The Effect of low birth weight on timing to BCG vaccination in a rural district of Northern Ghana

By

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Declaration

I, Emmanuel Yidana Ayamba (AYMEMM001), hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, is to be submitted for another degree in this or any other university.

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Thesis Abstract

Introduction: Early Bacille Calmette-Guérin (BCG) vaccination of low birthweight (LBW) infants has been shown to have heterologous immunological effects by increasing the in vitro cytokine responses which contribute to the maturation of the infant immune system and thereby protecting against fatal infections in the neonatal period. It has been noted to also reduce neonatal mortality in these LBW infants. In some low-income countries, BCG vaccination is usually postponed for children born with a low birthweight (LBW). This has resulted in delayed timing to BCG vaccination. Ghana, however, does not have any restrictions on receiving BCG vaccination for LBW infants. This study therefore assessed the effects of low birthweight on timing to BCG vaccination in a context where there are no restrictions on vaccinations.

Methods: The study used maternal and child health data collected from the Navrongo Health and Demographic Surveillance System (NHDSS). Age at BCG vaccination was the main outcome variable of interest whilst the weight at birth of the child was the main primary exposure variable. Frequencies, proportions, median and inter-quartile ranges (IQR) were used to describe the participants. Lognormal accelerated failure time (AFT) models were conducted, and time ratios obtained to assess the effect of birthweight on timing to BCG vaccination. Logistic regression models were also used to assess the factors associated with delays to BCG vaccination.

Results: About 12% of the infants were low birthweights (less than 2500 grams) with 17% weighing less than 2000 grams and 83% weighing between 2000 and 2490 grams. The results showed than low birth weight infants had a median vaccination age of 2 days compared with normal birth weight (≥2500 grams) infants who had a median of 3 days. No statistically significant difference in time to BCG vaccination by birthweight status was observed. However, other

characteristics which were statistically significantly associated with time to BCG included level of education of mother, place of delivery, socio-economic status of family and the age of mother.

Conclusions: The study shows that low birthweight infants in the study area receive BCG vaccination as timely as normal birthweight infants with several maternal and infant characteristics as well as socio-demographic and health system factors been associated with the timing. It demonstrates that low birthweight infants can receive BCG vaccination on time if there are no restrictions regarding vaccination schedules.

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To all my lectures and professors in the school of Public Health, I say thank you for the knowledge your impacted on me. God bless you all.

I would like to dedicate this mini dissertation to Late sister, Patience Ayamba, for your advice and encouragement throughout my career. I wish you lived longer to be able to read this.

List of Abbreviations

WHO	World Health Organization
TB	Tuberculosis
BCG	Bacille Calmette-Guérin
LBW	Low birthweight
NHDSS	Navrongo Health and Demographic Surveillance System
AFT	Accelerated Failure Time
CHPS	Community Health Planning and Services

Thesis Organization

Part A: The study protocol was submitted for departmental and ethical approvals and contains the background, objectives, and methodology for this Masters in Public Health mini-dissertation.

Part B: The journal-ready manuscript is presented according to the author guidelines for the BMC Global Health

Part C: The appendices include all additional documentation necessary for the presentation of the Masters in Public Health mini-dissertation.

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PART A: PROTOCOL

The Effect of low birth weight on timing to BCG vaccination in a rural district of Northern Ghana

Introduction

Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, continuous to be a public health concern globally. About one-quarter of the world's population are estimated to be infected with M. tuberculosis and 5–15% of these individuals will develop active TB during their lifetime.[1] In children, TB occurs most commonly in those aged less than five (5) years. Infants and young children (especially those aged less than two years) are at risk of developing severe disseminated disease associated with a high rate of mortality. Childhood TB is, therefore an indicator of ongoing transmission of M. tuberculosis in the general population.[2]

Efforts to control the spread of M. tuberculosis and to prevent TB-related morbidity and mortality is therefore necessary. Vaccination is one component of the integrated, patient-centred care and prevention strategy adopted by the World Health Organization (WHO) in preventing TB.[3] The Bacille Calmette-Guérin (BCG) vaccine has been recommended to be given to all healthy neonates at birth or as soon as possible after birth in countries or settings with high incidence of Tuberculosis.[4] BCG is one of the most widely used current vaccines on neonates and infants in countries where it is part of the national childhood immunization program. It has a documented protective effect against meningitis and disseminated TB in children.[5, 6] It is also known to provide non-specific benefits such as reducing neonatal mortality and infectious diseases.[7-9] A randomized control trial by Prentice et al noted a 25% reduction in episodes of physician-

diagnosed non-tuberculosis infections in the first week of life among infants who received BCG at birth compared to infants who received BCG after six weeks of age.[10]

Benefits of early BCG vaccination among low birthweight (LBW) infants have been noted in some observational studies and randomized controlled trials. Early BCG vaccination of LBW infants has heterologous immunological effects by increasing the in vitro cytokine responses which contribute to the maturation of the infant immune system and, thereby, protecting against fatal infections in the neonatal period.[11-13] Again, it has been noted to also reduce neonatal mortality in these low birth weight infants. Some studies have noted that the earlier BCG is given to an infant, the higher the chances of survival.[10, 14, 15] Other studies have documented no negative effects on infant growth when infants with low birth weight are vaccinated with BCG very early in life.[10, 16, 22]

Delays in BCG vaccination has been reported to have an increased risk of infections at infancy due to the shortening of the duration of the protective effect of the vaccine. Delayed BCG vaccination has also been recognized as an important indicator of the overall quality of the vaccine and has effects on vaccination coverage.[17]

That notwithstanding, several low-income countries usually postpone BCG vaccination in children born with LBW. This has resulted in delayed timing to BCG vaccination for LBW infants. For instance, in Kenya, pre-term and LBW infants (birthweight less than 2000 grams) receive BCG at the time of discharge from hospital.[18]

However, in other countries such as Ghana, there is no recommendation to delay BCG vaccination of LBW infants.

In addition, several factors have been reported to be associated with incomplete childhood vaccinations. Some studies have classified these factors into child and maternal characteristics and socio demographic factors.[19, 20] Less information is, however, known about the factors associated with delays to vaccinations.

This study will, therefore, seek to assess the effects of low birth weight on timing to BCG vaccination and to examine the factors associated with delay to BCG vaccination in a context where there are no restrictions on vaccinating low birthweight infants.

Objectives of the Study

The overall aim of the study is to assess the effects of LBW on timeliness to BCG vaccination in a rural district in Northern Ghana. Specifically, the study seeks to:

1. assess the effect of LBW on timing to BCG vaccination.
2. examine the factors associated with delay to BCG vaccination.
3. determine the median BCG vaccination age from 2012 to 2018.

Methods

a) Study Design

A retrospective secondary data analysis of infants born from 2012 to 2018 will be conducted to assess the effects of LBW on timeliness of BCG vaccination.

b) Study Setting

The study will be conducted in the Kassena-Nankana East municipal and Kassena-Nankana West district in the Upper East region of northern Ghana with an estimated population of 160 000 under

continuous demographic surveillance. The study area covers a land area of 1675 km2 and lies between latitude 10.30^0 and 11.10^0 north and longitude 1.10^0 west close to the Burkina Faso border. The area is characterized by Guinea Savannah vegetation with a short rainy season and a prolonged dry season from October to March. The mean annual rainfall is ~1300 mm with the heaviest usually occurring in August.[21] The area has two referral district hospitals and eight health centres. In addition, there are 57 community health compounds with resident community health officers providing door-to-door health services to the people.

c) Study population and data collection

The study will use maternal and child health data collected from the Navrongo Health and Demographic Surveillance System (NHDSS). The NHDSS monitors demographic and health changes of all persons and households in the Kassena-Nankana east and west districts. Trained field workers visit compounds every 4 to 6 months and interview heads of households using a compound registration book (CRB) which contains basic information of all individuals in a household. Where a new event is recorded, the CRB is filled to provide detailed information about that particular event. The data collection process also includes the community key informant system where individuals are selected by their respective communities and given some training by the research team to report events, such as pregnancies, births and child deaths (deaths to children aged <12 years). This complements the routine data collection machinery by recording in a timely manner, events that may occur after a fieldworker has passed a particular location during his or her routine rounds.

Data collected include pregnancies, live and stillbirths, morbidity, deaths, in- and out-migrations, childhood vaccinations and verbal autopsy on all deaths, educational status, marriage, religion and national health insurance coverage as well as socio-economic characteristics.

