January 2011

Outcome Of Extremely Low Birth Weight Infants In A Resource Limited Setting

Akua Adu-Boahene
Yale School of Medicine, akuaab@gmail.com

Outcome of Extremely Low Birth Weight Infants In a Resource Limited Setting

A Thesis Submitted to the

Yale University School of Medicine

In Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

By

Akua Adu-Boahene

2011

Abstract

Outcome of Extremely Low Birth Weight Infants in a Resource Limited Setting

Akua Adu-Boahene[+], Clare M. Thompson[*], Laura R. Ment[+], and Natasha Rhoda[*]

[+]Yale University School of Medicine. New Haven, CT. [*]Department of Neonatology, University of Cape Town, Cape Town, South Africa.

Background: In post-apartheid South Africa, low birth weight, and its associated complications, remains a leading cause of child mortality. While significant data have been collected on infants weighing more than a 1000g, there are no formal statistics yet for extremely low birth weight infants (ELBW), neonates weighing 401-1000g.

Objectives: To assess the neurodevelopmental outcome post-discharge from a neonatal unit with limited resources and to determine risk factors associated with unfavorable outcome.

Study Design: The 171 subjects were born between 22-35 weeks gestation, with weights ranging from 405-1000g. Subjects were treated in the neonatal unit at Groote Schuur Hospital, Cape Town, South Africa, between May 2003 and April 2005. Assessments of speech, cognition, audition, vision and motor function were made by a neurodevelopmental specialist during routine follow up. The Infant Neurological Assessment (a modified Dubowitz test) was performed when available. The mean age at follow up was 7.6 months.

Results: Subjects had a 68% survival to discharge with a 66% follow up rate. 71% were assessed as normal while 17% were assessed as having developmental delays and/or disabilities. For the remaining 12%, no assessment could be made, as data from follow up records were unavailable. Increasing birth weight and gestational age were associated with a greater survival up to discharge ($p < 0.0001$ for both). The incidence of neurodevelopmental handicap was found to decrease with female gender ($p = 0.048$) and increasing birth weight ($p = 0.050$) but not with increasing gestational age ($p = 0.607$). Necrotizing enterocolitis (NEC) in the neonatal period was associated with unfavorable outcome ($p=0.041$).

Conclusions: Favorable neurodevelopmental outcome at 7 months was associated with increasing birth weight and female gender.

Acknowledgements

I sincerely thank my family and friends for their continued support. I am also incredibly grateful to my thesis advisor, Dr Laura Ment, for her kindness, patience and guidance. Thank you to Dr Natasha Rhoda for establishing and developing this project. To Dr Clarissa Pieper, Dr Clare Thompson, Ms Gabeba Abass and Ms Karol Katz, thank you for your help and insight. I owe a debt of gratitude to the Office of Student Research for providing the support that made this project a reality. My greatest thanks go to all the children involved in this study. They, and their families, made this work possible.

Table of Contents

Introduction

The incidence of preterm births has become a major public health problem, a problem with significant medical and financial sequelae. Preterm births account for 28% of early neonatal deaths not related to congenital malformations.[1] In 2005, 12.9 million births (9.6% of all births) were preterm.[2] Of these preterm births, 11 million occurred in Africa and Asia. Although Asia has the largest number of preterm births, Africa has the highest rate of preterm births at 11.9%.[3] The very regions of the world that bear the greatest burden of preterm births are the ones least able to afford it. In the US alone, the financial impact of preterm births, in terms of medical and educational expenditure and lost productivity, was estimated at $26.2 billion in 2005.[4]

Successive post-apartheid South African governments have prioritized child health in an effort to eliminate racial disparities. Despite these efforts, the under-5 mortality rate—a key index of a country's development—has increased over the past two decades, from 56 in 1990 to 67 in 2008.[5] Underlying this finding is the parallel rise, from 44 to 48, in the infant mortality rate (under age 1) over this very period. In light of these facts, it becomes clear that South Africa is unlikely to achieve the stated aim of Millennium Development Goal (MDG) 4, to reduce the under-5 mortality rate by two thirds, between 1990 and 2015.

