

RESEARCH ARTICLE

Co-Occurrence of Malaria, Pneumonia, and Diarrheal Disease Among Households: A Cohort Study in Rural Western Uganda

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ABSTRACT

Objectives: This study aims to identify patterns associated with clustering and co-occurrence of malaria, pneumonia, and diarrhoea, the leading causes of death in children under age five in sub-Saharan Africa, in western Uganda to generate evidence for integrated prevention and control measures.

Methods: We conducted a prospective longitudinal study complemented by passive surveillance at local clinics. All households in the three selected villages were eligible to participate. Household-level socioeconomic and geographic data were linked to clinically diagnosed disease outcomes. Co-occurrence of diseases within households, defined as the diagnoses of two of the three diseases of interest (malaria, pneumonia, and diarrhoea) within a four-week period, was assessed using a Poisson model with a log link. Multinomial logistic regression models were fit to assess the association between patterns of malaria and pneumonia occurrence with socioeconomic and geographic factors.

Results: A total of 399 households were enrolled and completed baseline surveys. The smallest village accounted for 68.5%, 43.2%, and 38.1% of malaria, pneumonia, and diarrhoea cases, respectively. After adjusting for village, socioeconomic status, and the mean age of children in the home, households in Kasanzi had a higher relative risk of having both malaria and pneumonia versus neither disease compared to households in Bunyangoni (RRR: 33.84, 95% CI: 7.10, 161.24). For models replacing village with elevation, households in at higher elevations had a higher relative risk of having both malaria and pneumonia versus neither disease compared to households in at lower elevations (RRR: 26.59, 95% CI: 2.53, 279.84). No clear associations were found between malaria and pneumonia co-occurrence and SES.

Conclusions: Findings demonstrate that within small geographic areas, disease burden can vary dramatically across communities. Targeted, community-level interventions, rather than broad regional programs, are essential to address the distinct transmission dynamics and overlapping risks faced by high-burden communities.

1 | Introduction

Malaria, pneumonia, and diarrhoea remain the leading causes of death among children under 5 years of age across most of sub-Saharan Africa, including Uganda [1]. While most of the current literature focuses on individual diseases, research shows substantial spatial heterogeneity with some areas facing elevated burdens of either two or three of these diseases [1, 2]. This overlapping distribution creates the potential for co-occurrence of disease within the same households or individuals. Spatial analyses conducted in Malawi found positive associations between malaria and pneumonia in moderate and high endemicity regions, as well as indications of an association with diarrhoea, providing evidence that these diseases share similar spatial patterns and that there may be common risk factors [3].

However, studies explicitly examining the co-occurrence at the household level remain limited. The few observational studies that have looked at malaria and pneumonia co-infections find that patients with co-infections have increased disease severity and mortality compared to those with a single infection [4]. These findings highlight the need for greater horizontal focus in research and interventions to understand the full scope of burden at the local level [5].

Studies investigating these diseases individually find similar risk factors. All three diseases show strong socio-economic patterning, reflecting shared structural determinants of infection risk [6–8]. For example, diarrhoea is more common in households without improved toilet facilities and clean drinking water while pneumonia is associated with overcrowding in homes and indoor air pollution related to cooking [9–11]. In contrast, malaria is generally associated with household construction [6]. While the specific factors associated with each disease are distinct, they tend to occur within the same households which may suggest that clustering of these diseases within the same households may be driven by shared environmental, structural, and behavioural factors [12]. In Uganda, there are well documented disparities in the combined prevalence of ARI symptoms (i.e., pneumonia), fever (i.e., malaria), and diarrhoea between the highest and lowest socio-economic status (SES) households of 33% and 53%, respectively [13]. Further, the probability of multiple infections increases with less access to health services and lower SES [2].

Lower SES households, by nature, are less able to pay for medical care. While biologically, co-infections within the same individual can lead to more severe disease and death, infections among separate household members can also have a negative impact [14]. Co-occurrence of these infections within households may compound caregiving burdens and increase health expenditure, potentially creating a reinforcing cycle of illness and financial strain [15]. Repeated illness episodes within the same household can force families to repeatedly divert limited financial resources towards healthcare costs, including transport, consultation fees, and medication, while also reducing income through missed work [16]. The impact of SES may be modified by the level of rurality, with rural areas generally having lower SES, greater and higher disease burden than urban areas. This may be further exacerbated by differing access to

health care facilities and societal contexts between rural and urban communities [9, 17–19].

