								
77	8.8	10.0	9.3	7.6	6.0	5.6	4.6	5.4	3.5	4.4				
78		8.2	7.6	6.5	6.0	5.6	5.2	4.8						
79		9.6	5.8	5.2	5.0	4.8								
80	8.5	7.3	5.5	5.5	5.5	4.6	4.8	4.6	5.2	5.8	6.4	9.5	8.9	8.2
81		7.6	5.2	4.4										
82														
83	8.6	8.2	8.9	11.2	11.2	9.3	9.3	8.6	9.6	8.9	7.9	6.3	7.0	6.3
84	8.5	7.1	6.8	6.8	6.9	6.4	6.4	6.5	5.1	4.4	4.5	5.5	6.5	6.4
85		9.9	6.5	6.6	6.4	8.2	6.0	7.6	7.2	7.6	7.1	10.0	11.0	11.0
86	10.0	10.0	9.0	7.0	6.0	6.0	10.0	6.0	20.0	19.0	17.0	17.0	17.0	16.0
87	9.0	10.0	8.0	10.0	12.0	12.0	12.0	12.0	11.0	11.0	11.0	11.0	11.0	11.0
88	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0						
89	9.9	9.2	8.9	8.9	7.9	7.9	7.7	8.9	9.6	9.1	11.0	12.0	13.0	13.0
90	9.0	9.0	6.5	4.0	4.0	4.0	4.0	5.0	5.0	5.0				
91	12.0	11.0	7.0	7.0	6.0	6.0	5.0	5.0	5.0	5.0	4.0	5.0	5.0	5.0
92	11.0	11.0	3.9	3.3	3.2	3.3	5.1	3.5	4.0	4.0	4.0	4.0	4.0	4.0

No	Oxygen requirements													
	t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
93	36	49	100	70	90	75	80	75	100	50	65	57	55	70
94	28	21	21	21	21	21	21	21	21	21	21	21	21	21
95	100	21	34	27	25	21	21	21	21	21	21	21	21	21
96	25	96	96	76	73	62	55	40	37	29	40	55	41	49
97	43	70	26	21	50	25	21	32	29	38	43	43	27	35
98	40	40	21	21	21	21	21	21	21	21	21	21	21	21
99	50	72	100	100	70	90	100	88	70	79	80	70	62	68
100	100	100	90	80	100	70	80	48	36	50	75	55	40	32
101	21	21	21	21	21	21	21	21	21	21	21	21	21	21
102	44	49	40	71	39	41	39	25	21	21	21	21	21	21
103	84	100	23	21	21	22	21	21	21	21	21	21	21	21
104	70	91	59	94	100									
105	21	21	30	23	21	21	21	21	21	21	24	26	25	23
106	30	36	40	30	28	28	26	26	24	25	24	21	23	25
107	100	30	21	31	21	40	35	21	21	30	60			
108	80	22	21	35	21	21	21	21	21	27	21	22	21	21
109	100	21	38	43	35	50	50	50	40	40	100	100	100	100
110	25	21	21	21	21	21	21	21	21	21	30	32	39	35
111	27	21	21	21	21	21	21	21	21	21	21	30	21	24
112	100	21	21	31	27	21	28	21	21	21	21	21	21	21
113	80	21	21	21	25	21	24	21	25	21	21	21	21	21
114	100	50	51	71	29	33	50	100	38	43	30	39	34	30
115	28	78	90	80	91	60	35	33	49	53	54	40	57	60
116		30	21	21	27	25	23	25	23	21	25	22	21	24
117		21	21	44	37	22	21	21	21	21	21	21	21	21
118	60	90	100	100	100	100	100	100						
119	70	69	22	23	31	30	40	41	65	70	57	45	70	42
120	100	100	27	24	55	65	66	66	70	56	56	60	60	60
121		21	21	21	21	21	26	25	21	21	21	30	40	60
122	21	21	24	21	25	40	60	37	60	70	35	35	36	36
123	100	100	100	61	67	60	65	100	70	73	64	69	30	28
124	26	31	24	40	26	21	29	27	29	21	21	21	21	21
125	45	54	56	50	97	82	100	85	100	66	61	53	72	50
126	51	47	21	21	21	21	24	26	25	26	28	25	25	26
127														
128	100	55	39	30	21	26	21	29	27	29	30	21	21	21
129	70	70	75	60	70	93	64	100	100	100	100	100	100	100
130														
131	38	21	21	21	21	21	21	21	21	21	21	21	21	21
132	40	21	30	30	40	40	50	45	40	45	39	21	21	21
133	60	55	60	60	68	100								
134	32	30	21	21	21	21	21	25	25	21	21	21	21	21
135	50	30	21	21	21	21	21	21	21	21	21	21	21	21
136	28	21	21	21	21	21	21	21	21	21	21	21	21	21
137	36	21	80	35	30	25	21	21	21	21	21	21	21	21
138	38	21	21	21	21	21	21	21	21	21	21	21	21	21

No	Mean airways pressure													
	t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
93	11.0	12.0	17.0	14.0	14.0	1.0	12.0	12.0	10.0	10.0	8.0	9.0	9.0	9.0
94	7.5	7.9	7.3	7.8	6.0	5.2	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
95	8.0	8.0	7.2	7.0	7.5	7.8	7.6	7.7	7.0	7.0	7.0	6.9	6.4	5.8
96	15.0	18.0	15.0	14.0	14.0	15.0	12.0	12.0	11.0	11.0	11.0	11.0	9.8	10.0
97	8.0	9.0	9.0	5.0	6.0	5.0	5.0	5.0	5.0	6.0	5.0	5.0	5.0	5.0
98	5.0	10.0	10.0	5.3	4.9	4.0								
99	13.0	11.5	10.0	16.0	8.0	8.0	8.0	8.0	8.0	10.0	10.0	10.0	11.0	11.0
100	8.2	8.3	16.0	16.0	14.0	14.0	12.0	12.0	12.0	12.0	12.0	13.0	13.0	13.0
101	12.0	8.0	8.0	9.0	5.8	6.0	6.0	6.0	6.0	6.0	6.0	6.0	4.0	4.0
102	8.0	11.0	9.0	7.0	5.0	5.0	5.0	5.0	4.0	4.0	4.0	4.0		
103	7.5	9.7	8.3	8.0	8.0	5.1	5.0	4.0	4.5	3.0				
104	8.7	12.0	14.0	15.0	15.0									
105	9.0	8.0	5.0	4.0	3.0	5.0	4.0	4.0	4.0	4.0	4.0			
106	5.0	5.0	5.0	5.0	5.0	4.0	4.0	4.0	4.0	4.0	5.0	5.0	4.0	5.0
107	14.0	14.0	13.0	10.0	9.0	9.0	14.0	9.3	8.9	8.6	9.9			
108	10.0	8.0	8.0	8.0	8.0	8.0	8.0	6.0	6.0	6.0	5.0	5.0	4.0	4.0
109	14.0	12.0	12.0	12.0	10.0	10.0	11.0	11.0	11.0	12.0	16.0	12.0	16.0	16.0
110	9.5	6.4	5.3	5.2	3.8	3.5	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
111	9.2	8.0	6.2	5.5	3.8	3.7	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
112	13.0	10.0	7.0	7.0	6.0	6.0	5.0	5.0	5.0	5.0				
113	12.0	12.0	6.0	6.0	7.0	6.0	6.0	6.0	5.0	6.0	6.0	6.0	6.0	6.0
114	8.9	9.7	11.0	11.0	8.9	7.7	8.6	12.0	14.0	11.0	12.0	12.0	12.0	12.0
115	10.0	8.1	9.6	9.9	9.5	9.5	8.2	7.2	8.2	9.2	9.2	9.5	9.6	9.5
116		8.4	9.0	8.4	6.9	7.0	7.0	7.1	5.1	4.8	4.9	4.8	4.2	4.0
117		11.0	9.0	8.0	10.0	8.0	8.0	5.0	5.0	4.0	4.0	4.0	4.0	4.0
118	13.0	13.0	15.0	16.0	15.0	18.0	19.0	14.0						
119	13.0	10.0	9.8	8.5	7.5	7.1	5.8	5.6	9.4	8.7	10.0	9.9	10.0	11.0
120	12.0	15.0	15.0	11.0	6.9	7.0	7.0	7.0	5.7	5.8	5.8	5.8	5.8	5.8
121		11.0	8.0	8.0	7.0	7.0	8.0	7.0	7.0	7.0	6.0	4.0	4.0	4.0
122	9.0	9.0	9.0	7.0	7.0	6.0	4.0	4.0	10.0	13.0	12.0	10.0	10.0	10.0
123	11.0	20.0	21.0	20.0	20.0	12.0	13.0	14.0	11.0	14.0	14.0	14.0	13.0	15.0
124	10.0	10.0	10.0	7.0	8.0	6.0								
125	9.0	9.0	9.0	7.0	10.0	11.0	10.0	12.0	12.0	12.0	11.0	10.0	11.0	10.0
126	9.3	9.3	8.5	8.6	6.9	6.3	6.3	6.1	6.3	6.3	6.2	6.3	6.1	6.2
127														
128	14.0	13.0	14.0	14.0	8.0	8.0	8.0	8.0	5.0	5.0	5.0	5.0	5.0	5.0
129	4.0	4.0	14.0	13.5	12.0	18.0	16.0	14.0	12.0	13.0	12.0	12.0	14.0	14.0
130														
131														
132	11.5	11.5	10.3	6.4	5.4	7.4	7.4	5.4	10.0	8.0	10.0	10.0	10.0	10.0
133	13.0	13.0	13.0	11.8	11.8	13.0								
134	10.1	10.2	10.2	9.2	9.1	8.3	7.9	8.9	8.9	8.9	8.9	8.9	9.0	8.9
135	11.5	9.6	10.3	9.1	9.1	9.2	9.1	9.1	8.2	8.2	8.5	8.1	7.7	6.7
136	4.0	4.0	5.0	5.0	5.0	5.0	4.0	5.0	4.0	4.0				
137	5.0	5.0	12.5	13.9	10.0	8.5	8.4	8.4	8.4	7.6	7.6	7.6	8.4	6.8
138	9.3	7.7	6.7	4.5	4.2									

Oxygen requirements

No	t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
139	70	73	90	94	21	21	24	21	21	21	21	23	22	27
140	40	45	80	66	21	21	21	21	21	21	21	21	21	21
141	90	80	35	40	21	21	21	21	21	21	21	21	21	21
142	40	45	35	40	21	21	21	25	21	21	21	21	21	21
143	70	21	21	40	25	21	50	21	21	21	21	21	21	21
144	79	56	50	25	21	26	21	28	28	37	29	26	26	21
145	60	21	21	21	21	21	21	21	21	21	21	21	21	21
146	30	21	21	21	21	21	21	21	21	21	21	21	21	21
147	100	70	100	90	100	100	50							
148	100	100	100											
149	50	21	21	21	21	21	21	21	21	21	28	26	44	40
150	92	96	28	55	21	26	28	32	30	21	21	27	30	37
151	60	21	21	21	21	21	21	21	21	21	21	21	21	21
152	60	30	21	21	21	21	21	21	21	21	21	21	21	21
153		21	21	22	21	21	21	34	34	29	21	21	21	21
154	45	38	21	21	21	21	30	26	33	30	30	28	21	29
155	30	27	39	42	45	21	21	26	60	23	45	55	21	22
156	24	24	30	27	40	39	54	56	34	31	37	37	40	21
157	21	21	21	21	21	21	21	21	21	21	21	21	21	21
158	95	100	65	46	43	38	39	44	34	39	30	26	21	21
159	52	27	21	21	21	21	21	27	21	21	21	21	21	21
160	60	80	70	100	80	70	80	70	70	92	75	70	68	60
161	30	21	21	21	21	21	21	21	21	21	21	21	21	21
162	30	21	24	21	21	21	21	21	21	21	21	21	21	21
163	25	25	21	21	21	21	21	21	21	21	21	21	21	21
164	47	49	65	52	56	52	50	50	35	30	28	26	27	28
165	69	74	65	62	61	62	62	58	66	71	32	21	25	28
166	65	37	22	21	23	24	30	59	54	53	47	58	42	53
167	72	44	34	35	29	23	35	48	47	28	24	30	30	26
168	28	30	40	40	40	40	50	35	40	30	40	40	25	30
169	50	21	21	21	21	21	21	21	21	21	21	21	21	21
170	30	21	21	21	36	29	29	26	22	21	21	21	21	21
171	100	100	100											
172	60	40	29	33	29	28	25	22	21	21	21	24	21	21
173	30	30	32	21	25	24	23	21	21	21	21	21	26	21
174			80	59	48	49	46	55						
175	50	40	30	21	25	27	23	30	21	21	21	21	21	21
176	35	30	21	21	21	21	21	21	21	21	21	24	21	21
177	25	35	21	23	21	21	21	21	21	21	21	21	21	21
178	21	21	21	21	21	21	21	21	21	21	21	21	21	21
179	21	21	21	21	21	21	21	21	21	21	21	21	24	21
180	21	21	21	21	21	21	21	21	21	21	21	21	21	21
181		23	22	22	22	22	22	22	22	26	22	22	26	22
182	60	100	100	100	100									
183	21	21	21	21	21	21	21	21	21	21	21	21	21	21
184	75	30	44	25	21	22	22	21	21	21	21	21	21	21

Mean airways pressure

No	t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
139	5.0	4.0	16.0	16.0	17.0	16.0	15.0	14.0	14.0	16.0	11.0	10.0	10.0	9.0
140	14.0	16.4	12.0	9.7	9.1	8.4	7.8	7.8	7.8	4.8	5.8	5.8	5.2	5.2
141	16.0	18.0	16.0	15.0	12.0	11.0	10.0	10.0	9.0	9.0	8.0	8.0	9.0	10.0
142	12.0	10.0	9.0	9.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
143	9.6	10.1	9.8	10.5	11.5	9.9	7.3	7.0	7.6	7.8	6.9	7.0	7.3	7.4
144	14.0	14.0	12.0	12.0	12.0	10.0	8.0	8.0	8.0	9.0	9.0	8.0	7.0	7.0
145	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
146	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
147	13.6	14.0	11.0	16.0	11.0	11.0	11.0							
148	12.2	10.8	14.0											
149	16.0	13.0	12.0	12.0	9.0	8.0	8.0	8.0	8.0	8.0	8.0	10.0	8.0	8.0
150	15.5	16.5	20.0	17.0	14.0	14.0	14.0	14.0	14.0	14.0	12.0	9.2	9.2	9.2
151	13.5	13.5	13.5	17.0	16.0									
152	11.2	9.3	6.9	6.8										
153		10.7	9.3	7.3	7.3	6.1	6.1	6.8	6.8	6.8	7.5	8.3	8.0	8.8
154	11.2	9.6	9.0	8.0	7.0	7.0	7.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
155	5.0	5.0	5.0	5.0	14.0	14.0	12.0	12.0	24.0	20.0	12.0	13.0	14.0	14.0
156									5.0	5.0	5.0	5.0	5.0	5.0
157														
158			4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
159	9.0	8.0	6.0	6.0	5.0	5.0	4.0	7.0	6.0	6.0	5.0	6.0	6.0	6.0
160	10.7	11.7	12.5	9.1	9.8	9.7	9.6	9.4	8.7	10.2	10.8	10.1	9.9	9.1
161	8.0	8.0	7.0	7.0	7.0	7.0	4.0	4.0						
162	8.0	8.0	7.0	6.0	6.0	5.0	4.0	5.0	5.0					
163	8.5	8.9	7.5	6.5	5.3	5.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
164	9.0	11.0	10.0	11.0	11.0	11.0	11.0	10.0	9.0	8.0	8.0	8.0	7.0	6.0
165	11.0	11.0	9.3	9.5	9.5	9.9	10.0	11.0	11.0	13.0	11.0	10.0	10.0	10.0
166	11.0	8.0	8.0	8.0	10.0	10.0	8.0	10.0	10.0	10.0	10.0	10.0	10.0	20.0
167	8.0	8.0	9.0	9.0	9.0	10.0	10.0	12.0	12.0	10.0	10.0	8.0	8.0	8.0
168	11.0	9.2	7.2	7.4	8.1	8.3	8.5	8.6	7.9	7.2	7.8	7.8	6.9	6.7
169	8.5	8.1	6.3	6.4	4.0	7.2	4.9	5.0	5.0	4.9	4.7	4.0	4.0	4.0
170	12.0	12.0	11.0	10.0	9.0	9.0	8.0	8.0	8.0	7.0	5.0	5.0	5.0	5.0
171	17.0	17.0	20.0											
172	12.4	8.8	8.0	10.0	8.0	9.0	8.0	9.0	8.0	7.0	8.0	8.0	7.0	7.0
173	11.0	9.5	10.0	8.0	7.0	7.0	7.0	5.0	5.0	6.0	5.0	5.0	5.0	5.0
174			10.0	10.0	11.6	11.4	13.2	12.6						
175	8.9	8.7	8.2	7.5	7.6	8.0	7.6	7.4	7.8	7.5	6.7	5.6	5.0	5.6
176	10.0	9.0	8.0	7.0	6.0	6.0	5.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
177	10.2	10.8	10.0	8.3	7.5	7.0	5.9	5.7	5.2	5.3				
178														
179	8.8	7.5	7.2	5.5	6.0	6.2	6.3	6.3	6.1	6.2	6.9	6.4		
180	14.6	14.1	8.8	7.6	8.1	8.1	8.3	7.3						
181		9.6	7.2	6.7	6.8	6.3	5.8	7.8	5.7	5.6	6.3	6.9	7.2	7.6
182	8.3	13.1	19.5	23.3	29.2									
183	6.3	6.3	6.6	6.1	6.6	4.0	3.0	3.0						
184	7.3	7.3	8.8	7.8	7.9	9.3	7.7	8.3	8.2	8.2	8.3	8.3	8.3	8.3

