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Morphological Variants and Factors Associated With Neural Tube Defects at a Regional Referral Hospital

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ABSTRACT

Background: Neural Tube Defects (NTDs) remain a significant public health concern, especially in low-resource settings. This study investigated the morphological variants of NTDs and identified factors associated with their development among neonates at Mbarara Regional Referral Hospital (MRRH).

Methods: A retrospective cross-sectional descriptive study was conducted using medical records from January 2022 to December 2024. One hundred and six records of neonates diagnosed with NTDs were included. Data were analyzed using STATA version 17. Bivariate and multivariate logistic regression analyses were performed to assess associations between risk factors and NTD types.

Results: Open NTDs accounted for 70.75% of cases, with myelomeningocele being the most common. Most defects were posteriorly located (81.13%). Low birth weight (AOR = 4.09, CI: 1.00–6.67, $p = 0.049$) and lack of folic acid supplementation (AOR = 7.12, CI: 1.32–8.33, $p = 0.022$) were significantly associated with open NTDs.

Conclusion: Open NTDs are the predominant morphological variant at MRRH. Key risk factors include low birth weight, inadequate folic acid supplementation, and maternal HIV status.

1 | Background

Neural Tube Defects (NTDs) are a significant public health concern globally, particularly in low- and middle-income countries (LMICs) [1]. These congenital anomalies result from the incomplete closure of the neural tube during embryogenesis, leading to severe conditions such as spina bifida, anencephaly, and encephalocele [2]. NTDs can cause permanent neurological impairment, disability, or death in affected neonates, and they place a significant emotional and economic burden on families and health systems [3]. Globally, the prevalence of NTDs is estimated at 18.6 per 10,000 live births, with

approximately 200,000 cases annually, most of which occur in LMICs [1, 4]. A recent systematic review of over 6 million births from Africa reported a pooled prevalence of 21.42 per 10,000, with higher rates documented in Algeria (75/10,000), Ethiopia (61.43/10,000), and Nigeria (32.77/10,000) [5]. East Africa's NTD prevalence is also elevated, with pooled estimates of 33.30 per 10,000 births, which are five times higher than in Western countries. These numbers demonstrate the magnitude of the problem and highlight the severe regional disparity [4, 6].

Despite sporadic hospital-based reports in Uganda, there is no national birth defects registry, and comprehensive data on NTDs

Abbreviations: COR, crude odds ratio; DTG, Dolutegravir; LBW, low birth weight; LMICs, low- and middle-income countries; MRRH, Mbarara Regional Referral Hospital; MUST, Mbarara University of Science and Technology; NTD, neural tube defects.

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Summary

- Neural tube defects are still significant congenital conditions among children in rural areas, despite the wide promotion of folic acid use.
- Further attention must be directed to the study of in-utero predispositions, particularly within this population.
- Intense screening and diagnosis during pregnancy is also key to minimizing the occurrence of these defects.

remains scarce. Available studies report a prevalence ranging from 9.8 to 39.8 per 10,000 births [7–9]. Despite this evidence, a significant gap remains in the description of the morphological characteristics and associated factors of NTDs in Uganda.

Understanding these factors is crucial for informing targeted prevention strategies, such as folic acid supplementation programs, improved antenatal screening, and neonatal surgical planning. Additionally, studying these morphological variants, such as spina bifida occulta, myelomeningocele, and encephalocele, can aid in the timing of embryological failure and the different molecular pathways. These molecular pathways can further be evaluated for specific processes, such as folate metabolism and cell polarity signalling. Techniques such as bulk RNA sequencing and single-cell RNA sequencing can help map genes that are turned on or off at each developmental stage [10, 11]. Studying these variants can also help refine risk factor profiles. For example, morphological heterogeneity can help identify variant-specific risk factors rather than treating NTDs as a single entity. Some variants may be strongly linked to folate deficiency, while others may be associated with genetic syndromes, maternal diabetes, and environmental toxins [1, 12]. Also, classifying morphological variants can aid prognostic stratification, enabling health workers to provide sufficient information to parents and clearly map neurological, clinical, or orthopedic complications. This classification can also guide tailored clinical and surgical management and multidisciplinary care planning. This study aimed to fill this gap by determining the morphological variants of NTDs and identifying associated maternal and neonatal risk factors at MRRH.

