East African Medical Journal Vol. 95 No. 1 January 2018
OUTCOMES AND ASSOCIATED FACTORS AMONG PREMATURE NEONATES WITH RESPIRATORY DISTRESS SYNDROME MANAGED AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA
Prof. Winstone M. Nyandiko, Associate Professor & Paediatrician, Department of Child Health & Paediatrics, Moi University, School of Medicine, P.O. Box 4606, Moi University, Eldoret (30100), Dr. Eric Ng'etich, Paediatrician, Division of Paediatrics & Child Health, Moi Teaching & Referral Hospital, Eldoret, P.O. Box 7848, Eldoret (30100), Dr. Namulala Emma Sara, Resident, Department of Child Health & Paediatrics, Moi University, School of Medicine, Eldoret, P.O. Box 2310, Bungoma (50200).

Corresponding author: Dr. Namulala Emma Sara, Resident, Department of Child Health & Paediatrics, Moi University, School of Medicine. Email: efransa@yahoo.com

OUTCOMES AND ASSOCIATED FACTORS AMONG PREMATURE NEONATES WITH RESPIRATORY DISTRESS SYNDROME MANAGED AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

W.M. Nyandiko, E. Ng'etich and N.E. Sara

ABSTRACT

Background: **Globally, approximately over 4 million newborns die annually and the leading cause of death is directly from preterm complications which account for more than 1 million deaths. The most common complication is Respiratory distress syndrome (RDS).**
Objective: **To determine short-term outcomes of premature neonates with RDS managed in the newborn unit (NBU) at Moi Teaching & Referral Hospital (MTRH), Eldoret.**
Design: **Prospective descriptive study.**
Setting: **Riley Mother Baby Hospital, NBU (MTRH), Eldoret.**
Participants: **All admitted premature neonates clinically diagnosed with RDS.**
Main outcomes: **Death/survival on day 10 and broncho-pulmonary dysplasia (BPD) at 6 weeks.**
Results: **This study enrolled 94 premature neonates with RDS and 54 (57.4%) were females. Gestational age distribution: Below 28weeks (7.5%), 28-32weeks (54.3%) and 33-37 weeks (38.3%). Continuous Positive Airway Pressure was used on 62.8% (95% CI 52.2, 72.5), the rest received oxygen via nasal prongs and none received surfactant. Mortality at day 10 was 61% (0.61 95% CI: 0.51,0.71) with BPD reported in one neonate at 6weeks. Survival was 40% and 25% on day 10 and 40 respectively. Hypothermia and hyperglycemia were found in 65% and 55% respectively whereas suspected sepsis was treated in 77 (81.9%) of the neonates. None of the factors were independently associated with the outcome of death after adjusting by multiple logistic regression.**
Conclusion**: There was a high mortality mainly occurring in the first 10 days of life. Hypothermia, hyperglycemia and neonatal sepsis were common co-morbidities. None of the factors were independently associated with the outcome of death. Chronic complications like BPD were rare**

INTRODUCTION

Globally, there has been a decline in neonatal mortality rate from 36/1000 live births in 1990 to 19 in 2015 although this is slower than that of post-neonatal under 5's at 58% compared to 47%. This trend applies to most low and middle income countries. Kenya had a slower decline of 27 to 22/1000 live births (1).

The United nations Interagency Group for Child Mortality Estimation report (UN IGME) 2015 projected that if this trend continues, half of the under 5's deaths between 2016- 2030 are likely to occur in the neonatal period which will increase neonatal mortality from 45% of the under 5's deaths in 2015 to 52% in 2030. Preterm birth is the leading cause of newborn deaths and the second greatest killer of under 5's worldwide following pneumonia. Approximately 15 million babies are born preterm annually worldwide and this translates to 1/10 babies born preterm (2,3) with rates rising in almost all countries ranging from 5-18% of babies born across 184 countries (3,4). Of the eleven countries with highest rates of over 15%, all except two are in sub-Saharan Africa. Kenya recorded twelve premature births per every one hundred live births (3).

Complications of preterm birth were the main causes of mortality among the under 5's accounting for about 18% of the cases (1). Over one million children die annually due to complications of prematurity yet three quarters (75%) could be saved with current, cost-effective interventions, even without intensive care facilities (2).