No	Oxygen requirements t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
185	30	26	23	21	21	24	21	21	21	21	21	21	21	21
186														
187														
188	21	21	21	21	21	21	21	21	21	21	21	21	21	21
189	50	72	80	48	37	39	25	24	26	25	30	28	23	22
190	24	21	23	21	21	21	21	21	21	21	21	25	21	21
191		27	21	21	22	22	22	21	21	21	21	21	21	21
192			46	51	100	56	48	36	100	58	66	59	51	44
193	22	22	28	23	24	26	27	22	23	22	21	21	21	21
194	22	22	22	22	22	22	22	25	22	22	22	22	22	22
195			49	51	53	43	27	26	21	22	21	21	21	21
196														
197														
198	60	39	59	25	32	21	35	44	48	30	35	32	26	21
199	50	71	21	21	21	21	28	21	21	21	21	21	21	21

No	Mean airways pressure t = 0	t = 2	t = 6	t = 12	t = 18	t = 24	t = 30	t = 36	t = 42	t = 48	t = 54	t = 60	t = 66	t = 72
185	4.0	7.8	6.6	6.7	7.0	6.9	7.6	8.4	6.3	4.0				
186														
187														
188														
189														
190	10.4	9.2	11.5	8.7	8.8	8.8	9.2	9.0	8.9	8.9	9.2	9.5	9.2	8.5
191	9.3	12.3	10.6	9.6	7.9	8.1	7.3	6.8	6.7	7.8	7.5			
192		10.2	7.5	11.4	6.9	6.5	6.6	6.1	6.0	5.8	8.0	5.6	5.5	5.4
193			9.2	9.0	10.0	11.8	10.8	8.5	10.3	11.5	9.5	9.7	9.7	8.3
194	9.0	7.0	5.4	5.8	5.9	5.7	5.8	7.0	7.3	7.4	6.4	6.4	6.0	6.0
195	10.2	9.8	7.4	6.9	7.5	7.5	7.5	7.6	7.1	6.8	7.0	7.7	7.5	7.1
196			9.8	8.6	9.3	7.4	7.0	9.3	9.4	9.4	8.7	9.0	8.9	8.8
197														
198	12.0	12.0	10.0	14.7	14.2	11.0	6.1	7.9	8.3	9.1	7.8	8.0	6.4	4.6
199	13.0	9.5	9.4	6.7	6.7	5.9	5.9	4.5	4.5	4.2	4.2	4.0	4.0	4.0

APPENDIX 4

Data from infants <32 weeks gestation treated in the former Northern region 1998-99 (as used in chapter 10).

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
1	Darlington	Darlington	31	1620	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	30	22	6	FALSE	None	27
2	North Tees	North Tees	30	1610	1	1	Booked/born & ALL treatment level III	2	1	Discharged alive	30	21	2	FALSE	None	45
3	RVI	RVI	29	1275	1	1	Booked/born & ALL treatment level III	2	0	Discharged alive	21	21	7	FALSE	None	56
4	South Cleveland	North Tees	28	1160	1	1	Booked level III, IUT different level III	6	17	Died	80	25	3	FALSE	None	39
5	North Tees	North Tees	27	1100	1	1	Booked/born & ALL treatment level III	2	25	Discharged alive	45	21	2	FALSE	None	68
6	RVI	RVI	23	595	1	1	Booked/born & ALL treatment level III	16	0	Died	40	21	2	FALSE	None	16
7	Sunderland	Sunderland	27	1190	1	1	Booked/born & ALL treatment level III	10	3	Discharged alive	96	50	16	FALSE	None	52
8	RVI	RVI	30	1580	1	1	Booked/born & ALL treatment level III	3	1	Discharged alive	25	21	3	FALSE	None	35
9	North Tees	North Tees	27	871	1	1	Booked/born & ALL treatment level III	10	13	Discharged alive	100	50	11	FALSE	None	63
10	Sunderland	Sunderland	24	740	1	1	Booked/born & ALL treatment level III	19	1	Died	100	70	8	FALSE	None	19
11	North Tees	North Tees	31	1530	1	1	Booked/born & ALL treatment level III	1	1	Discharged alive	30	21	4	FALSE	None	38
12	South Cleveland	South Cleveland	24	760	1	1	Booked/born & ALL treatment level III	38	19	Discharged alive	100	45	10	FALSE	None	145
13	Gateshead	RVI	28	1250	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	59
14	North Tees	South Cleveland	31	1550	1	1	Booked level III, IUT different level III	0	0	Discharged alive	21	21	3	FALSE	None	31
15	Out of region	South Cleveland	31	1421	1	1	Booked ex-region (transferred)	3	1	Transferred	66	21	5	FALSE	None	21
16	North Tyneside	North Tyneside	31	1620	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	30	25	1	FALSE	None	24
17	Hartlepool	Hartlepool	28	920	1	1	Booked/born level I, PN transfer	10	7	Died	100	21	7	FALSE	None	41
18	RVI	RVI	25	510	1	1	Booked/born & ALL treatment level III	1	0	Died	100	100	13	FALSE	None	0
19	North Tyneside	North Tyneside	30	1720	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	24	21	6	FALSE	None	19
20	Dryburn	Dryburn	31	2090	1	1	Booked/born level I, PN transfer	3	3	Discharged alive	39	27	7	FALSE	None	31
21	Carlisle	Carlisle	31	1648	1	1	Booked/born level I, PN transfer	18	0	Died	90	48	4	TRUE	Myotonic dystrophy	18
22	South Cleveland	South Cleveland	30	1040	1	1	Booked/born & ALL treatment level III	7	1	Discharged alive	35	21	5	FALSE	None	100
23	North Tees	North Tees	30	1520	1	1	Booked/born & ALL treatment level III	3	1	Discharged alive	50	21	0	FALSE	None	36
24	North Tees	North Tees	30	1520	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	24	21	3	FALSE	None	32
25	South Cleveland	South Cleveland	25	790	1	1	Booked/born & ALL treatment level III	23	35	Discharged alive	55	30	8	TRUE	Ventricular septal defect	103
26	RVI	RVI	31	980	1	1	Booked/born & ALL treatment level III	0	8	Discharged alive	46	26	4	FALSE	None	50
27	South Tyneside	South Tyneside	31	1145	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	25	21	5	FALSE	None	42
28	South Cleveland	South Cleveland	28	1360	1	1	Booked/born & ALL treatment level III	4	3	Discharged alive	40	21	9	FALSE	None	64
29	RVI	RVI	31	1680	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	28	21	2	FALSE	None	22
30	RVI	RVI	29	1090	1	1	Booked/born & ALL treatment level III	1	0	Died	100	100	0	TRUE	Pulmonary hypoplasia	0
31	RVI	RVI	24	665	1	1	Booked/born & ALL treatment level III	10	0	Died	55	21	5	FALSE	None	10
32	South Cleveland	South Cleveland	29	1230	1	1	Booked/born & ALL treatment level III	5	1	Discharged alive	25	21	6	FALSE	None	38
33	North Tees	North Tees	31	1480	1	1	Booked/born & ALL treatment level III	0	3	Discharged alive	25	21	4	FALSE	None	27
34	RVI	RVI	30	1535	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	29
35	RVI	RVI	31	1690	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	61	42	0	FALSE	None	40
36	RVI	RVI	29	1450	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	48	21	5	FALSE	None	36
37	Hartlepool	Hartlepool	31	1580	2	1	Booked/born & ALL treatment level I	0	0	Discharged alive	28	21	5	FALSE	None	31
38	Hartlepool	Hartlepool	31	1830	2	2	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	31
39	Hartlepool	South Cleveland	28	870	1	1	Booked level I, IUT to level III	3	5	Discharged alive	60	30	9	FALSE	None	77
40	South Tyneside	South Tyneside	31	1570	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	52	28	9	FALSE	None	19
41	North Tees	North Tees	28	1290	1	1	Booked/born & ALL treatment level III	12	2	Discharged alive	100	60	6	FALSE	None	80
42	RVI	RVI	29	1260	1	1	Booked/born & ALL treatment level III	54	21	Discharged alive	60	40	1	FALSE	None	106
43	Gateshead	Gateshead	31	1440	1	1	Booked/born level I, PN transfer	9	3	Discharged alive	100	50	0	FALSE	None	15
44	Dryburn	Dryburn	30	1740	1	1	Booked/born level I, PN transfer	14	13	Discharged alive	97	36	10	FALSE	None	66
45	South Cleveland	South Cleveland	26	770	1	1	Booked/born & ALL treatment level III	3	9	Discharged alive	21	21	5	FALSE	None	76
46	Out of region	Out of region	25	1150	1	1	Booked ex-region (transferred)	20	27	Died	90	60	5	FALSE	None	48
47	Dryburn	Dryburn	28	1230	1	1	Booked/born level I, PN transfer	15	20	Discharged alive	100	82	3	FALSE	None	66

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
48	RVI	RVI	28	1270	1	1	Booked/born & ALL treatment level III	18	23	Discharged alive	27	21	5	TRUE	Fetal alcohol syndrome	86
49	RVI	RVI	28	905	1	1	Booked/born & ALL treatment level III	1	21	Discharged alive	22	21	5	FALSE	None	66
50	Sunderland	Sunderland	28	1350	1	1	Booked/born & ALL treatment level III	5	0	Discharged alive	50	22	0	FALSE	None	68
51	South Cleveland	South Cleveland	23	550	1	1	Booked/born & ALL treatment level III	1	0	Died	100	100	9	FALSE	None	0
52	South Cleveland	South Cleveland	29	1310	1	1	Booked/born & ALL treatment level III	1	1	Discharged alive	23	21	9	FALSE	None	68
53	Darlington	RVI	30	1350	1	1	Other	3	0	Discharged alive	70	35	6	FALSE	None	74
54	Out of region	Out of region	28	1270	1	1	Booked ex-region (transferred)	1	8	Transferred	100	21	4	FALSE	None	15
55	Sunderland	Sunderland	28	990	1	1	Booked/born & ALL treatment level III	20	14	Discharged alive	85	40	0	FALSE	None	74
56	North Tees	North Tees	29	1230	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	58	24	9	FALSE	None	29
57	Carlisle	Carlisle	28	1130	1	1	Booked/born level I, PN transfer	58	5	Discharged alive	100	40	13	FALSE	None	105
58	RVI	RVI	29	1460	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	31
59	North Tyneside	North Tyneside	31	1610	2	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	23
60	North Tyneside	North Tyneside	31	1750	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	32	27	0	FALSE	None	23
61	South Tyneside	South Tyneside	30	1045	1	1	Booked/born & ALL treatment level I	0	3	Discharged alive	50	35	9	FALSE	None	51
62	South Cleveland	South Cleveland	30	1320	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	10	FALSE	None	31
63	Bishop Auckland	Bishop Auckland	30	1330	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	29
64	RVI	RVI	30	1130	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	37	26	0	FALSE	None	45
65	Sunderland	Sunderland	30	1485	1	1	Booked/born & ALL treatment level III	0	5	Discharged alive	30	30	1	FALSE	None	37
66	RVI	RVI	31	1675	1	1	Booked/born & ALL treatment level III	0	2	Discharged alive	21	21	3	FALSE	None	30
67	South Tyneside	South Tyneside	30	1390	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	46
68	South Tyneside	RVI	27	910	1	1	Booked level I, IUT to level III	12	56	Discharged alive	100	38	9	FALSE	None	100
69	Hartlepool	Hartlepool	26	980	1	1	Booked/born level I, PN transfer	2	0	Discharged alive	40	30	3	FALSE	None	65
70	RVI	RVI	30	2540	1	1	Booked/born & ALL treatment level III	0	4	Discharged alive	31	21	4	FALSE	None	29
71	Hexham	Hexham	29	1660	1	1	Booked/born level I, PN transfer	11	37	Discharged alive	100	75	3	FALSE	None	73
72	South Cleveland	South Cleveland	29	980	1	1	Booked/born & ALL treatment level III	8	9	Discharged alive	30	21	0	FALSE	None	64
73	Bishop Auckland	Bishop Auckland	31	1750	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	26
74	RVI	RVI	29	1065	1	1	Booked/born level III, PN trans. level III	1	0	Discharged alive	70	21	8	TRUE	Left pulmonary artery hypoplasia	47
75	Dryburn	Sunderland	24	645	1	1	Booked level I, IUT to level III	35	13	Discharged alive	100	30	5	FALSE	None	93
76	RVI	RVI	25	950	1	1	Booked/born & ALL treatment level III	21	34	Discharged alive	47	25	0	FALSE	None	106
77	RVI	RVI	31	1470	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	47
78	RVI	RVI	31	1680	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	32	21	0	FALSE	None	38
79	RVI	RVI	31	1250	1	1	Transferred out of region	1	0	Discharged alive	30	24	0	FALSE	None	31
80	Dryburn	South Cleveland	28	960	1	1	Booked level I, IUT to level III	0	0	Discharged alive	30	21	4	FALSE	None	64
81	RVI	RVI	26	1030	1	1	Booked/born level III, PN trans. level III	5	37	Discharged alive	75	30	1	TRUE	ASD, VSD	102
82	Whitehaven	Whitehaven	31	1430	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	155
83	South Cleveland	South Cleveland	31	1690	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	32	21	6	FALSE	None	18
84	Whitehaven	Whitehaven	27	990	1	1	Booked/born level I, PN transfer	4	1	Discharged alive	30	21	0	FALSE	None	66
85	Whitehaven	Whitehaven	27	920	2	2	Booked/born level I, PN transfer	30	11	Discharged alive	100	54	9	FALSE	None	98
86	Whitehaven	Whitehaven	27	800	2	1	Booked/born level I, PN transfer	10	32	Discharged alive	90	38	5	FALSE	None	98
87	Whitehaven	Other	26	820	1	1	Other	16	5	Discharged alive	87	24	1	FALSE	None	66
88	Dryburn	RVI	30	1065	1	1	Booked level I, IUT to level III	0	6	Discharged alive	21	21	1	FALSE	None	45
89	Dryburn	North Tees	31	1270	2	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	27
90	Dryburn	North Tees	31	1570	2	2	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	27
91	Dryburn	Sunderland	27	1365	1	1	Booked level I, IUT to level III	3	1	Discharged alive	35	21	2	FALSE	None	45
92	South Tyneside	South Tyneside	27	1015	1	1	Booked/born level I, PN transfer	11	1	Discharged alive	100	23	6	FALSE	None	44
93	Hartlepool	RVI	23	590	1	1	Booked level I, IUT to level III	1	0	Died	100	65	4	FALSE	None	1
94	Whitehaven	RVI	31	1420	1	1	Booked level I, IUT to level III	0	1	Discharged alive	70	21	0	FALSE	None	40