Ethical consideration embarked by the NHDSS team includes consultations and partnership building with a wide range of stakeholders, including government and community members. Extensive community engagement activities, such as radio programmes or community meetings are used to sensitize the communities on the activities of the HDSS whilst consent for routine data collection is obtained at the household level.

All infants born from 2012 to 2018 will be eligible for inclusion in this study.

d) Sample size

All infants born from 2012 to 2018 with a birth weight and BCG vaccination recorded will be eligible. About 2000 infants per year are estimated to have records of both BCG vaccination and birth weight. This makes the estimated sample size for the study to be about 14000.

e) Variables of Interest

Age at BCG vaccination will be the main outcome variable of interest whilst the weight at birth of the child will be the main primary exposure variable. Birth weight will be categorized into low and normal birth weight for infants weighing less than 2500 grams and more or equal to 2500 grams respectively. Low birth weight will be further classified into those weighing below 2000 grams and those weighing 2000 to less than 2500 grams. Variables such as maternal age and education, ethnicity, religious affiliation, birth order of infant, sex, will be explored to determine their association with timing to BCG vaccination. Demographic characteristics such as place of

residence, place of delivery and socioeconomic status of the family will be explored to determine their association with delays in uptake of BCG vaccination.

f) Data Processing and Analysis

Descriptive statistics such as means, standard deviations, median and inter-quartile ranges will be reported for numerical variables depending on the distribution of the variables whilst frequencies will be reported for categorical variables. Survival analysis techniques will be used to assess the time to BCG vaccination. Kaplan-Meier curves will used to describe the age distribution of getting BCG for the three birth weight groups. Based on results from Kaplan-Meier curves, a cox regression or a parametric regression model will be fitted to assess the association between LBW and time to BCG vaccination. Factors associated with delays to BCG vaccination will also be evaluated using binary logistic regression models. Infants who receive BCG vaccination from birth to 4 weeks of age will be considered to be not delayed whilst those who received BCG vaccination more than 4 weeks of age will be considered to have delayed [19]. All statistical analyses will be conducted using STATA version 17.0.

g) Ethical Considerations

Ethical approval will be sought from the University of Cape Town Human Research Ethics Committee and the Navrongo Health Research Centre Institutional Review Board. These are review boards who guarantee participants safety in studies.

h) Risk and benefits

There will be no direct benefits for participation. Participants will not be paid in any form. This study is a low-risk study as it will only involve the use of secondary data and will not require the direct participation of any individuals.

i) Confidentiality

Unique identification numbers will be assigned to all participants to ensure confidentiality of the participants. The data will only be stored and backed-up in a database accessible to the researchers.

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PART B: JOURNAL MANUSCRIPT

The Effect of low birth weight on timing to BCG vaccination in a rural district of Northern Ghana: a cross-sectional study

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As per the MPH dissertation guidelines, co-authors are not listed on the journal ready manuscript. The contribution of collaborators and supervisors is listed in the acknowledgments section of this dissertation. This article is written according to the requirements in the Instructions for Authors for BMC Global Health Research and Policy. These instructions are included as Appendix 4.

Abstract

The World Health Organization (WHO) recommends that Bacille Calmette-Guérin (BCG) vaccine be given to all healthy neonates at birth or as soon as possible after birth in countries or settings with high incidence of Tuberculosis. In some low-income countries, BCG vaccination is usually postponed for children born with a low birthweight (LBW). This has resulted in delayed timing to BCG vaccination for LBW infants as witnessed in several low-income countries. However, there is no recommendation to delay BCG vaccination of LBW infants in Ghana. This study therefore assessed the effects of low birthweight on timing to BCG vaccination in a context where there are no restrictions on vaccinations.

A retrospective secondary data analysis of infants born from 2012 to 2018 in the Kassena-Nankana Districts of Ghana was conducted. A total of 18003 participants were included in the analysis. Lognormal accelerated failure time (AFT) model was used to assess the effect of low birth weight on timing to BCG vaccination.

About 12% of the infants were low birthweights (less than 2500 grams) with 17% weighing less than 2000 grams and 83% weighing between 2000 and 2490 grams. The results showed that low birth weight infants had a median vaccination age of 2 days compared with normal birth weight (≥2500 grams) infants who had a median of 3 days. No statistically significant difference in time to BCG vaccination by birthweight status was observed. However, other characteristics which were statistically significantly associated with time to BCG included level of education of mother, place of delivery, socio-economic status of family and the age of mother.

The study shows that low birthweight infants in the study area receive BCG vaccination as timely as normal birthweight infants with several maternal and infant characteristics as well as socio-demographic and health system factors been associated with the timing

Keywords

Bacille Calmette-Guérin (BCG) vaccination, low birthweight, time to BCG vaccination, delays.

Introduction

Every year 10 million people fall ill with tuberculosis (TB) which is caused by the bacterium Mycobacterium tuberculosis with about 1.5 million dying. In 2020, about 1.1 million children fell ill with TB globally. Childhood TB occurs mostly among those aged less than five (5) years. Infants and young children (especially those aged less than two years) are at risk of developing severe disseminated disease associated with a high rate of mortality.[1] Childhood TB is therefore an indicator of ongoing transmission of M. tuberculosis in the general population.[2]

The World Health Organization (WHO) recommends the Bacille Calmette-Guérin (BCG) vaccine to be given to all healthy neonates at birth or as soon as possible after birth in countries or settings with high incidence of Tuberculosis.[3] Bacille Calmette-Guérin (BCG) is one of the most widely used current vaccines on neonates and infants in countries where it is part of the national childhood immunization program. It has a documented protective effect against meningitis and disseminated TB in children.[4] It is also known to provide non-specific benefits such as reducing neonatal mortality and infectious diseases.[5, 6]

Benefits of early BCG vaccination among LBW infants have been noted in some observational studies and randomized controlled trials. Early BCG vaccination of LBW infants has heterologous immunological effects by increasing the in vitro cytokine responses which contribute to the maturation of the infant immune system and thereby protecting against fatal infections in the neonatal period.[7-9] Again, it has been noted to also reduce neonatal mortality in these low birth weight infants.[10]

It has been reported that when BCG vaccination is delayed, there is an increased risk of infections at infancy due to the shortening of the duration of the protective effect of the vaccine. Delay

vaccination has also been recognized as an important indicator of the overall quality of the vaccine and has effects on vaccination coverage.[11]

Despite these benefits, BCG vaccination is usually postponed in some low-income countries for children born with a LBW. This has resulted in delayed timing to BCG vaccination for LBW infants as witnessed in several low-income countries.[9, 12] For instance, in Kenya, pre-term and LBW infants (birthweight less than 2500 grams) receive BCG at the time of discharge from hospital [13] However, in other countries such as Ghana, there is no recommendation to delay BCG vaccination of LBW infants.

In addition, several factors have been associated with incomplete childhood vaccinations. Some studies have classified these factors into child and maternal characteristics as well as socio demographic factors.[14, 15] Less information is however known about the factors associated with timing and delays to BCG vaccinations.

This study therefore assessed the effects of low birthweight on timing to BCG vaccination, and examined the factors associated with delays to BCG vaccination in a context where there are no restrictions on vaccinating low birthweight infants.

Methods

a) Study Design

This study involved a retrospective secondary data analysis of infants born from 2012 to 2018 in the Kassena-Nankana Districts of Ghana. It assessed the effects of LBW on timeliness to BCG vaccination.

b) Study Population and data collection

The study used maternal and child health data collected from the Navrongo Health and Demographic Surveillance System (NHDSS). The NHDSS monitors demographic and health changes of all persons and households in the Kassena-Nankana east and west districts. Trained field workers visit compounds every 4 to 6 months and interview heads of households using a compound registration book (CRB) which contains basic information of all individuals in a household. Where a new event is recorded, the CRB is filled to provide detailed information about that particular event. The data collection process also includes the community key informant system where individuals are selected by their respective communities and given some training by the research team to report events, such as pregnancies, births and child deaths (deaths of children aged <12 years). This complements the routine data collection machinery by recording in a timely manner, events that may occur after a fieldworker has passed a particular location during his or her routine rounds.

