Child Mortality after Discharge from a Health Facility Following Suspected Pneumonia, Meningitis and Septicaemia in Rural Gambia.

By

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ABSTRACT

Background

Two years away from 2015, the decline in child mortality is not fast enough to reach Millennium Development Goal 4. The Integrated Management of Childhood Illness (IMCI) is a strategy that simplifies management of child health. Beyond effective disease management, IMCI recommendations for care *following* illnesses are based on limited evidence from the field. The aim of this project was to find (1) the magnitude of and (2) risk factors for child mortality following discharge from a health facility in a low-income setting.

Methods

This study used an established population-based surveillance system for suspected invasive pneumococcal disease in Upper River Region, The Gambia, West Africa. Children that survived admission for suspected pneumonia, meningitis or septicaemia at the Region's only referral centre (Basse Major Health Centre, Upper River Region) were followed for 180 days after discharge. Vitality status monitored by the DSS informed time-to-death information in a survival analysis that identified predictors of post-discharge mortality. Two multivariable Cox proportional hazards models were constructed. Model A described the clinical syndrome on admission (provisional diagnosis) and risk of post-discharge mortality. Model B used a reverse step-wise approach to find pre-discharge risk factors for mortality following discharge.

Results

The cohort that survived admission had higher mortality rates than the background rate in the community. Overall, 105 (2.8%) of 3735 patients died during the 6 months of follow-up. Half of the deaths occurred within 45 days of discharge. Approximately half as many patients died in the six months following discharge as died during hospital admission. Age stratified post-discharge mortality rates were three to six times higher than community mortality rates. In addition to demonstrating the protective effect of increasing age at discharge (HR 0.98 [95%CI: 0.96, 0.99] for every month increase in age), Model A showed that, compared to pneumonia alone, a provisional diagnosis of: pneumonia with visible signs of severe malnutrition had a HR 8.74 (95%CI: 4.93, 15.49); meningitis with visible signs of severe malnutrition had a HR of 13.90 (95%CI: 5.43, 35.58); sepsis with visible signs of severe malnutrition had a HR 18.79 (95%CI: 11.65, 30.32). Model B showed independent risk factors associated with post-discharge

mortality were: the presence of neck stiffness on assessment (HR 17.60 [95%CI: 7.36, 42.10]); low mid-upper arm circumference (MUAC) (<10.5cm, HR 11.52 [4.59, 28.90]); visible signs of severe malnutrition (HR 3.94 [95%CI: 2.11, 7.36]); non-medical discharge (HR 6.22 [95%CI: 2.98, 13.01]); discharge during dry season (HR 2.33 [95%CI: 1.44, 3.77]); decreasing peripheral arterial haemoglobin oxygen saturation (HR 0.95 [95%CI: 0.93, 0.98] per percent increase); decreasing haemoglobin concentration (HR 0.82 [95%CI: 0.74, 0.90]) per unit g/dL increase); and decreasing axillary temperature (HR 0.70 [0.58, 0.84] per unit ^{o}C increase).

Conclusion

Gambian children in Upper River Region with suspected invasive pneumococcal disease are at increased risk of death following discharge from a health facility, and most of these deaths occur early. There are identifiable risk factors for death, including neck stiffness, low MUAC, visible signs of severe malnutrition, non-medical discharge, discharge during dry season, decreasing peripheral arterial haemoglobin oxygen saturation, decreasing haemoglobin concentration and decreasing axillary temperature. These data add to the evidence base needed to inform the development key guidelines and may be helpful towards development of a tool with clinical utility to identify children for intervention after discharge from hospital.

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LIST OF ABBREVIATIONS

95%CI: 95 (Ninety-Five) Percent Confidence Interval

BHC: Basse Health Centre

BHDSS: Basse Health and Demographic Surveillance System

CRF: Case Report Form

CRR: Central River Region (The Gambia)

CSM: Clinical Severe Malnutrition

DSS: Demographic Surveillance System

EC: Ethics Committee

HIV: Human Immunodeficiency Virus

HR: Hazard Ratio

ID: Identifier

IMCI: Integrated Management of Childhood Illness

LBW: Low Birth Weight

MDG: United Nations Millennium Development Goal

MRC: The Medical Research Council

MUAC: Mid-upper Arm Circumference

NOS: Newcastle-Ottawa Scale (for Evaluation Cohort Studies)

PCV: Pneumococcal Conjugate Vaccine

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSP: Pneumococcal Surveillance System

RR: Relative Risk

SCC: Scientific Co-ordination Committee

SES: Socio-Economic Status

UN: United Nations

UNICEF: United Nations Children's Fund

URR: Upper River Region (The Gambia)

VLBW: Very Low Birth Weight

WHO: World Health Organisation

CHAPTER 1 – INTRODUCTORY CHAPTER

1.1 Overview of Topic

1.1.1 The United Nations and Millennium Development Goal 4

In the year 2000 the United Nations General Assembly passed the Millennium Declaration which marked the world's commitment to making the world a better place (1). From this, eight millennium goals were developed to be achieved by the year 2015.

At its current trajectory the United Nations Millennium Development Goal 4 (MDG4), to reduce the under-five mortality rate by two-thirds between 1990 and 2015, will not be met (2) (3) (4). Child mortality is reducing, but not fast enough, having reached a decrease of 41% up to 2011. Although difficult to estimate (5), about seven million children under the age of five die every year (2) (3). The highest rates of child mortality are in Sub-Saharan Africa where one in nine children will die before reaching their fifth birthday. Projections suggest possible stagnation or even worsening of child mortality rates in this region by 2050 (4).

Infectious diseases are responsible for nearly two-thirds of these deaths (4). Pneumonia is still the biggest killer of children under five, responsible for 18% of deaths while diarrhoea and malaria contributed to 11% and 7% of deaths respectively in 2011. Under-nutrition is a contributing factor in at least a third of under-five deaths globally(4).

1.1.2 The Integrated Management of Childhood Illness

In light of the complexity of managing child health in resource poor settings, in the late 1990s, the WHO and UNICEF developed the Integrated Management of Childhood Illness (IMCI) (6) (7). The IMCI focuses on delivery of rational, effective and affordable curative treatment of syndromic presentations at first-level health care facilities usually involving an oral antibiotic, an antimalarial and oral rehydration solution with zinc (8). Further, it includes advice on immunisation and nutrition for the child, enables health workers to counsel parents for any feeding difficulties and also teaches parents how to administer treatment at home. The IMCI receives on-going additions and updates (9). Implementation of the IMCI strategy may require adaptation on all levels of a participant country's health system, including adaptation of the IMCI guidelines themselves (10). Indeed it appears implementation of the IMCI lowers child mortality (11) .

1.1.3 Follow-up After Childhood Illness

The IMCI also outlines when follow-up care should be given, however, the evidence to guide management of child health *following* illness is of limited breadth and quality. To refine these guidelines and make an impact on child mortality following illness, a growing body of literature is attempting to shed light on the topic, but the current literature is unable to reach a consensus.

Child mortality after illness in high-income countries is confined to small high risk groups (12) (13) (14). In low-income settings, children appear to be at increased risk of mortality following any illness. In 1983, Roy et al. showed higher than expected mortality in a cohort of children who were sent home after recovering from diarrhoea- a majority of deaths occurring within the first three months (15). Subsequent studies have demonstrated increased yet variable post-discharge mortality following specific illnesses and further tried to find risk factors for mortality (16) (17) (18).

More recently two studies with cohorts of diverse diagnoses (rather than specific illnesses), somewhat representative of 'all discharges', have been published. Veirum et al. (19) in Guinea Bissau (West Africa) found 7.5% mortality in the year following discharge and suggested absconding from treatment as the predominating risk factor for mortality. Verium also showed that risk of death was higher than in the general community immediately following discharge but this risk slowly decreased and was not significant beyond six months post-discharge. Moisi et al.'s findings in Kenya (East Africa) contradicted Veirum et al.'s on all levels (20) - young age, malnutrition, hypoxia, enlarged liver, jaundice, long hospitalisations and numerous previous discharges were important predictors of a sustained frailty in children discharged from hospital, even beyond a year follow-up. More quality evidence from a variety of settings is needed to gauge the reality of post-discharge mortality.

1.1.4 The Rural Gambian Setting

For a long time, The Gambia has been (21) and continues to be (22) an important setting for child survival research. *Streptococcus pneumoniae* is a leading cause of bacterial pneumonia, meningitis and sepsis (23). Currently the Bill and Melinda Gates Foundation funded Pneumococcal Surveillance Project has systems in place in The Gambia collecting diverse information to assess the effectiveness of pneumococcal conjugate vaccines (PCVs) (24) (25). Utilising the large systems already established in rural Gambia, this study aimed to evaluate the magnitude of child mortality after discharge and further find if risk factors can identify children to prioritise for

intervention.

1.2 Thesis Outline

This thesis aims to answer a set of research questions on the topic of child mortality in a low-income setting, particularly after discharge from a health facility. The research questions are:

1. What is the post-discharge child mortality rate following admission for suspected pneumonia, sepsis or meningitis at Basse Health Centre?
2. What are the risk factors for child mortality following discharge?

The thesis is organised into chapters. Each chapter begins with a small synopsis. This chapter introduces the thesis and provides a brief overview of the topic.

Chapter 2 systematically reviews the current literature on child mortality following discharge from a health facility, focusing on mortality rates and risk factors for death.

The research methodology, the context in which the research was conducted and statistical analyses used to answer the research questions are detailed in Chapter 3.

Chapter 4 describes in detail the results of the research conducted and two multivariable models are presented.

Principal and secondary findings are discussed and comparisons to previous research are drawn in Chapter 5. The strengths and weaknesses of this project are stated and implications of the findings are explained.

1.3 My Role in the Study

I lived at the study site for nine months. I systematically reviewed the current literature, developed and refined the research idea and questions for this project, defined the study population and parameters, gained ethical approval for the study design, facilitated accurate extraction of sensitive data from two larger databases, worked closely with laboratory, clinical, field and data-management staff to maximise data quality, completed the entire analysis from inclusion to multivariable regression to tabulation of results. Data were available from two larger databases (Pneumococcal Surveillance System and Basse Health and Demographic Surveillance System), but were of variable quality. A large part of this project involved verifying volumes of missing information. I identified information that needed to be completed, organised the best possible approach, co-ordinated and encouraged the process to ensure a robust analysis was possible.

CHAPTER 2 – SYSTEMATIC LITERATURE REVIEW

Section 2.1 summarises the process and the findings from the review. Section 2.2 introduces the topic of the review. Section 2.3 outlines the literature review methodology. Section 2.4 details the findings of the search and reviews the literature, which is then discussed in section 2.5. Sources of funding are stated in section 2.6.

2.1 Summary of Literature Review

Based on the need for better understanding and recommendations, a systematic review of child mortality and risk factors for death following discharge from a health facility was conducted. MEDLINE and EMBASE databases were systematically searched for original articles. Expert engagement was another source of literature. After screening and assessment of full texts, 12 articles were included for review - highlighting paucity in the topic area. Although it appears that children are indeed at some increased risk of mortality following discharge, the current literature fails to cohesively estimate the magnitude and predictability of post-discharge mortality. The limited findings for rates and risk factors for post-discharge child mortality were reported on, but more evidence is clearly needed.

2.2 Introduction of Literature Review

Optimal management of child health *following* illness is poorly defined and rarely implemented. More evidence is needed to determine the magnitude of and risk factors for mortality following discharge from a health facility. This systematic literature review aimed to summarise current knowledge about child mortality following discharge from a health facility with a focus on risk factors.

2.3 Methodology of Literature Review

MEDLINE and EMBASE databases (via OvidSP) were searched for peer-reviewed articles published in the last ten years (2002 – current) using the limits ‘Full Text’ ‘English Language’ ‘Humans’ and the keywords:

"child" OR "infant" OR "toddler" AND
"follow up" OR "follow-up" OR "fatality" OR "mortality" OR "death" OR "survival"

OR "vitality" AND
"post-discharge" OR "postdischarge" OR "post discharge" OR "after discharge" OR "following discharge"

Additional publications were sought through expert engagement and reference list searching of articles included from the database searches.

Titles and abstracts were screened to determine scope of publications and their ability to inform the topic of interest.

Full texts needed to be original articles that described child mortality after discharge from a health facility in a low income setting to be eligible for inclusion in the review. There was no minimum follow-up length, but greater than six months was preferable. Post-discharge mortality and risk factor information was extracted from written text sections and tables of included articles.

The PRISMA statement (26) informed the systematic literature review design and reporting. The Newcastle Ottawa Scale (27) was adapted and used to assess study quality of included articles.

2.4 Results of Literature Review

Figure 1 illustrates the search process. The initial database search yielded 568 papers of which nearly half were duplicates. An expert submitted one paper for inclusion. Sixteen full articles were test for eligibility, but lack of scientific focus on mortality after discharge in low-income settings was evident. Older articles (pre-2002) were primarily found through reference lists. Ultimately twelve articles of mixed quality were included in the review.

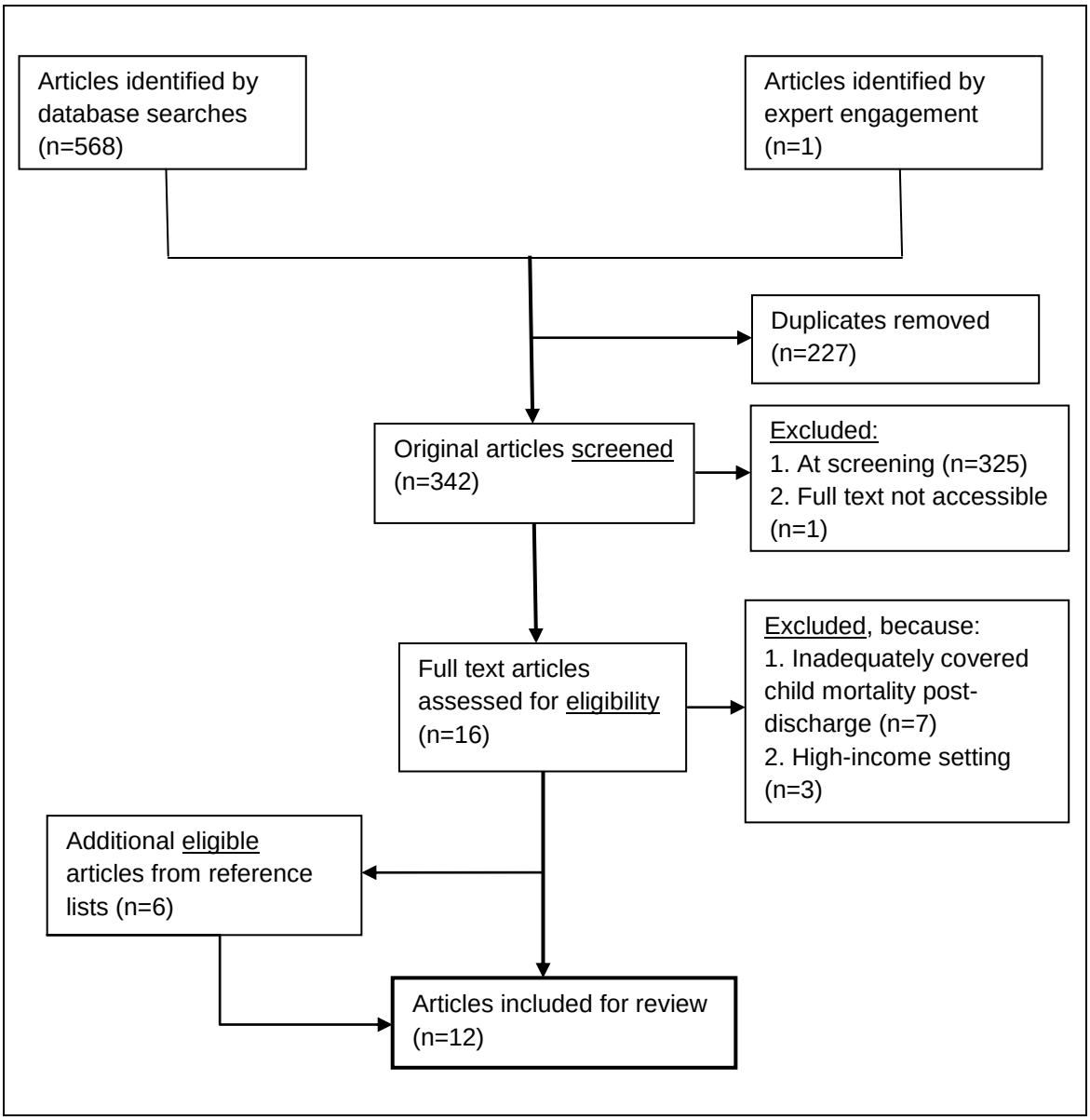

Figure 1. Flow diagram of Study Selection in this Systematic Literature Review

Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097(26)

In total 12 studies were identified, but only four received a NOS score of seven or higher (out of a possible nine). Eight studies were from Africa and four from Asia.

Publication dates ranged from 1983 to 2012, but only three dated pre-2000. Methodologically four studies used population-based systems to collect information on deaths, otherwise follow-up was conducted by field or clinic visits. Seven of the studies had greater than 75% follow-up, but follow up time varied greatly from a few weeks (28) (29), to one year (15) (20) or even more (17) (30). Studies with restricted sampling were common (e.g. follow-up of children after diarrhoea (15), pneumonia (17) or malaria (28)).

Post-discharge mortality rates

A combination of different study populations with different follow-up times made interpreting and comparing mortality rates and results difficult. Mortality rates were further reported inconsistently with a number of studies failing to formally calculate post-discharge mortality rates at all (17) (28). Reported post-discharge mortality rates in Africa varied from approximately 3.6% within a year of discharge (20) to 11% within 28 days (28). In 2007 Veirum et al conducted a high quality study (NOS score of eight) in a cohort of 'all discharges' into a demographic surveillance area and reported a mortality rate of approximately 4.6% per year- but a confidence interval for this estimate was not published. Moisi et al published a similar but larger study in 2012 (NOS score of five) and reported 3.6% mortality in the year following discharge. More restricted cohorts reported higher mortality rates, but do not give insight into the magnitude of post-discharge mortality as a whole.

Risk factors for post-discharge mortality

Cohorts of children that were followed after a specific (generally severe) illness had higher rates of post-discharge mortality than unrestricted cohorts (Table 1). Type of illness on admission was investigated formally in a few studies (19) (20) (17) (28) each showing an association between 'illness on admission' and 'post-discharge outcome'. To Villamor et al. it appeared that illnesses with acute mortality also had an effect on mortality following discharge (17). In a broad cohort, Moisi et al showed that those admitted with malaria had relatively lower post-discharge mortality than those admitted for other causes (20).

Age was repeatedly shown to be an important predictor of mortality (17) (19) (15) (31). Risk factors for post-discharge mortality from birth were reported in two studies from Asia. Chaudhari et al. (30) showed increased risk of mortality of VLBW (very low birth weight) children in a cohort of high risk children and further identified infection as a common cause of death. In a cohort of premature babies (<33 weeks gestation), Khan

et al. showed family income and parental education predicted mortality (32).

Moisi et al thoroughly investigated clinical predictors of post-discharge mortality, identifying under-nutrition, malaria parasitaemia, hypoxia, bacteraemia, jaundice, hepatomegaly, length of hospitalisation as candidate risk factors. West et al also found length of stay at hospital and under-nutrition to be important predictors of post-discharge mortality, but suggested longer stays at hospital were a marker of re-feeding interventions for malnourished children. However, West et al did not find hypoxia during admission as a risk factor for post-discharge mortality. Under-nutrition consistently associates with post-discharge mortality (15, 16) (17) (31). Low haemoglobin concentration (17) (19) and HIV positivity (17) (18) may be associated with increased post-discharge mortality.