Current practice in rural sub-Saharan Africa is to use integrated community case management (iCCM), a program that integrates community-level diagnosis and treatment of malaria, pneumonia, and diarrhoea by training and supplying community health workers (CHWs) to care for children under the age of 5 [20]. While this program has been effective and widely accepted, it does little to address potential opportunities for disease prevention beyond education [21]. Though this program can help reduce the financial burden for young children by reducing delays in care and avoiding travel and treatment costs, a supplementary intervention from a more preventative approach may be necessary. Furthermore, understanding patterns and factors associated with co-occurrence of these diseases at the household level could inform interventions that simultaneously address multiple diseases from the prevention perspective [2, 22]. The objective of this study was to identify patterns associated with co-occurrence of malaria, pneumonia, and diarrhoea within households in rural western Uganda to generate evidence for integrated prevention and control measures.

2 | Methods

2.1 | Study Design

We conducted a longitudinal, household-based prospective cohort study. After baseline surveys and household enumeration were completed, passive surveillance was conducted at neighbouring government health facilities to document episodes of malaria, pneumonia, and diarrheal disease among individuals of all ages living in enrolled households throughout the 7-month follow-up period.

2.2 | Study Area

This study was carried out in three villages in Bugoye sub-county in the Kasese District of western Uganda (Figure 1). This is a rural area characterized by deep river valleys and steep hillsides with elevations up to 2000m near the border of the Rwenzori Mountains National Park. The large variation in geographic factors including elevation and slope over relatively short distances fosters a wide range of malaria transmission intensity [23]. Most of the 43,000 residents of Bugoye sub-county are subsistence farmers living without access to water or electricity in the home [24].

Lower-level public health facilities, private drug shops, and CHWs are the primary sources of medical care. CHWs provide care to children under 5 years of age at no cost as part of a government-supported iCCM program.

Study villages including Kasanzi, Bunyangoni, and Rwakingi 1A were purposefully selected based on a sub-county-wide malaria indicator style survey with the goal of selecting villages of differing transmission intensity [23]. Kasanzi was selected as the community with the highest malaria transmission, with a

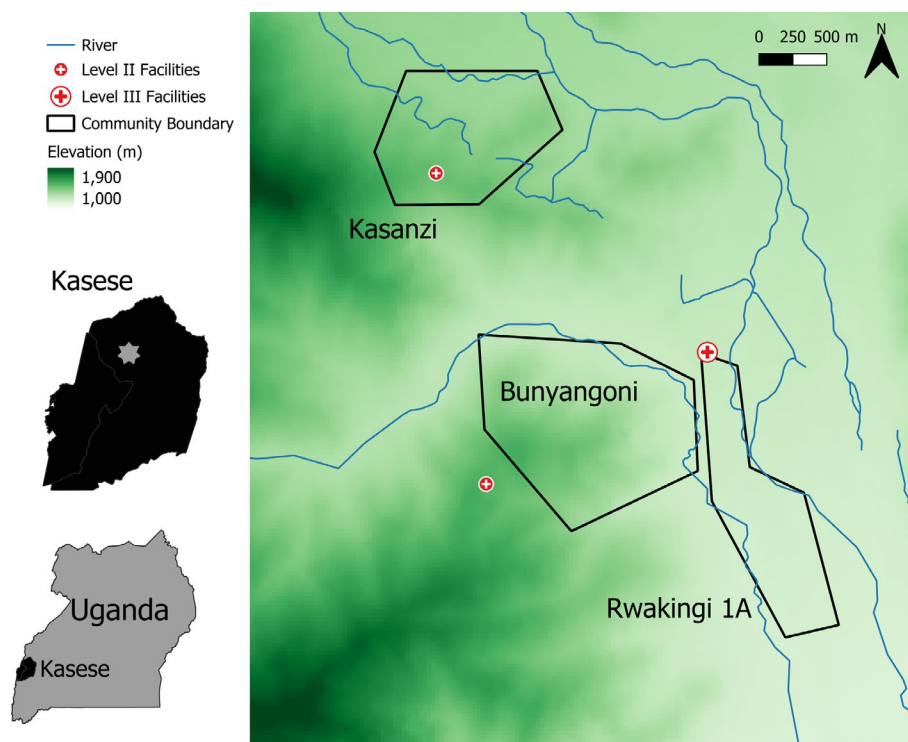


FIGURE 1 | Map of study area. The large map on the right shows the study area as denoted by the grey star inside the black cut out of Kasese District on the left. These maps were created in QGIS using shapefiles for administrative boundaries from the Humanitarian Data Exchange.

TABLE 1 | Study villages.