2 | Materials and Methods

This was a hospital-based retrospective analysis of records conducted at Mbarara Regional Referral Hospital (MRRH) in southwestern Uganda. MRRH is a government-owned tertiary hospital in Mbarara City, Western Uganda. It serves as the main referral center for the western region and provides specialised care to over 10 districts. The hospital is affiliated with Mbarara University of Science and Technology (MUST) and is a teaching hospital for medical students and other health trainees. With a bed capacity of approximately 600, MRRH offers a wide range of services, including internal medicine, surgery, pediatrics, obstetrics and gynecology, intensive care, and emergency care. It also houses speciality clinics like HIV/AIDS, dental, ophthalmology, and psychiatric services. The hospital plays a critical role in Uganda's healthcare system, particularly in rural health service delivery and the training of healthcare professionals. Despite being a major health facility, it often faces

overcrowding, limited resources, and understaffing, which are common issues in many public hospitals in low-income settings. MRRH handles high volumes of neonatal and obstetric cases from the southwestern region, making it an ideal setting for congenital anomaly surveillance.

The study population included all neonates delivered or referred to MRRH with a confirmed diagnosis of Neural Tube Defect between January 2022 and December 2024. The sample size was not calculated using statistical methods. Instead, all eligible cases documented over the 3-year period were included, thereby minimizing sampling bias and enhancing the representation of NTD patterns at MRRH. Inclusion criteria were partly set for patients with complete medical records and relevant maternal obstetric histories.

A census sampling method was used. All available medical records of neonates diagnosed with NTDs during the study period and meeting the inclusion criteria were reviewed. A total of 121 cases were eligible for inclusion. We used listwise deletion to handle missing data. Cases with missing values for variables included in the regression analysis were excluded. Fifteen cases were then excluded, resulting in a final sample size of 106, which were considered in the analysis. We compared complete and incomplete cases and found no significant differences in key demographic variables, suggesting that the missing data were due to random chance. The results of the regression analysis, therefore, are based on a complete-case analysis.

Data were collected using a structured data abstraction tool designed by the research team. The tool was pilot-tested and used to extract relevant variables from neonatal files, maternal health records, and delivery registers. Information collected included neonatal characteristics like sex, birth weight, type of NTD, site of lesion, outcome, and maternal factors, for example, age, HIV status, gravida, and folic acid supplementation. The data collection team consisted of trained research assistants supervised by the principal investigator, and the process was completed over 4 weeks.

Data were cleaned, entered, and analyzed using STATA version 17. Descriptive statistics summarised categorical variables as frequencies and percentages. Bivariable analysis was conducted using binary logistic regression to assess the association between the independent variables and NTD type (open vs. closed), reporting crude odds ratios (CORs) with 95% confidence intervals (CIs). A multivariate logistic regression model included variables with p values < 0.05 to control for potential confounders. Results were presented as adjusted odds ratios (AORs) with 95% CIs. Ethical approval was obtained from the Mbarara University Research and Ethics Committee. Administrative clearance was also obtained from the records department to access the documents, and all the data was handled anonymously and confidentially.

3 | Results

3.1 | Morphological Variants of Neural Tube Defects

Table 1 below shows the distribution of morphological variants of NTDs at MRRH. According to the table, most of the NTDs are

TABLE 1 | Morphological variants of NTDs.

Morphological variant of NTDs	Freq.	Percent
Open neural tube defects (more severe)		
Anencephaly	7	6.60
Encephalocele	10	9.43
Myelomeningocele	58	54.72
Closed neural tube defects (less severe)		
Spina bifida aperte	3	2.83
Spina bifida occulta	13	12.26
Other (mixed type)	15	14.15
Total	106	100.00

TABLE 2 | Location of NTD among children admitted at MRRH.