Data collected include pregnancies, live and stillbirths, morbidity, deaths, in- and out-migrations, childhood vaccinations, verbal autopsy on all deaths, educational status, marriage, religion and national health insurance coverage as well as socio-economic characteristics.[16] All infants born from 2012 to 2018 with birthweight and BCG vaccination recorded were included in the study.

c) Variables of Interest

Age at BCG vaccination was the main outcome variable of interest whilst the weight at birth of the child was the main primary exposure variable. Birth weight was categorized into low birth weight and normal birth weight for infants weighing less than 2500 grams and more or equal to 2500 grams respectively. Low birth weight was further sub-classified into those weighing below

2000 grams and those weighing 2000–2499 grams. Variables such as maternal age and education, ethnicity, religious denomination, birth order of infant, sex, were explored to determine their association with delays in BCG vaccination. Other sociodemographic variables of interest included in the analysis were place of residence, place of delivery and socioeconomic status of the household.

d) Data Analysis

Descriptive characteristics of the participants have been described in Table 1. The overall aim of the study was to assess the effect of LBW on timing to BCG vaccination. Survival analysis techniques were therefore used to assess the time to BCG vaccinations. BCG vaccination age ranged from 0 to 753 days. Majority of the participants received BCG vaccination before 90 days of age with only 1.5% of the participants receiving BCG vaccination after 90 days of age. Censoring was done at 90 days of age. Kaplan-Meier curves (Figure 1) were used to describe the age distribution of getting BCG vaccination for the three birth weights groups. A cox proportional hazards model was fitted to estimate the effect of LBW on the timing to BCG vaccination. Results from the Kaplan-Meier curves (Figure 1) and testing of the cox model showed a violation of the proportionality assumption which assumes proportionality of the hazard functions (Supplementary Figure 1). Parametric regression models were therefore fitted using different distribution such as the Weibull, exponential, lognormal, loglogistic and Gompertz to assess the association between LBW and time to BCG vaccination. These parametric models allow for the baseline hazards to vary and the hazard function does not need to be proportional. The Akaikes information criterion (AIC) and Bayesian information criterion (BIC) results were used to pick the best model that fits the dataset. The AIC and BIC suggested the lognormal accelerated failure time (AFT) model.

The dependent/outcome variable will be age at BCG vaccination whilst the main independent or primary exposure will be the weight at birth of infant. Other independent variables of interest will be socio-demographic characteristics of the participant as well as some health facility factors. These variables have been noted in some studies to be associated with time to BCG vaccination.

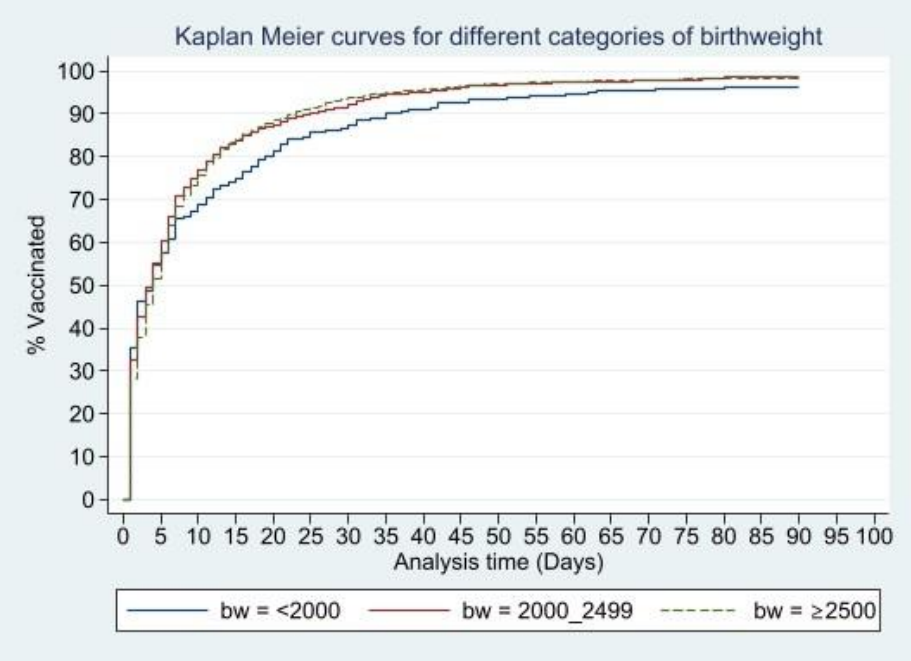
Unadjusted and adjusted regression models with time ratios were used to assess the effect of birthweight on timing to BCG vaccination. A time ratio is a comparison of rates at which subjects traverse the survival curve. In an accelerated failure-time model, everyone has the same "baseline" survival curve. Therefore, the effects of covariates serve to accelerate the passage of time. All variables irrespective of statistical significance in the univariable model were included in the adjusted models as some studies had shown associations of these variables with time to BCG vaccination.

Factors associated with delays to BCG vaccination after four weeks (28 days) of age were evaluated using binary logistic regression models. Delay to BCG vaccination was determined based on the World Health Organization's recommendations for childhood vaccinations [19]. All infants who received BCG vaccination from birth to 4 weeks of age were classified as not delayed whilst those who received BCG vaccination after 4 weeks of age were considered to have delayed. Median age at BCG vaccination was also calculated for each year. The dependent variable here was delayed/not delayed BCG vaccination whilst the independent or exposure variables were, participant characteristics, socio-demographic characteristics of the participant as well as some health facility factors.

Results are presented with 95% confidence intervals (CI) to demonstrate achieved precision and statistical significance was set at 5%. The Data was analyzed using Stata 17.0.

The study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee and the Navrongo Health Research Centre Institutional Review of Board.

Figure 1: Kaplan Meier curves for different categories of birthweight



Results

Descriptive Characteristics of participants

A total of 18003 participants were included in the study, of which 9087 (50%) were male. Infants who weighed below 2000 grams were 363 and had a median BCG vaccination age of 2 days; interquartile range (IQR) of 1-11 days whilst 1721 (10%) infants weighed between 2000–2499 grams with a median BCG vaccination age of 2 days with IQR of 1–7. The remaining 15919 (88%) had normal birth weight (≥2500 grams) with median BCG vaccination age of 3 days (IQR 1–8).

Infants born in a health facility, which constituted 96% of the participants, on average received BCG vaccination at 3 days (3 IQR 1-8) compared to 7days (IQR: 3-15) for those born at home or elsewhere. Those who were in urban locations, 2422 (13%) also averagely received BCG vaccination 2 days (median 1 IQR 1-5) earlier than those in rural locations (median 3 IQR 1-9). Infants whose mothers had no formal education received BCG vaccination later (median 4 IQR 1-10) compared to those who had some levels of education (Junior High; meadian 3, IQR 1-8, Senior High; median 2 IQR 1-7, and Tertiary; median 1 IQR 1-5). Infants born to families classified as the poorest generally received BCG vaccination (median 4 IQR 1-10) later compared to those in the least poor households (median 1 IQR 1-4). Infants born multiple (twins or more) on average received BCG vaccination 2 days earlier (median 1 IQR 1-6) than those who were born single (median 3 IQR 1-8). Both males and females had a median BCG vaccination age of 3 days (IQR 1-8). Details of the characteristics are shown in Table 1.

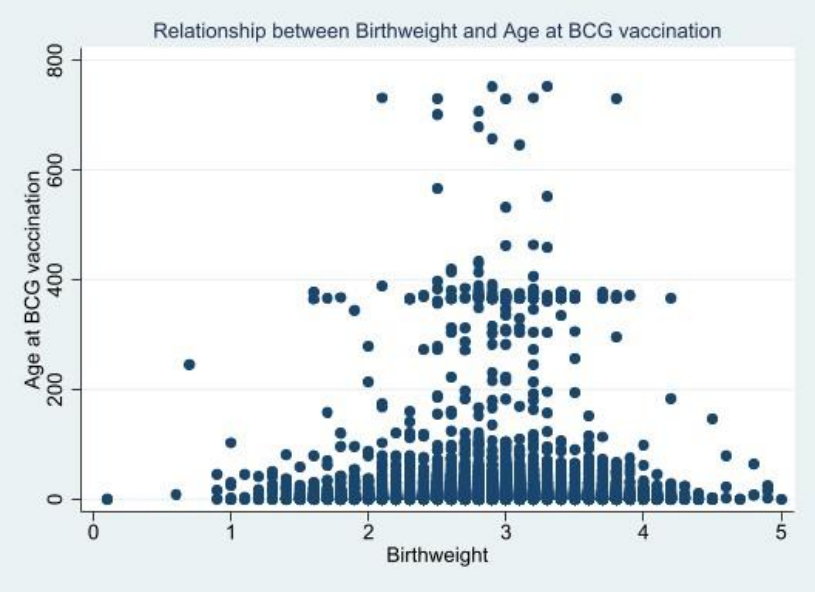
Table 1: Summary statistics of participant