According to UNICEF, 15% of South African infants born between 2003- 2008 were of low birth weight. In 2002, low birth weight and its associated complications, accounted for 11.2% of the under-5 mortality rate, second only to HIV/AIDS.[6] More recent data underscore this trend, with 46% of neonatal deaths caused by complications of immaturity.[7]

Despite the South African government's numerous child mortality initiatives, scant attention has been paid to extremely low birth weight (ELBW) infants, neonates weighing less than 1000g. In fact, until 1991, ELBW infants were offered limited or no treatment and to date, no co-ordinated management scheme for the care of these infants exists. While there are statistics on their survival to discharge, there are no data pertaining to their neurodevelopmental outcome after discharge.

In the developing country context, the lack of long-term survival data is not limited to South Africa. For many countries, it remains unrealistic to offer care to ELBW infants when the resources available are inadequate in meeting the needs of larger neonates. With this cost-benefit analysis in mind, many may question the merits of conducting long-term follow-up studies of ELBW children. However, the importance of such studies cannot be discounted.

The unfortunate reality is that the majority of ELBW children in South Africa have limited to no access to the therapeutic and support services routinely offered in developed countries. The findings of follow-up studies will be instrumental in raising awareness—at national and provincial levels—about the neurodevelopmental needs of this subpopulation of children. This could prompt the reallocation of resources toward therapeutic initiatives targeting ELBW children, and there is no disputing the need for such programs. Numerous studies from industrialized countries have shown that ELBW infants are more likely to develop cognitive, sensory and motor deficits.

Preterm subjects have been demonstrated to have significant developmental handicaps compared to term controls when examined in early childhood, at school age and during adolescence. A two-year follow up study of 78 ELBW Finnish children found the subjects to have deficits in multiple domains. The prevalence of all motor impairments was 24%, that of cerebral palsy was 11%, 23% had ophthalmic abnormalities and 42% had delayed speech.18% of all subjects had severe impairment.[8]

Voss et al followed a cohort of 159 German ELBW infants with a median birth weight and gestational age of 749g and 27 weeks respectively. School age children, between 6-10 years, were examined and categorized according to degree of impairment. 17% of subjects were found to have a major impairment (cerebral palsy, intelligence quotient (IQ) or development quotient (DQ) < 70, blindness and/or intractable epilepsy), 42% had minor impairment (IQ or DQ of 70-84 with motor, language, visual, auditory or socioemotional deficits) and 41% were normal. [9]

Similarly, an Australian study of 298 ELBW or very preterm children at age 8 identified long-term deficits. Compared to peers of normal birth weight, ELBW/ very preterm children were more likely to be diagnosed with developmental co-ordination disorder (DCD). DCD was, in turn, found to be associated with poor cognitive and academic performance as well as increased behavioural problems.[10]

Neurodevelopmental handicaps have been shown to continue into adolescence. A follow-up study of ELBW children at age 14 found them to have substantially higher rates of neurosensory impairments and disabilities than normal birth weight (NBW) controls. Of the 79 ELBW children assessed, 14% were severely disabled, 15% were moderately disabled, 25% were mildly disabled with the remaining 46% free of disability. In contrast, only 16% of the 42 NBW controls were disabled—2% were severely disabled and another 14% had a mild disability.[11]

Several perinatal factors have been linked with poor outcome in ELWB infants, one of them being gender. Hintz et al, assessed ELBWs born at <28 weeks, for degree of impairment at 18-22 months corrected age. Boys were found to be more likely than girls to have adverse outcomes (moderate to severe CP: 10.7% vs. 7.3%; Bayley Mental Developmental Index (MDI) <70: 49.1% vs. 27.1%). The prevalence of neurodevelopmental impairment was 48.1% for boys and 34.1% for girls.[12]