Location of NTD	Frequency	Percent
Anterior (brain/cranial)	19	17.92
Both	1	0.94
Posterior (spinal/caudal)	86	81.13
Total	106	100.00

TABLE 3 | Status of NTD admissions on discharge.

Variable	Frequency	Percent
Alive	89	83.96
Dead	13	12.26
Referred	4	3.77
Total	106	100.00

Open Neural Tube Defects (more severe cases), 75 (70.75%), and closed-ended types (less severe forms), 31 (15.09%), and 15 (14.15%) were other types of NTDs distributed between the more severe and less severe forms.

Table 2 below shows the distributions of NTDs. According to the table, most NTDs 86 (81.13%) were located in the posterior locations, while 19 (17.92%) were in the anterior locations, and 1 case (0.94%) had 1 NTD in both the anterior and posterior locations.

As shown in Table 3 below, most of the patients with NTDs were alive 89 (83.96%), while 13 (12.26%) died before discharge, and four of the patients were referred to other health facilities for specialised care of NTDs. This is shown below.

3.2 | Bivariate Analysis of Factors Associated With Neural Tube Defects (NTDs)

A series of bivariate logistic regression analyses was conducted to examine factors associated with the type of neural tube defect (NTD), comparing open versus closed NTDs. The outcome variable was NTD type (1 = Open, 0 = Closed). CORs with 95%

CI are reported. The results showed that mothers who had four or more pregnancies had significantly lower odds of having infants with open NTDs compared to those with 1–3 pregnancies. The COR was 0.25, with a 95% CI of 0.08–0.77, and a *p* value of 0.016. Infants with low birth weight were 5.5 times more likely to present with open NTDs than those with normal birth weight, with a 95% CI of 1.90–16.30, and a *p* value of 0.002. Further details are illustrated in Table 4.

3.3 | Multivariate Analysis of Different Variants of Neural Tube Defects

A multivariate logistic regression was conducted to examine the association between selected maternal and neonatal factors and the variant of NTD, categorized as open versus closed. The model included the following significant predictors at the bivariate level: gravida, maternal HIV status, birth weight, folic acid supplementation, and birth order. The results showed that maternal HIV-negative status was significantly associated with a lower likelihood of having an infant with an open NTD compared to HIV-positive status, AOR = 0.11, 95% CI [0.01, 0.84], *p* = 0.034. Furthermore, lack of folic acid supplementation during pregnancy was significantly associated with a higher likelihood of open NTDs, AOR = 7.12, 95% CI [1.32, 8.33], *p* = 0.022. Gravida (≥ 4 vs. 1–3) was not a statistically significant predictor of NTD type. The details of the multivariate analysis are shown in Table 5.

3.4 | Joint Effects of Significant Variables at the Multivariate Level

A binary logistic regression was conducted to examine the individual and joint effects of folic acid supplementation and birth weight on the type of NTD, specifically comparing open versus closed NTDs. The overall model was statistically significant, $\chi^2(3) = 22.81$, *p* < 0.001, indicating that the model distinguished between open and closed NTD cases. The model explained approximately 24.6% of the variance in NTD type (Pseudo $R^2 = 0.2459$). Infants whose mothers did not receive folic acid supplementation had significantly higher odds of presenting with an open NTD than those whose mothers did. Further details are shown in Table 6 and Figure 1.

4 | Discussion

This study revealed that open NTDs accounted for the majority of cases among neonates at MRRH, with myelomeningocele as the most frequent presentation. NTDs, especially open NTDs, have been reported across multiple settings, both globally and in SSA. The prevalence of open NTDs across Europe was estimated at 42% in Italy and 12.6 per 10,000 live births in Mexico [13, 14]. Kindie and Mulu [15] reported a 10.9% prevalence of open NTDs from a referral Hospital in North Shewa, Ethiopia. Another evaluation in Ethiopia reported a 5.71% prevalence of NTDs among 420 newborns [16, 17]. These demonstrate a variable prevalence, indicating significant variations in the predisposing factors. Studies across SSA have demonstrated

TABLE 4 | Bivariate analysis of factors associated with NTD variants.