Variable	N	%	Median age in days (IQR) of BCG vaccination
Birthweight (Kg)			
<2	363	2	2(1-11)
2-2.49	1721	10	2(1-7)
≥2.5	15919	88	3(1-8)
Sex			
Female	8916	50	3(1-8)
Male	9087	50	3(1-8)
Religion			
Traditional	7177	40	4(1-9)
Catholic	4452	25	2(1-7)
Other Christian	5056	28	2(1-8)
Islam	1262	7	2(1-6)
Others	56	0	1(1-4.50)
Mothers Age			
<19	2158	12	3(1-9)
20-34	12259	68	3(1-8)
≥35	3586	20	3(1-9)
Mothers Education			
No education	2659	15	4(1-10)
Primary	5231	29	4(1-10)
Junior high	5794	32	3(1-8)
Senior high	3136	17	2(1-7)
Tertiary	1183	7	1(1-5)
Residence			
Rural	15581	87	3(1-9)
Urban	2422	13	1(1-5)
Place of delivery			
Health facility	17217	96	3(1-8)
Home/Elsewhere (non-health facility)	786	4	7(3-15)
Ethnicity			
Kasem	9187	51	2(1-7)
Nankam	8091	45	4(1-9)
Buli	297	2	4(1-14)
Others	428	2	1(1-5)
Socio-economic status of family			
Poorest	4891	27	4(1-10)
Poorer	4082	23	3(1-9)
Poor	3341	18	3(1-8)
Less Poor	3579	20	1(1-7)
Least Poorer	2110	12	1(1-4)
Birth order of child			
1st	5839	32	2(1-8)
2nd	3938	22	3(1-8)
3rd	2860	16	3(1-8)
4th	2232	12	3(1-9)
5th	1633	9	4(1-9)
6th or more	1501	8	4(1-11)
Multiple Birth			
Single	17163	95	3(1-8)
Multiple	840	5	1(1-6)

Relationship between BCG vaccination age and birthweight of the participants.

The relationship between age at BCG vaccination and infant birthweight can be described as non-monotonic one. It is observe from Figure 2, that as the birthweight increases there is an increase in the age at vaccination up to some point and then subsequently begins to decrease.

Figure 2: Relationship between BCG vaccination age and Birthweight



Assessing the effect of low birthweight on timing to BCG vaccination

From Table 2, the result from the unadjusted lognormal model shows that infants with birthweight between 2000- 2499 grams received BCG vaccination earlier compared to those with normal birthweight (≥2500 grams). That is, infants who had birthweight 2000-2499 grams had a 3% reduced time ratio (TR=0.97, 95% CI: 0.91-1.04) of receiving BCG vaccination compared to those with normal birthweight whilst those with birthweight <2000 grams had time ratio of 1.15

compared to those with normal birthweight. This was however not statistically significant in both the adjusted and unadjusted models.

Other factors had statistically significant effects on timing to BCG vaccination as seen in the unadjusted model in Table 2. Infants in rural areas had a 20% increased time (TR=1.20, 95% CI: 1.12-1.29) of receiving BCG vaccination compared to those in urban areas. Similarly, infants born at home or elsewhere tended to receive BCG vaccination later (TR=1.54, 95% CI: 1.42-1.67) than those born in a health facility. Maternal age was also statistically significantly associated with time to BCG vaccination. Children born to mothers who less than 19 years had a 14% increased time (TR=1.14. 95% CI: 1.04-1.25) in receiving BCG vaccination compared to those who were in age groups more than 19 years.

The results also showed that children from relatively wealthy households (Less poor; TR=1.14, 95% CI: 1.05-1.24) were more likely to receive BCG vaccination earlier than those from poor households (Poorer; TR=1.17, 95% CI: 1.07-1.29, Poorest; TR=1.23, 95% CI: 1.13-1.35). Similarly, the lower the birth order of the infant, the earlier BCG vaccination is received. Infants who were born multiple (twins or more) were more likely to receive BCG vaccination earlier than those who were born single (TR=0.72, 95% CI: 0.65-0.80).

Religious denomination, educational level, and ethnic group of the mother were also statistically significantly associated with BCG vaccination age. Infants whose parents practice African Traditional Religion received BCG vaccination much later (TR=1.04, 95% CI: 0.95-1.13) than those who practice Islam. Also, infants whose mothers had no formal education received BCG vaccination later (TR=1.33, 95% CI: 1.20-1.48) compared to those children to mothers with tertiary level education. Also, infants from other ethnic groups (Kasem; TR=0.79, 95% CI: 0.67-

0.93, Nankam; TR=0.85, 95% CI: 0.72-1.00 and Others; TR=0.80, 95% CI: 0.64-0.99) tended, to receive BCG vaccine much later compared to those from the Buli ethnic group (. There was no statistically significant difference in time to BCG vaccination and sex of the infant.

Table 2: Unadjusted and adjusted lognormal models estimating effects of variables on timing of the BCG Vaccination

Characteristic	Univariable Model (N= 15155) Time ratio	95% CI	Overall p-value	Multivariable Model (N=15155) Time ratio	95% CI	Overall p-value
Birthweight categories (ref: ≥2500grams)						
<2000 grams	1.05	0.89-1.24	0.078	1.15	0.98-1.36	0.159
2000-2499 grams	0.93	0.86-0.99		0.97	0.91-1.04	
Sex (ref: Male)						
Female	1.01	0.97-1.05	0.505	1.02	0.98-1.06	0.348
Mothers Age (ref: ≥35 years)						
<19 years	1.02	0.94-1.09	**0.004**	1.14	1.04-1.25	**0.022**
20-34 years	0.94	0.89-.099		1.07	1.01-1.14	
Mothers Educational level (ref: Tertiary)						
No education	1.81	1.65-1.98	**<0.001**	1.33	1.20-1.48	**<0.001**
Primary	1.78	1.64-1.94		1.34	1.21-1.47	
Junior High School	1.54	1.42-1.68		1.22	1.11-1.34	
Senior High School	1.29	1.18-1.41		1.10	1.00-1.21	
Religion (ref: Islam)						
Traditional	1.38	1.27-1.49	**<0.001**	1.04	0.95-1.13	**0.015**
Catholic	1.06	0.98-1.15		0.95	0.87-1.04	
Other Christians	1.19	1.10-1.30		1.00	0.91-1.09	
Others	0.86	0.60-1.25		0.79	0.57-1.10	
Ethnicity (ref: Buli)						
Kasem	0.74	0.62-0.88	**<0.001**	0.79	0.67-0.93	**0.001**
Nankam	0.90	0.76-1.06		0.85	0.72-1.00	
Others	0.58	0.47-0.72		0.80	0.64-0.99	
Residence (ref: Urban)						
Rural	1.55	1.46-1.64	**<0.001**	1.20	1.12-1.29	**<0.001**
Socio-economic status (ref: Least Poor)						
Poorest	1.73	1.61-1.85	**<0.001**	1.23	1.13-1.35	**<0.001**
Poorer	1.63	1.52-1.75		1.17	1.07-1.29	
Poor	1.54	1.43-1.65		1.13	1.04-1.24	
Less poor	1.41	1.31-1.52		1.14	1.05-1.24	
Place of Delivery (ref: Health facility)						
Home/elsewhere	1.74	1.60-1.89	**<0.001**	1.54	1.42-1.67	**<0.001**
Birth Order of Child (ref: 6th or more)						
1st	0.75	0.69-0.81	**<0.001**	0.82	0.74-0.90	**0.004**
2nd	0.77	0.71-0.83		0.85	0.77-0.93	
3rd	0.79	0.72-0.86		0.86	0.78-0.94	
4th	0.81	0.74-0.88		0.85	0.77-0.93	
5th	0.88	0.80-0.96		0.90	0.82-0.99	
Multiple Birth (ref: Single)						
Multiple	0.73	0.66-0.81	**<0.001**	0.72	0.65-0.80	**<0.001**

Factors associated with delay to BCG vaccination in the first four weeks of age

The study also assessed factors associated with delay to BCG vaccination in the first four weeks of life using logistic regression and the results are presented in Table 3. In bivariate analysis, birthweight category, mothers age, ethnicity, religion, residence of family, place of delivery, birth order of infant and the socio-economic status of the family were all statistically significantly associated with delayed BCG vaccination in the first four weeks of life. In the multivariable model, birthweight category, mothers age and place of delivery were statistically significantly associated with delayed BCG vaccination in the first four weeks of life. Infants with birthweight less than <2000 grams birthweight category had twofold increased odds of delayed BCG vaccination in the first four weeks of life compared to those with normal birthweight 2.08(95% CI: 1.47-2.93). Additionally, infants who were born at home were 1.16 (95% CI: 1.14-1.88) times more likely to be delayed BCG vaccination in the first four weeks of life compared to those born in a health facility.