Decreasing birth weight and gestational age have also been identified as factors associated with poor cognitive performance among ELBW children. Relative to normal birth weight peers at age 8, a cohort of 298 ELBW/ very preterm (<28 weeks) children scored significantly lower on tests of full scale IQ, indices of verbal comprehension, perceptual organization, freedom from distractibility and processing speed. These children also performed significantly worse on tests of reading, spelling and arithmetic.[13]

Infection in the neonatal period has also been implicated in impaired cognitive and neuro-motor development. In a study by Stoll et al, neurodevelopmental and growth outcomes of ELBW children were assessed at 18-22 months corrected age and compared by infection group (uninfected, clinical infection alone, sepsis, sepsis and necrotizing enterocolitis (NEC), or meningitis with or without sepsis). In comparison with uninfected infants, those with infections were significantly more likely to have adverse outcomes at follow-up such as cerebral palsy, low MDI and psychomotor development index (PDI) scores, visual deficits and impaired head growth.[14]

The department of neonatology at Groote Schuur Hospital (GSH), a teaching hospital affiliated with the University of Cape Town, has been active in collecting data on ELBW infants treated in its neonatal unit. The 52 bed neonatal unit forms an integral part the Groote Schuur Maternity Centre, a referral centre for the southern part of the Western Cape Province of South Africa. The unit offers four levels of care—intensive care (level 1), high care (level 2), low care (level 3) and general care (level 4). Although both intensive and high care nurseries offer specialized neonatal care, intensive care is reserved for infants requiring ventilatory support while those needing oxygen therapy are assigned to high care. The unit offers ventilatory support to over 400 children every year.[15] In addition to sick infants born at the hospital, the unit accepts outborn children from within its regional service. Healthy infants born at term or close to term do not enter the unit; they remain with their mothers on the obstetric floors.

On admission to the unit, ELBW neonates are assigned to either intensive or high levels of care depending on their birth weight, gestational age and perinatal morbidities. The acuity of care provided is re-evaluated on a daily basis, and each child is assigned to the most appropriate of the four levels of care. Upon discharge, ELBW infants are seen in follow-up to assess their development. Referrals to specialists are provided as needed. Such follow-up services are only available at major tertiary care centres throughout the nation.

Although there is a clear understanding of survival until discharge, there is little information beyond this. The purpose of this study is to shed light on the longer-term survival and neurodevelopmental progress of ELBW infants treated in a resource limited setting. The influence of the following factors on outcome will be determined–gender, gestational age, birth weight and neonatal infection.

Hypotheses

The proposed hypotheses of this study were as follows:

1) The incidence of neurodevelopmental handicap will increase with decreased birth weight and gestational age.
2) Neonatal morbidities such as necrotizing enterocolitis and bronchopulmonary dysplasia will be associated with increased neurodevelopmental morbidity.
3) Male preterm subjects will be significantly more likely than female preterm subjects to experience developmental delay during early childhood.

Specific Aims of Study

To evaluate retrospectively:

1) The impact of birth weight and gestational age on neurodevelopmental outcome.
2) The influence of neonatal morbidities on outcome.
3) The association between gender and outcome at follow-up.

Research Methods

Review of neonatal admission charts

The charts of 180 ELBW infants admitted to Groote Schuur Hospital (GSH) between 05/01/2003 and 04/30/2005 were reviewed retrospectively. 11 subjects were known to be outborn; they were transferred to GSH soon after birth. Data on gender, height, birth weight, gestational age, head circumference, morbidity and mortality, maternal health and parity and length of hospital stay were collected from neonatal records. Auditory and ophthalmological assessments were not routinely performed; therefore, these data were unavailable.

The Follow-up Process

Upon discharge, subjects were seen for follow-up at Groote Schuur Hospital and at community health clinics where auditory, visual, speech and neuromotor assessments were performed. Testers were not blind to the subjects' neonatal histories.