The most common complication of prematurity is RDS with or without BPD (3) with approximately 50% of those born at 26-28 weeks gestation and less than 30% of those born at 30-31weeks gestation developing RDS (5).In developing countries such as Kenya, only about 46% of expectant mothers deliver in hospital with some parts like Nyanza and Western provinces having approximately 75% of them not delivering in hospital (6,7). This has led to RDS being less frequently reported and inaccurate records (8). RDS is a major contributor of neonatal mortality and morbidity worldwide (8). In Tanzania, Mlay GS et al found a mortality rate of 52% (9) whereas at Kenyatta National Hospital, Simiyu et al in 2002 recorded a morbidity of 43% amongst the total admissions (10). At MTRH in 2006, Njuguna et al found RDS to be the second commonest cause of morbidity after neonatal sepsis accounting for 37.1% amongst the admissions in the NBU11 and Makokha et al following her dissertation, in the same unit found a morbidity of 64.6% and RDS was the fourth commonest cause of admissions among premature neonates in 2014.

Management of RDS has evolved over the past five decades in developed countries and efficacy of various management modalities documented unlike in the developing countries (12). At MTRH, with the rising number of cases admitted with RDS, there is need for improved neonatal care focused on cost effective measures for treating RDS (10). Emerging new technologies such as use of oxygen therapy and CPAP together with observing fundamental principles of neonatal care in the developed countries have been associated with decreased mortality among RDS patients. With availability of oxygen and CPAP modalities in the NBU of MTRH, there is need to look at RDS management outcomes no study has previously been done addressing the same. The aim of this study was to determine RDS management outcomes in our unit and the factors associated with the same.

METHODS

This was a prospective descriptive study carried out at the Riley Mother Baby Hospital NBU of MTRH. Participants were

recruited within 24 hours of admission and followed up during their stay in the unit, taking note of all significant clinical events until discharge or death at day (10). A follow up was done at 6 weeks irrespective of whether they had been discharged or were still in the unit.

The study targeted all premature neonates admitted with a study population comprising those clinically diagnosed to have RDS managed at the unit during the period between January and September 2015. However, those with severe birth asphyxia (APGAR score < 4) and severe congenital malformations not compatible with life were excluded. The sample size was determined by the Fischer's formula with a total of 94 neonates recruited based on a study by Mlay G.S et al (9) on outcomes of RDS neonates admitted at Muhimbili medical centre, Dar es Salaam, Tanzania giving us an estimated P from the outcome death of 50% which gave us a sample size of 384. Adjustment for the finite population based on premature neonates admitted at the unit with a clinical diagnosis of RDS. On average, 12 neonates were admitted with RDS per month, for 9 months gave us a minimal sample size of 84. However, a further 10% was recruited to cater for any loss to follow up giving us a minimal final sample size of 94 sampled consecutively.

Short term outcomes of RDS defined as clinical features of respiratory distress in premature neonates (<37wks) who require oxygen support within 6 hours of life for at least 24 hours were looked out for. Primary outcomes were death or survival at day 10 and the secondary outcome was BPD defined as oxygen dependency at week six of life. Other outcomes included hypothermia, hyperthermia, hypoglycemia, hyperglycemia, neonatal sepsis and initiation of enteral feeds. Study participants were identified over 24 hrs with confirmation of the clinical diagnosis based on the findings; sub-costal recession, grunting, flaring of the alae nasi, apnea, cyanosis, intercostal recession, shallow breathing and tachypnea. At 24 hours if they were still on respiratory support, consent was obtained.

Data was collected using a pretested structured questionnaire and a follow up data Collection form. Data on demographic characteristics, neonatal and maternal characteristics were entered in the data collection form at 24 hours of admission following recruitment. Most of the data on maternal and infant characteristics were obtained from the nursery admission notes and any missing data was obtained through maternal interview and by checking the antenatal attendance booklets. Subsequently, a daily follow up was done till both primary and secondary outcomes were obtained up to a maximum of 6 weeks with the information entered to a data follow up chart. Those discharged before 6weeks had their contacts taken to be used as a reminder and were followed up in the neonatal outpatient clinic at 6 weeks from the day of delivery to examine for any secondary outcomes.

Data collected was entered into Microsoft access data base then exported to STATA version 13.0 for analysis. Descriptive statistics were used for continuous variables whereas frequency listings and percentages were used to describe categorical variables. The log-rank test was used to test for associations among various GA and birth weight categories presented in the Kaplan-Meir survival curves. The Fischer's exact and Pearson's Chi square tests were used to test for associations among socio-demographic and treatment variables with the outcome death. A p-value < 0.05 was considered statistically significant at 95% confidence interval. Multiple logistic regression (odds ratio) was used to determine independent variables for the outcome death. Data is presented in prose, tables, figures and curves.