Socioeconomic predictors such as quality of water supply, parental education level, parental employment status have shown associations with post-discharge morality in a few studies (17) (18) (19) (32).

Table 1 summarises the studies included in this review according to the parameters of the background population, cohort selection and characteristics, comparison groups, mortality and other results, assurance of initial patient status, how the study dealt with age and other confounders, how mortality was recorded and assessed, duration and completeness of follow-up.

	Study 1	Study 2	Study 3
Author (Year)	West (1999)	Veirum (2007)	Veirum (2005)
Background Population from which cohort was selected	Africa, The Gambia. Children (<5 years) admitted to hospital in The Gambia between May 1992 and November 1994 already selected for a casecontrol study investigating clinical predictors of hypoxia.	Africa, Guinea Bissau. 1991 and 1996 at the Bandim Health Project, Bissau and at the paediatric department at the national hospital in the capital Bissau, Guinea-Bissau.	Africa, Guinea Bissau Paediatric ward in the capital of Guinea Bissau. 6000 admission annually. About 14% of admissions come from Bandim Health Project area
Cohort selection	83 with hypoxaemia (<90% O2 sat) and 107 non-hypoxaemia patients were recruited in 1992-93 for a case control study; The combined cohort was attempted to be followed between May 1996 and July 1997 - 62% were traced.	Of an annual 6000 admissions to the paediatric ward, between 1991 and 1996, 4153 could be linked to population demographic surveillance. 3647 of these were live discharges and therefore eligible. The postdischarge period was defined as a 12-month period following discharge, and both community death and in-hospital death during this period were considered post-discharge deaths.	Hospital admissions that were in the BHP area.
Cohort Characteristics	Age from 1 week to 5 years	2950 children having 3647 live discharge	2079 hospitalisations, aged 1.5–17 months.1624 (78%) could be identified in the project's population of this 736 were 1.5–8 months old. Of these 736, 13/429 (3%) died in the month after discharge.
Comparison group selection method	107 control children with an SaO2 of >=90% were matched for age with cases and were recruited in 1993-94.	A restricted cohort of 8184 children registered during pregnancy and born in the study area between January 1991 and December 1996 were followed. In the cohort a total of 1113 deaths were registered during 15542 person-years of observation; 1399 of these children were admitted 1736 times and 271 children died at the hospital	Comparisons were made within the same cohort between those that died and did not.
Mortality Rate (if formally reported)	4.8 (95%CI: 2.4- 9.6) per 100 child-years in the hypoxemic group 2.2 (95%CI: 0.9-5.9) per 100 child-years in the non-hypoxaemia group.	46.1 per 1000 person years of observation (no 95% confidence provided)	*We can crudely observe that an additional 4% of deaths occurred within a month of discharge.*
Other Results	At follow up, mean weight-for-age was lower in those who died (p=0.03), mean length of hospital stay was higher in those who died (p= 0.06). differences between those that died and survived was p>0.05 for mean age on admission, for number of males in each	91.9% of discharges survived the first year after discharge. One third of the children that died, did within the first two weeks. 9% of discharged post-neonatal children died in the following year, 8.5% of those that were aged 1-2years, and 5% of the children aged	In children aged between 1.5-8 months that had received at least one DTP vaccination, 18% (35/197) of girls died in hospital, this increased to a total of 22% when included deaths one month after discharge. Rates were lower in boys with 11% (29/264) dying

	group, for number of people living in rural area in each group and number hypoxemic in each group. Mortality rate 2.2 and 4.4 per 100 person years. 10.2% mortality in the first 3 years. Weight for Age, Length of Hospital Stay correlated with mortality statistically significantly, but not hypoxia, age at admission, or sex or living in a rural area,	2-3years, only 2% of older children would die in the first year after discharge. Age at discharge (p<0.0001), Ethnic group (p=0.03), Mothers education (p=0.05), Non-medical discharge (p<0.0001), Admission Diagnosis (p<0.0001) were different between those that died and survived the year following discharge. Nonmedical discharge is a large riskfactor - especially in the first 14days after discharge (RR in first 14d 18.60 [95%CI: 9.45–36.60]). Other significant risk factors for postdischarge mortality included ethnic group, housing quality and maternal education, and these were similar to risk factors for community mortality. The same diagnoses that had high acute mortality, including anaemia, diarrhoea, were also associated with high postdischarge mortality.	in hospital and a total of 15% died if including those that died within a month of discharge. The female-male mortality rate ratio was 1.49 (95%CI: 1.00 – 2.25).
Assurance that children were alive before follow-up began	No	No	No
Did the study or analysis take into account age and sex	Yes	Yes	Yes
Did the study take into account other confounders (e.g. SES/ethnicity/etc)	No	Yes	No
How was outcome/death obtained	The date of death was obtained by asking the parents or recorded from the health card if it was available	Population Based Surveillance	Population deaths register.
How long was follow up?	mean length of follow up >34months	1 year	1 month after discharge
How complete was follow up? If	62%. Patients, both traced and not traced, had similar age on admission, weight-for-	Diagram shown and well explained. 66% (3647/5544) of admissions included for	78% patients matched to population register. But inpatient mortality similar in

<80%, described or explained?	age Z score and length of hospital stay. Matching of cases to controls would have been lost	analysis.	those matched and unmatched and those with and without missing data.
Funders of the Study	Ciba-Geigy and Glaxo-Wellcome.	Danish Council for Development Research, and DANIDA and Novo Nordisk Foundation.	Danish Council for Development Research, Danish Medical Research Council, DANIDA, Novo Nordisk Foundation and the EU Commission's INCO programme
Citation	(16) West TE, Goetghebuer T, Milligan P, Mulholland EK, Weber MW. Long-term morbidity and mortality following hypoxaemic lower respiratory tract infection in Gambian children. Bull World Health Organ. 1999;77(2):144-8. Epub 1999/03/20	(19) Veirum JE, Sodeman M, Biai S, Hedegård K, Aaby P. Increased mortality in the year following discharge from a paediatric ward in Bissau, Guinea-Bissau. Acta Pædiatrica. 2007;96(12):1832-8.	(29) Veirum JE. Routine vaccinations associated with divergent effects on female and male mortality at the paediatric ward in Bissau, Guinea-Bissau. Vaccine. 2005;23(9):1197-204.
NOS quality score (0= worst, 9=best)	6	8	5

Table 1. Tabulated Results from Systematic Literature Review (1 of 4)

	Study 4	Study 5	Study 6
Author (Year)	Biai (2007)	Moisi (2011)	Villamor (2004)
Background Population from which cohort was selected	Africa, Guinea Bissau. A paediatric ward in Guinea Bissau	Africa, Kenya. Poor, rural area on the coast in Kilifi District Hospital & Demographic Surveillance Area	Africa, Tanzania. Dar es Salaam, Tanzania, nested within a Vitamin A randomised controlled trial.
Cohort selection	Children 3m-5years of age admitted with malaria	< 15 years of age who were residents of the KHDSS area at some point in 2004–2008. Discharged from KDH	Dar es Salaam, Tanzania, among 687 children 6–60 months of age who were admitted to hospital with pneumonia
Cohort Characteristics	n=951 Median age 24 months, ~55%male, 88% had MUAC >130mm	12 203 discharges followed up. Not much known.	Mean age 17.6 months. 42% <12 months; 46% of children were female. Among the 624 children with known nutritional status at baseline, 29% were stunted and 18% were wasted; also, 25% were severely anaemic (haemoglobin concentration <7 g/dl), and 26% had positive blood smears for malaria.
Comparison group selection method	Same. Cohort selected and then randomised to receive intervention or not.	Community Comparison were in the same Surveillance area but not admitted & discharged from KDH	Comparisons were made within the same cohort between those that died and did not.
Mortality Rate (if formally reported)	Between 7% and 11% of patients that survived admission died within 28 days. (no 95% confidence interval was published)	3.3% (95% confidence interval, CI: 3.0–3.7).	Not formally reported.
Other Results	7% (29/443) of the intervention group died within 28 days of discharge compared to 11% (50/469) of controls, a risk ratio of 0.61 (95%CI: 0.40 to 0.95, p=0.02) Mortality significantly lower in children with confirmed malaria (p=0.04)	535 deaths observed in the >15,000 hospitalisations. In a multiple variable cox model, discharges aged 1–5 mo had a hazard ratio for death of 1.34 (95%CI: 0.93–1.92) those aged 6–11 mo HR=0.82 (95%CI: 0.57–1.18) Age 2–5 y HR=0.57 (95%CI: 0.36–0.90). Those with WAZ < −3 HR=3.42 (95%CI: 2.50–4.68) and WAZ < −4 6.53 (95%CI: 4.85–8.80). Parasitaemia was protective 0.45 (95%CI: 0.29–0.71). Admissions with hypoxia had a HR= 2.30 (95%CI: 1.64–3.23). Bacteraemia, HR=1.77 (95%CI: 1.15–2.74). Jaundice, HR=1.77 (95%CI: 1.08–2.91) Hepatomegaly, HR= 2.34 (95%CI: 1.60–3.42). Hospitalization > 13 d, HR=1.83 (95%CI: 1.33–2.52). ≥ 3 prior discharges HR=23.55 (95%CI: 10.70–51.84).	76/687 died in the first year, 21 during initial hospitalisation for pneumonia [*equates to approx 8% post-discharge mortality]*. In a multiple variable Cox model, HIV positive children had an adjusted HR (aHR) of 3.92 (95%CI: 2.34-7.49) for death after discharge. Risk of death decreased with increasing age (6-11m aHR=3.70 [95%CI: 1.72 to 7.95, p<0.001], 12-23m aHR=3.14 [95%CI: 1.44 to 6.88, p<0.004] when compared to children >=24m). Stunting increased the risk, aHR=2.12 (1.31–3.42, p=0.002) as did low MUAC aHR=1.88 (1.16– 3.03, p=0.01). Haemoglobin (g/dL) had adjusted p-value for trend =0.002 for mortality after discharge. Children with particularly Severe Pneumonia had aHR=2.47 (95%CI: 1.59–3.85, p=0.0001) for death. Quality of Tap water had had

			adjusted p-value for trend =0.006 with death after discharge.
Assurance that children were alive before follow-up began	Not reported	None.	Yes. Enrollment at discharge
Did the study or analysis take into account age and sex	Randomisation	Not sex. Age in places, not everywhere.	Yes
Did the study take into account other confounders (SES, ethnicity, etc)	Randomisation	No	Yes
How was outcome/death obtained	Collection of post-discharge mortality not reported	Linked to a Demographic Surveillance system with a Unique ID	Monthly clinic visits by mother and child, and home visits by fieldworkers.
How long was follow up?	28 days after admission	Analysis included deaths within 365days of discharge	Average of 25 month follow-up.
How complete was follow up? If <80%, described or explained?	89% followed up.	Not reported	89% follow-up
Funders of the Study	Not externally funded	Wellcome Trust (UK)	Thrasher Research Fund, Salt Lake City, UT, and the International Development Research Center, Ottawa, Canada
Citation	(28) Biai S. Reduced in-hospital mortality after improved management of children under 5 years admitted to hospital with malaria: randomised trial. BMJ British medical journal (Clinical research ed). 2007;335(7625):862-.	(20) Moïsi J. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. Bulletin of the World Health Organization. 2011;89(10):725-32.	(17) Villamor, E. (2004). "Child mortality in relation to HIV infection, nutritional status, and socio-economic background." International journal of epidemiology 34(1): 61-68.
NOS quality score (0= worst, 9=best)	5	5	9

Table 1. Tabulated Results from Systematic Literature Review (2 of 4)

	Study 7	Study 8	Study 9
Author (Year)	Phiri (2008)	Phiri (2012)	Roy (1983)
Background Population from which cohort was selected	Africa, Malawi. Children presenting to one of two hospitals in Malawi between July 2002 and July 2004. One with seasonal Malaria, One with intense Malaria all year around.	Africa, Malawi. One of four hospital inpatients in Malawi	Asia, Bangladesh. Rural Area of Matlab.
Cohort selection	Selected if presenting to one of two hospitals with severe anaemia, less than 5.0 g/dl, were aged 6–60 months and had not received a blood transfusion during the preceding four weeks excluded if history of trauma or malignancy	4–59 months age/ admitted with severe malarial anaemia, had received a blood transfusion, and had completed the inhospital course of intravenous quinine.	551 children between 3months and 3 years who in 1979 were admited to Matlab treatment centre for complaint of diarrhoea.
Cohort Characteristics	Average age of 20.4 months, 46% male, 15% below -2z score for wasting. 53% below -2zscore for stunting. 12.7% had HIV. 15.2% had bacteraemia. Average haemoglobin 3.6g/dL.	N=1414 for RCT, 708 placebo, 706 intervention. 24months average age, ~50% male, 80% HIVnegative.	80% less than 2years of age. 12% severely malnourish. Those >2 years were more malnourished.
Comparison group selection method	Comparison groups were selected, both hospital controls and community controls were selected, but survivorship was too high in the control groups so a survival analysis was run on cases (anaemic children) only	Randomisation	Community rates of death, United States comparisons for anthropometry.
Mortality Rate (if formally reported)	6.8% mortality in cases after discharge at 6 months follow-up	4.7 – 5.2 deaths per 100 person-years during 6month follow-up. (no 95% confidence interval published)	4.2% (23 children) of the group died during the 12 month during follow-up.
Other Results	Post-discharge mortality was 12.6% in (severely anaemic) cases, 2.9% in the Hospital Control group and 1.4% in the Community Control group at the end of 18month follow-up. 70% of deaths occurred in the first 6 months. 45% of those that died were HIV positive. In a multiple variable Cox model cases were less likely to die with every month increase in age (aHR=0.92 [95%CI:0.87–0.97, 0.001]) or had splenomegaly (aHR=0.36 [95%CI: 0.16–0.80, 0.01]), more likely to die if HIVpositive (aHR= 10.49 [95%CI:4.05–	During 6 month follow-up incidence of 4.7 and 5.2 deaths per 100 person-years were observed in the placebo and intervention group, respectively. There was no statistical difference between mortality in these two groups p=0.734.	4.2% (23 children) of the group died during follow up. 70% occurred in the first three months. Increased risk for death after discharge was only statistically significant for child 24-35months of age, otherwise mortality rates were lower than expected (when compared to community death rates), but this was not statistically significant.

	27.20) ,0.0001] or if their parents were unemployed (aHR= 4.15 [95%CI:1.61–10.74, 0.003]) Rural/urban status, Sex, Bacteraemia was included in the final model but not significant (p>0.05) “Malaria, study site, sickle cell disease, G6PD or hookworm infection did not significantly predict post-discharge death”		
Assurance that children were alive before follow-up began	Yes.	Children assessed for RCT before enrolment.	Yes, each child was weighed on discharge
Did the study or analysis take into account age and sex	Sex not Age	No	Age but not sex
Did the study take into account other confounders (SES, ethnicity, etc)	Yes.	No	No
How was outcome/death obtained	Follow up visits, information surrounding the death was collected using a verbal autopsy	Not reported	Demographic Surveillance
How long was follow up?	followed up at 1, 3, 6, 12 and 18 months from date of discharge	6months	1 year
How complete was follow up? If <80%, described or explained?	17.8 % lost to follow-up. There were no significant differences in baseline characteristics of the children lost to follow-up compared to those that completed the study follow-up period.	93%	mandatory registration - 100%
Funders of the Study	Wellcome Trust, Numico and Ter Meulen foundation, Gates Malaria Partnership	The Netherlands African Partnership for Capacity Development and Clinical Interventions Against Poverty Related Diseases, the UBS-Optimus Foundation, and the Gates Malaria Partnership.	Arab Gulf Fund, Australia, Bangladesh, France, Japan, Saudi Arabia, Sweden, Switzerland, United Kingdom and USAID.
Citation	(18) Phiri KS, Calis JC, Faragher B,	(33) Phiri K. Intermittent preventive therapy	(15) Roy SK, Chowdhury AK, Rahaman

	Nkhoma E, Ng'oma K, Mangochi B, et al. Long term outcome of severe anaemia in Malawian children. PLoS One. 2008;3(8):e2903. Epub 2008/08/07.	for malaria with monthly artemether–lumefantrine for the post-discharge management of severe anaemia in children aged 4–59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. The Lancet infectious diseases. 2012;12(3):191-200.	MM. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. Br Med J (Clin Res Ed). 1983;287(6399):1097-9. Epub 1983/10/15.
NOS quality score (0= worst, 9=best)	7	5	6

Table 1. Tabulated Results from Systematic Literature Review (3 of 4)

	Study 10	Study 11	Study 12
Author (Year)	Islam (1996)	Khan (2006)	Chaudhari (2000)
Background Population from which cohort was selected	Asia, Bangladesh. Diarrhoea Treatment Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) between November 1991 and December 1992 . 100000 patients treated each year, approximately 53percent are children <24months age. 10% of these young children are severely malnourished	Asia, Bangladesh. Randomized, controlled trial topical emollient therapy on the incidence of nosocomial infections in preterm infants at Dhaka Shishu (Children's) Hospital. infant survivors from the emollient trial at DSH who were enrolled on discharge. March 1999 to August 2003	Asia, India. Infants discharged from a Neonatal Special Care Unit were identified for follow up using predetermined risk criteria.
Cohort selection	1-23 months discharged between 9a.m. and 11a.m.	The 85 children that completed >1y follow-up had a mean age of 31months. 41% were from rural areas, and 42% were female. Mean age at first assessment was 1.2months	Infants discharged from a Neonatal Special Care Unit between October 1987 to April 1989 that had (i) gestation <37 weeks, (ii) birthweight <2000 g, (iii) Apgar score <5 at 5 minutes, (iv) septicemia/meningitis, (v) hyperbilirubinemia, (vi) apnea (vii) seizures, (viii) intraventricular hemorrhage and (ix) respiratory distress.
Cohort Characteristics	77% were less than 1 year of age. 39% were the only child in their family.	Normal development was observed in 32%, mild impairments were found in 45%, and serious impairments in 23%.	246 males and 158 females. Birth asphyxia was present in 56 (14%), hyperbilirubinemia in 72 (17.8%), Septicemia/meningitis in 81 (20%), seizures in 60 (14%); apneic spells in 48 (11%), intraventricular hemorrhage in 28 (6%) and respiratory distress in 48 (11%)
Comparison group selection method	Same cohort, dead compared with alive.	Comparisons were made within the same cohort between those that died and did not.	Some analyses were made within the post-discharge cohort. But normal full terms infants with birth weight more than 2500 g with a normal antenatal, natal and postnatal course, matched for socio-economic class, were enrolled as controls for other comparisons
Mortality Rate (if formally reported)	7% of the cohort died within 6 weeks (no 95% confidence interval published)	16% mortality over undefined period (no 95% confidence interval published)	38 of 404 high risk infants died in the first 6 months. (not formally reported)
Other Results	In a logistic regression children <6months had a RR=4.57 (95%CI: 2.90-7.18) of death compared to those >=6m, females were at higher risk of death than males (RR= 1.73 [95%CI:1.14-2.65]), if mothers had no schooling children were at increased risk (RR= [95%CI: 1.37-3.28]), If the child was not breastfed (RR= 2.35 [95%CI: 1.44-	16% (26 of 159) infants of those initially enrolled died, 19% (30 of 159) were lost to follow-up, and 65% (103 of 159) survived. Survivors had higher parental literacy rates and had higher family income (mothers' [P=.006] and fathers' [P =.024] literacy rates [defined as "able to read a newspaper"] and family income [P=.026])	38 of 40 deaths over the six year period occurred in the first year of follow-up/life. 60% of these were in infants less than 3 months of age. The mortality in the first year of follow-up/life was significantly higher in children with VLBW [p<0.05]. There was a trend for higher mortality in lower socioeconomic groups (p<0.001)