Village	Households	Population	PfPR
Bunyangoni	206	1299	10.5%
Rwakingi 1A	126	774	18.6%
Kasanzi	98	507	31.7%

Plasmodium falciparum prevalence rate (PfPR) of 31.7% in 2019, 2 to 3 years prior to data collection. Rwakingi 1A, located at low elevations along the river, and Bunyangoni, located on the hillside slopes, had lower transmission intensities than Kasanzi (Table 1). Village-specific incidence rates of pneumonia and diarrhoea were not known at the time of enrollment. However, the incidence of pneumonia has been shown to be as high as 7421 cases per 100,000 people in Kasese. Notably, the larger Tooro region, which encompasses Kasese, has the third highest prevalence of diarrhoea in Uganda at 22.9% among children under 5 due to high levels of faecal contamination of drinking water [25, 26].

2.3 | Enrollment and Data Collection

Enrollment and baseline surveys were conducted between November 29 and December 8, 2022. All households in each village were considered eligible and were invited to participate, including anyone living in the home at the time of the survey. Households with no one present at the time of visit were revisited up to three times before being excluded. Response rates were high at 88% (86/98), 94% (195/206), and 87% (110/126) in Kasanzi, Bunyangoni, and Rwakingi 1A, respectively. All

consenting household residents were enrolled. Study staff administered surveys modified from the most recent Uganda Malaria Indicator Survey including questions on household composition and demographics, household construction and amenities, malaria prevention and treatment behaviours, and general health seeking preferences [27].

2.4 | Surveillance Data

Seven months of passive surveillance for incident malaria, pneumonia, and diarrhoea cases was conducted at one level III health facility centrally located between the three villages and two level II health facilities between December 9, 2022 and July 3, 2023 (Figure 1). Participants brought their study identification card when presenting for care, which was then documented in the clinic registers. Each week, study staff abstracted data from registers regarding the reason for visit, diagnosis, laboratory testing results, and treatment of any study participants seeking care at one of the facilities or with a local CHW. Data were recorded in REDCap, a secure database using mobile devices [28]. No follow-up surveys were conducted after the baseline survey.

Malaria, pneumonia, and diarrhoea were diagnosed by clinicians at the participating government healthcare facilities in concordance with usual practice in the area. Children presenting to the facility were tested for malaria and diagnosed based on results of a rapid diagnostic test. Pneumonia was diagnosed among individuals with a cough, sounds of liquid in the lungs by use of a stethoscope, wheezing, and chest indrawing. In children, assessments of rapid breathing are also taken into consideration, defined as at least 60 breathes per minute (bpm), at least 50 bpm, and at least 40 bpm in children 0–2 months, 2–11 months, and

1–5 years old, respectively. Diarrhoea diagnosis was based on severity of dehydration and the presence of loose or watery stools.

2.5 | Analysis

The primary outcomes were the presence of malaria, pneumonia, and diarrhoea, each of which was defined as the diagnosis of anyone within the household with each respective disease at any point during the study. Co-occurrence was defined as diagnosis with two different diseases of interest within a four-week period for anyone in a given household to balance capturing both overlapping and sequential infections while reducing the potential for non-related events. Co-occurrences were analysed separately for pneumonia and malaria, pneumonia and diarrhoea, and malaria and diarrhoea. Data were collapsed to the household level for all analyses except descriptive statistics on timing of disease occurrence which utilized the longitudinal data structure.

Additionally, several predictor variables were considered. SES was calculated using a principal component analysis of asset and ownership data, which was then divided into tertiles [29]. Long lasting insecticidal net (LLIN) coverage was parameterized as a categorical variable indicating ownership of no LLINs, owning LLINs but not enough to meet the universal coverage threshold of 1 LLIN per 2 people in the home, and meeting universal coverage. Seasonality was categorized as rainy season (March–May; September–November) or dry season (December–February; June–August) with the first and last 2 weeks of each of these periods defined as a transition season between dry and rainy seasons. Elevation data were divided into tertiles categorized as low (1180–1247m), medium (1248–1382m), and high (1383–1580m). Distance to the nearest river was a categorical variable with categories for 0.1 km or less, 0.1–0.5 km, and greater than 0.5 km from the river. Normalized difference vegetation index (NDVI), calculated as $(NIR - Red) / (NIR + Red)$ where NIR is near infrared bands from Landsat raster satellite data, was divided into tertiles and categorized as low (0.177 to 0.311), medium (0.312–0.340), and high (0.341–0.417). Data for environmental variables were obtained from the Humanitarian Data Exchange and the Regional Centre for Mapping of Resources for Development (RCMRD).