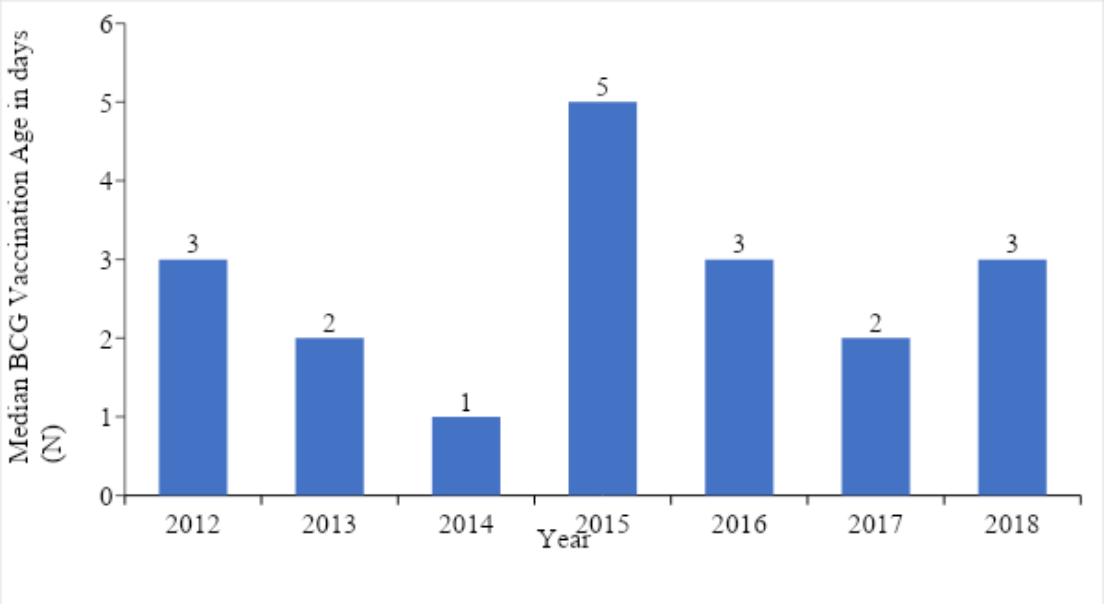
Table 3:Binary logistic regression models assessing factors associated with delayed BCG vaccination in the first four weeks of life

Characteristic	Univariable Model (N=18003)			Multivariable Model(N=18003)		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Birthweight categories (ref: ≥2500grams)						
<2000 grams	2.07	1.49-2.87	**<0.001**	2.08	1.47-2.93	**<0.001**
2000-2499 grams	1.23	1.01-1.49		1.24	1.01-1.51	
Sex (ref: Male)						
Female	0.97	0.86-1.10	0.678	0.97	0.86-1.09	0.583
Mothers Age (ref: ≥35 years)						
<19 years	1.02	1.01-1.53	**0.001**	1.34	1.00-1.78	0.065
20-34 years	0.90	0.77-1.05		1.05	0.86-1.29	
Mothers Educational level (ref: Tertiary)						
No education	1.31	0.97-1.75	**0.005**	1.07	0.76-1.51	0.147
Primary	1.28	0.96-1.67		1.03	0.75-1.42	
Junior High School	1.21	0.92-1.59		0.99	0.73-1.35	
Senior High School	1.23	0.67-1.23		0.80	0.58-1.11	
Religion (ref: Islam)						
Traditional	1.34	1.03-1.76	**0.016**	1.15	0.85-1.57	0.261
Catholic	1.07	0.80-1.42		1.02	0.75-1.39	
Other Christians	1.29	0.98-1.70		1.23	0.91-1.66	
Others	0.69	0.17-2.91		0.67	0.16-2.82	
Ethnicity (ref: Buli)						
Kasem	0.64	0.42-0.97	**0.002**	0.68	0.44-1.03	**0.026**
Nankam	0.80	0.53-1.22		0.81	0.53-1.24	
Others	0.65	0.36-1.16		0.81	0.43-1.50	
Residence (ref: Urban)						
Rural	1.23	1.02-1.49	**0.031**	0.98	0.78-1.24	0.896
Socio-economic status (ref: Least Poor)						
Poorest	1.48	1.18-1.86	**0.006**	1.16	0.86-1.57	0.092
Poorer	1.32	1.04-1.67		1.05	0.78-1.42	
Poor	1.18	0.92-1.51		0.96	0.71-1.31	
Less poor	1.39	1.09-1.76		1.23	0.93-1.63	
Place of Delivery (ref: Health facility)						
Home/elsewhere	1.59	1.24-2.04	**<0.001**	1.16	1.14-1.88	**0.003**
Birth Order of Child (ref: 6th or more)						
1st	0.84	0.68-1.04	**0.038**	0.82	0.61-1.11	0.408
2nd	0.70	0.56-0.89		0.74	0.56-0.99	
3rd	0.72	0.56-0.92		0.76	0.57-1.02	
4th	0.77	0.59-1.00		0.80	0.60-1.06	
5th	0.85	0.64-1.11		0.86	0.65-1.14	
Multiple Birth (ref: Single)						
Multiple	1.04	0.79-1.38	0.767	0.87	0.65-1.18	0.382

BCG Vaccination per year

The median age at BCG vaccination from 2012 to 2018 ranged from 1 day to 5 days. The least median age at BCG vaccination (1 day) was recorded in 2014 and the highest median age at vaccination (5 days) was in 2015.

Figure 3:Median age at BCG vaccination



Discussion

The study found that infants with low or very low birthweights had lower median BCG vaccination age than those with normal birthweight. This observed association however varies from other studies in other countries and areas which reported LBW infants receiving BCG vaccination several days later compared to normal birthweight children.[13, 17] This observation could be due to the Ghana Expanded Program of Immunization (EPI) following the recommendation by the World Health organization that BCG vaccination should be given to all healthy neonates at birth

or as soon as possible after birth in countries or settings with high incidence of Tuberculosis. Also, the increasing number of Community Health Planning and Services (CHPS) who render vaccination services both at home and the health facilities located in every community in the two districts could be a possible reason for the timely BCG vaccination of LBW infants.[18] It is common practice in some countries to delay BCG vaccination of low birthweight infants.[13] Several studies have documented that BCG may have non-specific and heterologous immunological effects that increase the in vitro cytokine responses which contribute to the maturation of the infant immune system and thereby protecting against fatal infections in the neonatal period.[5, 7, 8, 19] This therefore means that, LBW infants will not get these non-specific benefits early if BCG vaccination is delayed.[10]

This study also assessed the effect of other maternal and infant characteristics in association with time to BCG vaccinations. Mothers age and educational level, birth order of the child and multiple births (twins or more) were observed to statistically significantly associated with time to BCG vaccination. Place of delivery was also significantly associated with time to BCG vaccination. Infants born in a health facility received BCG vaccination earlier (median age of 3 days) compared to those born at home or elsewhere (median age of 7 days). This further emphasizes the importance of health care facilities in providing timely vaccinations. Other socio-demographic factors, socio-economic status of the household, residence of participants were also noted to be associated with time to BCG vaccination. Similar studies in Guinea-Bissau and South Africa found mothers educational level and socio-economic status of the family to be factors associated with time to BCG vaccinations.[20, 21] whilst two studies in Kenya and Uganda reported associations of place of delivery and timing to BCG vaccinations.[13, 22] These therefore highlights the need for

targeted vaccination strategies in order to reach out to all who are eligible children to ensure timely BCG vaccination in children.

Factors associated with delayed BCG vaccination in the first four weeks of life were also examined because receiving BCG vaccination between birth and the first four weeks of age is considered as timely vaccination Ghana. Similar factors as those associated with timing were seen to be significantly associated with delay to BCG vaccination in the first four weeks of life. However, in the multivariable model, only ethnicity of the family, birthweight of infant and place of delivery were found to be significantly associated with delay to BCG vaccination. These findings are consistent with previous findings from Ghana and other sub-Saharan African countries[17, 22]. It is critical that the health service sensitizes various communities on importance delivering in a health facility and receiving early BCG vaccination uptake for all infants irrespective of birthweight.