Approval was sought from IREC of MTRH and Moi University CHS with permission granted by the director of MTRH. Informed consent was obtained from the parents of the study participants.

Study limitations: There was lack of radiological investigation, surfactant level determination and lecithin sphingomyelin ratio to support the diagnosis of RDS by the clinicians and lack of access to an early echocardiogram to rule out congenital heart diseases that would also cause oxygen dependency.

RESULTS

Socio-demographic characteristics: We recruited 94 premature neonates clinically diagnosed to have RDS between January and September 2015 out of whom were 54 females.

Table 1:
Neonatal & Maternal characteristics

Variable	Frequency (%)	Median(IQR)
NEONATAL CHARACTERISTICS		
Sex		
Male	40(42.55%)	-
Female	54(57.45%)	-
Birth weight at admission		
<1000 grams	16(17.20%)	-
1000-1499grams	51(54.84%)	-
1500-2500grams	26(27.96%)	-
Age at admission(days)		0.63(0.17,2.5)
Length of hospital stay(days)		7(3,24)
Length of stay to Death		5(3,8)
Weight category discharged(n=23)		
<1000grams	1(4.35%)	-
1000-1499grams	4(17.39%)	-
1500-2500grams	18(78.26%)	-
Place of delivery		
Home	11 (11.7%)	-
Hospital	83 (88.3%)	-
Gestational age by the New Ballard Score(weeks)		
<28	5(5.43%)	-
28-32	51(55.43%)	-
33-37	36(39.13%)	-
Mode of delivery		
Spontaneous Breech Delivery	7(7.4%)	-
Spontaneous Vertex Delivery	69(73.4%)	-
Caeserian section	7(7.4%)	-
Unaware	11(11.7%)	-
APGAR score		
4-7	33(35.1%)	-
8-10	38(40.4%)	-
Born Before Arrival	16(17.0%)	-
Not indicated	7(7.4%)	-

MATERNAL CHARACTERISTICS		
Maternal age(yrs)	-	23(21,28)
Marital status		
Married	65(69.9%)	-
Single	28(30.1%)	-
		-
Educational level		
Primary	35(38%)	-
Secondary	40(43.5%)	-
Tertiary	17(18.5%)	-
Parity		
Primigravida	54(57.5%)	-
Multigravida	37(39.4%)	-

Clinical characteristics of the neonates: Most of the study participants presented with sub-costal recession (73.4%), grunting and flaring of the *alae nasi* (68.1% each). The rest included cyanosis (44.7%), intercostal recession (31.9%), shallow breathing (12.8%) and apnea (11.7%). Tachypnea (respiratory rate >60breaths/ minute) was noted in 69 (73.41%) of the neonates.