Descriptive statistics for baseline demographic and household characteristics were presented as frequencies and percentages for categorical data and medians and interquartile ranges for continuous data. Additional descriptive statistics for timing and locations of cases were calculated as frequencies, percentages, and incidence rates. Pairwise correlations between the presence of malaria, pneumonia, and diarrhoea were calculated to understand the relationship between the occurrence of each of the three diseases over the entire study period.

Due to the small number of co-occurrences within rolling four-week windows, unadjusted Poisson regression models were only fit for two outcomes: (1) malaria-pneumonia co-occurrence vs. no co-occurrence and (2) any co-occurrence of malaria, pneumonia, and diarrhoea vs. no co-occurrence. These models were restricted to Kasanzi due to few outcomes in the other communities. Predictor variables included household crowding, mean

age of children in the home, LLIN coverage, LLIN ownership, water source, location of water source, toilet location, toilet type, cooking location, if the household treated their water, previous admission for malaria, previous treatment with IV for malaria, SES, distance to the nearest river, NDVI, and elevation. From the fitted models, the prevalence ratio was estimated, and robust standard errors were used to calculate 95% confidence intervals (CIs).

Two multivariable multinomial logistic regression models were fit to identify household-level and environmental factors associated with presence of multiple diseases, while controlling for other risk factors. Because elevation and village were highly colinear, two versions of the model are included, one using village (village model) and the second model replacing village with elevation (elevation model). The outcome in these models was defined as a categorical variable with levels for neither malaria nor pneumonia, pneumonia only, malaria only, and malaria and pneumonia in a household during the entire surveillance period, not restricted to the 4-week rolling window used to assess co-occurrences. These models were also adjusted for SES and the average age of children in the home. From the fitted models, relative risk ratios (RRRs) were estimated and corresponding 95% CIs were computed. All analyses were conducted at the household level with the exception of the descriptive statistics on age distributions in Table 1. All analyses and data management were conducted in R version 4.4.2 [30].

2.6 | Ethics Statement

Ethical approval was provided by the institutional review boards of the University of North Carolina at Chapel Hill (19-1094), the Mbarara University of Science and Technology (06/05-18), and the Uganda National Council for Science and Technology (HS 2482). All participants provided written informed consent, with children ≥ 8 years of age provided written assent in the local language consistent with Ugandan guidelines.

3 | Results

3.1 | Study Sites and Population

A total of 430 households were listed on the 2019 CHW census, of which 399 (93.8%) were enrolled and completed baseline surveys with 8 (2.0%) households excluded from the analysis due to missing data (Table 2). Of the remaining 391 households, 195 households accounting for 1261 individuals were in Bunyangoni, 86 households with 512 individuals were in Kasanzi, and 110 households accounting for 764 individuals were in Rwakingi 1A. Similarly, 2 (2.2%) malaria and 7 (8.6%) pneumonia cases could not be linked to a household and were excluded.

Rwakingi 1A had the highest SES with 79.5% of its population in the highest SES tertile. The percentage of children hospitalized in the past year for malaria ranged from 15.0% in Kasanzi to 36.3% in Rwakingi 1A (Table 2). LLIN coverage also varied across villages with 28.5%, 52.3%, and 48.1% of households meeting the World Health Organization (WHO) definition of universal coverage and 44.0%, 16.3%, and 25.5% of households owning

TABLE 2 | Household characteristics.