Our study was strengthened by the comprehensive and high-quality data capturing of the NHDSS which provides population-based samples. Data on vaccination and birthweight are taken from the child welfare records and not based on recall. This gives us accurate records for analysis. This study adds to the evidence of timing to infant vaccinations in Ghana and similar sub-Saharan countries. A limitation of this study is the inability to estimate overall BCG uptake in the two districts as infants without BCG vaccination were not included in this analysis. Future studies on BCG vaccination uptake and qualitative studies to understand the reasons for delayed BCG vaccination in infants is required.

The study further shows that, low birthweight infants can receive BCG vaccination on time if there are no restrictions regarding vaccination schedules enabling these infants to receive the full

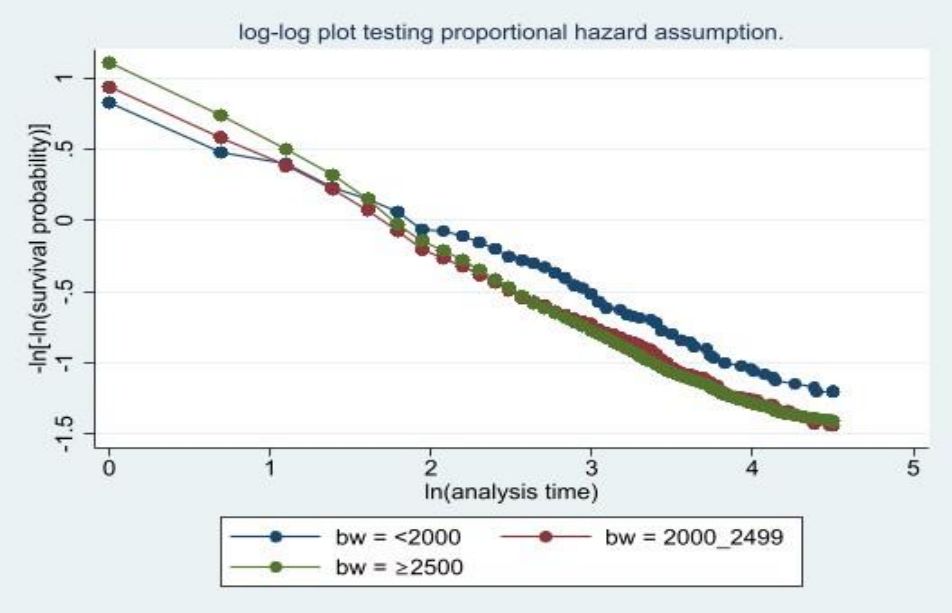
benefits of the vaccine as delayed vaccination can lead to an increased risk of infections at infancy and possibly neonatal deaths.

Conclusion

The study shows that low birthweight infants in the study area receive BCG vaccination as timely as normal birthweight infants with several maternal and infant characteristics as well as socio-demographic and health system factors been associated with the timing to BCG vaccination.

Supplementary Figure 1

Figure 4:Supplementary Figure: log-log survival curves testing for proportional hazard assumption



List of Abbreviations

WHO	World Health Organization
TB	Tuberculosis
BCG	Bacille Calmette-Guérin
LBW	Low birthweight
NHDSS	Navrongo Health and Demographic Surveillance System
AFT	Accelerated Failure Time
CHPS	Community Health Planning and Services

Declarations

Ethics approval and consent to participate

The Navrongo Health and Demographic Surveillance System team embarks on consultations and partnership building with a wide range of stakeholders, including government and community members. Extensive community engagements activities, such as radio programmes or community meetings are used to sensitize the communities on the activities of the HDSS whilst consent for routine data collection is obtained at the household level. This study was reviewed and approved by the University of Cape Town Human Research Ethics Committee (UCT HREC ref: 660/2022) and the Navrongo Health Research Institutional Review Board (NHRCIRB485). Approval letters are attached in appendix 2 and 3.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors received no specific funding for this work.

Authors' contributions

EYA conceived, designed, analysed the data and wrote the protocol and the manuscript.

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Prof. Landon Myer was the supervisor and Dr. Paul Welaga was the co-supervisor of the Study.

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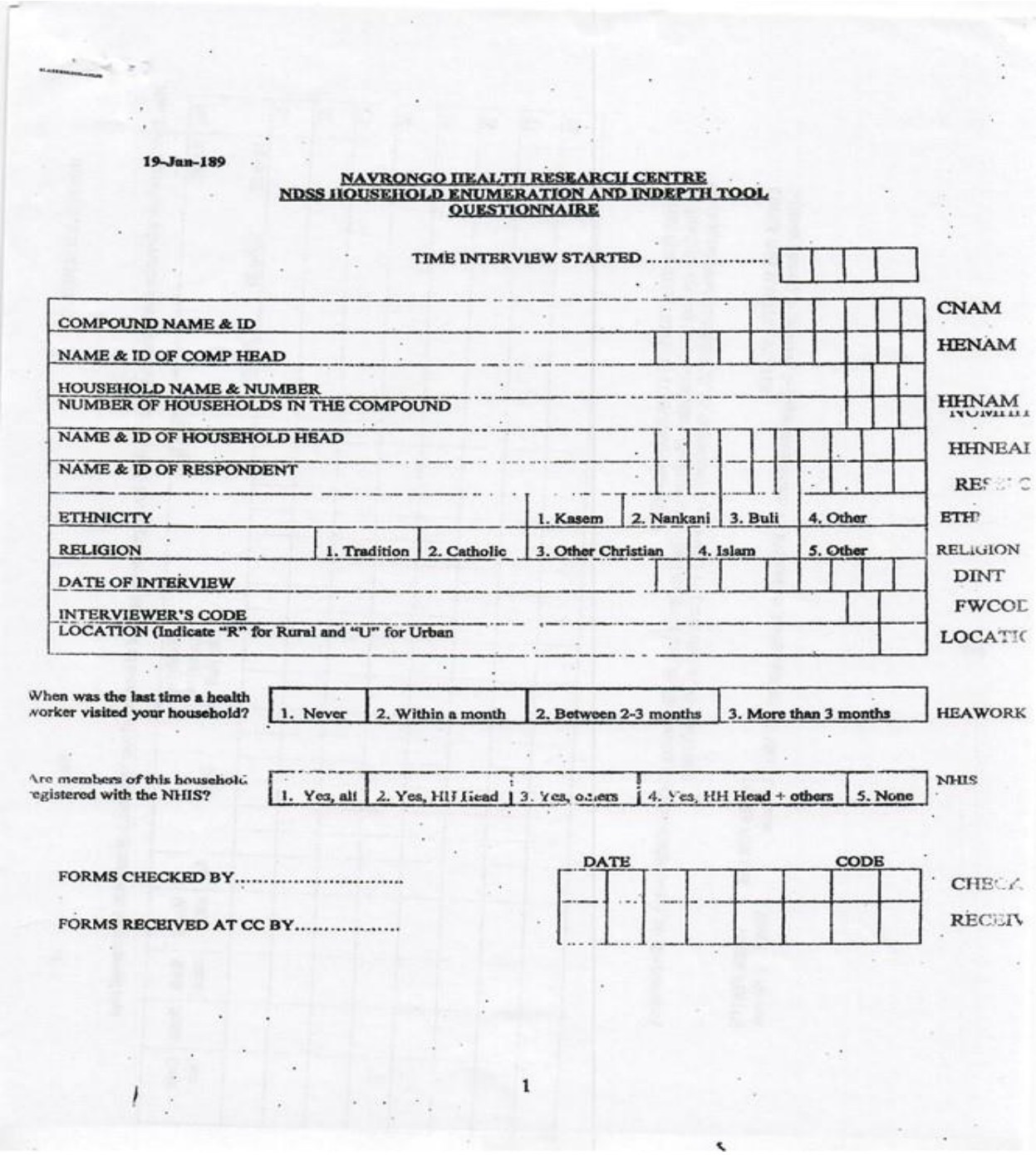
PART C: APPENDICES

Appendix 1: Navrongo Health and Demographic Surveillance System (NHDSS) Questionnaires



19-Jan-189

NAVRONGO HEALTH RESEARCH CENTRE
NDSS HOUSEHOLD ENUMERATION AND INDEPTH TOOL QUESTIONNAIRE

TIME INTERVIEW STARTED .....