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
95	North Tyneside	North Tyneside	27	1110	1	1	Booked/born level I, PN transfer	1	0	Died	100	100	6	FALSE	None	0
96	South Tyneside	South Tyneside	28	1160	2	1	Booked/born & ALL treatment level I	0	0	Discharged alive	35	25	8	FALSE	None	52
97	South Tyneside	South Tyneside	28	1140	2	2	Booked/born & ALL treatment level I	0	0	Discharged alive	39	25	7	FALSE	None	52
98	RVI	RVI	29	1000	2	1	Booked/born & ALL treatment level III	0	0	Died	21	21	0	TRUE	Holoprosencephaly, CLAP	0
99	RVI	RVI	29	1590	2	2	Booked/born & ALL treatment level III	2	1	Discharged alive	77	33	1	FALSE	None	31
100	Sunderland	Sunderland	26	855	1	1	Booked/born & ALL treatment level III	17	23	Discharged alive	50	30	0	FALSE	None	90
101	Sunderland	Sunderland	24	725	1	1	Booked/born & ALL treatment level III	13	0	Died	40	28	2	FALSE	None	12
102	South Tyneside	South Tyneside	30	1315	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	32
103	Whitehaven	Whitehaven	27	760	1	1	Booked/born & ALL treatment level I	1	0	Died	90	90	13	FALSE	None	1
104	Hartlepool	Hartlepool	31	1720	2	1	Booked/born level I, PN transfer	6	2	Discharged alive	100	32	6	FALSE	None	62
105	Hartlepool	Hartlepool	31	1860	2	2	Booked/born level I, PN transfer	5	0	Discharged alive	60	21	5	FALSE	None	62
106	Whitehaven	Whitehaven	24	700	1	1	Booked/born level I, PN transfer	13	45	Discharged alive	72	22	5	FALSE	None	101
107	Sunderland	Sunderland	30	1340	1	1	Booked/born & ALL treatment level III	6	6	Died	21	21	3	FALSE	None	20
108	Hartlepool	Hartlepool	23	560	1	1	Booked/born level I, PN transfer	54	15	Discharged alive	100	22	20	FALSE	None	201
109	Out of region	Out of region	27	840	1	1	Booked ex-region (transferred)	9	9	Transferred	100	50	0	FALSE	None	18
110	South Tyneside	South Tyneside	29	1225	1	1	Booked/born & ALL treatment level I	0	3	Discharged alive	72	62	7	FALSE	None	42
111	South Cleveland	South Cleveland	27	760	1	1	Booked/born & ALL treatment level III	19	13	Discharged alive	57	21	4	FALSE	None	88
112	South Cleveland	South Cleveland	27	1130	1	1	Booked/born & ALL treatment level III	7	0	Discharged alive	35	21	4	FALSE	None	78
113	Hartlepool	North Tees	26	1030	1	1	Booked level I, IUT to level III	21	11	Discharged alive	30	21	13	FALSE	None	97
114	RVI	RVI	25	760	1	1	Booked/born & ALL treatment level III	1	0	Died	100	100	11	FALSE	None	1
115	Whitehaven	Whitehaven	31	1560	1	1	Booked/born level I, PN transfer	6	2	Discharged alive	90	28	6	FALSE	None	50
116	North Tees	North Tees	27	850	1	1	Booked/born & ALL treatment level III	5	0	Died	60	21	7	FALSE	None	4
117	Bishop Auckland	South Cleveland	27	625	1	1	Booked level I, IUT to level III	28	7	Discharged alive	100	100	14	FALSE	None	163
118	South Cleveland	RVI	25	700	1	1	Booked level III, IUT different level III	41	1	Died	50	30	10	FALSE	None	41
119	Hartlepool	Hartlepool	28	1650	1	1	Booked/born level I, PN transfer	3	0	Discharged alive	60	25	6	FALSE	None	60
120	Out of region	Out of region	28	1370	1	1	Booked ex-region (transferred)	15	4	Transferred	80	37	0	FALSE	None	21
121	Dryburn	Dryburn	31	1420	1	1	Booked/born & ALL treatment level I	0	2	Discharged alive	28	21	0	FALSE	None	33
122	RVI	RVI	31	1770	1	1	Booked/born & ALL treatment level III	0	7	Discharged alive	25	21	4	FALSE	None	29
123	RVI	RVI	28	950	1	1	Other	3	6	Discharged alive	21	21	0	FALSE	None	58
124	Out of region	Out of region	28	1310	1	1	Booked ex-region (transferred)	7	0	Transferred	100	60	10	FALSE	None	11
125	North Tees	North Tees	30	1540	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	40	27	6	FALSE	None	31
126	Ashington	RVI	30	1170	1	1	Booked level I, IUT to level III	0	4	Discharged alive	38	21	3	FALSE	None	38
127	RVI	RVI	26	1110	1	1	Booked/born & ALL treatment level III	11	0	Died	100	75	4	TRUE	11 ribs	11
128	Dryburn	North Tees	30	1850	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	9	FALSE	None	41
129	North Tyneside	RVI	25	600	1	1	Booked level I, IUT to level III	3	0	Died	60	30	13	FALSE	None	0
130	Ashington	Ashington	25	800	1	1	Transferred out of region	1	0	Discharged alive	100	80	8	FALSE	None	102
131	South Tyneside	South Tyneside	31	1595	1	1	Booked/born & ALL treatment level I	0	2	Discharged alive	60	25	11	FALSE	None	43
132	Sunderland	Sunderland	26	1600	1	1	Booked/born & ALL treatment level III	10	3	Died	100	75	3	FALSE	None	12
133	Gateshead	Gateshead	31	1600	1	1	Booked/born & ALL treatment level I	3	5	Discharged alive	82	40	5	FALSE	None	39
134	Bishop Auckland	Bishop Auckland	29	1400	3	3	Booked/born level I, PN transfer	10	7	Discharged alive	90	60	13	FALSE	None	79
135	Bishop Auckland	Bishop Auckland	29	860	3	1	Transferred out of region	1	0	Discharged alive	40	21	6	TRUE	Large VSD	132
136	Bishop Auckland	Bishop Auckland	29	1370	3	2	Transferred out of region	1	0	Discharged alive	80	60	4	FALSE	None	45
137	South Cleveland	South Cleveland	31	1410	2	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	8	FALSE	None	31
138	South Cleveland	South Cleveland	31	1495	2	2	Booked/born & ALL treatment level III	0	2	Discharged alive	21	21	7	FALSE	None	31
139	Ashington	RVI	26	980	1	1	Booked level I, IUT to level III	18	15	Discharged alive	95	35	1	TRUE	Congenital dislocation of hip	95
140	North Tyneside	North Tyneside	31	1550	1	1	Booked/born & ALL treatment level I	0	4	Discharged alive	49	33	1	FALSE	None	61
142	Sunderland	Sunderland	29	1380	1	1	Booked/born & ALL treatment level III	3	2	Discharged alive	25	21	2	FALSE	None	49

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
143	RVI	RVI	31	1245	1	1	Booked/born & ALL treatment level III	2	4	Discharged alive	70	21	12	FALSE	None	42
144	RVI	RVI	25	750	3	3	Booked/born & ALL treatment level III	8	0	Died	100	50	6	FALSE	None	8
145	RVI	RVI	25	570	3	2	Booked/born & ALL treatment level III	28	0	Died	60	25	5	FALSE	None	28
146	RVI	RVI	25	550	3	1	Booked/born & ALL treatment level III	62	10	Died	51	25	8	FALSE	None	110
147	South Cleveland	RVI	30	1510	1	1	Booked level III, IUT different level III	55	18	Discharged alive	100	100	0	TRUE	TOF and VACTERL	115
148	South Cleveland	South Cleveland	28	1120	1	1	Booked/born & ALL treatment level III	6	10	Discharged alive	30	21	5	FALSE	None	63
149	South Cleveland	South Cleveland	31	1645	1	1	Booked/born & ALL treatment level III	5	9	Discharged alive	50	30	2	FALSE	None	50
150	South Cleveland	North Tees	28	660	1	1	Booked level III, IUT different level III	8	0	Died	60	21	13	FALSE	None	7
151	Hartlepool	Hartlepool	31	1270	1	1	Booked/born level I, PN transfer	7	3	Discharged alive	70	40	4	FALSE	None	59
152	North Tees	North Tees	25	920	1	1	Booked/born & ALL treatment level III	2	0	Died	100	50	3	FALSE	None	32
153	Carlisle	Sunderland	28	1230	1	1	Booked level I, IUT to level III	1	1	Discharged alive	21	21	0	FALSE	None	47
154	North Tees	North Tees	31	1650	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	18
155	Ashington	RVI	31	1460	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	5	FALSE	None	62
156	South Cleveland	South Cleveland	29	1360	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	55
157	Dryburn	Dryburn	29	1430	1	1	Booked/born level I, PN transfer	9	4	Discharged alive	100	82	9	FALSE	None	51
158	RVI	RVI	29	1340	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	21	21	0	FALSE	None	53
159	RVI	RVI	30	1210	2	1	Other	0	0	Discharged alive	21	21	0	FALSE	None	34
160	RVI	RVI	30	1585	2	2	Other	0	0	Discharged alive	21	21	0	FALSE	None	34
161	Carlisle	Carlisle	27	1164	1	1	Booked/born level I, PN transfer	13	37	Discharged alive	100	70	15	TRUE	Pulm Art branch stenosis	75
162	Ashington	RVI	24	770	2	2	Booked level I, IUT to level III	1	0	Died	100	58	15	FALSE	None	1
163	Ashington	RVI	24	695	2	1	Booked level I, IUT to level III	1	0	Died	100	70	6	FALSE	None	1
164	Out of region	RVI	30	2095	1	1	Other	38	3	Died	64	25	11	TRUE	Malignant sarcomata	61
165	North Tees	North Tees	31	1620	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	3	FALSE	none	33
166	Hartlepool	Hartlepool	30	1050	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	60	30	2	FALSE	None	49
167	Bishop Auckland	North Tees	29	1300	2	1	Booked level I, IUT to level III	2	1	Discharged alive	30	21	3	FALSE	None	62
168	Bishop Auckland	North Tees	29	1220	2	2	Booked level I, IUT to level III	2	1	Discharged alive	30	21	5	FALSE	None	62
169	North Tees	North Tees	27	1100	1	1	Booked/born & ALL treatment level III	5	8	Discharged alive	30	21	7	FALSE	None	56
170	Whitehaven	Whitehaven	24	750	1	1	Booked/born & ALL treatment level I	1	0	Died	100	40	18	FALSE	None	0
171	North Tees	North Tees	24	760	1	1	Booked/born & ALL treatment level III	2	0	Died	60	60	19	FALSE	None	1
172	Dryburn	Dryburn	29	1225	1	1	Booked/born level I, PN transfer	2	1	Discharged alive	41	25	1	FALSE	None	34
173	South Tyneside	South Tyneside	30	1775	1	1	Booked/born & ALL treatment level I	5	1	Discharged alive	69	34	12	FALSE	None	44
174	South Cleveland	South Cleveland	29	1010	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	40	21	6	FALSE	None	61
175	Darlington	South Cleveland	25	535	1	1	Booked level I, IUT to level III	68	18	Discharged alive	80	30	9	FALSE	None	132
176	Carlisle	Carlisle	24	708	1	1	Booked/born level I, PN transfer	27	13	Transferred	69	30	11	FALSE	None	40
177	South Cleveland	South Cleveland	26	820	1	1	Booked/born & ALL treatment level III	4	4	Discharged alive	40	21	13	FALSE	None	71
178	South Cleveland	South Cleveland	28	1190	2	1	Booked/born & ALL treatment level III	3	0	Discharged alive	34	24	5	FALSE	None	44
179	South Cleveland	South Cleveland	30	920	1	1	Booked/born & ALL treatment level III	0	8	Discharged alive	30	28	2	TRUE	CLAP	80
180	South Cleveland	South Cleveland	28	1190	2	2	Booked/born & ALL treatment level III	1	2	Discharged alive	60	32	5	FALSE	None	43
181	RVI	RVI	28	1080	1	1	Booked/born & ALL treatment level III	10	12	Discharged alive	30	21	4	FALSE	None	87
182	Ashington	RVI	27	810	1	1	Booked level I, IUT to level III	20	14	Discharged alive	100	57	4	FALSE	None	77
183	Dryburn	Sunderland	31	1520	2	1	Booked level I, IUT to level III	0	0	Discharged alive	24	21	1	TRUE	Trisomy 21	41
184	Dryburn	Sunderland	31	1202	2	2	Booked level I, IUT to level III	0	0	Discharged alive	21	21	1	FALSE	None	41
185	Ashington	RVI	29	450	2	1	Booked level I, IUT to level III	1	5	Discharged alive	50	21	10	TRUE	Hypospadias	117
186	Ashington	RVI	29	1460	2	2	Booked level I, IUT to level III	0	4	Discharged alive	30	21	2	FALSE	None	98
187	RVI	RVI	25	630	1	1	Booked/born & ALL treatment level III	50	34	Discharged alive	60	21	5	FALSE	None	137
188	RVI	Sunderland	29	1540	1	1	Booked level III, IUT different level III	0	10	Discharged alive	80	40	7	FALSE	None	54
189	North Tyneside	North Tyneside	29	1520	1	1	Booked/born level I, PN transfer	5	3	Discharged alive	50	21	6	FALSE	None	52
190	RVI	Sunderland	29	1240	1	1	Booked level III, IUT different level III	0	2	Discharged alive	32	21	3	FALSE	None	45