	3.84]), or up to date with vaccination (RR= 1.36[95%CI: 1.25-1.48]) they were at increased risk. Stunting (RR=2.97 [95%CI:1.43-6.16]) but not wasting (RR= 1.04[95%CI: 0.57-1.89]) lead to a statistically significant increase in risk in the logistic regression.		
Assurance that children were alive before follow-up began	Yes, interviewed at discharge	No	Not stated explicitly.
Did the study or analysis take into account age and sex	Yes	Explored, but not controlled for.	Age, but not sex
Did the study take into account other confounders (SES, ethnicity, etc)	Yes	Explored, but not controlled for.	Yes some what
How was outcome/death obtained	Follow up visit by educated and trained	Health worker escorted clinic visits or home visits. Verbal Autopsy for deaths where possible.	Monthly household visit for the first 2 and half years of follow up. Recalled for 6 year follow up.
How long was follow up?	follow up at 6 and 12 weeks	>1year.	6 years
How complete was follow up? If <80%, described or explained?	85% complete follow-up at 6 weeks 79% at 12 weeks. Baseline profile of those children lost to follow-up was comparable to those who were available for follow-up	85/159 fully completed follow up beyond 1 years of age. And 26/159 died during follow up. That is 69.8% follow up. Loss to follow up not very well defined.	404/425 in high risk group completed follow up. 86 controls.
Funders of the Study	Numerous international governmental, nongovernmental and private institutions that support ICDDR,B	Thrasher Research Fund; Save the Children-US through a grant from the Bill & Melinda Gates Foundation; and the Office of Health, Infectious Diseases and Nutrition, Global Health Bureau, US Agency for International Development	Indian Council of Medical Res earch, New Delhi.
Citation	(31) Islam MA, Rahman MM, Mahalanabis D, Rahman AK. Death in a diarrhoeal cohort of infants and young children soon after discharge from hospital: risk factors and	(32) Khan, N. Z. (2006). "Neurodevelopmental outcomes of preterm infants in Bangladesh." Pediatrics (Evanston) 118(1): 280-289.	(30) Chaudhari S, Kulkarni S, Pandit A, Deshmukh S. Mortality and morbidity in high risk infants during a six year follow-up. Indian Pediatr. 2000;37(12):1314-20. Epub

	causes by verbal autopsy. Journal of tropical pediatrics. 1996;42(6):342-7.		2000/12/19.
NOS quality score (0= worst, 9=best)	7	4	6

Table 1. Tabulated Results from Systematic Literature Review (4 of 4)

2.5 Discussion of Literature Review

Current literature on post-discharge child mortality is not exhaustive. A majority of current literature reports on sub-groups discharged from hospital and others report post-discharge child mortality as an ancillary finding. Limited inferences and conclusions can be made.

2.5.1 Child Mortality following Discharge from a Health Facility

The variable mortality rate in different sample populations highlights high risk groups (for example, 12% of severely anaemic children dying within 18months of discharge (18)) . The lower estimate of 3.6% mortality in the first year of discharge is from a very large study conducting in Kenya by Moisi et al. (20). It is one of two studies that included all discharges from a health facility. High risk groups within this cohort of 'all discharges' are described in Table 1.

Studies from Asia are few in number and of limited quality and generalisability, but report child mortality rates similar to Africa if not higher (up to 11.9% mortality in 8 months post-discharge(32)).

2.5.2 Risk Factors for Child Mortality following Discharge from a Health Facility

Evidence for risk factors of post-discharge child mortality is heterogeneous. Islam et al. (31) West et al. (16) and Veirum et al. (2005) (29) have conflicting reports of the importance of age and sex in various settings. Hypoxia (low oxygen saturation) is circumstantially dangerous (16) (20). According to Phiri et al. (2008) (18), bacteraemia may not be a risk factor in a partially anaemic HIV positive cohort; however bacteraemia in other settings is important (Moisi et al. (20)). Protective effects of parasitaemia and confirmed malaria have been shown by Moisi et al. (20) and Biai et al. (28), respectively.

A high quality study (NOS score of 8/9) by Veirum et al. (2007) (19) utilised a population based approach to compare an admitted-hospital cohort, with non-admitted-hospital cohort and a community control cohort. Non-medical discharge was the overpowering risk factor for post-discharge mortality in this setting. Illnesses with high inpatient mortality, such as anaemia and diarrhoea, also had high rates of post-discharge mortality. Risk factors for death in the post-discharge cohort such as ethnicity, housing quality and maternal education were shared by community control cohort.

Malnourished children have a consistently poor outcome (Roy et al. (15), Islam et

al. (31), West et al. (16), Villamor et al. (17), Moisi et al. (20). Parental literacy/education and SES factors tend to show predictive value when tested (Islam et al (31), Khan et al (32), Chaudhari (30), Veirum [2007](19)). Severely anaemic children were shown to have very poor prognosis in Malawi (18). Length of hospital stay may independently help predict post-discharge mortality (20) or might merely highlight re-feeding interventions for the undernourished (16).

2.5.3 Limitations and Conclusion of Literature Review

Roy et al (15) published about child mortality following discharge from a health facility nearly 30 years ago, but the body of evidence is still growing. A limited number of studies of varying quality and generalisability exist (as shown by fluctuations on NOS quality scale score in Table 1) and no definitive conclusions can be drawn yet. More quality research is needed in this area.

2.6 Funding of Literature Review

Funders of the project had no contribution to the design or completion of this systematic literature review. No additional funding was received for completion of this systematic literature review. University of Otago database subscriptions were used to access full-text articles when necessary. No conflicts of interest to declare.

CHAPTER 3 – METHODS

This chapter covers the methods used in this project. The research aims and questions are stated in sections 3.1 and 3.2 respectively, followed by a brief description of the study population in section 3.3. The larger projects, within which this project is nested, are described in section 3.4. Section 3.5 includes the design of this project, cohort selection, follow-up and outcomes of interest. Ethical issues are reported in section 3.6. The process of data extraction and cleaning is described in section 3.7. In section 3.8 the statistical analyses are described.

3.1 Research Aims

This project aimed to determine (1) the magnitude of and (2) risk factors for child mortality following discharge from a health facility.

3.2 Research Questions

1. What is the post-discharge child mortality rate following admission for suspected pneumonia, septicaemia or meningitis at Basse Health Centre?
2. What are the risk factors for child mortality *following* discharge?

3.3 Description of Study Population

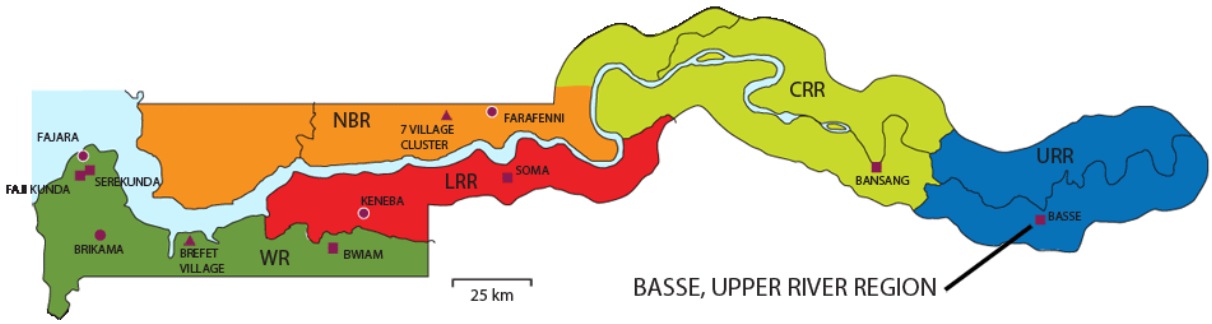

Figure 2: Map of The Gambia

The Upper River Region (URR) is highlighted in blue and Basse is indicated. The URR is bisected into north and south banks by the river Gambia, outlined in black.

With a rural population of approximately 191,000 people, the Upper River Region is located to the most east of the country. Difficulty accessing this remote area, primarily due to road conditions, has been an issue during previous research (22). The Region's only major health centre is located in its administrative centre, Basse Santa Su. The Basse Health and Demographic Surveillance System (BHDSS) monitors the south

river bank population in the Upper River Region. A total of 168, 989 people were resident in the BHDSS area on 30 April 2012 (unpublished data). In addition to servicing the Basse community, Basse Health Centre accepts referrals from five peripheral nurse-led clinics within the BHDSS area. From BHC, referrals are possible to Bansang Hospital in the Central River Region (CRR in Figure 1), or a tertiary level hospital on the coast (near Fajara in Figure 2). The mortality rates within the BHDSS area are reported below in Table 2.

Table 2. BHDSS Child Mortality Indicators

	2009	2010
Mortality rate per 1,000 person-years observation (95% Confidence Interval)		
1 – 11 months	22 (19 – 27)	23 (20 – 27)
12 – 59 months	9 (7 – 10)	12 (11 – 14)
Under-five mortality rate per 1,000 live births	67	78

Adapted from unpublished BHDSS data

3.4 Sources of Data

3.4.1The Basse Health and Demographic Surveillance System

Population census data from a previous randomised control trial conducted on the south bank of the URR in 2006 formed the basis of the BHDSS. The BHDSS has been funded by research projects that utilise the population demographic information.

How it works.

The BHDSS is based at the MRC Basse Field Station. Demographic surveillance started with a census of the entire south bank URR population of 136,387 in July 2007. Trained fieldworkers update census information (described below) every 4 months by household visits. Information is returned to the MRC Basse Field Station for single data entry and management using Microsoft SQL Server 2008.

Defining a BHDSS resident

DSS ID and BHDSS residency status are attained after an individual inhabits the BHDSS area for two consecutive update rounds (about 4 months). A resident is considered an exit from the surveillance system if absent from the BHDSS area for two consecutive update rounds.

What information is collected?

Every BHDSS resident is enumerated with a unique DSS ID that corresponds to their household, compound, and village. Identifying entry, exit or movement within the BHDSS area is possible with this DSS ID. Births and death information within each household is collected. Information on ethnicity, education level and household relationships is also collected. Each resident is accounted for, ticked off and if has had no notable event, then left intact in the database. A household socioeconomic survey begun in 2011 and data entry should be complete by 2014.

3.4.2 The Pneumococcal Surveillance System

The PSP is a population-based phase IV PCV effectiveness study within the BHDSS area and neighbouring Fuladu West district. Briefly, the introduction of PCVs is expected to significantly reduce child mortality in low income settings, but evaluation of other issues, such as the magnitude of replacement disease by non-vaccine serotypes of *S.pneumoniae,* is also needed. The PSP primarily aims to measure the incidence of radiological pneumonia and invasive pneumococcal disease by serotype. This project will continue until at least 2015.

How it works.

In partnership with the Gambian Government, the PSP performs surveillance for patients of any age presenting to government facilities in the BHDSS. The surveillance aims to detect cases of suspected pneumonia, meningitis and septicaemia. Any patient that is an outpatient or inpatient at a healthcare facility in the BHDSS area that meets screening criteria is referred to a PSP physician at Basse Health Centre (refer to Table 2). If the physician confirms that the patient meets surveillance criteria for suspected pneumonia, septicaemia, or meningitis, a standardised provisional diagnosis (adapted from previous literature (22) (34) (35)) is made (refer to Table 3) and standardised investigations (adapted from previous literature (36) (37)) are performed (laboratory and/or x-ray)). Treatment and admission are decided by the clinical acumen of the physician. Patient information is collected on Case Report Forms (CRFs) and returned to the MRC Basse Field Station for double data entry and management using Microsoft SQL Server 2008.

Screening Criteria for referral to a physician

PSP nurses screen any child presenting to a health facility within the BHDSS area. Routine screening of inpatients identifies children initially missed or who later developed symptoms suitable for referral. The standardised screening criteria are shown in Table 3.

Table 3: PSP Screening Criteria for Children ≥2 months and <60 months of age

Child to be referred for clinical assessment at Basse Health Centre if one or more of the following present for ≤14days.
History of cough or difficulty breathing, AND raised respiratory rate for age[a]
Axillary temperature of at least 38^0C, or less than 36^0C in a patient admitted or being admitted
History of convulsion
Impaired consciousness[b]
Bulging fontanelle
Stiff neck
Prostration[c]
Lower chest wall indrawing, nasal flaring, or grunting
Oxygen saturation less than 92%
Weight below -3 z-score for age
Local musculoskeletal swelling or tenderness
Any child with suspected meningitis

[a]Raised respiratory rate for age is defined as >50 breaths/min if 2-11months of age and >40 breaths /min if 12-59 months of age.
[b]Impaired consciousness is defined as anything other than Alert on AVPU scale of consciousness.
[c]Prostration is defined as the inability to drink or breastfeed or the inability to sit if usually able.

Adapted from: Mackenzie GA, Plumb ID, Sambou S, Saha D, Uchendu U, et al. (2012) Monitoring the Introduction of Pneumococcal Conjugate Vaccines into West Africa: Design and Implementation of a Population-Based Surveillance System. PLoS Med 9(1): e1001161. doi:10.1371/journal.pmed.1001161 (25)

Case definitions for provisional diagnosis

Standardised clinical criteria assist physicians to make a provisional diagnosis.

Table 4: Clinical Criteria for Suspected Pneumonia, Meningitis and Septicaemia

Provisional diagnosis	Clinical Criteria	
Suspected Pneumonia	A history of cough or difficulty breathing of less than 14 days duration, accompanied by one or more of:	1. Raised respiratory rate for age[a] 2. Lower chest wall indrawing, nasal flaring, or grunting 3. Oxygen saturation less than 92% 4. Focal chest signs (dull percussion note, coarse crackles, bronchial breathing)
Suspected Meningitis	Clinically unwell and if any of the following are present:	1. Neck stiffness 2. Impaired consciousness[b] 3. Prostration[c] 4. History of convulsion 5. Bulging fontanelle
Suspected Septicaemia	If one or more of the following is present:	1. Physician diagnosis of focal sepsis (including but not limited to: septic arthritis, osteomyelitis, endocarditis, peritonitis, liver abscess, soft tissue abscess, cellulitis) 2. Axillary temperature is<36^{o}C or >38^{o}C and no obvious cause of fever 3. For a patient admitted, or being admitted, the clinical impression is of severe malnutrition[d]

[a]Raised respiratory rate for age is defined as >50 breaths/min if 2-11months of age and >40 breaths /min if 12-59 months of age.
[b]Impaired consciousness is defined as anything other than Alert on AVPU scale of consciousness.
[c]Prostration is defined as the inability to drink or breastfeed or the inability to sit if usually able.
[d]Severe malnutrition is defined as per WHO definition.

Adapted from: Mackenzie GA, Plumb ID, Sambou S, Saha D, Uchendu U, et al. (2012) Monitoring the Introduction of Pneumococcal Conjugate Vaccines into West Africa: Design and Implementation of a Population-Based Surveillance System. PLoS Med 9(1): e1001161. doi:10.1371/journal.pmed.1001161 (25)

What Information is collected?

The PSP collects large volumes of information, but only information relevant for this project is discussed here. Patient information is collected on CRFs.

CRF1 and CRF2 (Appendix I) are completed by a nurse. Individual identification and PCV information is collected on CRF1 and each *admission* is allocated a unique PSP ID. This information is used to link *individuals* to their unique DSS ID – which is then also transcribed onto CRF1. Findings from patient history, examination including anthropometric measurements and point-of-care testing conducted by the screening nurse are collected on CRF2.

CRF4 (Appendix II) and CRF6 (Appendix III) are completed by a physician. If screening criteria are met the patient will be referred to a physician who will take a

patient history, complete an examination, order x-ray or laboratory investigations, make a diagnosis and decide to admit as necessary –this all collected on CRF4. Details about patient treatment and outcome upon departure from BHC are collected on CRF6.

CRF7 (Appendix IV) is completed for laboratory investigations by MRC Basse Field Station laboratory staff.

3.5 Study Design

A cohort of children (less than five years of age) was followed for mortality within 180 days of discharge following admission for suspected pneumonia, septicaemia or meningitis at Basse Health Centre.

3.5.1 Cohort Selection and Patient Information

The PSP database contains data on every individual screened by a project nurse. Only a proportion of those screened are referred to a physician. Referrals may be treated as outpatients or admitted. The decision to admit is made under the clinical acumen of the physician, but these are typically more severe presentations. Admissions were selected from the PSP database as per the inclusion and exclusion criteria (described below). Patient information was available through the same database.

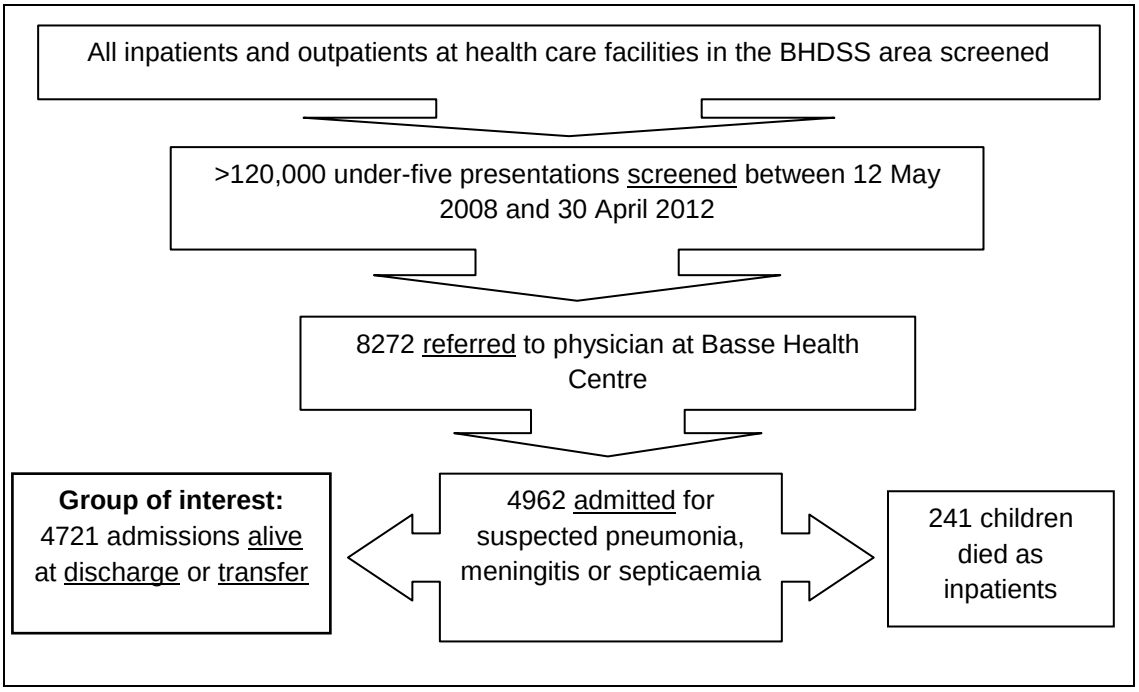

Figure 3. Flow Chart describing Cohort selection

3.5.2 Inclusion Criteria

Admissions between May 2008 and 30 April 2012 were included if:

- Less than five years of age AND
- Resident in the BHDSS area AND
- Admitted for suspected pneumonia, meningitis or septicaemia AND
- Discharged alive from Basse Health Centre OR
- Transferred to another health facility

3.5.3 Exclusion Criteria

Admissions were ineligible if:

- Less than two months of age at discharge (or transfer) from BHC
- Assessed and discharged on the same date
- Date of discharge (or transfer) from BHC and BHDSS date of death or exit were the same.