COMPOUND NAME & ID		CNAM
NAME & ID OF COMP HEAD		HENAM
HOUSEHOLD NAME & NUMBER		HHNAM
NUMBER OF HOUSEHOLDS IN THE COMPOUND		
NAME & ID OF HOUSEHOLD HEAD		HHNEAI
NAME & ID OF RESPONDENT		RES
ETHNICITY	1. Kasem 2. Nankani 3. Buli 4. Other	ETH
RELIGION	1. Tradition 2. Catholic 3. Other Christian 4. Islam 5. Other	RELIGION
DATE OF INTERVIEW		DINT
INTERVIEWER'S CODE		FWCOL
LOCATION (Indicate "R" for Rural and "U" for Urban		LOCATI

When was the last time a health worker visited your household? | 1. Never | 2. Within a month | 2. Between 2-3 months | 3. More than 3 months | HEAWORK

Are members of this household registered with the NHIS? | 1. Yes, all | 2. Yes, HH Head | 3. Yes, others | 4. Yes, HH Head + others | 5. None | NHIS

FORMS CHECKED BY..... DATE CODE CHEC

FORMS RECEIVED AT CC BY..... RECEI

1

HOUSEHOLD SCHEDULE

Sheet of

Now, I will like to have information about members of your household. Please, give me the names of all members of your household, beginning with the household head

No.	NAME Moth ID Father ID Husd ID	PERM ID	Relship of (name) to the HoH	DOB	Sex	Marital status	Work status	Status	Event Date
01									
02									
03									
04									
05									
06									
07									
08									

CODES FOR RELATIONSHIP TO HOUSEHOLD HEAD
01- (Head), 02- (spouse), 03- (Son/daughter), 04- (Parent), O5- (Son/Daughter-in-law), 06- (Grandchild), 07- (Mother/father-in-law), 08- (Brother/sister), 09- (Adopted/foster child/Stepchild), 10- (Not related), 11- (Co-wife), 12- (Other relative), 99-(Don't know)

CODES FOR MARITAL STATUS
1- (Never married), 2- (Married), 3- (Separated/divorced), 4- (Widowed), 5- (Living together)

CODES FOR SEX
1. Male 2. Female

WORK STATUS
1. Work 1 2. No work

2

II HOUSEHOLD CHARACTERISTICS QUESTIONS	CODING CATEGORIES		WATER
SOURCE OF DRINKING WATER: What is the main source of drinking water for members of your household?	BUYING WATER TAPS..... TANKS..... HAWKERS..... BOTTLED/SATCHET WATER..... PIPED WATER PIPED INTO RESIDENCE/COMPOUND..... PUBLIC TAP..... WELL WATER WELL ON RESIDENCE/COMP..... PUBLIC WELL..... BORE HOLE..... SURFACE WATER RIVER/STREAM..... DAM/POND/LAKE..... RAINWATER..... OTHER_____ (SPECIFY)	01 02 03 04 05 06 07 08 09 10 11 12 13	
TOILET FACILITY: What kind of toilet facility does your household use? (IF LATRINE: PROBE FOR THE TYPE)	FLUSH TOILET OWN FLUSH TOILET..... SHARED FLUSH TOILET..... PIT TOILET/LATRINE OWN TRADITIONAL PIT TOILET... SHARED TRADITIONAL PIT TOILET VENTILATED IMPROVED PIT TOILET OWN (VIP) LATRINE..... SHARED (VIP) LATRINE..... BUCKET/PAN..... NO FACILITY/BUSH/FIELD..... OTHER (SPECIFY)	01 02 03 04 05 06 07 08	TOILE
ROOMS OCCUPIED BY HOUSEHOLD: how many rooms your household occupies?	ROOMS.....		
ROOMS USED FOR SLEEPING: How many rooms in your household are usually used for sleeping?	SLEEPING ROOMS.....		SROC
MAIN MATERIAL OF THE FLOOR (Sleeping rooms)	NATURAL FLOOR MUD/SAND/GRAVEL..... SAND/GRAVEL/MUC MIXED WITH DUNG..... RUDIMENTARY FLOOR WOOD PLANKS..... FINISHED FLOOR POLISHED WOOD/TILES/TERRAZZO CEMENT..... CARPET..... OTHER (SPECIFY)	1 2 3 4 5 6 7	FLOC
MAIN MATERIAL OF THE ROOF RECORD ANY OBSERVATION	MUD ROOF..... GRASS/THATCH..... IRONSHEET/ZINC..... TILES..... OTHER_____ (SPECIFY)	1 2 3 4 5	RO
MAIN MATERIAL OF THE WALL RECOD ANY OBSERVATION	BRICKS (MUD)..... CEMENT BLOCKS..... IRONSHEETS (ZINC)..... WOOD/BOARDS..... GRASS/STOCKS..... OTHER (SPECIFY) _____	1 2 3 4 5 6	WA

TYPE OF COOKING FUEL: What is the main source of cooking fuel used by the household?	KEROSENE/PARAFFIN..... 1 GAS..... 2 ELECTRICITY..... 3 CHARCOAL..... 4 FIREWOOD..... 5 ANIMAL WASTE..... 6 CROP RESIDUE/SAW DUST..... 7 OTHER_____ 8 (SPECIFY)	CFU...
LIGHTING SOURCE: What is the main source of lighting for this household?	KEROSENE/PARAFFIN..... 1 GAS..... 2 ELECTRICITY..... 3 SOLAR..... 4 CANDLES..... 5 FIREWOOD..... 6 OTHER_____ 7 (SPECIFY)	LIGHT
DURABLE HOUSEHOLD GOODS: Does your household have?	YES NO	DGOOI
A Car/truck	CAR..... 1 2	
A motorcycle	MOTORCYCLE..... 1 2	
A Bicycle	BICYCLE..... 1 2	
Electricity	ELECTRICITY..... 1 2	
Solar light	SOLAR..... 1 2	
A Refrigerator	REFRIGERATOR..... 1 2	
A Television	TELEVISION..... 1 2	
DVD/VCD/VCR	DVD/VCD/VCR..... 1 2	
Radio	RADIO..... 1 2	
A Sewing machine	SEWING MACHINE..... 1 2	
A Stereo system	STEREO..... 1 2	
An Electric iron/box iron	IRON..... 1 2	
A fan	FAN..... 1 2	
Telephone	TELEPHONE..... 1 2	
An electric/gas stove	AN ELECTRIC/GAS STOVE..... 1 2	
A Donkey cart/push truck	DONKEY CART..... 1 2	
Tractor	TRACTOR..... 1 2	
Grinding mill	GRINDING MILL..... 1 2	
Kerosene stove	KEROSENE STOVE..... 1 2	
Personal Computer	PERSONAL COMPUTER..... 1 2	

H HOUSEHOLD CHARACTERISTICS CONTINUED

				LAND
1	LAND OWNERSHIP: Who owns the land where this compound is build?	LANDLORD	1	
		PUBLIC/GOVERNMENT LAND	2	
		SELF/FAMILY OWNED	3	
		OTHER (SPECIFY)	4	
		DON'T KNOW	9	
				TEN
2	TENURE OF DWELLING UNIT: Is your household renting or does it own this dwelling unit?	OWNED		
		PURCHASED	01	
		CONSTRUCTED	02	
		INHERITED	03	
		RENTED FROM:		
		INDIVIDUAL	04	
		GOVERNMENT	05	
		LOCAL AUTHORITY	06	
		PRIVATE COMPANY	07	
		FREE OF CHARGE	08	
		DON'T KNOW	09	
		OTHER (SPECIFY)	11	
				WAS
13	WASTE/GARBAGE DISPOSAL: what is the main method of waste/garbage disposal used by your household?	GARBAGE DUMP	01	
		IN THE RIVER	02	
		ON THE ROAD	03	
		IN DRAINAGE/TRENCH	04	
		IN PRIVATE PITS	05	
		IN PUBLIC PITS	06	
		GARBAGE DISPOSAL SERVICES	07	
		VACANT/ABANDONED HOUSE	08	
		BURNING	09	
		NO DESIGNATED PLACED/ALL OVER	10	
		OTHER (SPECIFY)	11	
14	Are there any mosquito nets in this household?	YES	1	
		NO	2	
15	How many are there?	NUMBER		
		DON'T KNOW	9	
		NA	8	
				PE
16	How many mobile phones does this HH have?			
17	If no, where can your HH members normally have access to a mobile phone?	1. No where	2. Within Compound	3. Within Community	8. NA