Variable	Category (closed NTD)	Category (open NTD)	COR (95% CI)	p value
Age				
30 years and below	9 (16.07%)	47 (83.93%)	1	
Above 30 years	7 (18.92%)	30 (81.08%)	0.78 (0.26–2.36)	0.666
Gravida				
1–3	5 (10.42%)	43 (89.58%)	1	
4 and above	15 (31.25%)	33 (68.75%)	0.25 (0.8–0.77)	0.016
Gender				
Female	9 (20.00%)	36 (80.00%)	1	
Male	11 (18.03%)	50 (81.97%)	1.13(0.42–3.002)	0.798
Gestational age				
Normal term	10 (17.24%)	48 (82.76%)	1	
Pre and post-term	7 (24.14%)	22 (75.86%)	0.65 (0.22–1.94)	0.446
Maternal HIV status				
HIV negative	12 (12.77%)	82 (87.23%)	1	
HIV positive	8 (66.67%)	4 (33.33%)	0.07 (0.0–0.28)	0.000
Birth weight				
Normal birth weight	14 (37.84%)	23 (62.18%)	1	
Low birth weight	6 (9.84%)	55 (75.0%)	5.5 (1.90–7.30)	0.002
Folic acid supplementation				
Yes	1 (20.00%)	4 (80.00%)	1	
No	15 (18.82%)	66 (90.16%)	8.72 (2.58–9.41)	0.000
Time of first ANC attendance				
1st trimester	2 (15.38%)	11 (84.62%)	1	
2nd trimester	8 (20.00%)	32 (80.00%)	0.72 (0.13–3.50)	0.713
3rd trimester	8 (24.24%)	25 (75.76%)	0.56 (0.10–3.12)	0.516
Did not attend	1 (25%)	3 (70.00%)	0.54 (0.04–8.27)	0.662
Number of ANC attendance				
Never attended	2 (50.00%)	2 (50.00%)	1	
1–3 times	5 (14.71%)	29 (85.29%)	5.8 (0.64–9.14)	0.114
More than 3 times	10 (19.23%)	42 (80.77%)	4.2 (0.53–8.54)	0.176

Note: Closed NTD (myelomeningocele, anencephaly, spinal bifida with hydrocephalus, encephalocele, craniorachischisis), Open NTD (meningocele, spinal bifida occulta, paracephalic cyst).

Abbreviation: COR = crude odds ratio.

variable prevalence of open NTDs; for example, Eritrea, Algeria, and Nigeria had 39, 75, and 32.77 per 10,000 live births prevalence, respectively [5, 18, 19]. NTD prevalence in South Africa was estimated at 0.8 per 1000 live births, demonstrating variability in distribution [20]. Other countries that have reported variable prevalences in NTDs include Ethiopia, Morocco, and South Sudan [4, 21–23].

Open NTDs are typically more severe, often visible at birth, and associated with a high risk of infection and neurological deficits. Their predominance may indicate gaps in periconceptional folic acid supplementation, delayed antenatal care, and limited access to prenatal screening [7]. Closed NTDs comprised 15.09%, and 14.15% were mixed or atypical forms. These often require imaging for diagnosis and may be underreported due to limited early detection. Most defects were located posteriorly, consistent with global data showing that lumbosacral defects

are the most common [24]. Only one case presented with both anterior and posterior lesions, consistent with embryological evidence that posterior closure sites are more prone to failure. At discharge, the majority of neonates were alive, suggesting good survival with timely care, though some died, reflecting the critical nature of some NTDs. Mortality likely resulted from sepsis, hydrocephalus, or associated anomalies.