	Bunyangoni N=195	Kasanzi N=86	Rwakingi 1A N=110	Total N=391
Family Size (Median (IQR))	5 (2)	5 (3)	5 (3)	5 (2)
Number of children under 5 years old (Median (IQR))	1 (1)	1 (1)	1 (1)	1 (1)
Age of children (Median (IQR)) ^a	6.5 (3.8)	6.0 (4.3)	6.8 (3.7)	6.5 (3.8)
Age of household members (Median (Q1-Q3))	6 (1–26)	7 (1–30)	5 (2–29)	6 (1–27)
Distance from the nearest river (km) (Median (IQR))	0.35 (0.41)	0.16 (0.15)	0.17 (0.09)	0.22 (0.22)
Elevation of household (m) (Median (IQR))	1330 (165)	1422 (116)	1203 (17)	1308 (199)
NDVI	0.33 (0.04)	0.34 (0.04)	0.30 (0.05)	0.33 (0.04)
Sex of the head of the household ^b				
Male	153 (78.9)	71 (82.6)	86 (80.4)	310 (80.1)
Female	41 (21.1)	15 (17.4)	21 (19.6)	77 (19.9)
Missing	1	0	3	4
Education level of the head of the household ^b				
No school	35 (18.0)	20 (23.3)	23 (21.4)	78 (20.2)
Primary school	115 (59.3)	50 (58.1)	45 (42.1)	210 (54.3)
Secondary school	39 (20.1)	14 (16.3)	31 (29.0)	84 (21.7)
University	5 (2.6)	2 (2.3)	8 (7.5)	15 (3.9)
Missing	1	0	3	4
Marital Status of the head of the household ^b				
Unmarried	13 (6.7)	7 (8.1)	12 (11.3)	32 (8.3)
Married	165 (85.1)	72 (83.7)	74 (69.8)	311 (80.6)
Divorced	4 (2.1)	1 (1.2)	7 (6.6)	12 (3.1)
Widowed	12 (6.2)	6 (7.0)	13 (12.3)	31 (8.0)
Missing	1	0	4	5
LLIN Coverage				
No LLINs	85 (44.0)	45 (52.3)	27 (25.5)	157 (40.8)
Below universal coverage	53 (27.5)	14 (31.4)	28 (26.4)	95 (24.7)
Meets universal coverage	55 (28.5)	27 (16.3)	51 (48.1)	132 (34.3)
Missing	2	0	4	6
Source of water				
Piped water	53 (27.2)	67 (77.9)	108 (100)	228 (58.6)
Tube well or borehole	9 (4.6)	0 (0)	0 (0)	9 (2.3)
Water from spring	28 (14.4)	0 (0)	0 (0)	28 (7.2)
Surface water (river, lake, stream, and irrigation channel)	105 (53.8)	19 (22.1)	0 (0)	124 (31.9)
Missing	0	0	2	2

(Continues)

TABLE 2 | (Continued)

	Bunyangoni N=195	Kasanzi N=86	Rwakingi 1A N=110	Total N=391
Location of water				
In own dwelling	31 (16.0)	8 (9.3)	20 (18.3)	59 (15.2)
In own yard or plot	11 (5.7)	29 (33.7)	67 (61.5)	107 (27.5)
Elsewhere	152 (78.4)	49 (57.0)	22 (20.2)	223 (57/3)
Missing	1	0	1	2
Treat their water	10 (5.2)	2 (2.4)	8 (7.3)	20 (5.0)
Missing	1	1	1	3
Type of toilet				
Flush or pour toilet	0 (0)	0 (0)	3 (2.8)	3 (0.8)
Pit Latrine	190 (97.4)	83 (96.5)	106 (97.2)	379 (97.2)
Hanging toilet	1 (0.5)	0 (0)	0 (0)	1 (0.3)
No facility/bush	4 (2.1)	3 (3.5)	0 (0)	7 (1.8)
Missing	0	0	1	1
Share a toilet	13 (6.8)	2 (2.3)	8 (7.3)	23 (5.9)
Missing	3	0	1	4
Location of toilet				
In own dwelling	6 (3.1)	1 (1.2)	16 (14.8)	23 (5.9)
In own yard or plot	186 (95.4)	83 (96.5)	92 (85.2)	361 (92.8)
Elsewhere	3 (1.5)	2 (2.3)	0 (0)	5 (1.3)
Missing	0	0	2	2
Cooking location				
In the house	2 (1.0)	0 (0)	1 (1.0)	3 (0.8)
In a separate building	174 (90.2)	82 (95.3)	95 (87.2)	351 (90.5)
Outdoors	17 (8.8)	4 (4.7)	13 (11.9)	34 (8.8)
Missing	2	0	1	3
Socioeconomic status				
T1 (Lowest)	74 (46.0)	27 (36.5)	7 (8.0)	108 (33.4)
T2	63 (39.1)	34 (45.9)	11 (12.5)	108 (33.4)
T3 (Highest)	24 (14.9)	13 (17.6)	70 (79.5)	107 (33.1)
Missing	34	12	22	68
If a child in the household had a fever, where would the caregiver take the child for care?				
Government health center	162 (83.1)	73 (84.9)	65 (59.1)	300 (76.7)
Private health center	2 (1.0)	2 (2.3)	3 (2.7)	7 (1.8)
Informal care ^c	13 (6.7)	7 (8.1)	20 (18.2)	40 (10.2)
CHW	18 (9.2)	4 (4.7)	22 (20.0)	44 (11.3)
Missing	0	0	0	0
Any children admitted for malaria	44 (24.6)	12 (15.0)	33 (36.3)	89 (25.4)
Missing	16	6	19	41

(Continues)

TABLE 2 | (Continued)

	Bunyangoni N=195	Kasanzi N=86	Rwakingi 1A N=110	Total N=391
Any children given intravenous fluids	44 (24.6)	12 (15.2)	32 (34.8)	88 (25.1)
Missing	16	7	18	41

Note: Values represent counts and the percentage in parentheses unless indicated as the median and IQR in parentheses Missing values are not included in percentage or IQR calculations.