I: FOOD SECURITY AND ANIMAL POSSESSIONS

QUESTIONS	CODING CATEGORY	CODE	
Does your household own any farming land?	YES	1	OWLAND
	NO	2	
	DON'T KNOW	9	
Is this land enough to grow food to feed members of your household?	YES	1	ENLAND
	NO	2	
	NA	8	
Did your household grow enough food to feed members of your household during the last farming season?	YES	1	ENFOOD
	NO	2	
	DON'T KNOW	9	
If no, how did you supplement your food requirements?	BOUGHT FROM THE MARKET	1	FAID
	FOOD FROM RELATIVES	2	
	MANAGED WITH STOCK	3	
	ASSISTANCE FROM FRIENDS	4	
	GOVERNMENT/NGO AID	5	
	NA	8	
What is the main staple food crop for your household?	MILLET	1	MSTAPLE
	RICE	2	
	MAIZE	3	
	POTATOES	4	
	BEANS	5	
	OTHER (SPECIFY)	6	
How many meals did this household take yesterday?	ONE	1	MEALS
	TWO	2	
	THREE	3	
	FOUR OR MORE	4	
	OTHER (SPECIFY)	5	
In the past one month or so, how many days did your household not have food to eat?			DFOOD
In the past 12 months, how many months did your household not have enough food to eat?			MFOOD
Do you think that this household has enough food to eat for the next three or four months?	YES	1	ADFOOD
	NO	2	
	DON'T KNOW	9	

Does your household possess any of the follow animals? If YES, ask and record number.

	YES	NO	Number	
CATTLE	1	2		CATTLE
SHEEP	1	2		SHEEP
DONKEYS	1	2		DONK
GOATS	1	2		GOAT
PIGS	1	2		PIG
HORSE	1	2		HOR
RABBITS	1	2		RAB
OTHER (Specify)	1	2		OTHE

Has anyone in this household had fever in the past two weeks?	1. Yes	2. No (End interview)	FEVER
If yes, who?			WHO
Did he/she take any anti-malaria?	1. Yes	2. No / 3. NA	ANTIMA

TIME INTERVIEW ENDED

BLANK VACCINATION DATA COLLECTION FORM - NHRC Round 80

Cluster: FW

Name
Individid Birth Date
Compound Name
Compid Sex
Int date Res: M=1, Oth=2

HC BC PO PE MV | B C G

Polio 0 1 2 3 | Penta 1 2 3 | Measle | Yfever | Pneumo-coccal 1 2 3 | Rotavirus 1 2 | Measle 18 | Vita A 1 2 3 | IPTi 1 2 3 | Visits 0-5 6-11 12-17 18-23 | BW Scar WFP NHIS | CMP 26-28 Oct | HL HOd HOm SBF | STm STy BNet ONet | Admission Adm Dur Rea Date

Fever Ftreat Diarrhea Dtreat ARTI Atreat Children who sleep in one bed MUAC SN REG

Fever Ftreat Diarrhea Dtreat ARTI Atreat Children who sleep in one bed MUAC SN REG

Fever Ftreat Diarrhea Dtreat ARTI Atreat Children who sleep in one bed MUAC SN REG

HC (Hcard):
1. Yes seen
2. Yes, not seen
3. No, never had a card
4. No, had a card but lost
5. No information

Reason not vaccinated for BCG, Polio, Penta and MV:
1. Was at heath centre to get vaccine but did not succed
2. Mother does not know of vaccination schedule
3. Mother considers child too small/sick for vaccination
4. Religious/Cultural reasons
5. Distance to health facility
6. Received but not indicated on card 7. other

ONet: How often does NAME sleep under the bednet?
1. Always
2. Sometimes
3. rainy season
4. Dry season
5. Never

Rea: Reason for admission
1. Respiratory infection
2. fever
3. Diarrhoea
4. Accident
5. Other

HL: How long after birth did you start BF
1. Immediate 2. Later same day
3. Day 2 4. 3/more days 5. Never

HOd: How old (in days) was NAME when you started giving NAME food or drinks?

HOm: How old (in months) was NAME when you started giving NAME food or drinks?

SBF: Still breastfeeding 1. Yes 2. no 8. NA

STm: How old (in months) was NAME when you stopped breastfeeding?

STy: How old (in years) was NAME when you stopped breastfeeding?

NHIS: 1. Yes, active 2. Yes, expired 3. No 4. card not seen

Appendix 2: University of Cape Town Human Research Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: https://health.uct.ac.za/home/human-research-ethics

31 October 2022

HREC REF: 660/2022

Prof L Myer
Public Health & Family Medicine
FHS
Email: Landon.myer@uct.ac.za
Student: AYMEMM001@myuct.ac.za

Dear Prof Myer

PROJECT TITLE: THE EFFECT OF LOW BIRTH WEIGHT ON TIMING TO BCG VACCINATION IN A RURAL DISTRICT OF NORTHERN GHANA-
(MASTERS CANDIDATE-MR EMMANUEL AYAMBA)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Mr Emmanuel Ayamba will also be involved in this study.

Please quote the HREC REF 660/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

HREC/ref 660.2022

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/ref 660.2022

Appendix 3: Navrongo Health Research Centre Institutional Review Board Ethics Approval Letter

OUR CORE VALUES

1. People-Centered
2. Professionalism
3. Team work
4. Innovation
5. Discipline
6. Integrity

My Ref: LBW Effects/10/2022
Your Ref:

GHANA HEALTH SERVICE
Your Health · Our Concern

Navrongo Health Research Centre
Institutional Review Board
Ghana Health Services
Post Office Box 114
Navrongo, UER

Mob: +233-591152102
E-mail: irb@navrongo-hrc.org
20th October 2022

Mr Emmanuel Yidana Ayamba
Navrongo Health Research Centre
P. O. Box 114
Navrongo

ETHICS APPROVAL ID: NHRCIRB485

Dear Mr Ayamba,

Approval of Protocol titled "The Effect of Low Birth Weight on Timing to BCG Vaccination in a Rural District of Northern Ghana"

I write to inform you that the Navrongo Health Research Centre Institutional Review Board (NHRCIRB) has reviewed your protocol and is happy to grant you approval.

The following documents were reviewed and approved;

- Study Protocol version 2.0 dated 11/10/2022
- Questionnaire (Navrongo Health Research Centre NDSS Household Enumeration and In-depth Tool)
- CV of Investigators (Emmanuel Yidana Ayamba and Professor Landon Myer)

Please, note that any amendment to these approved documents must receive prior NHRCIRB approval before implementation. This approval expires on **19th October 2023.**

The Board wishes you all the best in your study.

Sincerely,

Signed by candidate

Dr Emmanuel Kofi Dzotsi

(Chair, NHRCIRB)

Cc: The Director, NHRC - Navrongo

Apendix 4: Instructions for authors for preparing Manuscripts

Chosen Journal: BMC Global Health Research and Policy

Please refer to the link provided for all the authors guidelines which have been copied in below

https://ghrp.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors

- if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below

- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- Background: the context and purpose of the study
- Methods: how the study was performed and statistical tests used
- Results: the main findings
- Conclusions: brief summary and potential implications
- Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements

- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Authors are also encouraged to preserve search strings on searchRxiv https://searchrxiv.org/, an archive to support researchers to report, store and share their searches consistently and to enable them to review and re-use existing searches. searchRxiv enables researchers to obtain a digital object identifier (DOI) for their search, allowing it to be cited.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

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With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

If you wish to co-submit a data note describing your data to be published in BMC Research Notes, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each authors' competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

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Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

References

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Preparing tables

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.

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- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.

- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.

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- PowerPoint (suitable for diagrams and/or images, figures must be a single page)
- TIFF (suitable for images)
- JPEG (suitable for photographic images, less suitable for graphical images)
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For information and suggestions of suitable file formats for specific figure types, please see our author academy.

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Figures on the web:

- width of 600 pixels (standard), 1200 pixels (high resolution).

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- maximum height of 225 mm for figure and legend
- image resolution of approximately 300 dpi (dots per inch) at the final size

Figures should be designed such that all information, including text, is legible at these dimensions. All lines should be wider than 0.25 pt when constrained to standard figure widths. All fonts must be embedded.

Figure file compression

- Vector figures should if possible be submitted as PDF files, which are usually more compact than EPS files.
- TIFF files should be saved with LZW compression, which is lossless (decreases file size without decreasing quality) in order to minimize upload time.
- JPEG files should be saved at maximum quality.
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