Maternal HIV status was inversely associated with open NTDs. Infants born to HIV-positive mothers were significantly less likely to present with open NTDs. The observed inverse association between maternal HIV status and open NTDs may reflect increased healthcare engagement, nutritional support, and structured antenatal follow-up among women enrolled in HIV care programs, rather than a biological protective effect of HIV infection. However, our results contradict some other studies that found an association of NTDs among HIV positive

TABLE 5 | Multivariate analysis of factors associated with different NTD variants.

Variable	Category (closed NTD)	Category (open NTD)	Crude OR (95 CI)	p value	Adjusted OR (95%CI)	p value
Gravida						
1–3	9 (16.07%)	47 (83.93%)	1			
4 and more	7 (18.92%)	30 (81.08%)	0.25 (0.80–0.77)	0.016	0.24 (0.04–1.37)	0.110
Maternal HIV status						
HIV negative	17 (17.53%)	80 (82.47%)	1		0.11 (0.01–0.84)	0.034
HIV positive	3 (33.33%)	6 (66.67%)	0.43 (0.096–1.86)	0.258		
Birth weight						
Normal birth weight	11 (16.67%)	55 (83.33%)	1		4.09 (1.00–6.67)	0.049
Low birth weight	7 (25.0%)	21 (75.0%)	0.6 (0.205–1.754)	0.351		
Folic acid supplementation						
Yes	1 (20.00%)	4 (80.00%)	1			
No	15 (18.82%)	66 (81.48%)	8.72 (2.58–9.41)	0.000	7.12 (1.32–8.33)	0.022

TABLE 6 | Results for the interaction between FA supplementation and birth weight on NTD variants.

Variable	OR (95% CI)	p value
No folic acid	22.67 (12.32–28.09)	0.007
Low birth weight	40.00 (20.01–79.27)	0.016
No FA × low BW	0.07 (0.003–1.94)	0.118

mothers. For example, across Botswana, mothers living with HIV, especially those on dolutegravir (DTG), had an eightfold increased risk of giving birth to children with NTDs [25]. Further evaluation of these mothers living with HIV and on ART found a higher risk among mothers who were on a DTG-based regimen compared to a non-DTG regimen [26, 27]. Some in vitro studies have demonstrated antagonistic features with DTG toxicity reduction by folate supplementation [28]. An evaluation of 4489315 mothers in the United States found no significant association between DTG and non-DTG therapies and NTD development [29]. Another evaluation in the United States did not demonstrate any significant difference in the NTD prevalence among newborns among mothers living with HIV and the general population [30]. These contradictory results prompt further evaluation of the HIV status and its association with NTDs among children, especially considering other confounders such as socioeconomic status and duration of folate supplementation.

Lack of folic acid supplementation strongly predicted open NTDs, reaffirming its critical protective role. This supports WHO recommendations for universal periconceptional folic acid use to prevent NTDs. Evidence has consistently demonstrated the efficacy of Folate supplementation in minimizing NTDs among children [31]. Strategies to maximize folic acid supplementation have been successful in over 60 countries, including Angola, Benin, Egypt, Ethiopia, Ghana, Nigeria, and Morocco, by prioritizing the fortification of local foods [9, 32]. An estimated \$957 and \$14.9 are saved through death aversion and disability-adjusted life year following food fortification with

folic acid [33]. Therefore, mandating folic acid supplementation must be a high priority, with emphasis on its inclusion in maternal and child policies and regulations. Across eastern Uganda, several bottlenecks to iron and folic acid supplementation were identified, including limited health education among pregnant women and health workers and stock-outs [34]. Another evaluation in southwestern Uganda reported 22.37% self-reported adherence to folic acid supplementation among pregnant mothers [35]. The factors contributing to this low adherence must be addressed to achieve better outcomes and eliminate NTDs among children.