^aDoes not include homes with no children: 31 in Bunyangoni, 23 in Kasanzi, and 22 in Rwakingi 1A.

^bThe head of the household is typically the oldest male in the home but in the absence of a male adult that was not a child of the women in the home, the oldest female was considered the head of the household.

^cInformal care includes drug shops and traditional healers.

no LLINs in Bunyangoni, Kasanzi, and Rwakingi 1A, respectively [31].

3.2 | How Are Malaria, Pneumonia, and Diarrhoea Distributed Across Time and Space?

During the eight-month surveillance period, 89 cases of malaria were reported across 59 households with 15 (25.4%) households reporting multiple cases (Table 3). Over half (52.8%) of malaria cases occurred in the transition season. Kasanzi, the geographically smallest of the three villages, reported the most malaria cases, accounting for 68.5% of cases and 62.7% of households with a case (Table 3). Of the households in Kasanzi, 43.0% had a diagnosed malaria case during the study period compared to just 8.7% and 4.5% in Bunyangoni and Rwakingi 1A, respectively.

A total of 74 cases of pneumonia were reported among 55 households (Table 3) with 13 (23.6%) households reporting multiple cases. Similar to malaria, 52.7% of pneumonia cases occurred in the transition period. Pneumonia cases were more evenly distributed across Bunyangoni and Kasanzi, with 43.2% and 40.5% of pneumonia cases, respectively (Table 3). However, among villages, Kasanzi still has the highest relative burden, with 23.3% of houses having at least one pneumonia infection compared to 13.3% and 8.2% in Bunyangoni and Rwakingi 1A, respectively.

Diarrhoea cases were the least common with cases diagnosed among only 20 households (5.1%) (Table 3). The majority (64.9%) of diarrhoea cases occurred in the transition period. Diarrhoea cases were relatively evenly dispersed across the villages ranging from 23.8% of cases in Rwakingi 1A to 38.1% of cases in both Bunyangoni and Kasanzi. However, diarrhoea cases show a similar distribution pattern as seen for malaria and pneumonia. The prevalence of diarrhoea was at least twice as high in Kasanzi as in the other two villages, with 8.1%, 4.1%, and 4.5% of households having at least one case in Kasanzi, Bunyangoni, and Rwakingi 1A, respectively (Table 3). Temporal characteristics of disease co-occurrence are available in Table S1 and spatial distributions of cases and risk of disease individually and co-occurrences are available in Figures S1 and S2.

3.3 | Do Malaria, Pneumonia, and Diarrhoea Co-Occur Within the Same Households?

Households with malaria were more likely to also have pneumonia compared to other households, indicating a tendency for

these two diseases to co-occur (Phi correlation: 0.263, 95% CI: 0.17, 0.35) (Table 4). A smaller positive correlation was seen between pneumonia and diarrhoea. While the correlation between diarrhoea and malaria was large, the estimate was imprecise.

3.4 | Bivariate Associations

Since most cases of co-occurrence were in Kasanzi, results presented below were restricted to households in Kasanzi and two outcomes were considered, the co-occurrence of (i) pneumonia and malaria and (ii) any combination of malaria, pneumonia, and diarrhoea as the other co-occurrences were rare. SES was associated with co-occurrence of malaria and pneumonia, with all households with a co-occurrence in the lowest (6, 66.7%) and middle (3, 33.3%) SES tertiles. Elevation was also found to be associated with co-occurrence of pneumonia and malaria as well as any disease combination within Kasanzi with an estimated 8.9-fold and 5.33 higher prevalence for every 100-m increase in elevation, respectively (Table 5).

3.5 | Adjusted Analysis

Multivariable multinomial logistic regression models were fit using the occurrence of malaria, pneumonia, and both malaria and pneumonia over the entire study period as a categorical variable, in contrast to the previous models which defined co-occurrence based on rolling 4-week periods. Results from the elevation and village models indicate similar patterns.