Audition was evaluated by response to a ringing bell while vision and speech were assessed clinically. Neuromotor function was formally tested by means of the Infant Neurological Assessment (INA) when available. In absence of the INA, neuromotor development was assessed clinically. A global assessment of "normal" versus "developmentally delayed" was then made based on the results of the various assessments. This final assessment, and results of the INA when available, served as follow up data for this study. However, data pertaining to the nature of subjects' developmental handicaps were unavailable to this study.

Assessment tool: Infant Neurological Assessment (INA)

The INA is a modified Dubowitz test of 20 items, taking about 10-15 minutes to complete. It evaluates spontaneous movement, muscle tone, postural reactions and some primitive reflexes. Each item is rated as either appropriate or deviant for age with a deviancy score assigned. If more than one deviant sign is observed, the subject is to be followed until a normal assessment or definitive diagnosis is made.

Statistical Analyses

Nine subjects were excluded from the study because their gender was unknown. Data from the remaining 171 subjects were input into Excel and stripped of identifying information. The data were exported from Excel into SPSS v.19 for analyses. The quantitative prevalence of various prematurity related complications was established. Chi-squared tests were used to determine differences in binary and categorical variables while Student T-tests were employed in distinguishing group differences on continuous measures.

Roles of authors

Drs. Rhoda and Thompson were primarily responsible for chart review and initial data transfer into Excel. The student author of this paper was responsible for the creation and management of the secondary Excel database of de-identified data, as well as the exportation of data into SPSS and subsequent analyses. Dr. Ment served as the student author's primary advisor on this project.

Results

During the time interval 05/01/2003 to 04/30/2005 a total of 180 live born infants of 401-1000g birth weight were admitted to the neonatal unit at Groote Schuur Hospital. 11 subjects were outborn but were transferred to the unit soon after birth. Nine subjects were excluded from the study, as data on gender were unavailable. Of the remaining 171 infants, 116 survived until discharge. 76 of the discharged ELBW children were available for follow-up evaluations. The vast majority of subjects were either black or of mixed race.

Survival to discharge by birth weight and gestational age

For the 171 subjects (67 males, 104 females) involved in this study, the mean birth weight was 831.26 g ± 118.5g with a range between 405-1000g. Approximately 87% of subjects weighed between 701-1000g. There was no gender bias regarding birth weight (males: 839.10g ± 127.8g; females: 826.20g ± 112.4g);($p = 0.488$).

The birth weight distribution of the study's 171 subjects is shown below in Table 1

Birth weight (g)	**Frequency**	**Percent (%) of total**
401-475	2	1.2
475-550	6	3.5
551-625	2	1.2
626-700	12	7.0
701-775	27	15.8
776-850	39	22.8
851-925	41	24.0
925-100	42	24.6

Table 1: Distribution of birth weights (N=171)

Survival to discharge per birth weight category is shown below in Table 2

Birth weight (g)	**Number of survivors**	**Percent (%) Survival**
401-475	0	0
476-550	1	17
551-625	0	0
626-700	6	50
701-775	17	63
776-850	26	67
851-925	33	80
925-1000	33	79

Table 2: Survival-to-discharge rates according to birth weight (N=171)

Gestational age data were unavailable for subjects. The mean gestational age for the remaining 169 neonates was 29.01 weeks ± 2.5 weeks with a range between 22-35 weeks. Almost half (47%) of the infants were born between 27-29 weeks. 56% of infants were small for gestational age. There was no gender bias regarding gestational age (males: 29.08± 2.6 weeks; females: 28.96 ± 2.4 weeks); (p= 0.770).