Children less than two months of age were excluded because they were not part of systematic PSP surveillance and data collection. Discharge following admission was assured by exclusion of those assessed and discharged on the same date. To ensure death was after discharge, those that died on the same date as *discharge* (but, as death on same day after transfer is conceivable, not *transfer*) were excluded.

Any null values in above fields were also excluded, otherwise incomplete or unrealistic patient information was treated as missing information.

3.5.4 Exclusions from Analysis Due to Data Incompleteness and Inconsistency

Admissions were excluded from analysis due to data incompleteness or inconsistency if:

- The unique PSP ID for admission was duplicated
- Full (14-digit) individual DSS ID was not attainable
- Date of discharge from BHC was inconsistent with dates of birth, death or exit from BHDSS area.

3.5.5 Linkage to BHDSS

Patient admissions are linked to the BHDSS using a unique identifier (DSS ID). Individual deaths (and dates of death) are tracked by the BHDSS. Individual exits from the surveillance area (including dates) are also tracked by the BHDSS. This information allowed community follow-up after discharge from BHC. Additional patient demographic information was available through the BHDSS.

3.5.6 180 Day Follow-up

Follow-up for mortality (in the BHDSS) began on the date of discharge and lasted for 180 days. If no death had been recorded by the end of this period, vitality was assumed. Follow-up ceased on 01 May 2012 as BHDSS vitality status (as per update Round 15, conducted 01 May 2012 to 31 August 2012) could only be assured till this date.

Individuals with Multiple Discharges

Multiple discharges from an individual were included. If an individual was readmitted and discharged within a first 180 day post-discharge follow-up period, they would contribute person time to both 180 day post-discharge follow-up periods. If re-admitted and discharged for a third time within the first 180 day follow up, they would contribute person time to all three post-discharge follow-up periods and so on, until they completed follow-up for each respective discharge.

End of Follow-up for Admissions

Admissions contributed person-time to follow-up until the child died, exited the surveillance area, acquired five years of age, completed 180 day follow-up or until 01 May 2012, which ever occurred first

3.5.7 Primary Study Outcomes

Primary outcomes of interest were:

1. Mortality rates within the cohort.
2. Risk factors for mortality within the cohort.

3.6 Informed Consent and Ethical Approval

The population census that preceded the BHDSS proper, gained ethical approval under an earlier project. The BHDSS gained ethical approval to update this census data. Community consent was given by community leaders. The PSP gained ethical approval in May 2008 (SCC 1087).

The Gambia Government/MRC Joint Ethics Committee granted ethical approval for this project (L2012.41, Appendix V).

3.7 Data Extraction and Cleaning

Included admissions had variables extracted from CRF1, CRF2, CRF4, CRF6 and CRF7 from the PSP database. Through a unique DSS ID, admissions were followed up

for BHDSS vitality and residency status during the 180 day post-discharge period. Additional demographic information, such as ethnicity, parental education level and self-reported income was also available through the BHDSS database. Information was anonymised and stored under password protection.

Even with intrinsic quality control mechanisms, the PSP and the BHDSS databases had partially incomplete data and data consistency issues. Paper forms were checked for data entry error, BHC logbooks were crosschecked for accuracy and if necessary household visits were conducted to pinpoint the cause of the incomplete or inconsistent data. Any changes were rectified on paper forms and the respective database. Not all issues could be resolved within a reasonable time frame, however only 7% of the cohort were lost to follow-up due to data issues. Admissions without complete and consistent information central to cohort selection and study design such as DSS ID, date of birth, admission status, type of separation, date of separation, date of exit from BHDSS area or date of death were excluded from analysis.

3.8 Data Analysis

Statistical analysis was completed using STATA software, version 12.0 (StataCorp, College Station, United States of America). A survival analysis was used to model events within 180 days of discharge. Admissions entered the analysis on date of discharge from BHC and contributed person-time to follow-up until the child died, exited the surveillance area, acquired five years of age, completed 180 day follow-up or until 01 May 2012, which ever occurred first. Multiple admissions are discussed in section 3.5.6.

3.7.1 Calculation of Mortality Rates

The survival analysis estimated mortality rates (deaths per person-180days) within the cohort. For those that died during 180-day follow-up, ‘days alive’ was calculated by subtracting date of separation from date of death.

3.7.2 Risk Factor Analysis

Incomplete patient information was coded as missing, with the exception of clinical signs and symptoms where an incomplete field was understood as ‘not observed’. Unrealistic outliers were re-coded as missing information on a case-by-case basis. Length of admission was calculated by subtracting the date of assessment from the date of separation. Multiple *admissions* by an *individual* within the study period

could be calculated by observing the frequency of *individual* DSS IDs. Presence of text in one, two or three of the open text sections labelled "Other diagnoses", in addition to the provisional diagnosis, informed construction of the 'multiple diagnoses' variable. In the 'seasonality' variable 01 July to 30 November and 01 December to 30 June were considered the wet and dry season, respectively. Income was reported as two categorical estimates (income from agricultural sources and income from non-agricultural sources). The median numerical value of each category of income was used to convert each response to a continuous variable which were then summed together to get an estimate for 'total household income'. Parents reporting highest level of education as "Quranic" or "None" were coded as having 'no formal education', while 'formal education' was understood to include primary, secondary or tertiary study (38). 'Prostration' was defined as a patient history of inability to drink or breastfeed or to sit if usually able (39). The 'petechial rash' variable was generated from physician observations of any rash at assessment. 'Noted as recovering on discharge' and 'Noted as non-medical discharge' were generated to summate negative and missing findings together and construct a variable with clinical utility in this setting. Antibiotic delivery is noted as being "oral", "intravenous" or "other" - variables for analysis were generated accordingly. 'PCV completeness for age' was generated on the premise that below the age of 4 months children could be up-to-date with their vaccination schedule without receiving any dose of PCV, but by the end of the third month (i.e. once they reach four months of age) they should have received one dose, similarly by end of the fourth month of life they should have received two doses and by the end of the fifth month of life they should have received three doses.

Categorical variables were tabulated (with frequencies and percentages) by vitality status at end of 180day follow-up. Variables with less than five events in a particular table cell were excluded from further analysis.

The mean and standard deviation of continuous variables were tabulated by vitality status at end of 180 day follow-up. Box plots were used to observe patterns of distribution and identify outliers.

Variables missing more than 20% of data were noted. If a particular test was not clinically indicated (e.g. haemoglobin concentration) information for that variable was not collected. Rapid Diagnostic Test for malaria was done per protocol; randomly during the dry season unless clinically indicated and for every child during the wet season. For survival analysis, variables were assumed to have constant relative hazards and exclusions from analysis were assumed to be non-informative.

Similarities at baseline between individuals included and excluded from analysis due to data incompleteness or inconsistency were tested. Variances of continuous variables were tested and the appropriate t-test was conducted to assess the difference of two means. Skewed distribution of continuous variables was reported where relevant (i.e. nature or shape of distribution not relevant for Cox regression). For categorical variables Fishers exact test was used if there were less than 5 events in a table cell, otherwise Chi-squared test was used for testing differences between categorical variables.

3.7.3 Constructing Multiple Variable Cox Models

Univariate Cox regression was used to find unadjusted correlates of post-discharge mortality.

The Clinical Model

Variables with $p \leq 0.10$ on univariate analysis were entered into a multiple variable Cox model. Ethnicity and number of admissions (over the study period) were added as variables of interest. Any variable with a p-value>0.40 was excluded in a reverse stepwise approach (requiring 3 steps) after which, one-by-one the variables with highest p-value were sequentially removed from the model until all p-values were <0.05. Age and sex were reintroduced into the final model.

The Syndrome Model

The ability of the PSP provisional diagnosis, in presence or absence of clinical severe malnutrition, to predict mortality was tested in a syndrome based model. Multiple diagnoses were re-coded to a single diagnosis according to a mutually exclusive hierarchy of severity (meningitis>sepsis>pneumonia) with or without clinical severe malnutrition on assessment. Age and sex were then introduced into the model. Finally, a likelihood ratio test was used to find a possible interaction between clinical severe malnutrition and provisional diagnosis.

Table 5. Risk factors Initially Extracted from Databases

#	Risk factors initially included	#	Risk factors initially included
	Physicians records		**Nurses Records**
1	Cough	**38**	Sex
2	Difficulty breathing		
3	Irritability	**39**	First pneumococcal conjugate vaccine administered
4	Inability to drink or breastfeed	**40**	Second pneumococcal conjugate vaccine administered
5	Convulsion	**41**	Third pneumococcal conjugate vaccine administered
6	Inability to sit, if usually able	**42**	Days of sickness
7	Fever	**43**	Location of screening
8	Diarrhoea	**44**	Axillary temperature (^{o}C)
9	Rigors	**45**	Weight (kg)
10	Respiratory rate (breaths/min)	**46**	Height (cm)
11	Pulse rate (beats/min)	**47**	Mid-upper arm circumference (cm)
12	Rash	**48**	Were antibiotics taken in previous week?
13	Clinical severe malnutrition	**49**	Were antibiotics were given before referral to physician?
14	AVPU score	**50**	Result from Malaria Rapid Diagnostic Test?
15	Blantyre coma score	**51**	Does screening nurse suspect meningitis?
16	Oxygen saturation	**52**	DSS ID was used to identify re-admissions
17	Grunting		**Laboratory findings**
18	Lower chest wall indrawing	**53**	Was there bacteraemia?
19	Nasal flaring		
20	Crackles		**DSS information**
21	Wheeze	**54**	Ethnicity
22	Bronchial breathing	**55**	Mothers education level
23	Lethargy	**56**	Fathers education level
24	Musculoskeletal swelling or tenderness	**57**	Number of residents within household
25	Bulging fontanelle	**58**	Estimated total household income
26	Neck stiffness		
27	Ear discharge		
28	Dull percussion note		
29	Provisional diagnosis		
30	Any other diagnosis		
31	Result from malaria rapid diagnostic test		
32	Reason for investigation ordered but unable to test		
33	Antibiotics taken in previous week?		
34	Length of Admission		
35	Type of Separation		
36	Was child discharged against medical advice?		
37	Was there any persisting abnormality on discharge?		

CHAPTER 4 – RESULTS

This chapter presents the results from this project. Section 4.1 outlines the enrolment process, presents the demographics of the followed-up admissions and also compares those included or excluded from analysis.

Section 4.2 states the results relevant for the first primary aim, post-discharge mortality rates within the cohort.

From here the second primary aim of identifying risk factors for post-discharge mortality is explored, in section 4.3. Univariate Cox regression analysis is reported in section 4.3.1 and section 4.3.2 reports the results of the multiple variable Cox models.

4.1 Enrolment Process, Cohort Demographics and Exclusions from Analysis

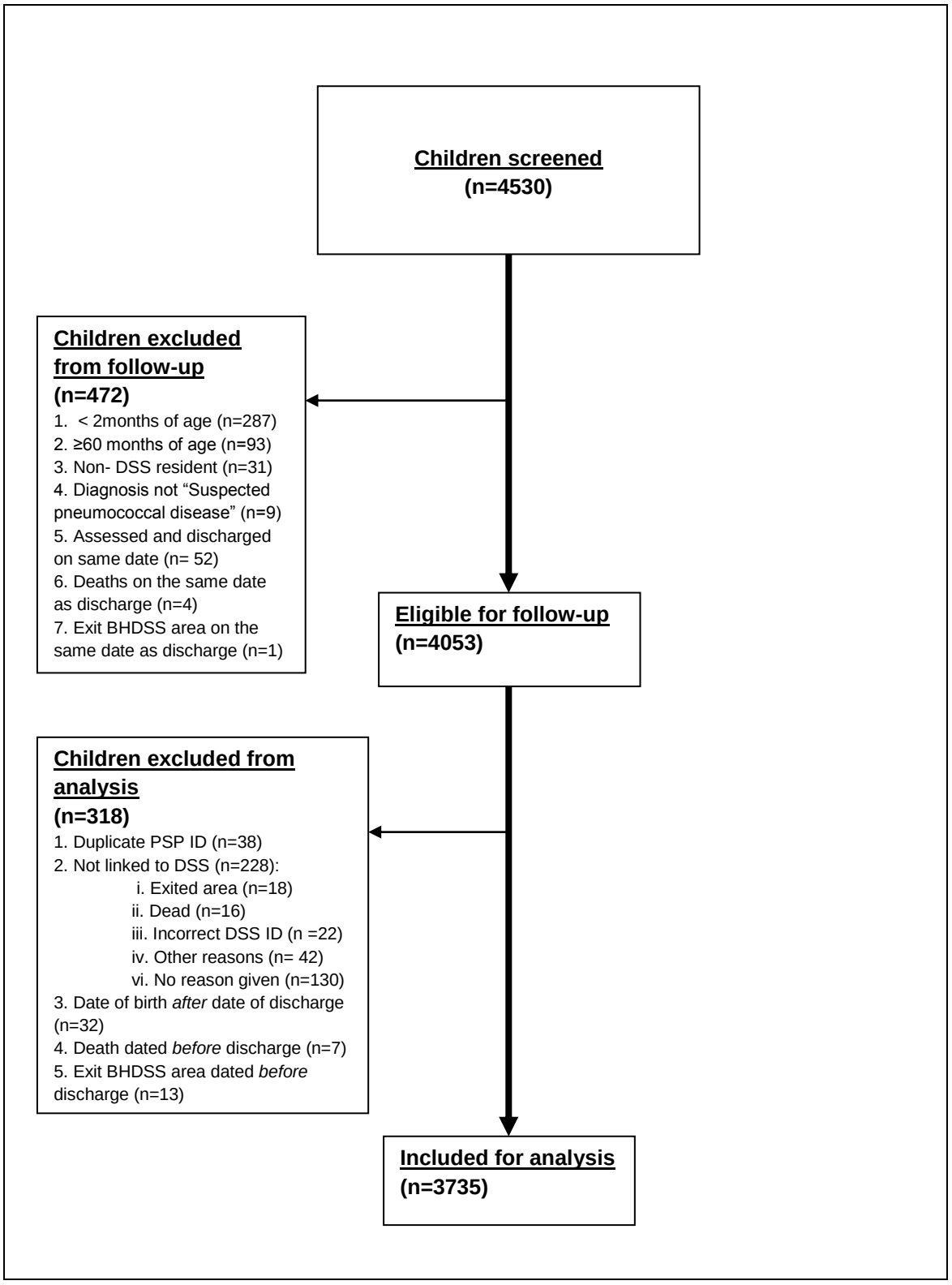

Figure 4. Flow Chart of Steps from Data Extraction to Analysis.

Cohort Demographics

The demographic information of the final cohort (n= 3735) included in analyses is shown in Table 6. Admissions had a mean age of 18 months. There were more boys than girls. Almost half of the cohort was of Sarahule ethnicity and the remaining nearly equal parts of Fula and Mandinka ethnicities.

Table 6. Demographic Information of those that were included and excluded from analysis due to data incompleteness or inconsistency

Demographic information	Complete and Correct information: Included in analysis (n=3735)	Incomplete and Inconsistent Information: Excluded from analysis (n=318)
Age at Discharge[a] (in months)		
Mean (95%CI)[b]	17.95 (17.53, 18.38)	13.59 (12.05, 15.13)
Age Group		
2-11 months n(%)	1,605(43%)	180(57%)
12-23 months n(%)	1,127(30%)	75(24%)
24-59 months n(%)	1,003(27%)	63(20%)
Sex[c]		
Male n(%)	2,110 (57%)	183(58%)
Female n(%)	1,614 (43%)	135(42%)
Missing n(%)	11 (0%)	0 (0%)
Ethinicity[d]		
Fula n(%)	972(26%)	-
Mandinka n(%)	963(26%)	-
Sarahule n(%)	1709(46%)	-
Wolof&Other n(%)	75(2%)	-
Missing n(%)	16(0%)	228(72%)

[a]Distribution showed signs of skewness
[b]Two-sample t test with equal variances Pr(T > t) = 0.0000
[c]Pearson chi2(1) = 0.0940 p = 0.759
[d]Ethinicity not reported in "Excluded from analysis group" because of 72% missing data, interaction not tested.

Analysis of those that were Excluded from Follow-up due to Data Incompleteness or Inconsistency

Of those patient admissions that passed eligibility criteria into the study (n=4054), 8% (n=318) were excluded from analysis because of incomplete or inconsistent data. Reasons for exclusion are stated in Figure 4. Ninety were able to be linked to the

demographic surveillance system for confirmation of vitality status, and 10 deaths were noted (11 including the artefact of duplicate PSP ID). Sixteen individuals were unable to be linked to the demographic surveillance system for the reason "Dead", but no date was given. Deaths may also be present in the 130 that had no reason given. Three hundred and eighteen patient admissions, among which there are at least 26 deaths, were excluded due to data incompleteness. Mortality was at least 8.2% in this excluded group.

Demographic (Table 6) and admission features (Table 7) between the two groups are briefly compared. Admissions excluded from analysis tended to be more from the first year of life (Table 6) and as a result their mean age was significantly lower (p=0.000). There was no significant difference in sex between the two groups. Differences in ethnicity could not be assessed due to missing data. The admissions excluded from analysis due to data incompleteness or inconsistency had a significantly different distribution of provisional diagnoses (Table 7), were significantly more wasted (as per weight-for-age) but not stunted (as per height-for-age), had significantly higher haemoglobin concentrations, but oxygen saturation was not significantly different.

Table 7. Admission features of those that were included and excluded from analysis due to data incompleteness or inconsistency

Admission Features	Complete and Correct information: Included in analysis (n=3735)	Incomplete and Inconsistent Information: Excluded from analysis (n=318)
Provisional diagnosis[a]		
Pneumonia n(%)	2,725 (72.96%)	193 (60.69%)
Meningitis n(%)	238 (6.37%)	18 (5.66%)
Septicaemia n(%)	326 (8.73%)	59 (18.55%)
Other focal sepsis n(%)	34 (0.91%)	3 (0.94%)
Pneumonia & Septicaemia n(%)	69 (1.85)	3 (0.94%)
Pneumonia & Septicaemia n(%)	287 (7.68%)	38 (11.95%)
Meningitis & Septicaemia n(%)	33 (0.88%)	2 (0.63%)
Pneumonia & Meningitis & Septicaemia n(%)	23 (0.62%)	2 (0.63%)
Total	3,735 (100%)	318 (100%)
Nutritional Indices		
Weight-for-age z-score[b]	[n= 3660][g]	[n=282][g]
Mean (95%CI)[c]	-1.69 (-1.74, 1.64)	-1.94 (-2.12, -1.75)
Height-for-age z-score	[n=3622][g]	[n=276][g]
Mean (95%CI)[d]	-1.19(-1.24, 1.14)	-1.29(-1.46, 1.11)

Haemoglobin concentration[b], g/dL	[n=2367][g]	[n=200][g]
Mean (95%CI)[e]	9.34 (9.26, 9.42)	9.75 (9.37, 10.14)
Oxygen Saturation[b], %	[n=2808][g]	[n=249][g]
Mean (95%CI)[f]	94.58 (94.41, 94.76)	94.64 (94.18, 95.11)

[a]Fisher's exact = 0.000
[b]Distribution showed signs of skewness
[c]Two-sample t test with unequal variances Pr(T > t) = 0.0055
[d]Two-sample t test with equal variances Pr(T > t) = 0.1529
[e]Two-sample t test with unequal variances Pr(T < t) = 0.0191
[f]Two-sample t test with unequal variances Pr(T > t) = 0.5928
[g]Number for admissions with information available.