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
191	Sunderland	Sunderland	31	1905	2	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	1	FALSE	None	27
192	Sunderland	Sunderland	31	1635	2	2	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	27
193	Hexham	Other	27	1140	1	1	Other	1	8	Discharged alive	0	0	0	FALSE	None	66
194	Dryburn	Dryburn	31	1375	1	1	Booked/born & ALL treatment level I	4	4	Discharged alive	78	62	0	FALSE	None	49
195	Bishop Auckland	Bishop Auckland	31	1800	1	1	Booked/born level I, PN transfer	4	1	Discharged alive	46	31	6	FALSE	None	7
196	Bishop Auckland	RVI	31	2500	1	1	Booked level I, IUT to level III	1	0	Died	100	100	10	TRUE	Pulm lymphangiectasia	0
197	Unbooked	North Tyneside	30	1630	1	1	Not booked prior to delivery	1	0	Died	100	90	13	FALSE	None	0
198	Dryburn	RVI	31	1490	3	1	Booked level I, IUT to level III	0	0	Discharged alive	27	21	0	FALSE	None	41
199	Dryburn	RVI	31	1265	3	2	Booked level I, IUT to level III	0	0	Discharged alive	25	21	0	FALSE	None	46
200	Dryburn	RVI	31	1130	3	3	Booked level I, IUT to level III	0	0	Discharged alive	24	21	0	FALSE	None	66
201	South Cleveland	South Cleveland	26	670	1	1	Booked/born & ALL treatment level III	24	6	Discharged alive	30	21	4	FALSE	None	136
202	Hartlepool	Hartlepool	27	1130	1	1	Booked/born level I, PN transfer	15	12	Discharged alive	90	74	10	FALSE	None	95
203	Whitehaven	Whitehaven	31	1580	1	1	Booked/born level I, PN transfer	15	12	Discharged alive	99	40	9	FALSE	None	43
204	Dryburn	RVI	26	505	1	1	Booked level I, IUT to level III	45	16	Discharged alive	50	25	0	FALSE	None	110
205	Gateshead	RVI	28	1180	1	1	Booked level I, IUT to level III	1	4	Discharged alive	30	21	0	FALSE	None	52
206	Carlisle	Carlisle	26	880	1	1	Booked/born level I, PN transfer	6	22	Discharged alive	60	30	10	FALSE	None	90
207	Sunderland	Sunderland	29	1585	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	31	21	2	FALSE	None	32
208	Ashington	Ashington	31	1770	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	21	21	0	FALSE	None	35
209	Ashington	Ashington	31	1830	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	60	21	0	FALSE	None	35
210	Bishop Auckland	RVI	27	1235	1	1	Booked level I, IUT to level III	3	4	Discharged alive	40	21	0	FALSE	None	69
211	North Tyneside	North Tyneside	29	1670	1	1	Booked/born & ALL treatment level I	0	2	Discharged alive	35	28	6	FALSE	None	30
212	Gateshead	RVI	29	1290	1	1	Booked level I, IUT to level III	1	2	Discharged alive	70	27	2	FALSE	None	48
213	Dryburn	Dryburn	30	1375	1	1	Booked/born level I, PN transfer	4	6	Discharged alive	100	27	4	FALSE	None	43
214	Sunderland	Sunderland	29	1315	1	1	Booked/born & ALL treatment level III	0	6	Discharged alive	30	21	1	FALSE	None	47
215	Ashington	Ashington	29	1435	1	1	Booked/born & ALL treatment level I	0	2	Discharged alive	53	35	19	FALSE	None	44
216	Whitehaven	RVI	29	1150	1	1	Booked level I, IUT to level III	2	1	Discharged alive	26	21	3	FALSE	None	48
217	Whitehaven	North Tees	26	680	1	1	Booked level I, IUT to level III	6	0	Died	80	40	5	FALSE	None	5
218	Bishop Auckland	Bishop Auckland	24	630	1	1	Booked/born level I, PN transfer	98	11	Died	100	50	12	FALSE	None	196
219	South Cleveland	South Cleveland	24	770	2	1	Booked/born & ALL treatment level III	1	0	Died	100	100	0	FALSE	None	0
220	South Cleveland	South Cleveland	24	740	2	2	Booked/born & ALL treatment level III	13	0	Died	100	100	0	FALSE	None	0
221	RVI	RVI	30	1405	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	1	FALSE	None	35
222	RVI	RVI	31	830	1	1	Booked/born & ALL treatment level III	0	3	Discharged alive	22	21	0	FALSE	None	74
223	Ashington	Ashington	26	875	1	1	Booked/born & ALL treatment level I	1	0	Died	100	100	30	FALSE	None	0
224	Bishop Auckland	South Cleveland	27	1030	1	1	Booked level I, IUT to level III	2	0	Discharged alive	21	21	0	FALSE	None	52
225	South Cleveland	North Tees	27	880	1	1	Booked level III, IUT different level III	5	6	Discharged alive	43	21	2	FALSE	None	89
226	South Cleveland	South Cleveland	31	1010	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	4	FALSE	None	27
227	South Tyneside	RVI	30	980	1	1	Booked level I, IUT to level III	0	3	Discharged alive	25	21	5	FALSE	None	57
228	South Cleveland	South Cleveland	25	575	1	1	Booked/born & ALL treatment level III	2	0	Died	55	45	10	FALSE	None	2
229	Out of region	Out of region	26	650	1	1	Booked ex-region (transferred)	11	29	Transferred	40	25	0	FALSE	None	44
230	RVI	RVI	31	1415	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	30
231	Carlisle	Carlisle	30	1338	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	26	25	8	FALSE	None	14
232	North Tyneside	RVI	27	1010	1	1	Booked level I, IUT to level III	37	43	Discharged alive	100	36	6	FALSE	None	118
233	North Tees	North Tees	31	1850	1	1	Booked/born & ALL treatment level III	4	3	Discharged alive	90	30	3	FALSE	None	34
234	RVI	RVI	29	700	1	1	Booked/born & ALL treatment level III	74	114	Died	30	21	1	TRUE	Gastro-intestinal malrotation	217
235	South Cleveland	South Cleveland	31	1685	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	19
236	RVI	Carlisle	31	1680	1	1	Other	6	3	Discharged alive	100	30	4	FALSE	None	45
237	Sunderland	Sunderland	26	870	1	1	Booked/born & ALL treatment level III	15	17	Discharged alive	45	35	10	FALSE	None	72

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
238	Whitehaven	Whitehaven	30	1840	1	1	Booked/born level I, PN transfer	6	2	Discharged alive	100	40	12	FALSE	None	42
239	Ashington	RVI	28	1020	1	1	Booked level I, IUT to level III	9	22	Discharged alive	80	48	4	FALSE	None	32
240	South Cleveland	South Cleveland	27	1270	1	1	Booked/born & ALL treatment level III	0	5	Discharged alive	40	21	0	FALSE	None	67
241	Hartlepool	Sunderland	28	1020	1	1	Booked level I, IUT to level III	0	0	Discharged alive	40	21	4	FALSE	None	65
242	South Cleveland	South Cleveland	28	1020	1	1	Booked/born & ALL treatment level III	0	26	Discharged alive	30	30	7	FALSE	None	103
243	South Cleveland	South Cleveland	31	2135	1	1	Booked/born & ALL treatment level III	2	1	Discharged alive	80	37	0	FALSE	None	16
244	RVI	RVI	28	1105	1	1	Booked/born & ALL treatment level III	4	7	Discharged alive	28	21	0	FALSE	None	84
245	South Tyneside	Sunderland	28	995	1	1	Booked level I, IUT to level III	21	20	Discharged alive	40	21	7	FALSE	None	73
246	North Tyneside	RVI	29	1355	1	1	Other	11	5	Discharged alive	58	33	0	FALSE	None	72
247	Out of region	RVI	25	780	1	1	Booked ex-region (transferred)	30	1	Transferred	100	42	4	FALSE	None	127
248	RVI	RVI	31	1765	1	1	Booked/born & ALL treatment level III	2	0	Discharged alive	25	21	0	FALSE	None	22
249	Out of region	North Tees	30	1680	3	1	Booked ex-region (transferred)	5	0	Transferred	30	21	11	FALSE	None	6
250	Out of region	North Tees	30	1750	3	2	Booked ex-region (transferred)	5	0	Transferred	33	21	8	FALSE	None	6
251	Out of region	North Tees	30	1430	3	3	Booked ex-region (transferred)	5	0	Transferred	80	30	11	FALSE	None	6
252	Carlisle	Carlisle	27	1240	1	1	Booked/born level I, PN transfer	2	14	Discharged alive	70	21	9	TRUE	Bilateral talipes equinovarus	60
253	South Tyneside	South Tyneside	27	1070	1	1	Booked/born level I, PN transfer	12	16	Discharged alive	73	32	10	FALSE	None	68
254	Whitehaven	RVI	31	1290	1	1	Booked level I, IUT to level III	5	0	Discharged alive	37	21	5	FALSE	None	73
255	Sunderland	Sunderland	25	810	1	1	Booked/born & ALL treatment level III	2	0	Died	60	60	19	FALSE	None	1
256	Dryburn	Dryburn	31	1350	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	26	21	2	FALSE	None	27
257	RVI	RVI	31	1940	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	47
258	North Tyneside	RVI	30	1070	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	4	FALSE	None	45
259	South Tyneside	South Tyneside	31	1795	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	TRUE	Amniotic band sequence R arm	23
260	Hartlepool	North Tees	27	1210	1	1	Booked level I, IUT to level III	5	27	Discharged alive	40	21	4	FALSE	None	78
261	Sunderland	Sunderland	31	1705	2	2	Booked/born & ALL treatment level III	0	5	Discharged alive	50	30	6	FALSE	None	27
262	RVI	RVI	31	1940	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	5	FALSE	None	33
263	Ashington	RVI	31	1720	1	1	Booked level I, IUT to level III	0	0	Discharged alive	25	21	4	FALSE	None	17
264	RVI	RVI	27	900	1	1	Booked/born & ALL treatment level III	6	43	Discharged alive	100	21	13	FALSE	None	86
265	North Tyneside	Sunderland	28	1135	2	1	Booked level I, IUT to level III	10	2	Discharged alive	50	21	2	FALSE	None	73
266	North Tyneside	Sunderland	28	1220	2	2	Booked level I, IUT to level III	10	2	Died	32	21	4	FALSE	None	11
267	Ashington	Ashington	31	1480	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	30	23	0	FALSE	None	26
268	South Cleveland	South Cleveland	24	560	1	1	Booked/born & ALL treatment level III	40	25	Discharged alive	75	33	6	FALSE	None	139
269	South Cleveland	South Cleveland	28	1010	2	1	Booked/born & ALL treatment level III	26	11	Discharged alive	56	44	5	FALSE	None	86
270	South Cleveland	South Cleveland	28	1280	2	2	Booked/born & ALL treatment level III	5	0	Discharged alive	35	24	5	FALSE	None	55
271	South Cleveland	South Cleveland	29	1460	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	23	21	0	FALSE	None	43
272	Bishop Auckland	South Cleveland	30	1440	1	1	Booked level I, IUT to level III	8	0	Discharged alive	100	21	4	FALSE	None	49
273	Sunderland	Sunderland	29	1385	2	1	Booked/born & ALL treatment level III	0	4	Discharged alive	28	21	4	FALSE	None	43
274	Sunderland	Sunderland	29	1280	2	2	Booked/born & ALL treatment level III	5	1	Discharged alive	50	21	4	FALSE	None	43
275	Ashington	North Tees	29	820	1	1	Booked level I, IUT to level III	18	9	Discharged alive	52	21	11	FALSE	None	69
276	South Cleveland	RVI	31	1195	1	1	Booked level III, IUT different level III	18	9	Died	21	21	5	TRUE	Atrioventricular septal defect	28
277	North Tees	North Tees	27	1070	1	1	Booked/born & ALL treatment level III	27	14	Discharged alive	100	60	12	TRUE	Obstructive uropathy (?type)	81
278	Whitehaven	Whitehaven	31	1380	1	1	Booked/born level I, PN transfer	1	0	Discharged alive	40	21	10	FALSE	None	44
279	North Tees	North Tees	30	1170	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	79
280	Bishop Auckland	RVI	30	1330	1	1	Booked level I, IUT to level III	0	4	Discharged alive	40	21	0	FALSE	None	49
281	Ashington	RVI	31	1810	1	1	Booked level I, IUT to level III	0	0	Discharged alive	25	21	2	FALSE	None	29
282	Hartlepool	Hartlepool	28	1045	1	1	Booked/born level I, PN transfer	23	45	Discharged alive	100	50	8	FALSE	None	96

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
283	South Cleveland	South Cleveland	31	1175	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	2	FALSE	None	20
284	North Tees	North Tees	31	1130	1	1	Booked/born & ALL treatment level III	0	3	Discharged alive	30	21	4	FALSE	None	36
285	South Tyneside	South Tyneside	31	1825	1	1	Booked/born & ALL treatment level I	0	4	Discharged alive	70	40	7	FALSE	None	42
286	Sunderland	Sunderland	28	1185	1	1	Booked/born & ALL treatment level III	1	10	Discharged alive	40	21	6	FALSE	None	54
287	Sunderland	Sunderland	31	2335	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	43
288	North Tyneside	RVI	30	1040	1	1	Booked level I, IUT to level III	0	9	Discharged alive	21	21	0	FALSE	None	15
289	South Cleveland	South Cleveland	27	1210	1	1	Booked/born & ALL treatment level III	4	0	Discharged alive	60	21	1	FALSE	None	51
290	Hartlepool	South Cleveland	28	1250	1	1	Booked level I, IUT to level III	3	0	Discharged alive	21	21	3	FALSE	None	57
291	South Cleveland	South Cleveland	31	2140	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	26
292	Hartlepool	Hartlepool	28	1200	1	1	Booked/born level I, PN transfer	31	13	Discharged alive	100	40	13	FALSE	None	103
293	Bishop Auckland	Sunderland	28	1210	1	1	Booked level I, IUT to level III	5	3	Died	45	21	5	FALSE	None	10
294	RVI	RVI	30	1430	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	22	21	0	FALSE	None	54
295	Whitehaven	RVI	30	1430	1	1	Booked level I, IUT to level III	7	2	Discharged alive	70	32	0	FALSE	None	49
296	North Tyneside	Sunderland	27	700	1	1	Booked level I, IUT to level III	17	2	Discharged alive	100	40	16	FALSE	None	75
297	North Tyneside	RVI	30	1390	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	35
298	Carlisle	Carlisle	30	1526	1	1	Booked/born level I, PN transfer	7	4	Discharged alive	100	21	3	TRUE	VSD, duplex ureter	37
299	Dryburn	RVI	28	1570	1	1	Booked level I, IUT to level III	2	1	Discharged alive	92	21	2	FALSE	None	47
300	South Cleveland	South Cleveland	29	1400	1	1	Booked/born & ALL treatment level III	2	0	Discharged alive	40	21	0	FALSE	None	29
301	Sunderland	Sunderland	31	1635	1	1	Booked/born & ALL treatment level III	3	1	Discharged alive	60	21	3	FALSE	None	33
302	Gateshead	RVI	25	700	1	1	Booked level I, IUT to level III	36	51	Discharged alive	100	80	2	FALSE	None	204
303	North Tees	North Tees	31	1370	1	1	Booked/born & ALL treatment level III	4	0	Died	30	21	4	FALSE	None	11
304	Sunderland	Sunderland	29	1320	1	1	Booked/born & ALL treatment level III	11	3	Discharged alive	95	65	3	FALSE	None	62
305	Sunderland	Sunderland	27	890	1	1	Booked/born & ALL treatment level III	35	25	Discharged alive	90	40	12	FALSE	None	86
306	Out of region	Out of region	30	1690	1	1	Booked ex-region (transferred)	10	3	Transferred	100	50	7	FALSE	None	14
307	RVI	RVI	26	805	1	1	Booked/born & ALL treatment level III	5	37	Discharged alive	76	21	0	FALSE	None	92
308	Sunderland	Sunderland	28	1355	1	1	Booked/born & ALL treatment level III	5	2	Discharged alive	90	25	1	FALSE	None	52
309	RVI	RVI	31	1680	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	44	21	7	FALSE	None	41
310	Ashington	RVI	30	1410	1	1	Booked level I, IUT to level III	0	1	Discharged alive	21	21	0	FALSE	None	31
311	Gateshead	RVI	30	1111	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	1	FALSE	None	40
312	Ashington	Ashington	25	580	1	1	Booked/born level I, PN transfer	5	0	Died	100	50	14	FALSE	None	5
313	RVI	RVI	31	1920	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	39	38	0	FALSE	None	29
314	Dryburn	RVI	25	785	1	1	Booked level I, IUT to level III	111	10	Died	100	76	3	TRUE	Atrial septal defect	147
315	South Cleveland	South Cleveland	30	1105	2	1	Booked/born & ALL treatment level III	11	12	Discharged alive	50	21	8	FALSE	None	82
316	South Cleveland	South Cleveland	30	895	2	2	Booked/born & ALL treatment level III	0	3	Discharged alive	32	21	6	FALSE	None	78
317	Bishop Auckland	North Tees	28	1310	2	1	Booked level I, IUT to level III	2	1	Discharged alive	30	21	0	FALSE	None	56
318	Bishop Auckland	North Tees	28	1410	2	2	Booked level I, IUT to level III	2	1	Discharged alive	30	21	4	FALSE	None	56
319	North Tyneside	RVI	28	1320	1	1	Booked level I, IUT to level III	0	1	Discharged alive	21	21	0	FALSE	None	38
320	RVI	RVI	27	1155	1	1	Booked/born & ALL treatment level III	3	30	Discharged alive	21	21	1	FALSE	None	79
321	RVI	RVI	31	1160	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	27	21	0	TRUE	Hypospadias	38
322	South Cleveland	South Cleveland	27	837	1	1	Booked/born & ALL treatment level III	7	16	Discharged alive	100	50	22	FALSE	None	51
323	North Tees	North Tees	31	1910	1	1	Booked/born & ALL treatment level III	0	2	Discharged alive	30	21	8	FALSE	None	24
324	Dryburn	Dryburn	24	690	1	1	Booked/born level I, PN transfer	1	0	Died	100	100	11	FALSE	None	1
325	South Cleveland	South Cleveland	26	995	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	60	30	0	FALSE	None	67
326	Bishop Auckland	Bishop Auckland	29	1180	1	1	Booked/born level I, PN transfer	2	0	Discharged alive	50	22	8	FALSE	None	63
327	Whitehaven	Whitehaven	29	1300	2	2	Booked/born level I, PN transfer	7	0	Died	80	40	8	FALSE	None	8
328	Whitehaven	Whitehaven	29	1460	2	1	Booked/born level I, PN transfer	2	12	Discharged alive	35	25	8	FALSE	None	8
329	South Tyneside	South Tyneside	31	1255	1	1	Booked/born & ALL treatment level I	1	3	Discharged alive	65	30	8	FALSE	None	42
330	RVI	RVI	31	1545	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	37
331	South Cleveland	South Cleveland	31	1750	1	1	Booked/born & ALL treatment level III	2	0	Discharged alive	72	21	7	FALSE	None	20