The gestational age distribution of 169 of the study's subjects is shown below in Table 3

Gestational age (weeks)	**Frequency**	**Percent (%) of total**
22-24	1	6
25-26	24	14.2
27-29	80	47.3
30-32	47	27.8
33-35	17	10.1

Table 3: Distribution of gestation ages (N=169)

Survival to discharge per gestational age category is shown below in Table 4

Gestational age (weeks)	**Number of survivors**	**Percent (%) Survival**
22-24	1	100
25-26	7	29
27-29	50	63
30-32	40	85
33-35	16	94

Table 4: Survival-to-discharge rates according to gestational age (N=169)

The most common morbidities observed among the subjects were sepsis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), patent ductus arteriosis (PDA) and necrotizing enterocolitis (NEC). 78% of subjects either had a presumed or confirmed diagnosis of sepsis. Neonatal RDS occurred in 78 (46%) infants. 40% showed evidence of IVH on diagnostic imaging. Frequencies of the various grades of IVH were as follows: 63% with grade 1; 30% with grade 2; 3% with grade 3 and 4% with grade 4. PDA was diagnosed in 25% of infants while 18% were found to have NEC.

Table 5: Distribution of neonatal morbidities (N=171)

Morbidity	**Frequency**	**Percent (%) of children with morbidity**
Sepsis	133	78
RDS	79	46
IVH	68	40
PDA	42	25
NEC	31	18
Bronchopulmonary dysplasia (BPD)	20	11
Pulmonary hypertension	11	8
Pulmonary hemorrhage	8	5

A total of 55 subjects (18 males, 37 females) died while on admission in the hospital, translating to a survival-to-discharge rate of 68%. The associations between multiple factors—gender, birth weight, gestational age and neonatal morbidity—and survival to discharge were investigated. No association was found between gender and survival to discharge ($p = 0.234$). Increasing birth weight and gestational age were associated with a greater survival up to discharge ($p < 0.0001$ for both). Of the neonatal morbidities previously discussed, RDS ($p < 0.0001$) and increasing IVH grade ($p = 0.033$) were associated with poor survival to discharge.

Neurodevelopmental Outcome at Follow-up

Of the ELBW infants who survived until discharge, 76 (33 males; 43 females) returned for follow-up, giving a follow-up rate of 66%. The average age at follow-up was 7.6 months corrected age (CA) with a range between 1.5 months preterm to 23 months CA. 71% of the children showed normal development while 17% had developmental delays/disabilities. Data for the remaining 12% were unavailable. 77% of females seen at follow-up were without neurodevelopmental handicap compared to 64% of males.

The associations between four factors—gender, birth weight, gestational age and neonatal morbidity—and neurodevelopmental outcome at follow-up was investigated. Although increasing gestational age was associated with greater survival to discharge, it was not found to be associated with favorable outcome at follow-up ($p = 0.607$). The incidence of neurodevelopmental handicap was found to decrease with female gender ($p = 0.048$) and increasing birth weight ($p = 0.050$). NEC was the only neonatal morbidity found to have an association with outcome at follow-up; it was associated with an increased incidence of developmental handicap ($p = 0.041$).

Table 6: Neurodevelopmental outcome according to birth weight (N=67)

Birth weight (g)	**Developmentally appropriate**	**Developmentally handicapped**	**Total**
401-475	0	0	0
476-550	0	1	1
626-700	3 (60%)	2	5
701-775	9 (90%)	1	10
776-850	10 (71%)	4	14
851-925	16 (89%)	2	18
925-1000	16 (84%)	3	19
Total	**54**	**13**	**67**

Percentage of developmentally appropriate children per birth weight class is found in parentheses. Data on outcome were unavailable for 9 of the 76 children known to have been seen in follow-up hence the N of 67 in Table 6.

Table 7: Summary statistics by gender (N=171 unless otherwise indicated)

	Male	**Female**	**p-value**
Number	67	104	
Survival	49 (73%)	67 (64%)	p= 0.234
Birth Weight (g)	839.10 ±127.8	826.20 ±112.4	p= 0.488
Gestational Age (weeks); N= 169	29.08 ± 2.6	28.96 ± 2.4	p= 0.770
Evaluated at follow up; N=76	33 (49% of all males in the study)	43 (41% of all females in the study)	p= 0.694
No disability at follow up; N=54	21 (64% of males seen in follow-up)	33 (77% o females seen in follow-up	p= 0.048