Low birth weight (LBW) was significantly associated with open NTDs. This aligns with previous evidence that poor fetal growth and micronutrient deficiencies contribute to both LBW and congenital anomalies [36]. Improving maternal nutrition may reduce the risk of NTDs and associated outcomes. Higher birth order and gravida were associated with decreased odds of open NTDs, suggesting that early pregnancies may carry a higher risk, possibly due to poorer antenatal preparedness or folate deficiency. These findings emphasize the need to scale up folic acid supplementation, improve maternal nutrition, and prioritize early antenatal engagement, especially among primigravidas and HIV-negative women who may be less targeted for intensive antenatal care. The study findings will contribute valuable evidence to support public health interventions, inform national birth defect surveillance systems, and enhance clinical care for affected neonates.

Other factors, such as gravida, birth order, and maternal age, showed no statistically significant trends. However, despite their insignificance, we noted more NTDs among mothers under 30 than among those over 30. Our study does not estimate the population risk of NTDs by maternal age. It rather describes the distribution of NTDs within the sampled population. Overall, we had 56 women below 30 years and 37 above 30 years, indicating that more women in this sample were below 30 years, which is typical of younger maternal age structures in rural SSA populations. A higher number of NTD cases in this group may simply reflect the underlying age

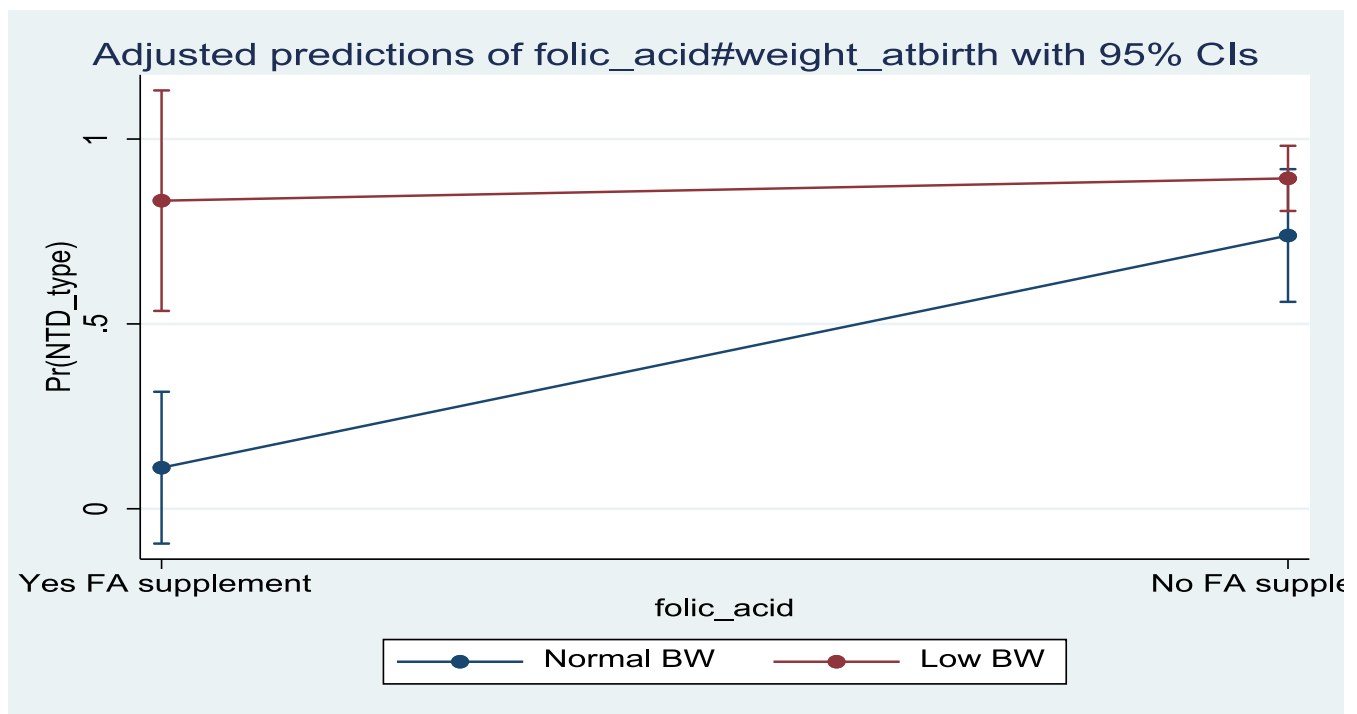


FIGURE 1 | Predicted probability of open neural tube defect by FA supplementation and birth weight. *Note:* This margin plot shows the predicted probabilities of having an open NTD across combinations of folic acid supplementation (Yes/No) and birth weight (Normal/Low), based on a logistic regression model with an interaction term.