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
332	RVI	RVI	24	545	1	1	Booked/born & ALL treatment level III	3	0	Died	90	55	4	FALSE	None	3
333	Gateshead	Gateshead	28	1070	1	1	Booked/born level I, PN transfer	34	28	Discharged alive	100	80	7	FALSE	None	66
334	Gateshead	Gateshead	29	965	1	1	Booked/born & ALL treatment level I	0	4	Discharged alive	30	24	5	FALSE	None	3
335	Out of region	Out of region	28	1200	1	1	Booked ex-region (transferred)	4	3	Transferred	90	26	13	FALSE	None	27
336	South Cleveland	South Cleveland	29	1160	1	1	Booked/born & ALL treatment level III	4	0	Discharged alive	100	50	13	FALSE	None	45
337	RVI	RVI	28	1185	1	1	Booked/born & ALL treatment level III	4	30	Discharged alive	28	21	3	FALSE	None	117
338	South Tyneside	RVI	31	1070	2	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	39
339	South Tyneside	RVI	31	1470	2	2	Booked level I, IUT to level III	3	0	Discharged alive	65	42	11	FALSE	None	39
340	Hartlepool	North Tees	29	1180	1	1	Booked level I, IUT to level III	3	15	Discharged alive	25	21	0	FALSE	None	63
341	RVI	RVI	27	755	1	1	Booked/born & ALL treatment level III	0	12	Discharged alive	29	21	3	FALSE	None	46
342	Dryburn	Sunderland	25	755	1	1	Booked level I, IUT to level III	7	1	Died	75	21	4	FALSE	None	7
343	Whitehaven	Whitehaven	30	1720	1	1	Booked/born level I, PN transfer	7	3	Discharged alive	100	53	6	FALSE	None	65
344	Bishop Auckland	Bishop Auckland	31	1660	1	1	Booked/born level I, PN transfer	4	0	Discharged alive	100	27	3	FALSE	None	26
345	South Cleveland	South Cleveland	26	1000	1	1	Booked/born & ALL treatment level III	14	15	Discharged alive	80	30	0	FALSE	None	101
346	Ashington	Ashington	28	1175	2	1	Booked/born level I, PN transfer	8	17	Discharged alive	100	70	16	FALSE	None	79
347	Ashington	Ashington	28	1140	2	2	Booked/born level I, PN transfer	8	19	Discharged alive	100	80	12	FALSE	None	79
348	Sunderland	Sunderland	29	1510	1	1	Booked/born & ALL treatment level III	13	4	Discharged alive	55	28	1	FALSE	None	48
349	South Cleveland	South Cleveland	24	690	1	1	Booked/born & ALL treatment level III	57	0	Discharged alive	90	50	11	FALSE	None	130
350	RVI	RVI	25	730	1	1	Booked/born & ALL treatment level III	3	47	Discharged alive	21	21	6	FALSE	None	91
351	RVI	RVI	28	1105	2	1	Booked/born & ALL treatment level III	0	2	Discharged alive	23	21	12	TRUE	ASD	74
352	RVI	RVI	28	1050	2	2	Booked/born & ALL treatment level III	1	19	Discharged alive	60	30	20	TRUE	Pulm Art branch stenosis	74
353	Gateshead	RVI	31	925	1	1	Booked level I, IUT to level III	0	2	Discharged alive	29	21	4	FALSE	None	53
354	Darlington	Darlington	31	2010	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	23
355	Darlington	Darlington	31	1770	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	24	21	8	FALSE	None	34
356	RVI	RVI	29	1280	1	1	Booked/born & ALL treatment level III	1	1	Discharged alive	21	21	8	FALSE	None	60
357	South Cleveland	South Cleveland	30	1615	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	25	25	6	FALSE	None	29
358	South Cleveland	South Cleveland	30	1580	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	21
359	South Tyneside	RVI	27	970	2	1	Booked level I, IUT to level III	0	18	Discharged alive	50	21	0	FALSE	None	60
360	South Tyneside	RVI	27	905	2	2	Booked level I, IUT to level III	0	20	Discharged alive	50	21	0	FALSE	None	60
361	RVI	RVI	25	775	1	1	Booked/born & ALL treatment level III	10	2	Died	60	27	0	FALSE	None	14
362	RVI	Sunderland	30	1305	2	1	Booked level III, IUT different level III	7	0	Discharged alive	50	21	0	FALSE	None	55
363	RVI	Sunderland	30	1150	2	2	Booked level III, IUT different level III	0	6	Discharged alive	40	21	7	FALSE	None	55
364	North Tees	North Tees	29	1390	1	1	Booked/born & ALL treatment level III	6	0	Discharged alive	66	47	3	FALSE	None	37
365	South Cleveland	South Cleveland	27	855	1	1	Booked/born & ALL treatment level III	4	10	Discharged alive	100	21	7	TRUE	Small VSD	70
366	South Cleveland	South Cleveland	30	1580	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	28	21	5	FALSE	None	31
367	Bishop Auckland	South Cleveland	31	1760	2	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	4	FALSE	None	33
368	Bishop Auckland	South Cleveland	31	1450	2	2	Booked level I, IUT to level III	0	0	Discharged alive	21	21	4	FALSE	None	33
369	South Cleveland	South Cleveland	29	1360	1	1	Booked/born & ALL treatment level III	8	0	Discharged alive	60	40	8	FALSE	None	54
370	South Cleveland	South Cleveland	27	1310	1	1	Booked/born & ALL treatment level III	1	0	Died	100	100	0	FALSE	None	1
371	South Cleveland	South Cleveland	27	1100	1	1	Booked/born & ALL treatment level III	9	8	Discharged alive	100	26	6	FALSE	None	74
372	Gateshead	Gateshead	28	1150	1	1	Booked/born level I, PN transfer	7	8	Discharged alive	100	49	2	FALSE	None	60
373	Out of region	North Tees	31	2100	1	1	Booked ex-region (transferred)	0	0	Transferred	21	21	8	FALSE	None	0
374	South Cleveland	South Cleveland	31	1310	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	6	FALSE	None	32
375	North Tees	North Tees	31	2060	1	1	Booked/born & ALL treatment level III	5	1	Discharged alive	50	25	7	FALSE	None	24
376	Out of region	Out of region	29	915	1	1	Booked ex-region (transferred)	10	2	Transferred	100	91	7	FALSE	None	16
377	RVI	RVI	29	1240	1	1	Booked/born level III, PN trans. level III	0	1	Discharged alive	57	21	0	FALSE	None	53
378	Bishop Auckland	Bishop Auckland	29	1320	1	1	Booked/born level I, PN transfer	3	3	Discharged alive	50	21	2	FALSE	None	51
379	Darlington	North Tees	28	1120	1	1	Booked level I, IUT to level III	6	0	Discharged alive	47	21	0	FALSE	None	53

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
380	Darlington	Darlington	31	1390	1	1	Booked/born & ALL treatment level I	1	0	Died	100	35	12	FALSE	None	0
381	Sunderland	Sunderland	25	765	1	1	Booked/born & ALL treatment level III	37	38	Discharged alive	40	21	3	FALSE	None	172
382	Hartlepool	North Tees	24	560	1	1	Booked level I, IUT to level III	82	6	Discharged alive	90	21	13	FALSE	None	200
383	RVI	RVI	27	1125	1	1	Booked/born & ALL treatment level III	1	16	Discharged alive	21	21	4	FALSE	None	82
384	RVI	RVI	28	1065	1	1	Booked/born & ALL treatment level III	7	11	Discharged alive	95	37	2	FALSE	None	63
385	Carlisle	Carlisle	28	1346	1	1	Booked/born level I, PN transfer	5	11	Discharged alive	40	21	7	FALSE	None	69
386	South Cleveland	South Cleveland	30	1000	1	1	Booked/born & ALL treatment level III	1	1	Discharged alive	21	21	11	FALSE	None	39
387	Hartlepool	North Tees	30	1570	1	1	Booked level I, IUT to level III	9	37	Discharged alive	100	90	17	FALSE	None	129
388	RVI	RVI	31	1590	2	1	Booked/born level III, PN trans. level III	5	0	Discharged alive	100	27	9	FALSE	None	31
389	RVI	RVI	31	1540	2	2	Booked/born level III, PN trans. level III	4	0	Discharged alive	45	21	2	FALSE	None	31
390	Gateshead	Gateshead	26	630	1	1	Booked/born level I, PN transfer	19	14	Discharged alive	80	21	5	TRUE	Duplex L kidney/ureter	101
391	Dryburn	Dryburn	26	880	2	1	Booked/born & ALL treatment level I	1	0	Died	100	79	7	FALSE	None	0
392	Dryburn	Dryburn	26	765	2	2	Booked/born level I, PN transfer	7	1	Died	100	55	7	FALSE	None	7
393	Darlington	South Cleveland	31	1370	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	4	FALSE	None	30
394	Gateshead	RVI	28	1270	1	1	Booked level I, IUT to level III	15	0	Died	100	70	2	FALSE	None	15
395	Ashington	Ashington	28	1040	1	1	Booked/born level I, PN transfer	0	0	Discharged alive	21	21	6	FALSE	None	58
396	Sunderland	Sunderland	28	775	1	1	Booked/born & ALL treatment level III	22	28	Discharged alive	80	25	11	FALSE	None	85
397	Hartlepool	North Tees	30	1360	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	4
398	South Tyneside	South Cleveland	29	1710	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	4	FALSE	None	37
399	North Tyneside	North Tyneside	27	1150	2	1	Booked/born level I, PN transfer	6	3	Discharged alive	100	21	5	FALSE	None	68
400	North Tyneside	North Tyneside	27	1330	2	1	Booked/born level I, PN transfer	5	3	Died	100	51	4	FALSE	None	5
401	Bishop Auckland	Bishop Auckland	31	1520	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	33
402	RVI	RVI	24	730	3	1	Booked/born & ALL treatment level III	1	0	Died	100	60	16	FALSE	None	1
403	RVI	RVI	24	640	3	2	Booked/born & ALL treatment level III	1	0	Died	100	100	0	FALSE	None	1
404	RVI	RVI	24	610	3	3	Booked/born & ALL treatment level III	30	1	Died	50	21	0	FALSE	None	31
405	Carlisle	Carlisle	27	960	1	1	Booked/born & ALL treatment level I	1	0	Died	100	95	18	TRUE	Pulmonary hypoplasia	1
406	South Cleveland	South Cleveland	27	945	1	1	Booked/born & ALL treatment level III	22	21	Discharged alive	80	21	7	FALSE	None	76
407	North Tees	North Tees	31	1970	1	1	Booked/born & ALL treatment level III	7	4	Discharged alive	40	28	8	FALSE	None	40
408	South Cleveland	South Cleveland	30	1760	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	28	21	5	FALSE	None	18
409	Sunderland	Sunderland	29	820	1	1	Booked/born & ALL treatment level III	3	2	Discharged alive	60	21	9	FALSE	None	47
410	RVI	RVI	26	800	2	1	Booked/born & ALL treatment level III	2	29	Discharged alive	100	21	10	FALSE	None	91
411	RVI	RVI	26	880	2	2	Booked/born & ALL treatment level III	1	0	Died	100	90	9	FALSE	None	1
412	Dryburn	South Cleveland	27	1180	1	1	Booked level I, IUT to level III	5	1	Discharged alive	50	26	10	FALSE	None	56
413	South Cleveland	South Cleveland	30	1850	1	1	Booked/born & ALL treatment level III	6	0	Discharged alive	33	24	6	FALSE	None	39
414	Sunderland	Sunderland	26	910	2	1	Booked/born & ALL treatment level III	2	0	Died	100	70	10	FALSE	None	1
415	Sunderland	Sunderland	26	765	2	2	Booked/born & ALL treatment level III	37	5	Died	21	21	5	FALSE	None	61
416	Hexham	RVI	27	1055	1	1	Booked level I, IUT to level III	1	2	Discharged alive	30	21	4	FALSE	None	75
417	South Cleveland	South Cleveland	31	1960	1	1	Booked/born & ALL treatment level III	0	2	Discharged alive	50	21	0	FALSE	None	15
418	Sunderland	Sunderland	26	795	1	1	Booked/born & ALL treatment level III	2	0	Died	100	90	8	FALSE	None	1
419	Out of region	South Cleveland	29	670	1	1	Booked ex-region (transferred)	1	1	Transferred	21	21	3	FALSE	None	7
420	Carlisle	Carlisle	31	1762	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	45	21	7	FALSE	None	31
421	North Tyneside	North Tyneside	29	1170	2	2	Booked/born level I, PN transfer	8	3	Discharged alive	100	83	8	FALSE	None	65
422	North Tyneside	North Tyneside	29	1330	2	1	Booked/born level I, PN transfer	8	2	Discharged alive	100	50	6	FALSE	None	65
423	RVI	RVI	31	1650	2	1	Booked/born & ALL treatment level III	0	1	Discharged alive	21	21	0	FALSE	None	33
424	RVI	RVI	31	1890	2	2	Booked/born & ALL treatment level III	0	1	Discharged alive	21	21	4	FALSE	None	33
425	North Tyneside	North Tyneside	31	1680	2	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	20
426	North Tyneside	North Tyneside	31	1700	2	2	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	20