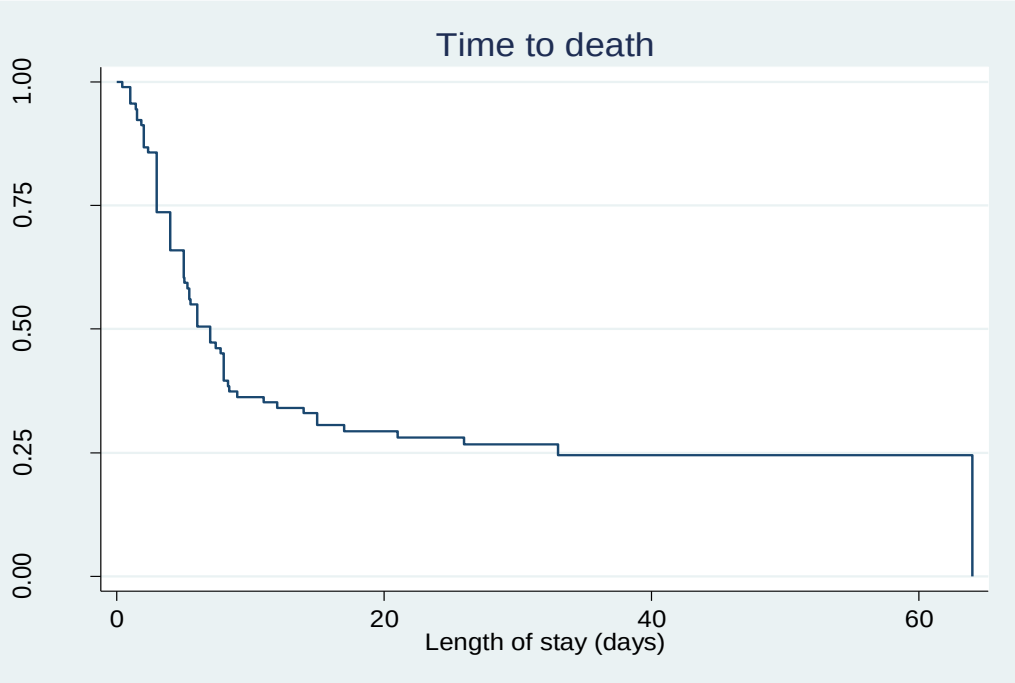
OUTCOMES

Mortality: There were 68 (72.3%) deaths during the study period with 58 occurring within the first 10 days of life. Mortality rate at day 10 was 61% (0.61, 95%CI: 0.51,0.71). Oxygen therapy was an initial treatment modality for 88 (93.6%) of the neonates. Majority, 59 (62.8%) with 95% CI 52.2, 72.5) were managed on continuous positive airway pressure (CPAP) subsequently. None of the neonates received surfactant therapy. CPAP was started as an initial treatment modality for only 6 (6.4%) neonates with 53 (56.4%) being put on CPAP later during the hospital stay. Average time to start of CPAP was 3.08 days. Of the 6 neonates whose initial treatment was CPAP, half (3) of them died within the first 10 days of life while 2 were discharged and one (1) was on supplemental oxygen at 6 weeks. BPD was found in 1 (1.1%) of the neonates.

Survival: Survival was about 40%, 30%, 28% and 25% on day 10, 20, 30 and 40 respectively as shown in the Kaplan-Meir survival curve in figure 1 below.

Figure 1

Neonates' Overall survival (time to death) - Kaplan -Meir survival curve



Survival by gestational age is illustrated by figure 2 below. None of those born with a GA of < 28weeks survived beyond 5 days of life. However, for those with GA of 28 weeks and above, survival was 40%, 30% and 25% on day 10, 20 and 30 respectively. From the log rank test, survival distribution of different GA categories comparing those born with a GA of < 28weeks and those above was statistically significant (P=0.039) indicating that having a GA above 28 weeks is significantly associated with better survival.

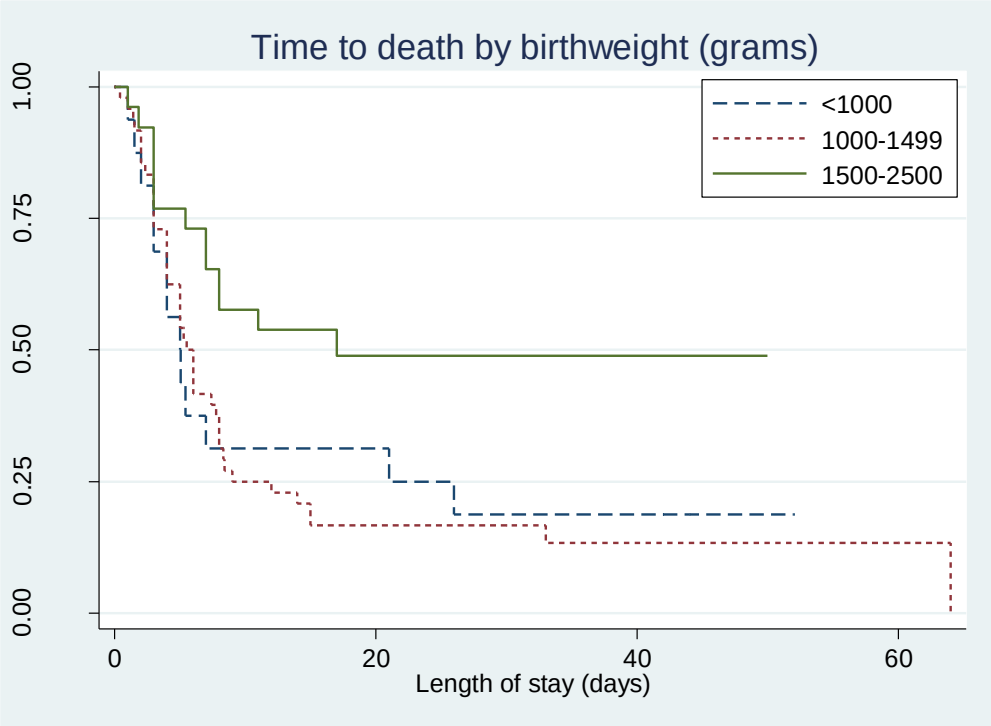
Figure 2

Neonates' Time to death by gestational age -Kaplan-Meir survival curve

Figure 3 below indicates survival by birth weight. For those born with a birth weight of <1000 grams, it was 30%, 25% and 20% on day 10, 20 and 30 respectively; those between 1000-1499 grams, it was 25%, 15% and 13% on day 10, 20 and 30 respectively whereas for those between 1500-2500grams it was 60% and 50% on day 10 and 20 respectively. From the log rank test, the survival distribution of different birth weight categories was statistically significant (P=0.016) indicating that those with a birth weight of more than 1500g were more likely to survive than those with a lesser weight.