distribution of all births. Without denominator data, for example, the total births per age group, we cannot conclude that a younger age confers a higher risk despite the association.

Some evidence has demonstrated a higher prevalence of some NTDs, such as Spina bifida, among young mothers below 30 years [37, 38]. However, these young mothers had some underlying comorbidities such as type 2 diabetes. Other evidence has demonstrated an increased risk of infants having NTDs among older mothers compared to the young ones; for example, mothers older than 35 years in Ethiopia had a 1.9 chance of giving birth to infants with NTDs [39]. More evidence from a community-based study of 891 women demonstrated a 3.5 times higher risk of delivering infants with NTDs among mothers aged above 30 [40]. These literature findings warrant extensive studies concerning the influence of age on NTD development.

5 | Strengths and Weaknesses

A major strength of this study is its inclusion of all eligible NTD cases over 3 years, providing comprehensive insights into the burden and characteristics of NTDs at a regional referral hospital. The study also used a robust data abstraction tool and multivariate analysis to identify significant predictors, enhancing the validity of findings. However, the study had limitations. It relied on retrospective secondary data, which was incomplete and subject to documentation errors. Additionally, the hospital-based nature of the study may limit generalizability to the broader population, as only facility-delivered or referred cases were included. Lastly, the cross-sectional design does not allow for causal inference or the assessment of temporal trends.

6 | Conclusion and Recommendations

The study highlights the significant burden of NTDs among neonates at Mbarara Regional Referral Hospital, reinforcing the need for targeted public health responses. The predominance of open NTDs echoes the importance of early prevention strategies, primarily through folic acid supplementation. While mortality was not overwhelming, the presence of severe complications such as sepsis, hydrocephalus, and neurological impairment emphasizes the urgency for timely diagnosis, surgical intervention, and post-natal care. The observed inverse association between maternal HIV status and open NTDs challenges existing assumptions. It reveals potential protective factors, such as enhanced antenatal follow-up or nutritional interventions in this subgroup. However, inconsistencies in global data necessitate further investigation to identify the underlying mechanisms and contextual influences, including ART regimens and folate interactions, especially in the local setting. These findings also call for strengthening maternal health systems, with a focus on universal access to folic acid before conception and throughout early pregnancy. Addressing barriers to supplementation, such as knowledge gaps, supply shortages, and health system inefficiencies, should be central to intervention efforts. Additionally, improving perinatal surveillance, especially in rural and underserved regions, is essential for early detection and referral. We recommend conducting a prospective longitudinal study to establish further evidence on the factors associated with open and closed NTDs in this setting.

Author Contributions

Benard Owere: conceptualization, writing – original draft, writing – review and editing. **Patience D. Nalumaga:** writing – original draft,

writing – review and editing, methodology. **Dauglas Nkoyooyo**: formal analysis, writing – original draft, writing – review and editing. **Innocent Ayesiga**: writing – original draft, writing – review and editing.

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The authors have nothing to report.

Ethics Statement

The Faculty of Medicine Research and Ethics Committee initially reviewed the study. It was then reviewed by the Mbarara University of Science and Technology Research Ethics Committee and given approval number MUST-2024-1944. Informed consent was not obtained since we reviewed records. Administrative approval was obtained to access the hospital records concerning these pediatric patients.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data is available following a reasonable request from the authors.

Transparency Statement

The lead author, Benard Owere, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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