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
427	RVI	RVI	31	1310	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	50
428	North Tees	North Tees	30	1730	1	1	Booked/born & ALL treatment level III	4	1	Discharged alive	60	21	6	FALSE	None	39
429	Sunderland	Sunderland	29	1355	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	41
430	Out of region	South Cleveland	24	450	3	1	Booked ex-region (transferred)	1	0	Died	40	25	8	FALSE	None	0
431	Out of region	South Cleveland	24	300	3	2	Booked ex-region (transferred)	2	0	Died	100	40	9	FALSE	None	2
432	Carlisle	RVI	31	1490	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	0	FALSE	None	43
433	Out of region	Out of region	27	770	1	1	Booked ex-region (on holiday)	17	1	Discharged alive	100	40	7	FALSE	None	19
434	Sunderland	Sunderland	31	2065	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	27
435	RVI	RVI	31	1380	1	1	Booked/born & ALL treatment level III	0	3	Discharged alive	44	21	8	FALSE	None	36
436	Sunderland	RVI	27	920	1	1	Other	2	0	Died	100	30	4	TRUE	Gastrochisis	1
437	Dryburn	South Cleveland	24	815	3	1	Booked level I, IUT to level III	1	0	Died	100	100	25	FALSE	None	0
438	Dryburn	South Cleveland	24	645	3	2	Booked level I, IUT to level III	1	0	Died	100	70	15	FALSE	None	0
439	Dryburn	South Cleveland	24	705	3	3	Booked level I, IUT to level III	1	0	Died	100	100	15	FALSE	None	0
440	RVI	RVI	30	1680	1	1	Booked/born & ALL treatment level III	3	6	Discharged alive	62	22	4	FALSE	None	52
441	Sunderland	Sunderland	30	1045	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	28	21	0	FALSE	None	51
442	Out of region	South Cleveland	30	1545	2	1	Booked ex-region (transferred)	0	3	Transferred	47	21	6	FALSE	None	8
443	Out of region	South Cleveland	30	1470	2	2	Booked ex-region (transferred)	0	3	Transferred	27	21	8	FALSE	None	8
444	Out of region	South Cleveland	27	1060	1	1	Booked ex-region (transferred)	0	0	Transferred	21	21	0	FALSE	None	13
445	Gateshead	Gateshead	23	570	1	1	Booked/born level I, PN transfer	4	0	Died	100	30	11	FALSE	None	4
446	South Tyneside	South Tyneside	29	1150	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	34	21	7	FALSE	None	39
447	Ashington	RVI	24	710	2	1	Booked level I, IUT to level III	1	0	Died	100	38	9	FALSE	None	1
448	Ashington	RVI	24	665	2	2	Booked level I, IUT to level III	1	0	Died	100	100	9	FALSE	None	1
449	Sunderland	Sunderland	31	1540	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	5	FALSE	None	38
450	Sunderland	Sunderland	31	1610	1	1	Booked/born & ALL treatment level III	3	1	Discharged alive	38	21	0	FALSE	None	42
451	North Tees	North Tees	31	1880	1	1	Booked/born & ALL treatment level III	2	9	Discharged alive	97	31	5	TRUE	TGA	51
452	Ashington	RVI	31	615	2	1	Booked level I, IUT to level III	3	1	Died	58	21	0	FALSE	None	4
453	Ashington	RVI	31	1490	2	2	Booked level I, IUT to level III	0	5	Discharged alive	40	28	1	FALSE	None	28
454	South Tyneside	South Tyneside	29	1100	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	38	21	16	FALSE	None	41
455	South Cleveland	South Cleveland	26	890	1	1	Booked/born & ALL treatment level III	5	0	Died	100	33	13	FALSE	None	5
456	Carlisle	Carlisle	31	1328	1	1	Booked/born level I, PN transfer	0	0	Discharged alive	35	21	0	TRUE	Congenital hydrocephalus	51
457	Carlisle	Carlisle	31	1656	1	1	Booked/born & ALL treatment level I	1	1	Discharged alive	39	26	7	FALSE	None	48
458	North Tees	North Tees	28	790	1	1	Booked/born & ALL treatment level III	52	33	Discharged alive	82	57	3	FALSE	None	161
459	South Cleveland	South Cleveland	23	650	1	1	Booked/born & ALL treatment level III	37	9	Discharged alive	41	21	5	FALSE	None	84
460	RVI	RVI	26	1080	2	1	Booked/born & ALL treatment level III	1	0	Died	77	33	4	FALSE	None	1
461	RVI	RVI	26	1000	2	2	Booked/born & ALL treatment level III	23	31	Discharged alive	60	41	3	FALSE	None	90
462	North Tyneside	North Tyneside	31	1430	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	30	21	0	FALSE	None	26
463	Whitehaven	RVI	28	980	1	1	Booked level I, IUT to level III	2	0	Discharged alive	37	21	0	TRUE	Meckel's diverticulum	68
464	Unbooked	South Cleveland	30	1540	1	1	Not booked prior to delivery	0	0	Discharged alive	21	21	4	FALSE	None	28
465	Dryburn	Dryburn	28	1195	1	1	Booked/born & ALL treatment level I	0	6	Discharged alive	40	28	9	FALSE	None	52
466	RVI	RVI	28	1300	1	1	Booked/born & ALL treatment level III	28	22	Discharged alive	28	21	5	FALSE	None	93
467	Out of region	Out of region	31	1485	2	1	Booked ex-region (transferred)	0	0	Transferred	21	21	0	FALSE	None	11
468	Out of region	Out of region	31	1720	2	2	Booked ex-region (transferred)	3	0	Transferred	29	26	12	FALSE	None	11
469	Darlington	Darlington	31	1555	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	4	FALSE	None	19
470	Ashington	Ashington	30	1000	1	1	Booked/born & ALL treatment level I	0	2	Discharged alive	34	26	4	FALSE	None	48
471	South Cleveland	South Cleveland	30	2200	2	1	Booked/born & ALL treatment level III	5	0	Discharged alive	100	40	8	FALSE	None	54
472	RVI	RVI	29	830	1	1	Booked/born & ALL treatment level III	3	0	Died	100	55	6	FALSE	None	3
473	Unbooked	RVI	26	840	2	1	Not booked prior to delivery	13	17	Discharged alive	21	21	1	TRUE	Hypospadias	86

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
474	Unbooked	RVI	26	1000	2	2	Not booked prior to delivery	14	8	Discharged alive	60	21	1	TRUE	Hypospadias	86
475	Sunderland	Sunderland	31	1690	1	1	Booked/born & ALL treatment level III	3	1	Discharged alive	21	21	1	FALSE	None	28
476	Sunderland	Sunderland	25	690	1	1	Booked/born & ALL treatment level III	1	0	Died	100	100	20	FALSE	None	0
477	RVI	RVI	31	1470	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	4	FALSE	None	54
478	Darlington	South Cleveland	30	1480	3	1	Booked level I, IUT to level III	3	0	Discharged alive	48	27	6	FALSE	None	38
479	Darlington	South Cleveland	30	1440	3	2	Booked level I, IUT to level III	0	0	Discharged alive	40	21	8	FALSE	None	38
480	Darlington	South Cleveland	30	1460	3	3	Booked level I, IUT to level III	0	1	Discharged alive	30	27	5	FALSE	None	38
481	North Tees	North Tees	31	1380	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	29
482	RVI	Born at home	29	1300	1	1	Other	7	0	Discharged alive	35	28	18	FALSE	None	50
483	RVI	RVI	31	2085	3	1	Booked/born & ALL treatment level III	0	2	Discharged alive	40	21	1	FALSE	None	34
484	RVI	RVI	31	1775	3	2	Booked/born & ALL treatment level III	5	0	Discharged alive	32	21	5	FALSE	None	45
485	RVI	RVI	31	1510	3	3	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	3	FALSE	None	34
486	Out of region	North Tees	28	840	1	1	Booked ex-region (transferred)	5	0	Died	28	21	5	FALSE	None	4
487	Ashington	Ashington	28	1215	2	1	Booked/born level I, PN transfer	4	0	Died	100	45	4	FALSE	None	3
488	Ashington	Ashington	28	1135	2	2	Booked/born level I, PN transfer	12	0	Died	100	50	13	FALSE	None	11
489	South Cleveland	South Cleveland	31	1540	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	5	FALSE	None	18
490	Hartlepool	RVI	26	620	1	1	Booked level I, IUT to level III	3	0	Died	100	21	11	FALSE	None	3
491	Bishop Auckland	Bishop Auckland	28	1060	1	1	Booked/born level I, PN transfer	14	9	Discharged alive	100	25	8	FALSE	None	74
492	Carlisle	Carlisle	30	856	1	1	Booked/born level I, PN transfer	3	1	Discharged alive	35	21	12	FALSE	None	61
493	South Cleveland	South Cleveland	30	1600	1	1	Booked/born & ALL treatment level III	1	0	Discharged alive	50	24	8	FALSE	None	22
494	Dryburn	RVI	27	1020	1	1	Other	27	27	Discharged alive	100	30	1	FALSE	None	100
495	North Tyneside	RVI	23	855	1	1	Booked level I, IUT to level III	1	0	Died	100	80	7	TRUE	69XXY	0
496	Out of region	South Cleveland	31	1085	3	1	Booked ex-region (transferred)	0	0	Transferred	21	21	2	FALSE	None	9
497	Out of region	South Cleveland	31	1170	3	2	Booked ex-region (transferred)	0	0	Transferred	21	21	2	FALSE	None	9
498	Out of region	South Cleveland	31	1085	3	3	Booked ex-region (transferred)	0	0	Transferred	21	21	0	FALSE	None	9
499	North Tees	North Tees	24	630	1	1	Booked/born & ALL treatment level III	7	0	Died	100	100	19	FALSE	None	6
500	RVI	RVI	26	1110	1	1	Booked/born & ALL treatment level III	2	44	Discharged alive	40	21	0	TRUE	Talipes L foot	76
501	South Cleveland	South Cleveland	29	1400	1	1	Booked/born & ALL treatment level III	2	0	Discharged alive	26	21	3	FALSE	None	39
502	South Cleveland	South Cleveland	26	990	1	1	Booked/born & ALL treatment level III	10	3	Discharged alive	25	21	5	FALSE	None	69
503	Ashington	RVI	25	700	1	1	Booked level I, IUT to level III	56	3	Discharged alive	100	21	4	FALSE	None	152
504	Sunderland	Sunderland	30	1480	2	1	Booked/born & ALL treatment level III	0	3	Discharged alive	26	21	1	FALSE	None	47
505	Sunderland	Sunderland	30	1300	2	2	Booked/born & ALL treatment level III	0	3	Discharged alive	34	21	1	FALSE	None	47
506	South Cleveland	South Cleveland	28	880	1	1	Booked/born & ALL treatment level III	18	8	Discharged alive	65	26	8	FALSE	None	83
507	RVI	RVI	27	1040	2	1	Booked/born & ALL treatment level III	2	33	Discharged alive	25	21	6	FALSE	None	83
508	RVI	RVI	27	960	2	2	Booked/born & ALL treatment level III	5	28	Discharged alive	41	21	4	FALSE	None	83
509	RVI	RVI	28	1150	1	1	Booked/born & ALL treatment level III	10	39	Discharged alive	100	38	4	FALSE	None	76
510	RVI	Sunderland	31	1635	2	1	Booked level III, IUT different level III	0	1	Discharged alive	40	35	4	FALSE	None	35
511	RVI	Sunderland	31	1465	2	2	Booked level III, IUT different level III	0	1	Discharged alive	21	21	0	FALSE	None	35
512	RVI	RVI	28	1150	1	1	Booked/born level III, PN trans. level III	1	1	Discharged alive	30	21	13	FALSE	None	84
513	Sunderland	Sunderland	30	1410	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	25	21	1	FALSE	None	31
514	RVI	North Tees	31	1940	1	1	Booked level III, IUT different level III	0	0	Discharged alive	21	21	0	FALSE	None	29
515	Darlington	North Tees	31	990	2	1	Booked level I, IUT to level III	4	0	Died	43	21	0	FALSE	None	3
516	Darlington	North Tees	31	1330	2	2	Booked level I, IUT to level III	3	0	Died	96	40	16	FALSE	None	2
517	Gateshead	Gateshead	28	1325	1	1	Booked/born level I, PN transfer	7	1	Died	100	45	3	FALSE	None	8
518	South Cleveland	South Cleveland	30	1260	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	6	FALSE	None	31
519	North Tees	North Tees	26	1020	1	1	Booked/born & ALL treatment level III	6	39	Discharged alive	76	30	12	FALSE	None	95
520	Carlisle	Carlisle	31	1900	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	50	25	9	FALSE	None	36
521	RVI	RVI	29	1485	1	1	Booked/born & ALL treatment level III	1	1	Discharged alive	29	21	0	FALSE	None	46
522	Ashington	North Tees	28	1140	1	1	Booked level I, IUT to level III	5	1	Discharged alive	60	40	6	FALSE	None	50

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
523	Whitehaven	Whitehaven	29	1440	1	1	Booked/born level I, PN transfer	33	16	Discharged alive	100	50	3	FALSE	None	210
524	RVI	RVI	27	1080	2	2	Booked/born & ALL treatment level III	8	0	Died	100	27	9	FALSE	None	8
525	North Tees	North Tees	31	1890	1	1	Booked/born & ALL treatment level III	6	0	Discharged alive	50	27	10	TRUE	Trisomy 21	28
526	Darlington	Other	28	810	1	1	Other	0	0	Discharged alive	21	21	0	FALSE	None	58
527	South Cleveland	South Cleveland	31	1540	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	16
528	North Tees	Born at home	24	550	1	1	Other	1	0	Died	100	100	0	FALSE	None	0
529	Darlington	South Cleveland	28	1230	1	1	Booked level I, IUT to level III	6	0	Discharged alive	24	21	5	FALSE	None	61
530	Gateshead	North Tees	29	1110	1	1	Booked level I, IUT to level III	3	2	Discharged alive	50	21	8	FALSE	None	60
531	Dryburn	RVI	28	1190	1	1	Booked/born level I, PN transfer	0	8	Discharged alive	35	21	1	FALSE	None	48
532	Gateshead	Gateshead	31	1870	1	1	Booked/born & ALL treatment level I	4	0	Discharged alive	100	38	6	FALSE	None	27
533	South Cleveland	South Cleveland	28	945	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	21	21	5	FALSE	None	43
534	Ashington	Ashington	28	1215	2	2	Booked/born level I, PN transfer	32	16	Discharged alive	100	65	4	FALSE	None	118
535	Ashington	Ashington	28	1115	2	1	Booked/born level I, PN transfer	16	62	Discharged alive	68	30	1	FALSE	None	118
536	Hartlepool	Hartlepool	26	990	1	1	Booked/born level I, PN transfer	16	21	Discharged alive	100	21	11	FALSE	None	97
537	North Tees	North Tees	31	1890	1	1	Booked/born & ALL treatment level III	0	3	Discharged alive	21	21	4	FALSE	None	18
538	RVI	RVI	30	1055	2	1	Booked/born & ALL treatment level III	3	4	Discharged alive	58	21	6	FALSE	None	44
539	RVI	RVI	30	970	2	2	Booked/born & ALL treatment level III	4	8	Discharged alive	38	21	6	FALSE	None	44
540	South Tyneside	South Tyneside	31	1715	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	12
541	Darlington	South Cleveland	23	580	1	1	Booked level I, IUT to level III	57	20	Discharged alive	60	30	11	FALSE	None	138
542	South Cleveland	South Cleveland	27	1165	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	6	FALSE	None	32
543	Sunderland	Sunderland	28	720	1	1	Booked/born & ALL treatment level III	10	1	Died	30	21	6	FALSE	None	10
544	Ashington	Sunderland	27	745	2	2	Booked level I, IUT to level III	2	0	Died	100	31	14	TRUE	Tracheo-oesophageal fistula	1
545	Ashington	Sunderland	27	895	2	1	Booked level I, IUT to level III	44	14	Discharged alive	95	30	12	FALSE	None	1
546	South Cleveland	South Cleveland	28	800	1	1	Booked/born & ALL treatment level III	1	0	Died	100	80	4	TRUE	Trisomy 13	0
547	South Tyneside	South Tyneside	29	1530	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	43	24	6	FALSE	None	44
548	Darlington	South Cleveland	29	1850	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	8	FALSE	None	28
549	Hartlepool	North Tees	29	930	2	1	Booked level I, IUT to level III	1	0	Died	100	92	18	TRUE	Pulmonary hypoplasia	7
550	Hartlepool	North Tees	29	1099	2	2	Booked level I, IUT to level III	5	0	Discharged alive	36	21	7	FALSE	None	51
551	Bishop Auckland	Bishop Auckland	31	1440	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	23	21	0	FALSE	None	29
552	Hartlepool	Hartlepool	27	1010	1	1	Booked/born level I, PN transfer	10	0	Died	100	22	8	FALSE	none	9
553	Darlington	Darlington	31	1700	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	23	21	4	FALSE	None	37
554	Hartlepool	Hartlepool	31	1760	1	1	Booked/born & ALL treatment level I	0	3	Discharged alive	54	21	3	FALSE	None	28
555	Out of region	Whitehaven	31	1820	1	1	Booked ex-region (on holiday)	1	5	Discharged alive	50	44	5	FALSE	None	24
556	Hartlepool	RVI	29	1300	1	1	Booked level I, IUT to level III	20	26	Discharged alive	100	48	1	FALSE	None	94
557	Darlington	RVI	28	1255	1	1	Booked level I, IUT to level III	2	3	Discharged alive	60	21	1	FALSE	None	57
558	Bishop Auckland	Bishop Auckland	31	1260	1	1	Booked/born level I, PN transfer	30	0	Discharged alive	80	44	5	FALSE	None	94
559	Other mat. hosp.	RVI	25	965	1	1	Booked level I, IUT to level III	10	0	Died	71	30	9	FALSE	None	10
560	Other mat. hosp.	RVI	25	970	1	1	Booked level I, IUT to level III	48	18	Discharged alive	90	28	7	FALSE	None	168
561	South Tyneside	South Tyneside	31	1675	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	TRUE	Isolated dextrocardia	22
562	Hexham	RVI	31	1710	1	1	Booked level I, IUT to level III	3	8	Discharged alive	27	21	4	FALSE	None	25
563	Sunderland	Sunderland	30	1450	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	39
564	Out of region	Out of region	31	1500	2	1	Booked ex-region (transferred)	1	2	Transferred	30	21	3	FALSE	None	5
565	Out of region	Out of region	31	1536	2	2	Booked ex-region (transferred)	1	0	Transferred	30	21	4	FALSE	None	5
566	North Tyneside	RVI	31	1095	1	1	Booked level I, IUT to level III	0	0	Discharged alive	40	21	0	FALSE	None	42
567	Out of region	South Cleveland	26	960	1	1	Booked ex-region (transferred)	22	31	Transferred	82	49	7	FALSE	None	132
568	Gateshead	Gateshead	28	1100	1	1	Booked/born & ALL treatment level I	1	0	Died	100	100	29	FALSE	None	0
569	Ashington	Ashington	29	1330	2	1	Booked/born level I, PN transfer	3	20	Discharged alive	27	21	4	FALSE	None	69