The village model indicates that households in the highest SES tertile have a lower relative risk of pneumonia versus neither disease (RRR: 0.24, 95% CI: 0.06, 0.99) compared to households in the poorest tertile. Households with the average age of their children under the age of 5 have a higher relative risk of pneumonia versus neither disease compared to households with the average age of children 5 years or older (RRR: 2.39, 95% CI: 1.03, 5.58). In Kasanzi, there was a higher relative risk of both malaria and a co-occurrence of malaria and pneumonia versus neither disease compared to Bunyangoni (malaria RRR: 7.08, 95% CI: 2.83, 17.71; co-occurrence of malaria and pneumonia RRR: 33.84, 95% CI: 7.10, 161.24) (Table 6).

The elevation model similarly indicates a protective effect of SES on the risk of pneumonia versus neither disease (RRR: 0.24, 95% CI: 0.06, 0.92) and an increased risk for pneumonia versus neither disease when the children are on average younger than

TABLE 3 | Characteristics of disease occurrence.

	Malaria	Pneumonia	Diarrhoea	Any Reason^a
Number of households with a positive case	59	55	20	119
Number of cases	89	74	21	221
Number of cases ^b				
Season ^c				
Dry	18 (20.2)	9 (12.2)	2 (9.5)	34 (15.4)
Rainy	24 (27.0)	26 (35.1)	8 (38.1)	66 (29.9)
Transition	47 (52.8)	39 (52.7)	11 (52.4)	121 (54.8)
Village				
Bunyangoni	21 (23.6)	32 (43.2)	8 (38.1)	85 (38.5)
Kasanzi	61 (68.5)	30 (40.5)	8 (38.1)	107 (48.4)
Rwakingi 1A	7 (7.9)	12 (16.2)	5 (23.8)	29 (13.1)
Number of households ^d				
Village				
Bunyangoni (<i>n</i> = 195)	17 (28.8)	26 (47.3)	8 (40.0)	58 (48.7)
Kasanzi (<i>n</i> = 86)	37 (62.7)	20 (36.4)	7 (35.0)	43 (36.1)
Rwakingi 1A (<i>n</i> = 110)	5 (8.5)	9 (16.4)	5 (25.0)	18 (15.1)
Proportion of households ^{d,e}				
Village				
Bunyangoni (<i>n</i> = 195)	17 (8.7)	26 (13.3)	8 (4.1)	58 (29.7)
Kasanzi (<i>n</i> = 86)	37 (43.0)	20 (23.3)	7 (8.1)	43 (50.0)
Rwakingi 1A (<i>n</i> = 110)	5 (4.5)	9 (8.2)	5 (4.5)	18 (16.4)
Incidence rates				
Village ^f				
Bunyangoni (<i>n</i> = 195)	0.033	0.050	0.013	0.134
Kasanzi (<i>n</i> = 86)	0.225	0.111	0.030	0.395
Rwakingi 1A (<i>n</i> = 110)	0.019	0.033	0.014	0.080
Incidence rate ^g				
Dry	0.043	0.022	0.005	0.081
Rainy	0.155	0.128	0.036	0.398
Transition	0.053	0.057	0.018	0.145

Note: Values represent counts and the percentage in parentheses unless indicated as the median and IQR. Missing values are not included in percentage or IQR calculations. Households may be represented multiple times in the table as each household may have had at least one case of each disease.

^aAny reason includes households that visited the health facility for a diagnosis for any of these three diseases, malaria, pneumonia, or diarrhoea but also those who received other diagnoses to provide context for general care seeking patterns.

^bThe number of cases uses the "Number of cases" row as the denominator for percentage calculations. In these rows, different cases may represent the same household.

^cSeason is defined as the rainy season from March to May, the dry seasons from December to February and June to August. The transition season was calculated as the first and last 2 weeks of each of the rainy and dry seasons. Year to year these cut-offs could differ, particularly with changes in season timing because of climate change. Weeks in each season were relatively evenly distributed, with 35%, 39%, and 26% of the surveillance period in the dry, transition, and rainy seasons, respectively.

^dIncludes each household just once regardless of the number of cases occurring in each household. It uses "Number of households with a positive case" row as the denominator for percentages.

^eThe denominator is the "n" value provided for each village.

^fIncidence rates are calculated per person-year using 234 days of person-time for all community members over the surveillance period.

^gIncidence rates are calculated per person-year based on season with person-time split between 11 (35%), 12 (39%), and 8 (26%) weeks in the dry, transition, and rainy seasons, respectively.

TABLE 4 | Correlations of disease occurrence.

Disease 1	Disease 2	Households with both infections (n)	Phi Correlation (95% CI)
Malaria	Pneumonia	21	0.263 (0.17, 0.35)
Pneumonia	Diarrhoea	6	0.108 (0.01, 0.20)
Diarrhoea	Malaria	5	0.066 (−0.03, 0.16)

TABLE 5 | Household characteristics associated with co-occurrence.