Discussion

The aim of this study was to assess the neurodevelopmental outcome of ELBW children post-discharge from a neonatal unit, and to determine risk factors associated with unfavourable outcome. There were a total of 171 subjects born between 22-35 weeks gestation, with weight ranging from 405-1000g. Subjects had a 68% survival to discharge rate. Increasing birth weight and gestational age were associated with greater survival to discharge ($p < 0.0001$ for both). Respiratory Distress Syndrome ($p < 0.0001$) and higher IVH grade ($p = 0.033$) were associated with poor survival to discharge. The follow-up rate was 66% with an average age of 7.6 months CA at follow-up. 71% of subjects were assessed as developmentally normal and 17% were found to have developmental delays/disabilities. No assessment could be made of the remaining 12%, as data from follow-up were unavailable. The incidence of neurodevelopmental handicap was found to decrease with female gender ($p = 0.048$) and increasing birth weight ($p = 0.050$) but not with increasing gestational age ($p = 0.607$). NEC was the sole neonatal morbidity associated with an increased incidence of developmental handicap ($p = 0.041$). Based on these findings, the authors conclude that favourable neurodevelopmental outcome at 7 months was associated with increasing birth weight and female gender.

Previous South African studies of low birth weight infants have focused on those of very low birth weight (VLBW). Velaphi et al conducted a retrospective study of 2164 VLBW infants who were born alive at or admitted to Chris Hani Baragwanath Hospital, a major public sector referral hospital. Birth weight and gestational age ranged between 500-1495g and 22-40 weeks respectively. The survival to discharge rate was 32% for infants weighing <1000g and 84% for those weighing between 1000-1499g. This considerable difference in survival rates was partly due to the fact that ELBW infants were not offered mechanical ventilation, as resources were limited. Overall survival to discharge was 72%. Increasing birth weight and gestational age, and female gender were associated with increased survival to hospital discharge.[16] Another South African retrospective study of 474 VLBW infants showed a 34.9% survival rate for children born below 1001g, with an overall survival rate of 70.5%. In this instance as well, mechanical ventilation was limited. Mechanical ventilation was only available to neonates weighing above 900g. The determinants of survival to discharge included female gender ($p=0.001$) and increasing birth weight ($p<0.001$). The presence of NEC was associated with poor survival to discharge ($p<0.001$).[17]

The 68% survival to discharge rate of the ELBW infants in our study compares favourably with survival rates of the larger infants in the previously discussed VLBW studies. This suggests that ELBW mortality rates can be lowered significantly, even in resource limited settings, as long as ventilatory support is included in the care protocols of these infants. Our findings of female gender and increasing birth weight being key determinants of survival are corroborated by the two VLBW infant studies.

Upon review of the existing literature, no long-term outcome studies of African ELBW infants could be found, although two long-term outcome studies have been conducted on very low birth weight infants (i.e. those 1250g BW or less). Clinicians at Groote Schuur Hospital (GSH) evaluated infants born between July 1988 and June 1989 who weighed less than 1250g.[18] In this prospective 2-year follow-up study of 235 VLBW infants, overall survival to discharge was 61%. Of note, there were 126 ELBW subjects of which 53 survived until discharge. In this instance, ELBW infant survival was 42%

compared to 68% in our study. The difference in survival may be attributed to changes in ventilatory support of this patient population. At the time of the VLBW study, GSH did not routinely mechanically ventilate infants weighing less than 900g. Only 18% of infants weighing less than 900g and 37% of those weighing 900-1000g were given ventilatory support. Infants more likely to survive until discharge were born weighing greater than 900g, were delivered at greater than 30 weeks and were born to mothers who attended prenatal care. Follow-up rates were 83% and 91% at ages 1 and 2 years, respectively, compared to 66% in our study. As the VLBW study was done prospectively, specific mechanisms were implemented to ensure consistent follow-up. The presence of a social worker, who undertook home visits, made it easier to track children who would have otherwise been lost to follow-up.