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
570	Ashington	Ashington	29	1495	2	2	Booked/born level I, PN transfer	4	12	Discharged alive	50	21	4	FALSE	None	69
571	RVI	RVI	28	690	2	1	Booked/born & ALL treatment level III	1	0	Died	100	100	0	TRUE	Trisomy 18/diaphragmatic hernia	0
572	RVI	RVI	28	1370	2	2	Booked/born & ALL treatment level III	2	0	Died	100	60	14	FALSE	None	2
573	Hartlepool	North Tees	27	850	1	1	Booked level I, IUT to level III	0	5	Discharged alive	45	25	5	FALSE	None	51
574	Out of region	Out of region	30	1250	1	1	Booked ex-region (transferred)	11	1	Transferred	84	40	6	FALSE	None	79
575	South Cleveland	South Cleveland	25	850	1	1	Booked/born & ALL treatment level III	1	1	Discharged alive	80	30	8	FALSE	None	108
576	Hartlepool	Hartlepool	25	850	1	1	Booked/born level I, PN transfer	76	16	Discharged alive	60	21	11	FALSE	None	147
577	North Tyneside	North Tyneside	24	700	1	1	Booked/born level I, PN transfer	1	0	Died	100	80	7	FALSE	None	31
578	Hartlepool	Hartlepool	26	670	1	1	Booked/born level I, PN transfer	33	2	Died	50	21	6	FALSE	None	34
579	RVI	RVI	30	1255	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	36	21	1	FALSE	None	48
580	Dryburn	Dryburn	31	1930	2	1	Booked/born & ALL treatment level I	0	0	Discharged alive	40	21	0	FALSE	None	17
581	Dryburn	Dryburn	31	2080	2	2	Booked/born & ALL treatment level I	0	2	Discharged alive	45	41	9	FALSE	None	21
582	Bishop Auckland	Bishop Auckland	29	1620	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	48
583	Darlington	Darlington	29	1270	2	1	Booked/born level I, PN transfer	0	0	Discharged alive	32	25	7	FALSE	None	55
584	Darlington	Darlington	29	1205	2	2	Booked/born level I, PN transfer	4	0	Discharged alive	100	40	11	FALSE	None	55
585	South Cleveland	South Cleveland	29	1092	1	1	Booked/born & ALL treatment level III	6	2	Discharged alive	22	22	8	FALSE	None	49
586	South Cleveland	South Cleveland	29	1100	2	1	Booked/born level III, PN trans. level III	3	1	Discharged alive	30	21	7	FALSE	None	54
587	South Cleveland	South Cleveland	29	965	2	2	Booked/born level III, PN trans. level III	3	1	Discharged alive	50	21	6	FALSE	None	54
588	Bishop Auckland	Bishop Auckland	31	1820	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	26
589	South Cleveland	North Tees	30	1570	1	1	Booked level III, IUT different level III	0	0	Discharged alive	33	21	7	FALSE	None	22
590	RVI	RVI	30	1140	2	1	Booked/born & ALL treatment level III	1	5	Discharged alive	80	21	1	FALSE	None	55
591	RVI	RVI	30	1120	2	2	Booked/born & ALL treatment level III	0	2	Discharged alive	40	21	2	FALSE	None	64
592	Unbooked	South Cleveland	28	950	1	1	Other	22	18	Discharged alive	60	35	13	FALSE	None	93
593	Out of region	Out of region	28	1160	1	1	Booked ex-region (transferred)	0	9	Transferred	60	21	4	FALSE	None	17
594	Hartlepool	Hartlepool	26	890	1	1	Booked/born level I, PN transfer	6	41	Discharged alive	60	21	8	FALSE	None	113
595	Carlisle	Carlisle	31	1426	1	1	Booked/born & ALL treatment level I	0	3	Discharged alive	59	25	6	FALSE	None	39
596	Carlisle	Carlisle	29	1630	1	1	Booked/born level I, PN transfer	1	1	Discharged alive	30	21	0	FALSE	None	43
597	Ashington	RVI	31	2055	1	1	Booked level I, IUT to level III	0	2	Discharged alive	30	22	7	FALSE	None	25
598	Bishop Auckland	South Cleveland	30	1550	1	1	Booked level I, IUT to level III	5	1	Discharged alive	37	21	7	FALSE	None	32
599	Carlisle	Carlisle	29	1240	1	1	Booked/born level I, PN transfer	1	1	Discharged alive	26	21	2	FALSE	None	47
600	Ashington	Ashington	30	1385	2	1	Booked/born level I, PN transfer	0	1	Discharged alive	21	21	2	FALSE	None	42
601	Ashington	Ashington	30	1425	2	2	Booked/born level I, PN transfer	0	1	Discharged alive	26	21	2	FALSE	None	42
602	Sunderland	Sunderland	31	1655	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	26
603	Gateshead	Gateshead	31	1520	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	7	FALSE	None	36
604	RVI	RVI	29	630	2	1	Booked/born & ALL treatment level III	44	34	Discharged alive	70	21	1	FALSE	None	176
605	Bishop Auckland	South Cleveland	28	990	1	1	Booked level I, IUT to level III	0	9	Discharged alive	21	21	5	FALSE	None	95
606	Darlington	Darlington	30	1640	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	30	23	8	FALSE	None	32
607	Sunderland	Sunderland	29	1010	2	1	Booked/born & ALL treatment level III	3	0	Discharged alive	55	21	0	FALSE	None	48
608	Sunderland	Sunderland	29	1280	2	2	Booked/born & ALL treatment level III	2	1	Discharged alive	60	21	0	FALSE	None	48
609	South Cleveland	South Cleveland	29	1770	1	1	Booked/born & ALL treatment level III	0	2	Discharged alive	27	21	10	FALSE	None	29
610	North Tees	North Tees	30	1730	1	1	Booked/born & ALL treatment level III	2	3	Discharged alive	35	21	5	FALSE	None	36
611	South Cleveland	South Cleveland	30	1125	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	12	FALSE	None	46
612	North Tyneside	RVI	31	2080	1	1	Booked level I, IUT to level III	0	1	Discharged alive	30	21	4	FALSE	None	15
613	RVI	RVI	26	870	1	1	Booked/born & ALL treatment level III	10	37	Discharged alive	80	45	5	FALSE	None	84
614	Hartlepool	Hartlepool	30	1020	1	1	Booked/born level I, PN transfer	2	3	Discharged alive	90	28	7	FALSE	None	34
615	Out of region	Out of region	25	760	1	1	Booked ex-region (on holiday)	2	0	Died	100	50	13	FALSE	None	2
616	Ashington	RVI	29	865	1	1	Booked level I, IUT to level III	7	0	Died	100	27	11	TRUE	Hydropsn (?cause)	7

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
617	Hartlepool	Hartlepool	28	1040	1	1	Booked/born level I, PN transfer	2	0	Died	100	59	4	FALSE	None	2
618	Whitehaven	Whitehaven	31	1640	1	1	Booked/born & ALL treatment level I	0	2	Discharged alive	42	24	2	FALSE	None	32
619	North Tees	North Tees	28	1350	4	1	Booked/born & ALL treatment level III	4	1	Discharged alive	55	21	8	FALSE	None	56
620	Ashington	RVI	31	1980	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	4	FALSE	None	18
621	Ashington	Ashington	30	1075	1	1	Booked/born level I, PN transfer	4	11	Discharged alive	100	72	10	FALSE	None	46
622	Sunderland	Sunderland	28	920	1	1	Booked/born & ALL treatment level III	13	8	Discharged alive	50	21	17	FALSE	None	91
623	Bishop Auckland	South Cleveland	25	900	1	1	Booked level I, IUT to level III	42	29	Discharged alive	35	21	7	FALSE	None	144
624	Ashington	RVI	25	670	1	1	Booked level I, IUT to level III	5	37	Discharged alive	26	21	7	FALSE	None	89
625	Out of region	Out of region	29	990	1	1	Booked ex-region (transferred)	11	7	Discharged alive	30	21	2	FALSE	None	23
626	Sunderland	Sunderland	28	1195	1	1	Booked/born & ALL treatment level III	0	2	Died	32	28	1	FALSE	None	33
627	RVI	RVI	28	1320	2	1	Booked/born & ALL treatment level III	3	25	Discharged alive	40	22	2	FALSE	None	50
628	RVI	RVI	28	1220	2	2	Booked/born & ALL treatment level III	8	0	Died	100	100	9	TRUE	Hydrops (?cause)	8
629	Out of region	North Tees	30	1490	2	1	Booked ex-region (transferred)	0	2	Transferred	25	21	7	FALSE	None	9
630	Out of region	North Tees	30	1000	2	2	Booked ex-region (transferred)	3	1	Transferred	35	21	8	FALSE	None	9
631	North Tyneside	RVI	28	1015	1	1	Booked level I, IUT to level III	11	26	Discharged alive	100	50	5	FALSE	None	62
632	South Cleveland	South Cleveland	27	1100	1	1	Booked/born & ALL treatment level III	4	0	Discharged alive	21	21	5	FALSE	None	66
633	Gateshead	Gateshead	28	1460	1	1	Booked/born level I, PN transfer	48	1	Died	55	23	6	FALSE	None	51
634	North Tyneside	North Tyneside	29	1860	1	1	Booked/born level I, PN transfer	5	0	Discharged alive	100	45	4	FALSE	None	46
635	South Cleveland	South Cleveland	29	1491	1	1	Booked/born & ALL treatment level III	2	0	Discharged alive	22	21	5	FALSE	None	34
636	Sunderland	Sunderland	29	1140	1	1	Booked/born & ALL treatment level III	0	4	Discharged alive	28	21	8	FALSE	None	71
637	RVI	Out of region	29	1500	1	1	Other	0	0	Discharged alive	21	21	3	FALSE	none	52
638	RVI	RVI	26	875	1	1	Booked/born & ALL treatment level III	8	0	Died	100	53	13	FALSE	None	8
639	Hartlepool	South Cleveland	29	1100	2	1	Booked level I, IUT to level III	1	0	Discharged alive	29	21	11	FALSE	None	50
640	Hartlepool	South Cleveland	29	1040	2	2	Booked level I, IUT to level III	0	0	Discharged alive	21	21	10	FALSE	None	54
641	North Tyneside	North Tyneside	29	1150	1	1	Booked/born level I, PN transfer	1	3	Discharged alive	24	21	10	TRUE	Talipes equinovarus	46
642	Hartlepool	RVI	30	1380	1	1	Other	91	21	Discharged alive	36	21	2	TRUE	Congenital laryngeal atresia	158
643	Hartlepool	Hartlepool	29	1400	1	1	Booked/born level I, PN transfer	4	3	Discharged alive	30	21	8	FALSE	None	58
644	RVI	RVI	26	1340	1	1	Booked/born & ALL treatment level III	1	43	Discharged alive	40	21	5	FALSE	None	80
645	Sunderland	Sunderland	26	735	1	1	Booked/born & ALL treatment level III	8	0	Died	100	45	3	FALSE	None	7
646	Ashington	RVI	31	1940	1	1	Booked level I, IUT to level III	0	0	Discharged alive	24	22	1	FALSE	None	22
647	Hexham	RVI	31	1735	1	1	Booked level I, IUT to level III	0	0	Discharged alive	40	21	4	FALSE	None	35
648	Carlisle	Carlisle	27	1152	2	1	Booked/born level I, PN transfer	1	9	Discharged alive	35	21	4	FALSE	None	67
649	North Tyneside	North Tees	25	920	2	1	Booked level I, IUT to level III	14	40	Discharged alive	54	21	10	FALSE	None	81
650	North Tyneside	North Tees	25	940	2	2	Booked level I, IUT to level III	10	19	Discharged alive	28	21	10	FALSE	None	81
651	RVI	RVI	27	870	1	1	Booked/born & ALL treatment level III	56	18	Discharged alive	70	38	4	FALSE	None	100
652	South Cleveland	South Cleveland	29	1440	1	1	Booked/born & ALL treatment level III	9	2	Discharged alive	100	50	12	FALSE	None	30
653	Bishop Auckland	South Cleveland	30	915	1	1	Booked level I, IUT to level III	1	0	Discharged alive	30	21	9	FALSE	None	57
654	Whitehaven	RVI	31	1195	1	1	Booked level I, IUT to level III	1	1	Discharged alive	52	21	5	FALSE	None	50
655	Hartlepool	Hartlepool	27	1030	1	1	Booked/born level I, PN transfer	40	5	Discharged alive	100	50	10	FALSE	None	92
656	Ashington	Sunderland	26	780	1	1	Booked level I, IUT to level III	10	1	Died	45	21	6	FALSE	None	10
657	RVI	RVI	26	780	1	1	Booked/born & ALL treatment level III	47	14	Discharged alive	51	21	5	FALSE	None	132
658	Bishop Auckland	Bishop Auckland	30	1400	1	1	Booked/born level I, PN transfer	4	0	Discharged alive	80	52	7	FALSE	None	44
659	Ashington	RVI	26	980	1	1	Booked level I, IUT to level III	9	28	Discharged alive	88	33	8	FALSE	None	75
660	Out of region	South Cleveland	23	630	1	1	Booked ex-region (on holiday)	2	0	Died	60	21	10	FALSE	None	1
661	North Tees	North Tees	27	940	1	1	Booked/born & ALL treatment level III	27	16	Discharged alive	90	22	7	FALSE	None	96
662	Dryburn	Sunderland	29	1385	1	1	Booked level I, IUT to level III	4	0	Discharged alive	32	24	2	FALSE	None	30
663	Sunderland	Sunderland	29	1515	1	1	Booked/born & ALL treatment level III	10	1	Discharged alive	50	45	2	FALSE	None	7051
664	South Cleveland	South Cleveland	28	1450	3	1	Booked/born & ALL treatment level III	1	0	Discharged alive	30	22	5	FALSE	None	45