4.2 First Primary Outcome: Mortality Rates within the Cohort

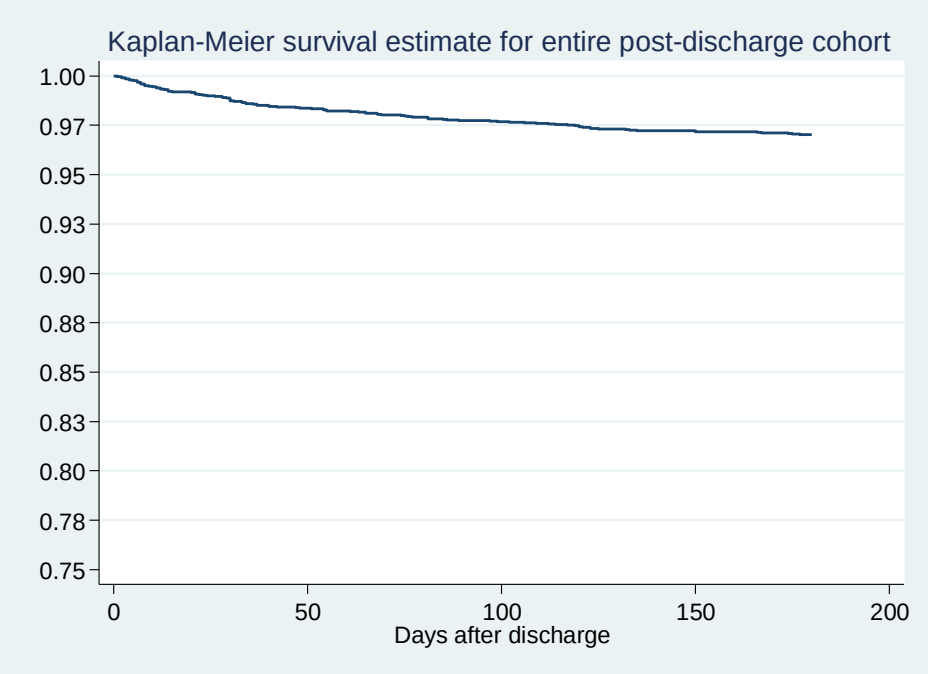

Figure 5. Kaplan Meier Estimate Showing Mortality in the 180 days after Discharge (or Transfer) Alive Following Admission to Basse Health Centre for Suspected Meningitis, Septicaemia or Pneumonia

The survival analysis contained 105 deaths over 605148.50 person-days of observation – 31.23 (=105/[(605148.50/180)*1000]) deaths per 1000 person-180 days of follow-up. At the end of the 180 day follow-up 2.8% of the original 3735 that started follow-up had died. The crude mortality rate was 28.5 deaths for every 1000 discharges that completed 180 days follow-up.

Table 8. Exits and Deaths During Follow-up for the Entire Cohort by Age Group

Age Group	N at start of follow-up	Exited during follow-up	Death during follow-up	Mortality Rate per 1000 complete 180 day follow-ups
2-11m	1,605	26	47	29.77
12-59m	2,130	29	58	27.61
Total	3,735	55	105	28.53

The annual mortality indicators for the BHDSS area are presented in Table 2. Crude estimates were that in a six month period, approximately 11 in 1000 children aged 1 – 11 months, and five in 1000 children aged 12 – 59 months would die in the BHDSS community. The six month (180 day) mortality rate in the post-discharge cohort stratified by age groups is presented in Table 8. Post-discharge mortality rates were roughly three times higher for younger children and roughly six times higher in older children when compared to community mortality rates. Although higher in the younger children, there was less marked difference in mortality rates between the age groups in the post-discharge cohort, than seen in the community.

One hundred and five patients died in the post-discharge cohort. This number would have been higher if data was complete (Figure 4). Two hundred and forty one patients died during admission (Figure 3), meaning of all deaths between admission and 6 months post-discharge, 30.3% died after discharge.

Table 9. Exits and Deaths During Follow-up for the Entire Cohort by Post-Discharge Period

Days after discharge	Exits during follow-up	Deaths during follow-up	Total
1-14 days	3(0.08%)	29(0.78%)	32(0.86%)
15-30 days	4(0.11%)	17(0.46%)	21(0.56%)
31-45 days	2(0.05%)	12(0.32%)	14(0.37%)
46-60 days	2(0.05%)	7(0.19%)	9(0.24%)
61-75 days	6(0.16%)	9(0.24%)	15(0.4%)
76-90 days	5(0.13%)	7(0.19%)	12(0.32%)
91-105 days	4(0.11%)	3(0.08%)	7(0.19%)
105-180 days	29(0.78%)	21(0.56%)	50(1.34%)
Completed Follow-up	3,575(95.72%)	0(0%)	3,575(95.72%)
Total	3,630(97.19%)	105(2.81%)	3,735(100%)

Table 9 describes events that occurred within the 180 day post-discharge follow-up. Post-discharge deaths were most common directly after discharge: 25% of deaths

occurred within the first 14 days. Half of the deaths occurred in the first 1.5 months (45 days) and nearly 80% occurred in the first three months (90 days). The distribution of deaths during the 180 day post-discharge follow-up is graphically presented in Figure 6.

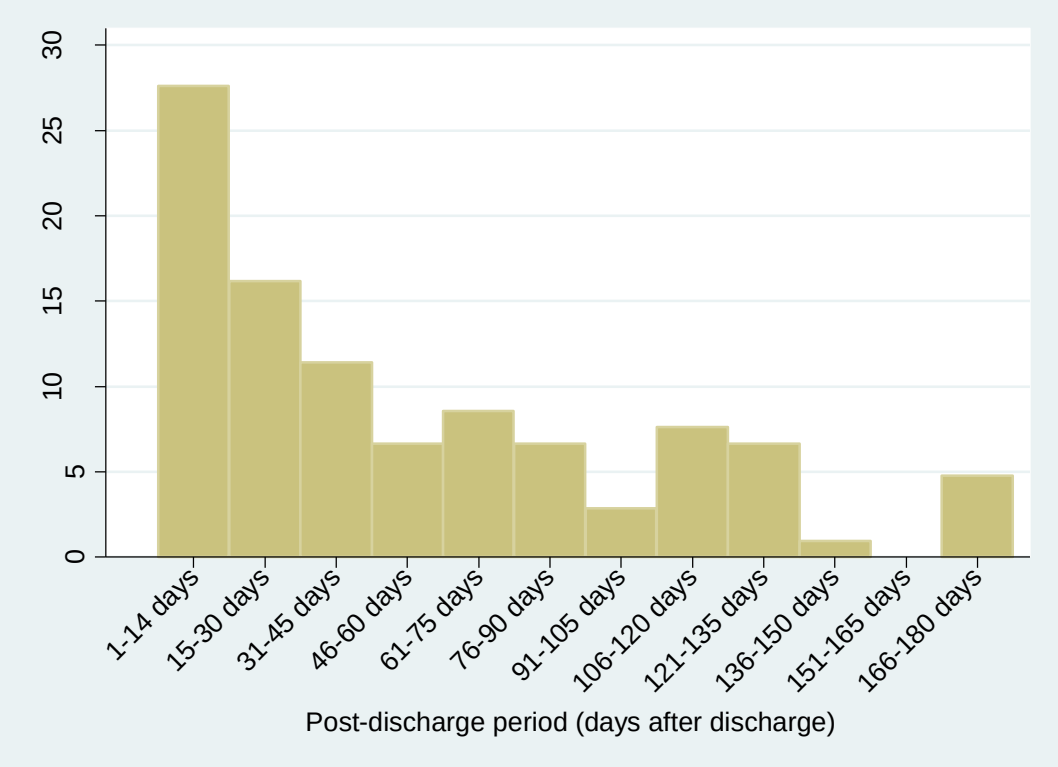

Figure 6. Temporal Distribution of 105 deaths that occurred during 180 day follow-up after discharge from Basse Health Centre

4.3 Second Primary Outcome: Risk Factors for Post-discharge Mortality

4.3.1 Univariate Analyses

Table 10. Univariate Cox Survival Analysis: Demographic and Socio-economic Information For The Post-Discharge Cohort

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	p value
DEMOGRAPHIC INFORMATION				
Age (in months) at Discharge	[n= 3630][a]	[n=105]		
Mean(SD[b])	18.0(13.35)	15.65(10.95)	0.99 [.97, 1.00]	0.09
Age Group				
2-23months	2,646(73%)	86(82%)		
24-59months	984(27%)	19(18%)	0.61 [0.37, 0.996]	0.048
Sex				
Male n(%)	2,055(56.61%)	55(52.38%)	1.00	-
Female n(%)	1,565(43.11%)	49(46.67%)	1.17 [0.79, 1.71]	0.43
Missing information n(%)	10(0.28%)	1(0.95%)		
Ethnicity				(p=0.888)
Fula n(%)	949(26.14%)	23(21.90%)	1.00	-
Mandinka n(%)	929(25.59%)	34(32.38%)	1.52[0.89, 2.58]	0.12
Sarahule n(%)	1,664(45.84%)	45(42.86%)	1.12[0.68, 1.85]	0.66
Wolof&Other n(%)	73(2.01%)	2(1.90%)	1.11[0.26, 4.71]	0.89
Missing information n(%)	15 (0.41%)	1 (0.95%)		
PARENTAL EDUCATION				
Mother received any formal education				
No	1,913 (52.7%)	59 (56.19%)		
Yes	446 (12.29%)	6 (5.71%)	0.45 [0.19, 1.03]	0.06
Missing Information	1,271 (35.01%)	40 (38.10%)		
Father received any formal education				
No	1,404 (38.68%)	40 (38.1%)	1	
Yes	196 (5.4%)	5 (4.76%)	0.91 [0.36, 2.32]	0.85
Missing Information	2,030 (55.92%)	60 (57.14%)		
OTHER SOCIO-ECONOMIC				
Number of residents in same household	[n= 3549]	[n= 82]		
Mean(SD)	34.73(22.26)	32.26(17.71)	0.99 [0.98, 1.01]	0.32
Estimated Total Household Income (in GMD1000)	[n= 2716]	[n= 69]		

Mean(SD)	19.71(23.42)	13.05(15.75)	0.98 [0.97, 0.998]	0.02

[a]Numbers in square brackets, above Mean(SD) values, refers to number of admissions with valid information that were able to contribute to this variable.
[b]SD = standard deviation

Demographic and socioeconomic information is presented in Table 10. On univariate Cox analysis, age at discharge in months was not significant as a continuous variable. When stratified, children two years of age and above at discharge were more likely to survive the 180-day follow-up period (p=0.048). Sex and ethnicity were not significantly associated with post-discharge mortality on univariate analysis.

Parental education variables (extracted from the BHDSS database) had high levels of missing information and did not reach statistical significance in Table 10. Post-hoc 'Missing Information' and 'No Formal Maternal Education' were grouped together as a 'negative finding', 'Formal Maternal Education' as a 'positive finding' was a protective predictor of post-discharge mortality (data not shown, univariate HR= 0.44 [95%CI: 0.1923, 0 .9994, p=0.050]). This was not the case with paternal education. Half of the patients had mothers with no formal education.

Total household income as estimated by the BHDSS socio-economic study significantly predicted post-discharge mortality on univariate analysis (p=0.02), however this BHDSS information was missing for 25% of survivors and 34% of deceased (25% of the entire cohort). Number of household co-habitants did not significantly predict post-discharge mortality in univariate analyses.

Table 11. Univariate Cox Survival Analysis: Screening Related Information For The Post-Discharge Cohort

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	p value
Screened at Outlying Clinic				
No n(%)	2,061(57%)	72(69%)		
Yes n(%)	1,569(43%)	33(31%)	0.61 [0.41, 0.93]	0.02
Screening Nurse Administered Antibiotics Before Referral				
No n(%)	2,530(70%)	64(61%)		
Yes n(%)	201(6%)	7(7%)	1.28 [0.59, 2.77]	0.53
Missing information n(%)	899(25%)	34 (32%)		
Screening Nurse Suspected Meningitis				
No n(%)	3,335(92%)	97(92%)		
Yes n(%)	283(8%)	7(7%)	0.88 [0.41, 1.89]	0.74
Missing information n(%)	12(0%)	1(1%)		
Pneumococcal Conjugate Vaccine: Dose 1 received				
No n(%)	1,075(30%)	23(22%)		
Yes n(%)	1,526(42%)	45(43%)	1.48 [0.9, 2.45]	0.13
Missing information n(%)	1,029(28%)	37(35%)		
Pneumococcal Conjugate Vaccine: Dose 2 received				
No n(%)	1,379(38%)	29(28%)		
Yes n(%)	1,212(33%)	38(36%)	1.6 [0.98, 2.59]	0.06
Missing information n(%)	1,039(29%)	38(36%)		
Pneumococcal Conjugate Vaccine: Dose 3 received				
No n(%)	1,600(44%)	41(39%)		
Yes n(%)	991(27%)	28(27%)	1.19 [0.74, 1.93]	0.47
Missing information n(%)	1,039(29%)	36(34%)		
PCV completeness (for age)				
Complete n(%)	1,189(33%)	32(30%)		
Partially incomplete n(%)	349(10%)	14(13%)	1.42 [0.76, 2.66]	0.27
Fully incomplete n(%)	866(24%)	19(18%)	0.75 [0.42, 1.32]	0.32
Missing information n(%)	1,226(34%)	40(38%)		

Table 11 presents information collected by the screening nurse on presentation to a health facility. Being screened at an outlying clinic (rather than at Basse Health Centre) was a protective predictor for post-discharge mortality on univariate Cox analysis (p=0.02). The nurses' judgement of 'suspected meningitis' did not significantly predict post-discharge mortality.

All other variables in Table 11 (namely, receipt of antibiotics before referral and doses of pneumococcal conjugate vaccine) failed to predict post-discharge mortality but

also had high levels of missing information.

Even with missing information, about a quarter of the cohort was known to be fully PCV-incomplete (i.e. received none of the PCV schedule) and another ten percent had started their PCV schedule, but had missed at least one dose.

Table 12. Univariate Cox Survival Analysis: Patient History Related Information For The Post-Discharge Cohort

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	p value
Days unwell[a]	[n= 3629][b]	[n= 104]		
	3.36 (2.43)[c]	6.06 (8.34)	1.23 [1.17, 1.30]	0.00
Days unwell (categories)				
0-3days	2,547(70%)	45(42.86%)		
4-7days	958(26.39%)	44(41.9%)	2.54 [1.68, 3.85]	0.00
>7days	124(3.42%)	15(14.29%)	6.43 [3.58, 11.53]	0.00
Missing information	1(0.03%)	1 (0.95%)		
Patient History of Cough				
No n(%)	274(8%)	15(14%)		
Yes n(%)	3,356(92%)	90(86%)	0.48 [0.28, 0.83]	0.01
Patient History of Difficulty Breathing				
No n(%)	835(23%)	39(37%)		
Yes n(%)	2,795(77%)	66(63%)	0.51 [0.34, 0.75]	0.00
Patient History of Irritability				
No n(%)	2,852(79%)	83(79%)		
Yes n(%)	778(21%)	22(21%)	1.01 [0.63, 1.62]	0.96
Patient History of Prostration				
No n(%)	3,354(92%)	89(85%)		
Yes n(%)	276(8%)	16(15%)	2.17 [1.27, 3.7]	0.00
Patient History of Convulsion				
No n(%)	3,317(91%)	96(91%)		
Yes n(%)	313(9%)	9(9%)	0.98 [0.49, 1.93]	0.95
Patient History of Fever				
No n(%)	130(4%)	4(4%)		
Yes n(%)	3,500(96%)	101(96%)	0.94 [0.35, 2.55]	0.90
Patient History of Diarrhoea				
No n(%)	2,803(77%)	69(66%)		
Yes n(%)	827(23%)	36(34%)	1.72 [1.15, 2.58]	0.01
Patient History of Vomiting				
No n(%)	2,768(76%)	81(77%)		
Yes n(%)	862(24%)	24(23%)	0.93 [0.59, 1.47]	0.75
Antibiotics Taken in Previous Week?				
No n(%)	2,486(68%)	69(66%)		
Yes n(%)	359(10%)	14(13%)	1.41 [0.79, 2.5]	0.24
Unknown n(%)	759(21%)	22(21%)	1.02 [0.63, 1.65]	0.94
Missing information n(%)	26(1%)	0(0%)		

[a] Days unwell= Reported length of illness at presentation
[b] Numbers in square brackets, above Mean(SD) values, refers to number of admissions with valid information that were able to contribute to this variable.
[c] Mean (SD)
[d] Prostration is defined as the loss of ability to sit, drink or breastfeed

Percentages within grouped columns may not add to 100% due to missing information
p=0.00 is equivalent to p<0.005

Table 12 presents the patient history information that was collected before admission. The reported length of illness at presentation ("days unwell") strongly predicted post-discharge mortality on univariate analysis both as a continuous (p<0.005) and categorical (p<0.005) variables – compared with admissions that were zero to three days unwell at presentation, those that were unwell for longer than seven days had between 3.58 and 11.58 times the risk of death (95% confidence). History of diarrhoea (p=0.01) and history of prostration (defined as any loss of the ability to sit, drink or breastfeed) (p<0.005) also predicted post-discharge mortality on univariate Cox analysis.

History of cough and difficulty breathing were significantly associated with reduced post-discharge mortality (p=0.01 and p<0.005, respectively) on univariate Cox analysis.

History of irritability, convulsion, fever, vomiting and antibiotic use in previous week were not significantly predictive of post-discharge mortality.