Figure 3

Neonates' Time to death by birth weight -Kaplan and Meir survival curve



Other outcomes: Hypothermia was found in 60 (64%) from at least one reading from the 3 hourly temperatures taken daily with the remaining having normal temperature. Only 1 (1%) neonate had hypoglycemia, 41 (43.6%) had a normal glucose control whereas the remaining 52 (55.3%) had hyperglycemia from at least a reading recorded 3 hourly over 24hours on a daily basis. All neonates were put on intravenous fluids for the first 24 hours, 10% dextrose was initiated and electrolytes subsequently introduced after 24 hours. Enteral feeds were initiated as tolerated on day 3 of life. A total of 77 (61%) neonates were treated for neonatal sepsis out of whom 27 (35%) had blood cultures with 23 (85%) found to be positive for bacterial growth.

FACTORS ASSOCIATED WITH THE OUTCOME DEATH

Univariate analysis: On univariate analysis of the various factors associated with the outcome death, we found that having a birth weight of less than 1500 grams (P=0.007), being born of a primi-gravida (P=0.031) and lack of antenatal clinic attendance (P=0.016) were significantly associated with the outcome of death.

Multivariate analysis: The table 4 below indicates multivariate analysis (odds ratio) for independent factors for the outcome death. None of the factors were significantly associated with the outcome death.

Table 4

Multiple logistic regression for the outcome of death

DEAD	ODDS RATIO	95% CI		P-VALUE
Sex				
Male vs. Female	2.066876	0.627657	6.806233	0.232
Birth weight				
1000-1499 vs. <1000	0.757692	0.125552	4.572576	0.762
1500-2500 vs. <1000	0.191322	0.027610	1.325767	0.094
Parity				
Primi vs. Multi	2.466389	0.821588	7.40405	0.107
Antenatal clinic attendance				
ANC vs. No ANC	0.329641	0.089344	1.216241	0.096

DISCUSSION

The mortality in this study is higher as compared to Mlay et al[9] study conducted at Muhimbili medical centre in Dares Salaam, Tanzania which is similarly a teaching and second referral hospital in the country. This may be due to indifferences in the sample size such that in this study we had a smaller sample size without controls and only included premature neonates clinically diagnosed with RDS unlike Mlay et al whereby they included all neonates with respiratory distress. Morbidity due to RDS at our facility is four times higher as compared to Muhimbili hospital leading to higher mortality in our set up. Ghafoor et al[13] in Pakistan at Rawalpindi Military Hospital recruited both term and preterm neonates hence our outcomes having been skewed to favour poor outcome among prematures. In Mlay et al[9] and Perez[14] et al studies, 60% and 100% of the neonates respectively had an X-ray of the chest which aided in diagnosis of RDS unlike our study which was highly dependent on the clinical diagnosis hence a possibility of overdiagnosis of RDS with overlap of other comorbidities such as neonatal pneumonia, sepsis, congenital heart diseases and birth asphyxia which highly impact on neonatal mortality. At MTRH, only two modalities are employed in treatment of RDS (CPAP and oxygen via nasal prongs) unlike at Muhimbili whereby despite having the two also had neonate given surfactant which is the definitive treatment resulting in a lower mortality as compared to our study.

Myhre et al[15] in a two arm study (prospective and retrospective arms) and Omoding et al[16] in a short longitudinal study at Kijabe AIC mission Hospital found a better survival as compared to this study. The difference might have been in the treatment modalities. CPAP at Kijabe was initiated earlier within 24 hours in over 90% of the neonates unlike in our study whereby it was started late (on average day 3) leading to poor survival as CPAP is associated with a better outcome if started early. There were inadequate CPAP machines to those who really required them early as initiation on the same was dependent on availability leading to poor survival. We didn't have options to CPAP failure denying neonates chances of survival with modalities such as mechanical ventilation and Surfactant as it were at Kijabe.