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
665	South Cleveland	South Cleveland	28	1240	3	2	Booked/born & ALL treatment level III	1	0	Discharged alive	21	21	4	FALSE	None	45
666	South Cleveland	South Cleveland	28	1290	3	3	Booked/born & ALL treatment level III	4	0	Discharged alive	30	21	7	FALSE	None	45
667	Gateshead	Gateshead	26	1105	1	1	Booked/born level I, PN transfer	2	0	Died	100	60	8	FALSE	None	1
668	Carlisle	Carlisle	31	2454	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	54	21	6	FALSE	None	30
669	North Tees	North Tees	30	1570	1	1	Booked/born & ALL treatment level III	5	1	Discharged alive	100	30	12	FALSE	None	29
670	North Tees	North Tees	26	760	1	1	Booked/born & ALL treatment level III	4	8	Died	35	21	6	FALSE	None	11
671	Out of region	RVI	26	790	1	1	Booked ex-region (on holiday)	30	8	Transferred	54	21	5	FALSE	None	38
672	Darlington	Darlington	31	2160	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	31	23	4	FALSE	None	33
673	North Tees	North Tees	28	1350	1	1	Booked/born & ALL treatment level III	3	0	Discharged alive	35	21	8	FALSE	None	54
674	Out of region	South Cleveland	24	870	2	1	Booked ex-region (transferred)	63	0	Died	21	21	8	FALSE	None	63
675	Out of region	South Cleveland	24	570	2	2	Booked ex-region (transferred)	51	20	Transferred	44	22	6	FALSE	None	90
676	Out of region	South Cleveland	31	1375	1	1	Booked ex-region (transferred)	0	0	Transferred	21	21	2	FALSE	None	5
677	Darlington	South Cleveland	31	1160	2	1	Booked level I, IUT to level III	1	0	Died	30	21	9	TRUE	Congenital diaphragmatic hernia	0
678	Darlington	South Cleveland	31	1480	2	2	Booked level I, IUT to level III	1	0	Discharged alive	21	21	11	TRUE	Congenital diaphragmatic hernia	41
679	South Cleveland	South Cleveland	30	1690	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	29
680	South Cleveland	South Cleveland	27	1100	1	1	Other	5	0	Discharged alive	25	24	7	FALSE	None	61
681	Ashington	Sunderland	30	1340	1	1	Booked level I, IUT to level III	7	6	Discharged alive	95	50	8	TRUE	Diaphragmatic eventration	42
682	South Cleveland	South Cleveland	30	1040	2	1	Booked/born & ALL treatment level III	1	0	Died	100	100	16	TRUE	Renal aplasia/pulm hypoplasia	0
683	South Cleveland	South Cleveland	30	1600	2	2	Booked/born & ALL treatment level III	1	1	Discharged alive	40	21	7	FALSE	None	29
684	Hartlepool	Hartlepool	28	1080	1	1	Booked/born level I, PN transfer	3	0	Discharged alive	25	21	3	FALSE	None	67
685	Bishop Auckland	Bishop Auckland	29	1420	1	1	Booked/born level I, PN transfer	5	5	Discharged alive	100	49	13	FALSE	None	44
686	RVI	RVI	30	1320	2	1	Booked/born & ALL treatment level III	0	0	Discharged alive	25	21	2	FALSE	None	48
687	RVI	RVI	30	1135	2	2	Booked/born & ALL treatment level III	11	1	Discharged alive	35	21	4	FALSE	None	48
688	Gateshead	Sunderland	29	1280	1	1	Booked level I, IUT to level III	5	1	Discharged alive	45	21	3	FALSE	None	64
689	North Tyneside	RVI	30	1760	1	1	Booked level I, IUT to level III	0	1	Discharged alive	24	21	1	FALSE	None	27
690	Dryburn	South Cleveland	28	950	1	1	Booked level I, IUT to level III	1	0	Died	50	21	10	FALSE	None	1
691	Out of region	RVI	23	485	2	1	Booked ex-region (on holiday)	1	0	Died	100	65	18	FALSE	None	0
692	RVI	RVI	24	680	1	1	Booked/born & ALL treatment level III	127	8	Died	43	21	0	FALSE	None	151
693	Carlisle	Carlisle	30	1489	2	1	Booked/born & ALL treatment level I	0	1	Discharged alive	43	22	3	FALSE	None	48
694	Carlisle	Carlisle	30	1488	2	2	Booked/born & ALL treatment level I	0	3	Discharged alive	36	24	2	FALSE	None	48
695	South Cleveland	South Cleveland	30	985	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	25	21	2	FALSE	None	66
696	North Tees	North Tees	31	1390	1	1	Booked/born & ALL treatment level III	0	5	Discharged alive	40	21	7	FALSE	None	36
697	Gateshead	Gateshead	31	1405	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	0	FALSE	None	35
698	North Tees	North Tees	31	1670	1	1	Booked/born & ALL treatment level III	0	3	Discharged alive	30	21	6	FALSE	None	26
699	Sunderland	Sunderland	27	530	1	1	Booked/born & ALL treatment level III	37	13	Discharged alive	85	36	9	FALSE	None	95
700	South Cleveland	South Cleveland	28	1140	1	1	Booked/born & ALL treatment level III	2	2	Discharged alive	21	21	8	FALSE	None	33
701	RVI	RVI	27	1020	1	1	Booked/born & ALL treatment level III	7	40	Discharged alive	100	21	17	FALSE	None	85
702	North Tees	South Cleveland	31	1210	2	1	Booked level III, IUT different level III	0	2	Discharged alive	21	21	11	FALSE	None	53
703	North Tees	South Cleveland	31	1720	2	2	Booked level III, IUT different level III	7	2	Discharged alive	49	46	9	FALSE	None	53
704	Ashington	Sunderland	30	1350	1	1	Booked level I, IUT to level III	18	14	Died	30	21	1	TRUE	Cleft lip and palate. ?syndromic	85
705	Dryburn	South Cleveland	28	1220	1	1	Booked level I, IUT to level III	7	0	Died	60	23	10	FALSE	None	7
706	Darlington	Darlington	31	1640	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	35	21	10	FALSE	None	28
707	North Tees	North Tees	30	1430	2	1	Booked/born & ALL treatment level III	8	5	Discharged alive	24	21	11	FALSE	None	51
708	North Tees	North Tees	30	1300	2	2	Booked/born & ALL treatment level III	2	0	Discharged alive	60	21	9	FALSE	None	51

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
709	Sunderland	Sunderland	29	1440	1	1	Booked/born & ALL treatment level III	1	10	Discharged alive	30	21	4	FALSE	None	41
710	Sunderland	Sunderland	31	1460	1	1	Booked/born & ALL treatment level III	0	1	Discharged alive	38	21	3	FALSE	None	34
711	Gateshead	Born at home	31	1460	1	1	Other	1	0	Died	100	86	5	TRUE	Tracheal oesophageal fistula	1
712	Hexham	Sunderland	31	1680	1	1	Booked level I, IUT to level III	0	0	Discharged alive	25	21	0	FALSE	None	37
713	Ashington	Ashington	30	1275	2	1	Booked/born level I, PN transfer	3	8	Discharged alive	33	25	8	TRUE	Coarctation, VSD, ASD	72
714	Ashington	Ashington	30	1009	2	2	Booked/born level I, PN transfer	0	0	Died	31	28	6	FALSE	None	9
715	Ashington	Ashington	24	685	1	1	Booked/born level I, PN transfer	23	55	Discharged alive	100	21	12	FALSE	None	115
716	RVI	RVI	30	1060	1	1	Booked/born & ALL treatment level III	6	1	Discharged alive	33	21	3	FALSE	None	46
717	South Cleveland	South Cleveland	29	1480	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	4	FALSE	None	34
718	Sunderland	Sunderland	30	1220	2	1	Booked/born & ALL treatment level III	0	3		40	21	1	TRUE	Coarctation	43
719	Sunderland	Sunderland	30	1620	2	2	Booked/born & ALL treatment level III	5	0	Discharged alive	55	30	2	FALSE	None	45
720	Darlington	Darlington	31	1420	2	1	Booked/born & ALL treatment level I	0	0	Discharged alive	25	21	0	FALSE	None	35
721	Darlington	Darlington	31	1520	2	2	Booked/born & ALL treatment level I	0	1	Discharged alive	31	22	8	FALSE	None	35
722	Darlington	Darlington	30	1540	1	1	Booked/born level I, PN transfer	4	1	Discharged alive	60	35	6	FALSE	None	41
723	South Tyneside	RVI	28	1185	2	1	Booked level I, IUT to level III	0	1	Discharged alive	21	21	2	FALSE	None	62
724	South Tyneside	RVI	28	945	2	2	Booked level I, IUT to level III	8	6	Discharged alive	24	21	4	TRUE	VSD/absent L kidney/microcolon	107
725	Hexham	Hexham	25	930	1	1	Booked/born level I, PN transfer	16	0	Died	21	21	7	FALSE	None	16
726	Dryburn	Dryburn	29	680	1	1	Booked/born level I, PN transfer	2	1	Discharged alive	70	21	10	FALSE	None	69
727	Hartlepool	South Cleveland	24	705	1	1	Booked level I, IUT to level III	118	1	Discharged alive	100	27	0	FALSE	None	124
728	North Tees	North Tees	24	720	1	1	Booked/born & ALL treatment level III	127	4	Died	40	21	14	FALSE	None	130
729	Darlington	Darlington	27	1160	1	1	Booked/born level I, PN transfer	4	13	Discharged alive	100	90	18	FALSE	None	78
730	Dryburn	Dryburn	25	830	1	1	Booked/born level I, PN transfer	1	0	Died	100	100	9	FALSE	None	2
731	Whitehaven	Whitehaven	30	1470	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	3	FALSE	None	30
732	South Cleveland	South Cleveland	28	1500	1	1	Booked/born & ALL treatment level III	2	0	Died	82	22	12	FALSE	None	2
733	Ashington	Sunderland	30	1575	1	1	Booked level I, IUT to level III	0	0	Discharged alive	26	26	3	FALSE	None	25
734	Dryburn	North Tees	29	1020	1	1	Booked level I, IUT to level III	4	5	Discharged alive	70	50	6	FALSE	None	62
735	Darlington	North Tees	28	1120	1	1	Booked level I, IUT to level III	6	0	Discharged alive	47	21	0	FALSE	None	-6
736	Sunderland	Sunderland	28	1190	1	1	Booked/born & ALL treatment level III	0	2	Discharged alive	26	21	0	FALSE	None	50
737	Ashington	RVI	29	1150	1	1	Booked level I, IUT to level III	0	2	Discharged alive	35	22	0	FALSE	None	43
738	Hartlepool	Hartlepool	28	1610	1	1	Booked/born level I, PN transfer	7	6	Discharged alive	80	21	6	FALSE	None	45
739	Out of region	South Cleveland	24	820	1	1	Booked ex-region (transferred)	16	29	Transferred	52	26	9	FALSE	None	54
740	RVI	RVI	27	1360	1	1	Booked/born & ALL treatment level III	15	26	Discharged alive	100	30	9	FALSE	None	67
741	Out of region	RVI	26	1070	1	1	Booked ex-region (transferred)	24	9	Transferred	100	50	4	FALSE	None	53
742	South Cleveland	South Cleveland	30	1070	1	1	Booked/born & ALL treatment level III	4	1	Discharged alive	42	21	4	FALSE	None	33
743	Out of region	South Cleveland	27	1090	1	1	Booked ex-region (transferred)	8	8	Transferred	26	22	4	FALSE	None	38
744	North Tees	North Tees	31	1220	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	0	FALSE	None	32
745	Ashington	RVI	31	880	2	2	Other	0	0	Died	39	21	3	FALSE	None	60
746	Ashington	RVI	31	1500	2	1	Other	6	0	Discharged alive	100	50	9	FALSE	None	38
747	North Tees	North Tees	25	820	1	1	Booked/born & ALL treatment level III	31	0	Died	75	47	7	FALSE	None	30
748	Out of region	South Cleveland	31	1310	2	1	Booked ex-region (transferred)	0	0	Transferred	21	21	2	FALSE	None	13
749	Out of region	South Cleveland	31	1670	2	2	Booked ex-region (transferred)	0	1	Transferred	21	21	5	FALSE	None	13
750	Bishop Auckland	South Cleveland	26	1100	1	1	Booked level I, IUT to level III	2	1	Discharged alive	23	21	6	FALSE	None	69
751	North Tyneside	Out of region	29	1140	1	1	Transferred out of region	0	0	Discharged alive	32	21	6	FALSE	None	34
752	Whitehaven	Whitehaven	29	1200	2	2	Booked/born level I, PN transfer	8	0	Died	100	45	9	FALSE	None	8
753	Whitehaven	Whitehaven	29	1100	2	1	Booked/born level I, PN transfer	6	0	Died	100	47	7	FALSE	None	5
754	North Tees	North Tees	30	1940	1	1	Booked/born & ALL treatment level III	0	5	Discharged alive	23	21	6	FALSE	None	38

No.	Booked at	Born at	Gest	BWt	Fetuses	Order	Early neonatal course	Vent days	CPAP days	Outcome	Max O2	Min O2	BD	Malform	Type malf.	Age out
755	Bishop Auckland	Bishop Auckland	30	1970	1	1	Booked/born & ALL treatment level I	0	3	Discharged alive	33	26	0	FALSE	None	38
756	Sunderland	Sunderland	29	1360	1	1	Booked/born & ALL treatment level III	6	0	Discharged alive	35	21	0	FALSE	None	41
757	Darlington	Darlington	30	1950	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	30	21	6	FALSE	None	24
758	Whitehaven	Out of region	30	920	1	1	Transferred out of region	0	0	Discharged alive	29	21	0	FALSE	None	32
759	South Cleveland	South Cleveland	31	1660	1	1	Booked/born & ALL treatment level III	0	0	Discharged alive	21	21	8	FALSE	None	18
760	Bishop Auckland	South Cleveland	29	1540	1	1	Booked level I, IUT to level III	0	0	Discharged alive	25	21	4	FALSE	None	29
761	Bishop Auckland	Bishop Auckland	29	760	1	1	Booked/born level I, PN transfer	16	40	Discharged alive	70	21	8	FALSE	None	149
762	Carlisle	Carlisle	31	1794	1	1	Booked/born & ALL treatment level I	0	1	Discharged alive	28	21	6	FALSE	None	39
763	South Cleveland	RVI	24	490	2	1	Booked level III, IUT different level III	3	0	Died	100	60	9	FALSE	None	2
764	South Cleveland	RVI	24	415	2	2	Booked level III, IUT different level III	1	0	Died	100	54	7	FALSE	None	0
765	Ashington	RVI	31	1550	1	1	Booked level I, IUT to level III	0	0	Discharged alive	21	21	1	FALSE	None	32
766	Ashington	Ashington	26	750	1	1	Booked/born level I, PN transfer	46	20	Discharged alive	100	21	6	FALSE	None	97
767	Whitehaven	Whitehaven	30	1660	1	1	Booked/born level I, PN transfer	2	6	Discharged alive	70	21	5	FALSE	None	41
768	Hartlepool	Hartlepool	30	1410	1	1	Booked/born & ALL treatment level I	0	0	Discharged alive	21	21	2	FALSE	None	47
769	South Tyneside	RVI	26	705	1	1	Booked level I, IUT to level III	14	28	Discharged alive	36	26	6	FALSE	None	75
770	RVI	RVI	26	920	1	1	Booked/born & ALL treatment level III	14	35	Discharged alive	100	43	4	FALSE	None	72
771	Out of region	South Cleveland	24	685	1	1	Booked ex-region (transferred)	1	0	Died	92	21	23	FALSE	None	1