Table 13. Univariate Cox Survival Analysis: Clinical Assessment Related Information For The Post-Discharge Cohort

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	p value
Musculoskeletal Swelling or Tenderness				
No n(%)	3,552(98%)	103(98%)		
Yes n(%)	78(2%)	2(2%)	0.88 [0.22, 3.58]	0.86
VITAL SIGNS				
Axillary Temperature, ^{o}C	[n= 3630] [a]	[n= 105]		
Mean (SD)	38.23 (1.38)	37.78 (1.17)	0.72 [0.61, 0.84]	0.00 [b]
Pulse Rate, beats/min	[n=3624]	[n=105]		
Mean (SD)	156.10 (21.99)	148.03 (29.60)	0.98 [0.98, 0.99]	0.00
Respiratory Rate, breaths/min	[n=3629]	[n=104]		
Mean (SD)	59.41 (17.35)	54.79 (21.37)	0.98 [0.97, 0.99]	0.00
Oxygen Saturation, %	[n=2736]	[n=72]		
Mean (SD)	94.64 (4.68)	92.49 (8.00)	0.95 [0.93, 0.98]	0.00
NUTRITION STATUS				
Clinical Severe Malnutrition				
No n(%)	3,330(92%)	53(50%)		
Yes n(%)	300(8%)	52(50%)	9.89 [6.75, 14.5]	0.00
Haemoglobin	[n=2291]	[n=76]		

concentration, g/dL				
Mean (SD)	9.36 (1.99)	8.62 (2.36)	0.85 [0.77, 0.94]	0.00
Mid upper arm circumference, cm				(p=0.00)
>13.0cm	2,455(68%)	22(21%)		
11.5-13.0cm	879(24%)	30(29%)	3.71 [2.14, 6.43]	0.00
10.5-11.4cm	162(4%)	22(21%)	14.13 [7.83, 25.52]	0.00
<10.5cm	117(3%)	30(29%)	25.38 [14.64, 44.00]	0.00
Missing Information	17(0%)	1(1%)		
Height-for-age z-score	[n=3526]	[n=96]		
Mean (SD)	-1.15 (1.47)	-2.52 (1.85)	0.57 [0.51, 0.65]	0.00
Weight-for-age z-score	[n=3568]	[n=92]		
Mean (SD)	-1.64 (1.44)	-3.39 (1.57)	0.48 [0.42, 0.55]	0.00
Weight-for-height z-score	[n=3511]	[n=87]		
Mean (SD)	-1.31 (1.42)	-2.63 (1.45)	0.51 [0.44, 0.60]	0.00
LEVEL OF CONCIOUSNESS				
Lethargic on Assessment				
No n(%)	2,753(76%)	56(53%)		
Yes n(%)	877(24%)	49(47%)	2.62 [1.78, 3.84]	0.00
AVPU scale				(p=0.63)
Unresponsive n(%)	24(1%)	0(0%)		
Pain n(%)	71(2%)	2(2%)	Variable omitted due	
Voice n(%)	71(2%)	2(2%)	to too few events	
Alert n(%)	3,460(95%)	100(95%)		
Missing information n(%)	4(0%)	1(1%)		
Blantyre Coma Score				(p=0.97)
0 n(%)	3(0%)	0(0%)		
1 n(%)	8(0%)	0(0%)		
2 n(%)	42(1%)	1(1%)	Variable omitted due	
3 n(%)	51(1%)	2(2%)	to too few events	
4 n(%)	59(2%)	2 (2%)		
5 n(%)	3,459(95%)	100(95%)		
Missing information n(%)	8(0%)	0(0%)		
RESPIRATORY SIGNS				
Grunting				
No n(%)	3,122(86%)	94(90%)		
Yes n(%)	508(14%)	11(10%)	0.7 [0.37, 1.3]	0.26
Lower Chest Wall In-drawing				
No n(%)	1,330(37%)	51(49%)		
Yes n(%)	2,300(63%)	54(51%)	0.58 [0.4, 0.85]	0.01
Nasal Flaring				
No n(%)	1,712(47%)	64(61%)		
Yes n(%)	1,918(53%)	41(39%)	0.56 [0.38, 0.83]	0.00
Crackles				
No n(%)	1,772(49%)	65(62%)		
Yes n(%)	1,858(51%)	40(38%)	0.6 [0.41, 0.89]	0.01
Wheeze				
No n(%)	2,720(75%)	92(88%)		
Yes n(%)	910(25%)	13(12%)	0.42 [0.23, 0.74]	0.00

Bronchial Breathing				
No n(%)	3,132(86%)	93(89%)		
Yes n(%)	498(14%)	12(11%)	0.87 [0.48, 1.58]	0.64
Dull Percussion Note				
No n(%)	3,193(88%)	89(85%)		
Yes n(%)	437(12%)	16(15%)	1.25 [0.73, 2.13]	0.41
SIGNS OF MENINGITIS				
Petechial Rash				
No n(%)	3,485(96%)	100(95%)		
Yes n(%)	145(4%)	5(5%)	1.17 [0.48, 2.87]	0.73
Bulging Fontanelle				
No n(%)	3,592(99%)	104(99%)		
Yes n(%)	38(1%)	1(1%)	0.95 [0.13, 6.82]	0.96
Neck Stiffness				
No n(%)	3,600(99%)	100(95%)		
Yes n(%)	30(1%)	5(5%)	6.16 [2.51, 15.13]	0.00
Ear Discharge				
No n(%)	3,588(99%)	102(97%)		
Yes n(%)	42(1%)	3(3%)	2.48 [0.79, 7.82]	0.12

[a]Numbers in square brackets, above Mean(SD) values, refers to number of admissions with valid information that were able to contribute to this variable.
[b]p=0.00 is equivalent to p<0.005

Table 13 presents the information collected during assessment. Each of the 'vital signs' (increasing axillary temperature, respiratory rate, pulse rate, oxygen saturation were protective) had strong statistically significant relationships ($p<0.005$) with post-discharge mortality on univariate Cox analysis. Discharges that survived the 180 day follow-up tended to have higher temperature, higher pulse rate, higher respiratory rate and higher oxygen saturation.

Under-nourished children were clearly over-represented in the group that died during 180 day post-discharge follow-up ($p<0.005$ for all nutritional indices tested with univariate Cox analysis). Additionally there was a statistically strong trend of increased hazard for death with decreasing mid upper arm circumference ($p<0.005$). Discharges that died during follow-up had a significantly lower haemoglobin concentration than those that survived, and each increase in unit (g/dL) of haemoglobin concentration reduced the hazard of death by 15% (6% to 23%, with 95% confidence) on univariate analysis.

Lethargy on assessment had a statistically strong relationship with post-discharge mortality on univariate analysis ($p<0.005$), but AVPU Scale or Blantyre Coma Score could not be formally analysed due to insufficient events.

Presence of respiratory signs on assessment suggested less hazard of death during the 180 day post-discharge period; even clinical signs of severe respiratory illness (e.g.

lower chest wall indrawing, nasal flaring) showed significant protective effect on univariate Cox analysis.

Neck stiffness was a strong predictor of mortality ($p<0.005$). However, presence of petechial rash, bulging fontanelle or ear discharge did not statistically significantly predict 180 day post-discharge mortality.

Table 14. Univariate Cox Survival Analysis: Admission Related Information For The Post-Discharge Cohort

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	p value
Length of Admission, days	[n= 3557][a]	[n= 103]		
Mean(SD)	3.74 (2.48)	6.21 (4.35)	1.19 [1.14, 1.23]	0.00[c]
Number of admissions during follow-up	[n= 3630]	[n= 105]		
Mean(SD)	1.37 (0.77)	1.25 (0.51)	0.77 [0.56,1.06]	0.11
Provisional diagnosis				(p=0.00)
Pneumonia n(%)	2,677(74%)	48(46%)		
Meningitis n(%)	233(6%)	5(5%)	1.19 [0.47, 2.98]	0.71
Septicaemia n(%)	298(8%)	28(27%)	5.12 [3.21, 8.16]	0.00
Other focal sepsis n(%)	32(1%)	2(2%)[b]	3.68 [0.89, 15.14]	0.07
Pneumonia & Meningitis n(%)	65(2%)	4(4%)[b]	3.4 [1.23, 9.44]	0.02
Pneumonia & Septicaemia n(%)	272(7%)	15(14%)	3.27 [1.83, 5.84]	0.00
Meningitis & Septicaemia n(%)	31(1%)	2(2%)[b]	3.5 [0.85, 14.42]	0.08
Pneumonia & Meningitis & Septicaemia n(%)	22(1%)	1(1%)[b]	2.58 [0.36, 18.73]	0.35
Number of diagnoses (incl. Provisional diagnosis				(p=0.00)
1 n(%)	2,208(61%)	46(44%)		
2 n(%)	1,139(31%)	39(37%)	1.58 [1.03, 2.42]	0.04
3 n(%)	235(6%)	17(16%)	3.19 [1.83, 5.57]	0.00
4 n(%)	48(1%)	3(3%)[b]	2.76 [0.86, 8.87]	0.09
Lumbar Puncture Requested by Physician				
No n(%)	3,298(91%)	94(90%)		
Yes n(%)	312(9%)	10(10%)	1.12 [0.58, 2.15]	0.73
Unable to Investigate n(%)	11(0%)	1(1%)[b]	2.84 [0.4, 20.4]	0.3
Missing information n(%)	9(0%)	0(0%)		
Lung Aspirate Requested by Physician				
No n(%)	3,458(95%)	105(100%)	Variable omitted	
Yes n(%)	161(4%)	0(0%)	due to	
Missing information n(%)	11(0%)	0(0%)	too few events	
Pleural Aspirate Requested by Physician				
No n(%)	3,610(99%)	105(100%)	Variable omitted	
Yes n(%)	9 (0%)	0(0%)	due to	
Missing information n(%)	11(0%)	0(0%)	too few events	
Malaria RDT result				
Negative n(%)	2,460(68%)	71(68%)		

Positive n(%)	251(7%)	5(5%)	0.68 [0.27, 1.67]	0.4
Not done n(%)	856(24%)	25(24%)	0.99 [0.62, 1.55]	0.95
Missing information n(%)	63(2%)	4 (4%)		
Confirmed Bacteraemia				
No	3,480(96%)	98(93%)		
Yes	150(4%)	7 (7%)	2.02 [1.06, 3.86]	0.03
Oral antibiotics given				
No n(%)	3,394(93%)	100(95%)		
Yes n(%)	236(7%)	5(5%)	0.69 [0.28, 1.69]	0.41
Intravenous antibiotics given				
No n(%)	335(9%)	5(5%)		
Yes n(%)	3,295(91%)	100(95%)	2.12 [0.86, 5.21]	0.1
Non-oral, Non-IV antibiotics given				
No n(%)	3,596(99%)	102(97%)		
Yes n(%)	34(1%)	3(3%)[b]	2.89 [0.92, 9.12]	0.07

[a]Numbers in square brackets, above Mean(SD) values, refers to number of admissions with valid information that were able to contribute to this variable.
[b]Less than 5 events in table cell.
[c]p=0.00 is equivalent to p<0.005
Percentages within grouped columns may not add to 100% due to missing information

Table 14 presents details of admission for the cohort. Length of Admission was significantly longer in those that died during 180 day post-discharge follow-up on univariate Cox analysis. Every additional day of admission conferred an increase of 19% hazard of death (p<0.005). Those that died in the 180 days after discharge had fewer PSP admissions (during the study period), but this relationship did not reach statistical significance.

Provisional diagnosis was strongly associated with post-discharge mortality as a whole/continuous variable (p<0.005) on univariate Cox analysis. Proportionally there were less diagnoses of pneumonia and more diagnoses of 'septicaemia' (p<0.005), 'pneumonia and meningitis' (p=0.02) and 'pneumonia and septicaemia' (p<0.005) in those that suffered post-discharge mortality. Low number of events were noted for the diagnoses of 'other focal sepsis' 'pneumonia and meningitis' 'meningitis and septicaemia' 'pneumonia and meningitis and septicaemia'.

Those that died during post-discharge follow-up proportionally had more concurrent diagnoses than those that survived follow up. The relationship between number of diagnoses and post-discharge mortality was particularly strong for three diagnoses (p<0.005), but low number of events decreased the power to estimate the risk at four diagnoses.

Rapid Diagnostic Test for Malaria did not associate with post-discharge mortality on univariate Cox analysis. Laboratory confirmed bacteraemia doubled the hazard of death on univariate Cox analysis (p=0.03). Route of antibiotic delivery did not confer

any significant association with post-discharge mortality on univariate analysis.

Table 15. Univariate Cox Survival Analysis: Discharge Related Information For The Post-Discharge Cohort

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	p value
Type of Separation				
Discharged alive n(%)	3,589(99%)	97(92%)		
Transferred alive n(%)	41(1%)	8(8%)	6.84 [3.32, 14.06]	0.00[a]
Month of Discharge				(p=0.39)
1 n(%)	201(6%)	5(5%)		
2 n(%)	216(6%)	7(7%)	1.36 [0.43, 4.29]	0.6
3 n(%)	340(9%)	8(8%)	1.04 [0.34, 3.19]	0.94
4 n(%)	410(11%)	6(6%)	0.73 [0.22, 2.39]	0.6
5 n(%)	281(8%)	11(10%)	1.5 [0.52, 4.31]	0.45
6 n(%)	258(7%)	18(17%)	2.62 [0.97, 7.07]	0.06
7 n(%)	332(9%)	10(10%)	1.15 [0.39, 3.38]	0.79
8 n(%)	390(11%)	13(12%)	1.29 [0.46, 3.62]	0.63
9 n(%)	384(11%)	10(10%)	1 [0.34, 2.93]	1
10 n(%)	342(9%)	6(6%)	0.68 [0.21, 2.24]	0.53
11 n(%)	293(8%)	6(6%)	0.8 [0.24, 2.61]	0.71
12 n(%)	183(5%)	5(5%)	1.09 [0.32, 3.77]	0.89
Season of Discharge				
Wet (Jul-Nov) n(%)	1,741(48%)	45(43%)		
Dry (Dec-Jun) n(%)	1,889(52%)	60(57%)	1.34 [0.91, 1.97]	0.14
Year Quarter of Discharge				(p=0.18)
1 (Jan-Mar) n(%)	757(21%)	20(19%)		
2 (Apr-Jun) n(%)	949(26%)	35(33%)	1.39 [0.8, 2.41]	0.24
3 (Jul-Sept) n(%)	1,106(30%)	33(31%)	1.02 [0.59, 1.78]	0.94
4 (Oct-Dec) n(%)	818(23%)	17(16%)	0.72 [0.38, 1.38]	0.33
Noted as Recovering on Discharge				
No n(%)	114(3%)	17(16%)		
Yes n(%)	3,516(97%)	88(84%)	0.18 [0.11, 0.3]	0.00
Noted as non-medical discharge				
No n(%)	3,583(99%)	98(93%)		
Yes n(%)	47(1%)	7(7%)	5.12 [2.38, 11.03]	0.00

Percentages within grouped columns may not add to 100% due to missing information
[a]p=0.00 is equivalent to p<0.005

Table 15 displays discharge information for the post-discharge cohort. Patients transferred from Basse Health Centre to another health facility were at 6.84 times the hazard of death compared with those discharged alive.

The month of discharge when tested as a whole variable showed no significant relationship with post-discharge mortality. No individual month had a poorer outcome than the first (as shown in Table 15), but statistically significant higher hazards were found in the month 6 (June) when compared to months 3, 4, 7, 9, 10, 11 ($p<0.05$, data

not shown) and others came close to reaching significance (month 1 p=0.056, month 8, p=0.051, month 12 p=0.083, data not shown). No quarter of the year had significantly higher hazards than the first, although the second had 1.92 times the hazards than the fourth (p=0.028, data not shown). The season (wet or dry) had no statistically significant association with post-discharge mortality on univariate Cox analysis.

If an admission was noted to be of recovering status on discharge (compared with 'persistent abnormality' and 'missing information') the child had 82% less hazard of post-discharge mortality on univariate Cox analysis. This is difficult to interpret as malnutrition may be considered a persistent abnormality. Those that were noted as non-medical discharge (compared with 'medical discharge' and 'missing information') had five times the hazard of post-discharge mortality on univariate Cox analysis.

4.3.2 Multiple Variable Cox Models

Table 16 presents a multiple variable Cox model comprised of disease syndromes. Each month-of-life increase was independently associated with a 2% decrease in hazard of mortality (p=0.01). Sex was not a significant risk factor for post-discharge mortality. Compared to pneumonia without clinical severe malnutrition, children with sepsis and clinical severe malnutrition had a 19-fold hazard of post-discharge death, children with meningitis and clinical severe malnutrition had a 14-fold hazard of post-discharge death. When sepsis with clinical severe malnutrition and meningitis with clinical severe malnutrition are compared in this model there was no statistical difference (p=0.529, data not shown). A syndrome with presence of clinical severe malnutrition resulted in a 5- to 9-fold increase hazard in post-discharge mortality compared to a syndrome without clinical severe malnutrition (the most marked difference noted in pneumonia). In absence of clinical severe malnutrition the magnitude of hazard is relatively low, compared to when clinical severe malnutrition is present. This relationship was later tested and there was no significant interaction between clinical severe malnutrition and any provisional diagnosis.

Table 16. Model A: Syndrome based-Multiple Variable Cox Regression

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	Multivariate Cox HR [95% CI]	p value
Age at Discharge (in months)[a]	18.02 (13.35)	15.65 (10.95)	0.99 [.97, 1.00]	0.98 [0.96, 0.99]	0.01
Sex[b]					
Male n(%)	2,055(56.61 %)	55(52.38%)	1.00		
Female n(%)	1,565(43.11 %)	49(46.67%)	1.17 [0.79, 1.71]	1.06 [0.74, 1.50]	0.76
Sepsis with CSM	134(3.69%)	33(31.43%)		18.79 [11.65, 30.32]	0.00
Meningitis with CSM[c]	16(0.44%)	3(2.86%)[d]		13.90 [5.43, 35.58]	0.00
Pneumonia with CSM	150(4.13%)	16(15.24%)		8.74 [4.93, 15.49]	0.00
Meningitis without CSM	335(9.23%)	9(8.57%)		2.98 [1.66, 5.36]	0.00
Sepsis without CSM	468(12.89 %)	12(11.43%)		2.72 [1.50, 4.93]	0.00
Pneumonia without CSM	2,527(69.61 %)	32(30.48%)		1.00	-

[a]Mean(SD).
[b]Percentages do not add to 100% because of missing information.
[c]CSM, clinical severe malnutrition on assessment by physician.
[d]less than 5 events in this cell.
p=0.00 is equivalent to p<0.005

Table 17 presents a multiple variable Cox regression, a model comprised of clinical observations and measurements. Age and sex did not have an independent relationship with post-discharge mortality. The other variables in the model had strong associations with post-discharge mortality (all $p<0.005$). Every unit (^{o}C) increase in axillary temperature led to a decrease in hazard of post-discharge mortality by 30%. Every unit (%) increase in oxygen saturation led to a decrease in hazard of mortality by 5%. Every unit (g/dL) increase in haemoglobin concentration led to an 18% decrease in hazard of death.

There was a trend of increasing hazard of post-discharge mortality with decreasing mid upper arm circumference. Those with the lowest mid upper arm circumference (<10.5cm) were at 11.5 times the hazards of post-discharge mortality.

On assessment, clinical severe malnutrition independently increased the hazard of post-discharge mortality by about four times, neck stiffness by about 18 times.

Discharge during the dry season (see methods for inclusion of season) independently approximately doubled the hazard of post-discharge mortality. Observed non-medical discharge resulted in a six-fold increase in hazard of post-discharge mortality.

Table 17. Model B: Admission information-based Multiple Variable Cox Model

Risk factor	Survived or Exited 180 day follow-up (N= 3630)	Died during 180 day follow-up (N= 105)	Univariate Cox HR [95% CI]	Multivariate Cox HR [95% CI]	p value
Age at Discharge (in months)[a]	18.02 (13.35)	15.65 (10.95)	0.99 [.97, 1.00]	1.00 [0.98, 1.03]	0.69
Sex					
Male n(%)	2,055(56.61%)	55(52.38%)	1.00		
Female n(%)	1,565(43.11%)	49(46.67%)	1.17 [0.79, 1.71]	0.89 [0.56, 1.42]	0.63
Neck Stiffness	30/3630 (1%)	5/105 (5%)	6.16 [2.51, 15.13]	17.60 [7.36, 42.10]	0.00
Mid upper arm circumference					
>13.0cm	2,455(68%)	22(21%)		1.00	
11.5-13.0cm	879(24%)	30(29%)	3.71 [2.14, 6.43]	4.78 [2.30, 9.93]	0.00[b]
10.5-11.4cm	162(4%)	22(21%)	14.13 [7.83, 25.52]	9.29 [3.83, 22.50]	0.00
<10.5cm	117(3%)	30(29%)	25.38 [14.64, 44.00]	11.52 [4.59, 28.90]	0.00
Clinical Severe Malnutrition	300/3630 (8%)	52/105 (50%)	9.89 [6.75, 14.5]	3.94 [2.11, 7.36]	0.00
Noted as non-medical discharge	47/3630 (1%)	7/105 (7%)	5.12 [2.38, 11.03]	6.22 [2.98, 13.01]	0.00
Dry Season	1889/3630 (52%)	60/105 (57%)	1.34 [0.91, 1.97]	2.33[1.44, 3.77]	0.00
Axillary Temperature (^oC) [a]	38.23 (1.38)	37.78 (1.17)	0.72 [0.61, 0.84]	0.70 [0.58, 0.84]	0.00
Haemoglobin concentration (g/dL) [a]	9.36 (1.99)	8.62 (2.36)	0.85 [0.77, 0.94]	0.82 [0.74, 0.90]	0.00
Oxygen Saturation (per %)[a]	94.64 (4.68)	92.49 (8.00)	0.95 [0.93, 0.98]	0.95 [0.93, 0.98]	0.00

[a]Mean(SD).
[b]p=0.00 is equivalent to p<0.005

CHAPTER 5 – DISCUSSION

This chapter discusses the findings from this project in section 5.1 and relates it to previous literature in section 5.2. Section 5.3 discusses the biological plausibility of relationships (or lack thereof) that were found. Sections 5.4 and 5.5 review the strengths and weaknesses of the research, respectively.