Follow-up evaluations consisted of a clinical assessment and testing with Griffiths development scales. 91 out of 106 children (86%) were assessed as developmentally normal at age 1 while 72 out of a total of 96 children (78%) were free of handicap at age 2. The rate of major handicap went from 11% at 1 year to 22% at 2 years. Follow-up in our study occurred, on average, at 7.6 months at which time 71% of subjects in our study were assessed as normal. Although our study's handicap rate is greater, it must be remembered that our subjects were born smaller than those in the VLBW study. Consistent with our study's results, infants with NEC were more likely to have poor outcome. No difference in neurodevelopmental outcome was demonstrated between ELBW and larger infants. The authors attributed this finding to the low survival rate of ELBW subjects relative to the rest of their cohort.

The GSH VLBW study was unable to identify any perinatal predictors of long-term outcome. However, a long-term outcome study of VLBW children in Soweto, South Africa, identified an association between higher maternal education levels and favourable developmental outcome.[19] As maternal socio-demographic data were unavailable, we were unable to assess its effect on the outcome of our cohort.

Our data may also be compared to those from developed countries. In their multicentre outcome study of American ELBW children at 18 to 22 months of age, Vohr et al had a 78% follow-up rate. [20] Our 66% follow-up rate is comparatively low. Fifty-one percent of their subjects were without handicap compared to 71% in our study. Although our handicap rate is less, the average age at follow-up in our study was 7.6 months CA, which is too young to definitively diagnose conditions such as cerebral palsy. If our cohort had been followed for a longer period, it is possible that their rate of handicap would be higher than the 17% demonstrated at 7 months. Vohr et al's study found female gender and increasing birth weight to be associated with favourable outcome. NEC was shown to be associated with poor outcome. While these associations are consistent with our results, others are not.

The Vohr study demonstrated an association between high grade IVH and adverse outcome. Our study found no such association, primarily because most of the infants with high grade IVH died prior to hospital discharge. Neither did we identify an association between decreasing gestational age and neurodevelopmental handicap at follow-up as has been demonstrated, albeit inconsistently, in the literature. A German outcome study of 135 ELBW children evaluated from ages 3 through 10, associated decreasing gestational age with adverse neurodevelopmental outcome.[21] Our follow-up period was far short of 7 years. As to whether the effect of gestational age on outcome would have become apparent as our cohort matured, this remains unknown.

Despite the important insights provided, our study is not without its limitations. Following our subjects after hospital discharge proved to be challenging, as evidenced by the study's 66% follow-up rate. Vital data were unavailable. There was no information on maternal socio-demographics. For subjects found to be handicapped, we had no access to records detailing the nature and extent of their disability. The use of the INA presented challenges. It was performed inconsistently; not all subjects underwent INA testing. Although it is a simple test to administer, not all testers were equally experienced. None of our testers was blind to the subjects' history and this could have been a source of bias during follow-up assessments. While NEC was found to be associated with adverse outcome, it is impossible to separate its effect from that of sepsis given that all subjects with NEC who were evaluated at follow-up also had sepsis as neonates.

In as much as possible, future South African ELBW studies should be prospective in nature. Some might argue about the cost of "re-doing" a study. A prospective trial would allow for greater emphasis on follow-up be it through a social worker as was done in a past study or by using short message service (SMS) technology to maintain contact with families. South Africa is reported to have a 100% cellular phone penetration rate[22] so SMS would be an ideal tool—inexpensive, time efficient and accessible to families, regardless of socio-economic standing.

Preterm birth remains a significant global public health concern, particularly in sub-Saharan Africa. Its considerable burden of morbidity comes at a tremendous cost. While our study has shed some light on the neurodevelopmental outcome of South

African ELBW children, additional studies are needed in order to design and implement cost-effective interventions for these children. These interventions could then serve as models for other developing countries, models that could be adapted to each country's unique socio-cultural context. None of this can be accomplished without funding. Providing funding for the follow-up of ELBW children is more than a public health issue. Funding would affirm the South African government's commitment to ensuring the wellbeing of ***all*** South African children.