BPD associated with ventilation and oxygen treatment was rare as compared to

Omoding et al study[16]. The difference may have been due to a lesser number of neonates started on CPAP as an initial modality and that most of them died within the first 10 days of life not having a chance to be assessed for the same at week 6. Lastly, the difference in the definition of BPD for both studies may have contributed to the insignificant finding of BPD as the duration was lesser in our study.

On multivariate analysis, the odds of males dying from RDS was 2.01 times more than females whereas the odds of dying from RDS after being born of a primigravida was 2.47 times more likely than those born of multigravida. However, none of these factors were significantly associated with the outcome death.

CONCLUSION

There was a high mortality with majority of the deaths occurring within the first 10 days of life. Hypothermia, hyperglycemia and neonatal sepsis were common co-morbidities. None of the factors were independently associated with the outcome of death with chronic complications like BPD reported rarely.

REFERENCES

1. United Nations Children's Fund. (2015). IGME report 2015 child mortality final.pdf. Retrieved from http://www.childmortality.org/files_v20/download/IGME report 2015 child mortality final.pdf
2. Wang, M. L., Dorer, D. J., Fleming, M. P., & Catlin, E. a. (2004). Clinical outcomes of near-term infants. *Pediatrics*, *114*(2), 372–376. http://doi.org/10.1542/peds.114.2.372
3. WHO. (2013). Preterm birth. Retrieved from http://www.who.int/mediacentre/factsheets/fs363/en/
4. Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2009). Preterm Birth 1: Epidemiology and Causes of Preterm Birth. *Obstetric Anesthesia Digest*, *29*(1), 6–7. http://doi.org/10.1097/01.aoa.0000344666.82463.8d
5. Pramani AK, Rosenkrantz MD, Pesonen AK et al,Respiratory distress Syndrome, Medscape, Sep 2012
6. Ikamari, L., Izugbara, C., & Ochako, R. (2013). Prevalence and determinants of unintended pregnancy among women in Nairobi, Kenya. *BMC Pregnancy and Childbirth*, *13*(1), 69. http://doi.org/10.1186/1471-2393-13-69
7. KNBS. (2015). Key Indicators 2014 Kenya Demographic and Health Survey.
8. Kamath, B. D., Macguire, E. R., McClure, E. M., Goldenberg, R. L., & Jobe, A. H. (2011). Neonatal mortality from respiratory distress syndrome: lessons for low-resource countries. *Pediatrics*, *127*(6), 1139–46. http://doi.org/10.1542/peds.2010-3212
9. Mlay, G. S., & Manji, K. P. (2000). Respiratory distress syndrome among neonates admitted at Muhimbili Medical Centre, Dar es Salaam, Tanzania. *Journal of Tropical Pediatrics*, *46*(5), 303–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11077942
10. Kiptoon, P. (2014). An assessment of the overall mortality of low birth weight neonates at the new birth units of the Moi Teaching and Referral Hospital in Eldoret, Kenya (2014). *East African Medical Journa; 2*(3), 63–71.
11. Levesque, B. M., Kalish, L. a, LaPierre, J., Welch, M., & Porter, V. (2011). Impact of implementing 5 potentially better respiratory practices on neonatal outcomes and costs. *Pediatrics*, *128*(1), e218–e226. http://doi.org/10.1542/peds.2010-3265
12. D.E., S. (2004). Morbidity and mortality of low birth weight infants in the new born unit of Kenyatta National Hospital, Nairobi. *East African Medical Journal*. Retrieved from

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=15490710

13. Ghafoor, T., Mahmud, S., Ali, S., & Dogar, S. A. (2003). Incidence of respiratory distress syndrome. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP*, *13*(5), 271–273. http://doi.org/05.2003/JCPSP.271273
14. Perez Molina, J. J., Blancas Jacobo, O., & Ramirez Valdivia, J. M. (2006). [Hyaline membrane disease: mortality and maternal and neonatal risk factors]. *Enfermedad de Membrana Hialina: Mortalidad Y Factores de Riesgo Maternos Y Neonatales.* Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16970125
15. Myhre, J., Okeyo, B., Letchford, S., Nduku, I., Anand, M., & Okeyo, L. (2014). Effect of Treatment of Premature Infants with Respiratory Distress Using Low-cost Bubble CPAP in a Rural African Hospital. In *International Congress of Tropical Paediatrics*.
16. Omoding A.A, Wafula E, Murila F et al, A short longitudinal survey describing the use of bubble CPAP in premature neonates with respiratory distress syndrome at the AIC Kijabe. 18th nov, 2012