5.1 Principal Findings

Post-discharge mortality rate was three to six times higher than the background community rate with a majority of deaths occurred within 45 days of discharge. Children that were malnourished (even children above WHO "severely malnourished" cut-off (40)) on admission were at a significantly higher risk of post-discharge mortality. In the clinical syndrome model (Model A) there was a gradual increase in risk with increasing severity of provisional diagnosis (suspected meningitis or suspected sepsis rather than suspected pneumonia), and there was an additive relationship with visible signs of severe malnutrition.

Neck stiffness on admission was a very strong independent predictor of post-discharge mortality: Those with neck stiffness were at 17.6 times the risk of death compared to those without. However only 1% of the cohort presented with neck stiffness. Non-medical discharge, discharge during dry season, decreasing axillary temperature, decreasing haemoglobin concentration and decreasing peripheral arterial haemoglobin oxygen saturation were all independent predictors of mortality following discharge. MUAC may be a combination measure of risk of under-nutrition and age. Presence of severe clinical malnutrition on assessment independently further increases the risk for death. Sex was not a predictor of post-discharge mortality in this setting.

5.2 How Findings Relate to Previous Literature

We showed the risk of mortality was higher in the post-discharge cohort when compared with background community rates. Previous studies also concluded higher risk of mortality in post-discharge cohorts than in the background population (15) (19) (20). We further showed the number that died in the six months following discharge is in the same order of magnitude of those that died as inpatients.

This study reported a mortality rate of 31.23 deaths per 1000 person-180 days of follow-up post-discharge following admission for suspected invasive bacterial disease.

Other studies with similarly broad cohorts showed similar mortality rates (20) if not slightly higher (19).

Time to death has been reported in previous studies and our findings confirm that there is a concentration of post-discharge mortality directly after discharge (15) (18) (20) (29) (31) (39). Of the deaths that occurred in the first six months following discharge, Moisi et al. showed 35% (20) and Veirum et al. showed 53% (19) occurred in the first four weeks.

The importance of nutritional status on admission has been studied in previously (15) (16) (17) (20) (33) (31). Our analysis yielded MUAC and clinical severe malnutrition on assessment as independent nutritional risk factors. Beyond MUAC and Clinical Severe Malnutrition, other nutritional indices (namely weight-for-age, height-for-age and weight-for-height z-scores) failed to add any significant predictive value to our model, but have been implicated as important by other studies (15) (16) (17) (20) (31). In a multivariate model, weight-for-age below minus four z-score independently contributed to a HR of 6.54 according to Moisi et al. Villamor et al. showed low MUAC contributed to an independent increase in risk of 88%.

In the syndrome model, preliminary diagnosis (suspected disease syndrome on clinical assessment) modified risk of post-discharge mortality, but risk was almost an order of magnitude of risk higher when visible signs of severe malnutrition were present. Syndrome of illness on admission has been previously shown to be important for predicting post-discharge (17) (20). Moisi et al. could not adjust their model for age and Villamor et al. could only compare children with pneumonia and severe pneumonia. This is the first evidence to show an age and sex adjusted effect of suspected invasive bacterial disease syndrome on post-discharge mortality together with the effect of severe malnutrition. Similar relationships between under-nutrition and disease and population child mortality have been published previously (41) (42). Caulfield et al. (41) estimated that 52% of all deaths in young children were attributable to malnutrition.

Neck stiffness on admission, although uncommon, was a very strong predictor of post-discharge mortality. Although tested in previous research (20), this is the first study to show the predictive value neck stiffness on admission as a predictor of post-discharge mortality.

If a discharge was noted to be against medical advice (“non-medical discharge”) then there was an increased risk of post-discharge mortality. This finding adds to the body of literature suggesting non-medical discharge (fleeing/absconding patients) are at

higher risk of mortality (19), a finding that was previously refuted by Moisi et al. (20).

Post-discharge mortality decreased with decreasing peripheral arterial haemoglobin oxygen saturation and haemoglobin concentration. Moisi et al. found no relationship between severe anaemia (low haemoglobin concentration) and post-discharge mortality in Kenya (20). Other studies showed anaemia to be an important independent predictor of mortality post-discharge (17) (19). A previous low-power study in The Gambia concluded that hypoxia during admission was not an important predictor of post-discharge mortality. Subsequent literature (20) has shown otherwise, attributing hypoxia an independent HR of 2.3 (95% CI: 1.64–3.23).

Moisi et al. tested axillary temperature as a possible risk factor, but failed to demonstrate an independent relationship with post-discharge mortality (20). This is the first evidence to show an independent and protective relationship of increasing axillary temperature.

This is the first study to show a relationship between season and post-discharge mortality. Although a previous study reported no effect of season on mortality (20), in this setting discharge during dry season increased risk of post-discharge mortality.

We showed decreased risk of post-discharge mortality with increasing age, but when analysed together with MUAC (in Model B) age became non-significant. Age has been shown to have a relationship with post-discharge mortality in other studies (15) (17) (19) (20) (31), with older children generally having better outcomes. The results from this study agree with the current literature that consistently shows no relationship between sex and post-discharge mortality in an African setting (16) (17) (18) (20), but this might be different in Asia, where females have poorer outcomes in some settings (31).

There was no independent effect of confirmed malaria (as detected by rapid diagnostic test) on post-discharge mortality; Phiri et al. showed malaria did not predict post-discharge mortality in a severely anaemic cohort (18), yet in a more diverse post-discharge cohort there was decreased risk of post-discharge mortality following admission associated with malaria (20). In a cohort with clinically diagnosed malaria, those with slide positive malaria had better post-discharge survival than those with negative slide findings (28).

This study did not confirm the findings from a previous study that length of admission, number of admissions (across the study period), laboratory confirmed bacteraemia have independent predictive relationships with post-discharge mortality (20).

Information on HIV status, jaundice, hepatomegaly were not available in this study, but these have been implicated as risk factors elsewhere (17) (18) (20).

5.3 Biological Plausibility of Findings and their Fit into Context

The suspected disease syndrome (i.e. type of invasive bacterial disease, either; pneumonia septicaemia or meninigitis) on admission predicted mortality following discharge. There is no evidence to suggest or refute that deaths may be due to early discharge following childhood illness or subclinical disease on discharge. It is conceivable that children are more frail and undernourished following a more severe infection (meningitis rather than pneumonia, for example) which may leave them vulnerable post-discharge. Neck stiffness, which is a sign of meningism and also proved to be strong predictor, might exert its influence on post-discharge mortality in a similar way. Hypoxia too is a sign of severe illness. Alternatively, or perhaps synergistically, following discharge the child may return and later succumb to the unfavourable environment responsible for their more severe illness in the first instance. For example, anaemia might have a direct physiological role in mortality, but may also be a marker for an unfavourable environment.

The addition of MUAC into Model B and the subsequent loss of significance of age at discharge as a risk factor may indicate that MUAC can measure combined risk of malnutrition and young age, rendering it a tool with very high clinical utility. Interestingly the trend of better nutritional status and decreasing risk of post-discharge mortality extended above the WHO cut-off for severe acute malnutrition of 11.5cm (40). Findings from this study support previous research that suggests malnutrition has an exponential effect on population child mortality and there is no threshold for this effect (43).

Discerning the relationship between nutritional status and post-discharge mortality is complex and needs to be the aim of further research. Underlying disease may precede malnutrition in the first instance (44) (45). Malnutrition dampens immune function and compounds HIV effects (46). Malnutrition may be a marker for lower socio-economic status and exposure to poorer social determinants of health. Admittedly treatment of the underlying cause of the malnutrition is important, but direct amelioration of a malnourished physiological state improves immune function (46) (47).

Inadequate or culturally insensitive medical treatment may increase discharge against medical advice (19) and this would lead to an obvious decline for a sick child. In this setting increasing axillary temperature was protective. Children unable to mount

a strong febrile response may be malnourished, immunosuppressed or moribund. A strong febrile immune response may be protective and anecdotally patients with very high fevers also attract more medical attention. Admissions with high axillary temperature and discharged during the wet month had better post-discharge outcomes, a possible indirect measurement of easily curable malaria parasitaemia observed elsewhere (20).

5.4 Strengths of this Study

This is one of the largest studies to date looking at child mortality following discharge from a health facility. It uncovered important risk factors, supports previous knowledge gained and also contributes new information to the field.

A majority of previous research in the field had limited generalisability. The cohort in this study, children discharged following admission for suspected pneumonia, meningitis or septicaemia, was diverse. Results from previous child mortality research in the Upper River Region, The Gambia have been considered generalisable (16) (22) and informed policy across Africa and the world.

All outpatient and inpatients in the study area were screened by a nurse for possible inclusion into the study. Clinical information was collected by physicians and nurses at point of care on standardised Case Report Forms (described in section 3.4.2). The population-based surveillance system allowed patient tracing in the community. Information was collected systematically and prospectively, limiting the introduction of bias during data collection. The cohort was representative with 7.8% of discharges lost due to data inconsistency or incompleteness.

5.5 Weaknesses of this Study

5.5.1 Information Bias

Diarrhoea is a major cause of childhood mortality and has been implicated as a risk factor for post-discharge mortality in some studies (19) but not others (20). Although information on diarrhoea was collected, children that had diarrhoea without signs consistent with signs of suspected pneumococcal disease would not have been included in the cohort. The same applies to other illnesses. Results and comparisons with other studies must be interpreted accordingly.

Microscopic detection, the gold standard for malaria diagnosis (48), was not available for the cohort. The parent study of this project in The Gambia is focused on

suspected invasive pneumococcal disease and there are clear indications for malaria testing. These may not be optimal for a purely malaria focused question. Some relationships observed could be proxy measurements of malaria infection (discussed above).

Of the 4053 discharges that were eligible for inclusion into the analysis, 318 (7.8%; including at least 23 known deaths) were excluded due to data incompleteness. Discharges excluded were younger, more wasted (weight-for-age z score) and had a different distribution of presentations (with less pneumonia-only more septicaemia-like syndromes). This possibly explains the high proportion of deaths in this group.

During risk factor analysis some variables (particularly from the BHDSS) had substantial amounts of missing data which may have attenuated or overlooked associations. For example total household income, maternal education and paternal education had 25%, 35% and 56% missing data, respectively.

5.5.2 Measurement Bias

The BHDSS collects population information for various different projects. The design and implementation is different to that of the PSP. The PSP is a well-resourced system where most of the real time information is elicited and collected by trained nurses (often the best in the country) and physicians. Fieldworkers (usually graduates of secondary school) with basic numeracy and literacy elicit most of the BHDSS information, but at times events like births and deaths require recall, leading to an element of imprecision. This imprecision may attenuate relationships.

5.5.3 Analytical Bias

Although Cox proportional hazards modelling is the analysis method of choice in previous literature (20) (28), there are other techniques to analyse time-to-death (survival) data (19), each with their own strengths and weaknesses (49)

5.5.4 Confounding

Previous research has highlighted potential confounders that we do not have data for (e.g. HIV status), and others that we have poor data for (e.g. maternal education).

Birth information such as prematurity or LBW was not available, but may be important for mortality post-discharge (32) (30). HIV statistics in the The Gambia are largely unknown, especially for children, but adult estimates are estimated to be low (50). Similarly, HIV status of the cohort was unknown, but HIV may influence post-discharge survivorship (17) (18).

CHAPTER 6 – CONCLUDING CHAPTER

This chapter summarises the project in section 6.1 and further states the implications of the findings for practice and future research in section 6.2

6.1 Summary

Child mortality needs to be curtailed more quickly to reach Millennium Development Goal 4. Children were at increased risk of mortality post-discharge following admission for suspected pneumonia, meningitis and septicaemia in this rural West African setting (Upper River Region, The Gambia). Of the deaths that occurred following admission, two thirds died during admission and one third of children died post-discharge. Most of the post-discharge deaths occurred within 45 days.

With two multivariable models, this study uncovered novel and reaffirmed previous risk factors for post-discharge child mortality. Model A showed younger children that presented with visible signs of severe malnutrition had poorer outcomes post-discharge, particularly if they have a more severe provisional diagnosis on admission. Older children with a provisional diagnosis of pneumonia without visible signs of severe malnutrition fared the best outcome post-discharge. Model B showed predictors that can be used to develop a tool to identify those at high risk of post-discharge mortality. Neck stiffness on admission, low MUAC, visible signs of severe malnutrition, non-medical reason for discharge, discharge during the dry season, decreasing axillary temperature, decreasing peripheral arterial haemoglobin haemoglobin concentration, decreasing oxygen saturation were associated with increased risk of post-discharge mortality.

6.2 Implications for Practice

It is clear that post-discharge child mortality is important in a rural West African setting, particularly in the first few weeks following discharge. This relatively neglected group of children deserve more attention. Physician- and nurse-led inquiry into child health following discharge will explain relationships further. With better clinical record keeping and better reporting of deaths in the community, more situations can be investigated and more lessons learned.

In a rural African setting where access is already difficult (51), every opportunity to maximise interactions and outcomes with healthcare providers should be taken. The body of literature is slowly growing to assist healthcare workers identify high risk

children and their families that might need extra attention. Preventative interventions may include nutritional rehabilitation in the community, prophylactic chemotherapy for possible subsequent infections or even counselling parents when to seek help and more intensive follow-up of high-risk children.

6.3 Unanswered Questions/Future Research

Future research should focus on the following:

1) Completing missing information, particularly socioeconomic variables from the BHDSS and retrieving the 7% that were lost due to data inconsistency.
2) Analysing community population data for population attributable risk.
3) Finding prevalence of risk-factors for post-discharge mortality in the general population. Are post-discharge risk-factors also prevalent in the community at large, warranting a community intervention rather than clinical?
4) Collecting verbal autopsies to identify the causes of post-discharge mortality.
5) Developing the cut-points for continuous variables in the multiple variable models that best predict post-discharge mortality.
6) Developing a scoring system and a screening tool with clinical utility to identify individuals at highest risk.
7) Determining the median time to death for each preliminary diagnosis?
8) Whether MUAC is a measure of vulnerability. Can it account for age and level of malnutrition? MUAC will have high clinical utility in settings where it is difficult to ascertain patient age.
9) Conducting large studies to show that relationships are consistent and coherent in other settings whilst ensuring data is collected on all possible confounders.
10) Although the issue of post-discharge child mortality is important and predictable... is it preventable in this low-resource setting?
11) Which intervention will best prevent post-discharge mortality?

APPENDICES

Appendix I. Pneumococcal Surveillance Project Case Report Form 1 and 2

Form 1 and 2 – Screening of children under 5 years *Pneumococcal Surveillance Project, The Gambia*

Form 1 - Demographic Information

1.01 Surveillance Number : 0 6 - 0 5 - 1 0 1.02 Age (In Days <60) 1.03 Age (In Months 2 to 59)

1.05 Name (First name Second name Surname) 1.06 Sex (Male =1, Female=2)

1.07 Mother's name (First name Second name Surname) 1.08 Village code (ND=99)

1.09 Household head (First name Second name Surname)

1.10 Directions to house/ local contact person

1.11 Is patient resident in BHDSS area? (Y=1, N=2) 1.12 Village name (ND=99)

1.13 Basse HDSS ID (ND=99) 1.14 Health card No (ND=99)

1.15 Date of birth known? (Y=1, N=2) 1.16 If Y, date of birth (DD/MM/YY)

1.17 PCV1(Y=1,N=2,ND=99) 1.18 Date 1.19 PCV2 1.20 Date

1.21 PCV3 1.22 Date 1.23 PCV4 1.24 Date

1.25 Signed 1.26 ID

Form 2 - Screening criteria for children under 5 years (and at least 2 months)

2.01 How long has patient been unwell? (days) 2.02 Screened at: Basse clinic=1, Gambissara=2, Fatoto=3, Garawol=4, Damba Kunda=5, Koina=6, Basse ward=7, Other=9

Part A Is there a history of any of the following? (Yes=1, No=2)

2.03 Cough 2.04 Difficulty breathing

2.05 Unable to sit (if usually able) 2.06 Unable to drink / or to breastfeed

2.07 Fever 2.08 Diarrhoea

2.09 Irritability 2.10 Convulsion

Part B Are any of the following present? (Yes=1, No=2)

2.11 Grunting 2.12 Lower chest wall indrawing

2.13 Nasal flaring 2.14 Lethargy

2.15 Bulging fontanelle 2.16 Neck stiffness

2.17 Musculoskeletal swelling or tenderness

Part C Record the following observations:

2.18 Axillary Temperature °C 2.19 Pulse Rate (/min) 2.20 Oxygen Saturation (%) 2.21 Respiratory Rate (/min)

2.22 Above resp rate for age (Y=1, N=2) 2.23 Weight (kg) 2.24 Weight below -3z score for age? (Y=1,N=2) 2.25 Height/Length (cm)

2.26 Mid upper arm circumfer. (cm) 2.27 AVPU Score (Alert=4, responds to Voice=3, Pain=2, Unresponsive=1) 2.28 Antibiotic/s taken in the previous week? (Yes=1, No=2, ND=99)

2.29 If Y, name/s of antibiotic/s? 1 2.30 Route (1=po, 2=iv, 3=other)

2.31 2 2.32 Route (1=po, 2=iv, 3=other)

2.33 Antibiotic given in clinic before referral (Y=1, N=2) 2.34 If Y, time (24H)

2.35 Blood culture taken (Yes=1, No=2) 2.36 If Y, BC before antibiotic (Yes=1, No=2) 2.37 Malaria test done (Yes=1, No=2) 2.38 If Y, test result (Positive=1, Negative=2, ND=99)

2.39 Haematocrit test (Yes=1, No=2) 2.40 If haematocrit, result (Circle if % or g/dL) 2.41 Does the patient have suspected meningitis? (Yes=1, No=2)

2.42 Does patient meet screening criteria? (Y=1, N=2) 2.43 Patient for referral (Y=1, N=2) 2.44 Referral plan? (Now=1, Declined=2, No transport=3, Mx o'night=4, Admit=5)

2.45 Signed 2.46 ID 2.47 Date (DD/MM/YYY) 2.48 Time (24H)

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DSS ID

OK FOR DATA ENTRY (ID NO) (D D/M M/Y Y) DATA ENTRY 1 COMPLETE (ID NO) (D D/M M/Y Y) DATA ENTRY 2 COMPLETE (ID NO) (D D/M M/Y Y) OK TO FILE (ID NO) (D D/M M/Y Y)