References

[1] Lawn, J.E., Wilczynska-Ketende, K., and Cousens, S.N. 2006. *Estimating the causes of 4 million neonatal deaths in the year 2000*. Int. J Epidemiol. 35:706-18.

[2,] Beck, S., Wojdyla, D., Say, L., Betran, A.P., Merialdi, M, et al. 2010. *The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity.* Bull World Health Org .88: 31-38.

[3] ibid

[4] ibid

[5] UNICEF Country Factsheet, South Africa:

http://www.unicef.org/infobycountry/southafrica_statistics.html

[6] Saloojee, H., and Pettifor, J.M. 2005. *International child health: 10 years of democracy in South Africa.* Current Pediatrics. 15(5): 429-436.

[7] *Saving Babies Lives 2006-2007*: *Sixth Report on Perinatal Care in South Africa*. 2009. Ed R.C. Pattinson. Tshepesa Press, Pretoria.

[8] Tommiska, V., Heinonen, K., Kero, P., Pokela, M-L., Tammela, O., et al. 2003. *A national two year follow up study of extremely low birthweight infants born in 1996-1997.* Arch Dis Child Fetal Neonatal Ed.88: F29-F35.

[9] Voss, W., Neubauer, A.P., Wachtendorf, M., Verhey, J.F., and Kattner, E. 2007. *Neurodevelopmental outcome in extremely low birth weight infants : what is the minimum age for reliable developmental prognosis?* Acta Pediatrica. 96(3)342-347.

[10] Davis, N.M., Ford, G.W., Anderson, P.J., and Doyle, and L.W. 2007. *Developmental Coordination Disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants.* Dev Med Child Neurology. 49(5):325-330.

[11] Doyle, L.W., and Casalaz, D. 2001. *Outcome at 14 years of extremely low birthweight infants: a regional study.* Arch Dis Child Fetal Neonatal Ed. 85:F159- F164.

[12] Hintz, S.R., Kendrick, K.E., Vohr, B., Poole, W.K., and Higgins, R.D. 2006. *Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birth weight infants.* Acta Paediatrica. 95:1239-1248.

[13] Anderson, P., and Doyle, L.W. 2003. *Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s.* JAMA. 289(4): 3264-3272.

[14] Stoll, B.J., Hansen, N.I., Adams-Chapman, I., Fanaroff, A.A., Vohr, B., et al, .2004. *Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection.* JAMA. 292(19): 2357-2365.

[15] Newborns Groote Schuur Trust: www.newborns.org.za

[16] Velaphi, S.C., Mokhachane, R.M. Mphahlele, R.M., Beckh-Arnold, E, Kuawanda, M.L., et at al. 2005. *Survival of very-low-birth-weight infants according to birth weight and gestational age in a public hospital.* SAMJ. 95(7): 504-509.

[17] Ballot, D.E., Chirwa, T.F., and Cooper, P.A. 2010. *Determinants of survival in very low birth weight neonates in a public sector hospital in Johannesburg.* BMC Pediatr. 10: 30.

[18] Thompson, C.M., Buccimazza, S.S., Webster, J., Malan, A.F., and Molteno, C.D. 1993. *Infants of less than 1250 grams birth weight at Groote Schuur Hospital: outcome at 1 and 2 years of age.* Pediatrics. 91(5): 961-968.

[19] Cooper, P.A., and Sandler, D.L. 1997. *Outcome of very low birth weight infants at 12 to 18 months of age in Soweto, South Africa.* Pediatrics 99(4): 537-544.

[20] Vohr, B.R., Wright, L.R., Dusick, A.M. Mele, L. Verter, J., et al. 2000. *Neurodevelopment and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994*. Pediatrics 105(6): 1216-1226.

[21] Neubauer, A., Voss, W., and Kattner, E. 2008. *Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on development.* Eur J Pediatr. 167: 87-95.

[22] Transcript of Public Radio International's "The World" radio broadcast on Cellular Phone Learning in South Africa: http://www.theworld.org/2010/10/cell-phone-learning-south-africa/