Form 1&2 PSPv4 12_29Jan10

Appendix II. Pneumococcal Surveillance Project Case Report Form 4

Form 4 - Assessment of children under 5 years ***Pneumococcal Surveillance Project, The Gambia***

4.01 Surveillance Number ☐☐☐—☐☐☐—☐☐ **4.02** Patient location (Outpatient=1, Inpatient=2) ☐

4.03 Does the patient meet screening criteria? (Yes=1, No=2) ☐ **4.04** If No, reason ☐
(Non-DSS res=1, Enrolled PSP last 14 days=2, other=3)

4.05 Patient admitted in last 14 days? ☐

Part A **Is there a history of the following?** (Yes=1, No=2)

4.06 Cough ☐ **4.07** Difficulty breathing ☐ **4.14** Other notes:

4.08 Irritability ☐ **4.09** Unable to drink/breastfeed ☐

4.10 Convulsion ☐ **4.11** Unable to sit, if usually able ☐

4.12 Fever ☐ **4.13** Diarrhoea ☐

4.15 Resp. rate /min ☐☐☐ **4.16** Pulse Rate /min ☐☐☐

4.17 Rash (no=1, petechial=2 purpuric=3, other=4) ☐ **4.18** Clinical severe malnutrition (Yes=1,No=2) ☐

4.19 AVPU (A=4, V=3, P=2, U=1) ☐ **4.20** Blantyre Coma Score (0 to 5) ☐

4.21 Oxygen saturation ☐☐☐ %

Part B **On examination is the following present?** (Yes=1, No=2)

4.22 Grunting ☐ **4.23** Lower chest wall indrawing ☐

4.24 Nasal flaring ☐ **4.25** Crackles on auscultation ☐

4.26 Wheeze ☐ **4.27** Bronchial breathing ☐

4.28 Lethargy ☐ **4.29** Musculoskeletal swelling or tenderness ☐ **4.30** Bulging fontanel ☐

4.31 Neck stiffness ☐ **4.32** Ear discharge ☐ **4.33** Dull percussion note ☐

4.34 Suspected surveillance diagnosis (Pneumonia=1, Meningitis=2, Septicaemia=3, Other focal sepsis=4, Pneumococcal disease not suspected=5, Pneumonia & Meningitis=6, Pneumonia & Septicaemia=7, Meningitis & Sepsis=8, Pneumonia & Meningitis & Septicaemia=9) ☐

4.35 Other diagnoses 1. ☐ **4.36** 2. ☐ **4.37** 3. ☐

4.38 Key clinical findings if sepsis/meningitis <2 mo 1. ☐ **4.39** 2. ☐ **4.40** 3. ☐

Part C **Investigations Ordered** (Yes=1, No=2, Unable to investigate=9)

4.41 Chest X-Ray ☐ **4.42** Lung Aspirate ☐ **4.43** Blood culture ☐

4.44 CSF Culture ☐ **4.45** Pleural aspirate ☐ **4.46** CRP ☐

4.47 Haematocrit ☐ **4.48** If haematocrit, result (Circle if % or g/dl) ☐☐ **4.49** Antibiotic activity detection ☐

4.50 Rapid malaria test ☐ **4.51** If Y, result (pos=1, neg=2, ND=99) ☐ **4.52** If other test, specify ☐ **4.53** If CXR, BC, or CSF required but not collected, why not? ☐/☐

4.55 Antibiotic received in previous week? (Yes=1, No=2, unknown=3) ☐

(no electricity=1, faulty X-ray=2, no X-ray tech=3, no vein seen=4, venepuncture unsuccessful=5, BC consent declined=6, BC declined=7, LP unsuccessful=8, LP contraindicated=9, LP declined=10, other=11)

4.56 If Yes, 1 ☐ **4.57** Route (1=po, 2=iv, 3=oth) ☐

4.58 2 ☐ **4.59** Route ☐

4.60 To be admitted? (Yes=1, No=2) ☐ **4.54** If other, specify ☐

4.61 Signed ☐ **4. 62** ID ☐☐☐ **4.63** Date ☐☐☐☐☐☐ **4.64** Time (24 H) ☐☐☐☐

NB: *If suspected pneumonia, septicaemia, or other pneumococcal infection, complete outcome form & request forms.*

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OK FOR DATA ENTRY		DATA ENTRY 1 COMPLETE		DATA ENTRY 2 COMPLETE		OK TOFILE	
(ID NO)	(D D / M M / Y Y)	(ID NO)	(D D / M M / Y Y)	(ID NO)	(D D / M M / Y Y)	(ID NO)	(D D / M M / Y Y)
☐☐☐	☐☐☐☐☐☐	☐☐☐	☐☐☐☐☐☐	☐☐☐	☐☐☐☐☐☐	☐☐☐	☐☐☐☐☐☐

Form 4 PSPv4.10_24May09.doc

Appendix III. Pneumococcal Surveillance Project Case Report Form 6

Form 6- Clinical Outcome

Pneumococcal Surveillance Project, The Gambia

Part A *(Complete if suspected pneumococcal disease)*

6.01 Surveillance Number ___ — ___ — ___ **6.02** Age (In Days <60) ___ **6.03** Age (In Months 2 to 59) ___

6.05 Name *First name* **6.04** Age (In Years, if 5 years or greater) ___

6.06 Sex (Male=1, Female=2) ___ **6.07** Antibiotic/s prescribed/administered? (Yes=1, No=2) ___

6.08 Time 1st dose antibiotics (24 HR, ND=99) ___ **6.09** If Y, which ___ **6.10** Route (1=po,2=iv,3=oth) ___

6.11 antibiotic/s? ___ **6.12** Route (1=po,2=iv,3=oth) ___

6.13 Date of assessment: (DD/MM/YY) ___ **6.14** Signed ___ **6.15** ID ___

Part B *(To be completed at separation of patient from Basse HC)*

1. Penicillin 6. Tetracycline 11. Amoxicillin
2. Ampicillin 7. Co-trimoxazole 12. Chloroquine
3. Cloxacillin 8. Ciprofloxacin 13. Quinine
4. Chloramph 9. Erythromycin 14. Artem/Lum
5. Ceftriaxone 10. Gentamicin 15. Other specify

6.16 Type of separation (Not admitted=1, Discharge following admission=2, Transfer=3, Died=4, ND=99) ___

6.17 Date of separation (DD/MM/YY) ___

6.18 Was antimicrobial therapy changed during admission? (Yes=1, No=2, ND=99) ___ **6.19** If yes, reason for change (Sensitivity result=1, Organism isolated=2, Failure to improve=3, Other=4, ND=99) ___

6.20 Other antimicrobials administered during admission? (Yes=1, No=2, ND=99) ___ **6.21** If yes, specify, 1. ___ **6.22** 3. ___ **6.23** 2. ___ **6.24** 4. ___

6.25 If discharge after admission, discharged against advice? (Yes=1, No=2, ND=99) ___

6.26 If discharge after admission, outcome (Recovering=1, Persistent abnormality=2, ND=99) ___ **6.27** If persistent abnormality, specify ___

6.28 If transferred, to which health facility? (Bansang=1,RVTH=2, Other=3, ND=99) ___ **6.29** If other, specify ___

6.30 If died, date of death (DD/MM/YY) ___ **6.31** Time of death (24H) ___

List of possible diagnoses:

0. No diagnosis identified	9. Bronchiolitis	18. Dysentery	27. Pericarditis	36. Skin Infection/ Boil/Pustules
1. Abdominal pain	10. Cerebral palsy	19. Glomerulonephritis	28. Malnutrition	37. Tetanus
2. Abscess	11. Cholera	20. HIV	29. Trauma	38. Tuberculosis - pulmonary
3. Acute Gastroenteritis	12. Chronic Discharging Ear	21. Measles	30. Malaria	39. Tuberculosis - extrapulmonary
4. Acute Otitis Media	13. Chronic Gastroenteritis	22. Meningitis,	31. Urticarial rash	40. Jaundice
5. Pneumonia	14. Bronchiectasis	23. Nephrotic syndrome	32. Heart failure	41. Chicken pox
6. Anaemia	15. Chronic Viral Infection	24. Osteomyelitis,	33. Worms	42. Congenital malformation
7. Anaphylactic Shock	16. Conjunctivitis	25. Panophthalmitis	34 Sepsis,	43. URTI
8. Asthma	17. Diabetes	26. Peritonitis	35 Septic arthritis	44. Other 45. Unknown

6.32 Primary diagnosis precipitating admission / treatment (1 to 45 from list above) ___ **6.33** If any other, specify ___

6.34 1st underlying diagnosis contributing to death / morbidity (1 to 45 from list above) ___ **6.35** If other, specify ___

6.36 2nd underlying diagnosis contributing to death / morbidity (1 to 45 from list above) ___ **6.37** If other, specify ___

6.38 Primary diagnosis at discharge (1 to 45 from list above) ___ **6.39** If other, specify ___

6.40 Date of review: (DD/MM/YY) ___ **6.41** Signed ___ **6.42** ID No ___

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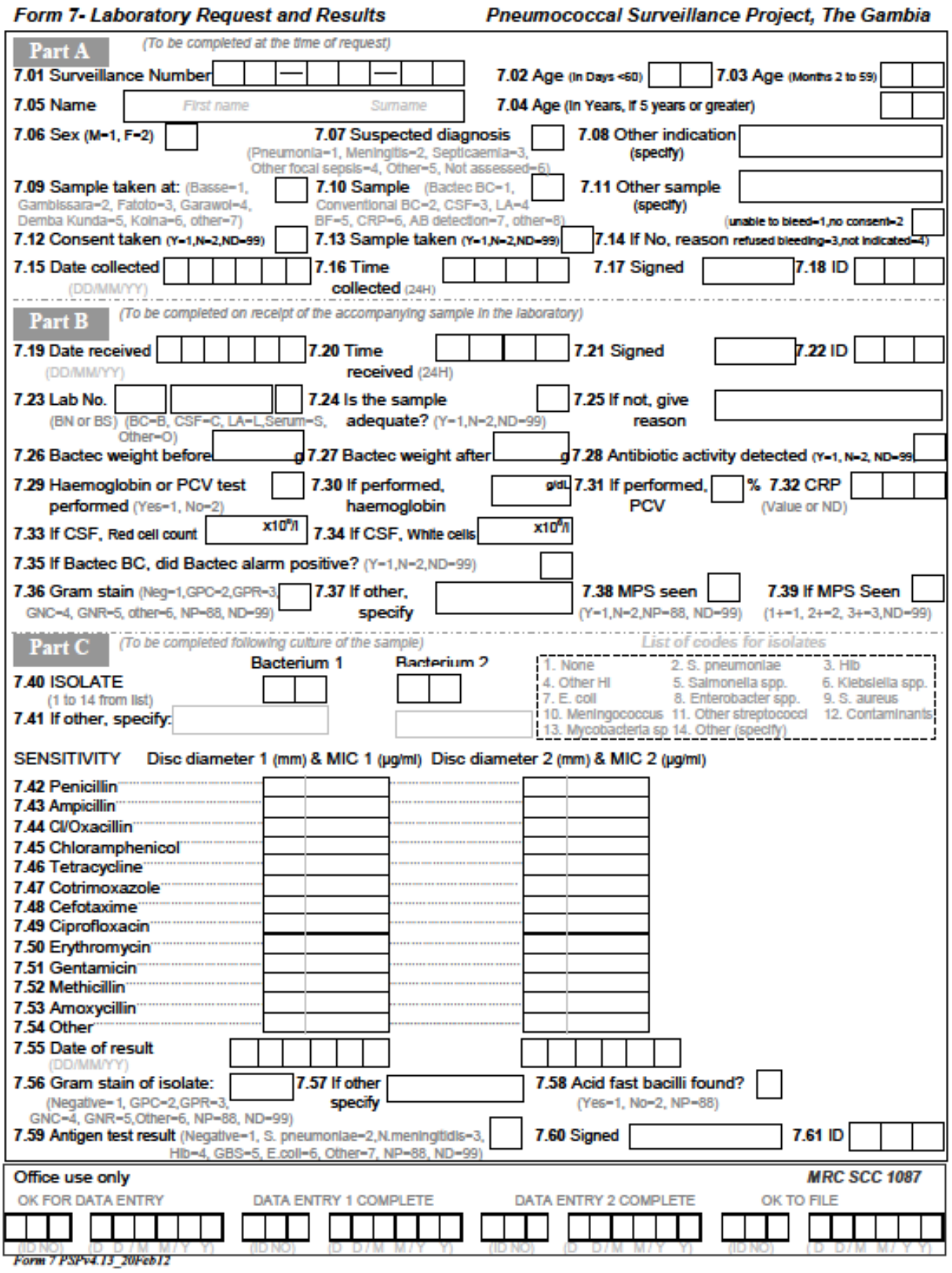
OK FOR DATA ENTRY		DATA ENTRY 1 COMPLETE		DATA ENTRY 2 COMPLETE		OK TO FILE	
(ID NO)	(D D / M M / Y Y)	(ID NO)	(D D / M M / Y Y)	(ID NO)	(D D / M M / Y Y)	(ID NO)	(D D / M M / Y Y)

Form 6 PSPv4.9_3Jul09.doc

Appendix IV. Pneumococcal Surveillance Project Case Report Form 7



Form 7- Laboratory Request and Results ***Pneumococcal Surveillance Project, The Gambia***

Part A *(To be completed at the time of request)*

7.01 Surveillance Number ___ ___ — ___ ___ — ___ ___ **7.02** Age (In Days <60) ___ ___ **7.03** Age (Months 2 to 59) ___ ___

7.05 Name First name Surname **7.04** Age (In Years, if 5 years or greater) ___ ___

7.06 Sex (M=1, F=2) ___ **7.07** Suspected diagnosis (Pneumonia=1, Meningitis=2, Septicaemia=3, Other focal sepsis=4, Other=5, Not assessed=6) ___ **7.08** Other indication (specify)

7.09 Sample taken at: (Basse=1, Gambissara=2, Fatoto=3, Garawol=4, Demba Kunda=5, Koina=6, other=7) ___ **7.10** Sample (Bactec BC=1, Conventional BC=2, CSF=3, LA=4 BF=5, CRP=6, AB detection=7, other=8) ___ **7.11** Other sample (specify)

7.12 Consent taken (Y=1,N=2,ND=99) ___ **7.13** Sample taken (Y=1,N=2,ND=99) ___ **7.14** If No, reason refused bleeding=3,not indicated=4 (unable to bleed=1,no consent=2 ___

7.15 Date collected (DD/MM/YY) ___ ___ ___ ___ ___ ___ **7.16** Time collected (24H) ___ ___ ___ ___ **7.17** Signed ___ **7.18** ID ___ ___ ___

Part B *(To be completed on receipt of the accompanying sample in the laboratory)*

7.19 Date received (DD/MM/YY) ___ ___ ___ ___ ___ ___ **7.20** Time received (24H) ___ ___ ___ ___ **7.21** Signed ___ **7.22** ID ___ ___ ___

7.23 Lab No. (BN or BS) ___ ___ ___ (BC=B, CSF=C, LA=L,Serum=S, Other=O) **7.24** Is the sample adequate? (Y=1,N=2,ND=99) ___ **7.25** If not, give reason

7.26 Bactec weight before ___ g **7.27** Bactec weight after ___ g **7.28** Antibiotic activity detected (Y=1, N=2, ND=99) ___

7.29 Haemoglobin or PCV test performed (Yes=1, No=2) ___ **7.30** If performed, haemoglobin ___ g/dL **7.31** If performed, PCV ___ % **7.32** CRP (Value or ND) ___ ___ ___

7.33 If CSF, Red cell count ___ x10⁶/l **7.34** If CSF, White cells ___ x10⁶/l

7.35 If Bactec BC, did Bactec alarm positive? (Y=1,N=2,ND=99) ___

7.36 Gram stain (Neg=1,GPC=2,GPR=3, GNC=4, GNR=5, other=6, NP=88, ND=99) ___ **7.37** If other, specify ___ **7.38** MPS seen (Y=1,N=2,NP=88, ND=99) ___ **7.39** If MPS Seen (1+=1, 2+=2, 3+=3,ND=99) ___

Part C *(To be completed following culture of the sample)*

List of codes for isolates

1. None	2. S. pneumoniae	3. Hib
4. Other HI	5. Salmonella spp.	6. Klebsiella spp.
7. E. coli	8. Enterobacter spp.	9. S. aureus
10. Meningococcus	11. Other streptococci	12. Contaminants
13. Mycobacteria sp	14. Other (specify)	

	Bacterium 1	Bacterium 2	Disc diameter 1 (mm) & MIC 1 (µg/ml)	Disc diameter 2 (mm) & MIC 2 (µg/ml)
7.40 ISOLATE (1 to 14 from list)	___ ___	___ ___		
7.41 If other, specify:				
7.42 Penicillin				
7.43 Ampicillin				
7.44 Cl/Oxacillin				
7.45 Chloramphenicol				
7.46 Tetracycline				
7.47 Cotrimoxazole				
7.48 Cefotaxime				
7.49 Ciprofloxacin				
7.50 Erythromycin				
7.51 Gentamicin				
7.52 Methicillin				
7.53 Amoxycillin				
7.54 Other				
7.55 Date of result (DD/MM/YY)			___ ___ ___ ___ ___ ___	___ ___ ___ ___ ___ ___

7.56 Gram stain of isolate: (Negative=1, GPC=2,GPR=3, GNC=4, GNR=5,Other=6, NP=88, ND=99) ___ **7.57** If other specify ___ **7.58** Acid fast bacilli found? (Yes=1, No=2, NP=88) ___

7.59 Antigen test result (Negative=1, S. pneumoniae=2,N.meningitidis=3, Hib=4, GBS=5, E.coli=6, Other=7, NP=88, ND=99) ___ **7.60** Signed ___ **7.61** ID ___ ___ ___

Office use only **MRC SCC 1087**

OK FOR DATA ENTRY		DATA ENTRY 1 COMPLETE		DATA ENTRY 2 COMPLETE		OK TO FILE	
(ID NO)	(D D/M M/Y Y)	(ID NO)	(D D/M M/Y Y)	(ID NO)	(D D/M M/Y Y)	(ID NO)	(D D/M M/Y Y)
___ ___ ___	___ ___ ___ ___ ___ ___	___ ___ ___	___ ___ ___ ___ ___ ___	___ ___ ___	___ ___ ___ ___ ___ ___	___ ___ ___	___ ___ ___ ___ ___ ___

Form 7 PSPv4.13_20Feb12

Appendix V: Letter of Ethical Approval

The Gambia Government/MRC Joint
ETHICS COMMITTEE

C/o MRC Unit: The Gambia, Fajara
P. O. Box 273, Banjul
The Gambia, West Africa
Fax: +220 – 4495919 or 4496 513
Tel: +220 – 4495442-6 Ext. 2308

02 October 2012

Mr Aakash Chhibber
Medical Student
Basse Field Station

Dear Mr Chhibber

L2012.41, A sub-analysis using data from the Pneumococcal Surveillance Project (SCC 1087)

Thank you for submitting your letter dated 20 August 2012 for consideration by the Gambia Government/MRC Joint Ethics Committee at its meeting held on 28 September 2012.

The Committee reviewed your request to use data collected by the ongoing Pneumococcal Surveillance Project to conduct a sub-analysis for your BSc thesis.

Members were pleased to approve your request.

With best wishes

Yours sincerely

Mr Malcolm Clarke
Chairman, Gambia Government/MRC Joint Ethics Committee

Additional documents submitted for review:-

- N/A

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