	Malaria and pneumonia N=9 PR (95% CI)	Any co-occurrence N=12 PR (95% CI)
Crowding (people per room)	0.11 (0.01, 0.82)	0.16 (0.03, 0.79)
Mean age of children in the home (Ref: Under 5 years old)		
5 years or older	0.94 (0.21, 4.23)	1.06 (0.32, 3.54)
LLIN coverage (Ref: No nets)		
Below universal coverage	1.07 (0.24, 4.72)	0.80 (0.19, 3.35)
Meets universal coverage	0.28 (0.04, 2.19)	0.42 (0.10, 1.82)
LLIN ownership (binary)	0.55 (0.15, 2.05)	0.55 (0.18, 1.69)
Water source (Ref: Piped water)		
Surface water	1.01 (0.23, 4.46)	1.18 (0.35, 3.92)
Water location (Ref: In your home)		
In own plot/yard	0.55 (0.06, 5.33)	0.55 (0.06, 5.34)
Elsewhere	0.98 (0.14, 7.10)	1.47 (0.21, 10.08)
Previous admission for malaria	0.35 (0.10, 1.22)	0.53 (0.17, 1.68)
Previous treatment with IV for malaria	0.30 (0.08, 1.09)	0.48 (0.15, 1.55)
SES (Ref: T1 (poorest))		
T2	0.40 (0.11, 1.44)	0.30 (0.09, 1.02)
T3 (richest)	NA	NA
Distance to the nearest river (Ref: less than 100 m)		
100–499 m	NA	NA
500–1 km	1.24 (0.28, 5.53)	1.07 (0.32, 3.58)
NDVI (Ref: Low)		
Medium	0.63 (0.13, 2.92)	0.63 (0.13, 2.92)
High	0.35 (0.07, 1.86)	0.71 (0.17, 3.03)
Elevation (per 100 m)	8.9 (2.13, 37.26)	5.33 (1.98, 14.40)

Note: Outcome is a binary variable for co-occurrence of (i) malaria and pneumonia and (ii) any combination of malaria, pneumonia, and diarrhoea within the home within a 4-week period for disease from unadjusted models. Limited to only cases from Kasanzi due to sample size small sample size in the other communities. Toilet location, toilet type, cooking location, and if the household treated their water were also considered but were homogenous within Kasanzi and not included in the table. NA—not applicable, indicating that no one in Kasanzi were in that category. Abbreviation: PR = prevalence ratio.

5 (RRR: 2.54, 95% CI: 1.08, 5.94) compared to households with the average age of children 5 years or older. A higher elevation of between 1383 and 1580 m was associated with a higher risk of co-occurrence of malaria and pneumonia versus neither disease (RRR: 26.59, 95% CI: 2.53, 279.84) compared to households

at the lowest elevations (Table 6). Estimates for SES were small but imprecise while the estimated relative risk ratios between the average age of children within the home and co-occurrence compared to the presence of neither disease was estimated to be close to the null value of 1.

TABLE 6 | Adjusted associations between diseases of interest.

	Pneumonia RRR (95% CI)	Malaria RRR (95% CI)	Malaria and pneumonia RRR (95% CI)
Number of observations	34	38	21
Village model			
Village (Ref: Bunyangoni)			
Kasanzi	0.73 (0.19, 2.73)	7.08 (2.83, 17.71)	33.84 (7.10, 161.24)
Rwakingi 1A	1.43 (0.45, 4.53)	1.05 (0.28, 3.92)	NE
SES (Ref: T1)			
T2	1.04 (0.42, 2.59)	0.82 (0.31, 2.14)	0.41 (0.11, 1.50)
T3	0.24 (0.06, 0.99)	0.66 (0.20, 2.16)	0.49 (0.10, 2.38)
Mean age of children in the home (Ref: Under 5 years old)			
5 years or older	2.39 (1.03, 5.58)	0.53 (0.18, 1.56)	0.95 (0.26, 3.43)
Elevation model			
Elevation (m) (Ref: Low (1180–1247 m))			
Medium (1248–1382 m)	0.66 (0.22, 1.96)	1.09 (0.35, 3.36)	2.54 (0.20, 32.64)
High (1383–1580 m)	0.57 (0.18, 1.82)	1.72 (0.53, 5.52)	26.59 (2.53, 279.84)
SES (Ref: T1)			
T2	1.07 (0.43, 2.67)	0.93 (0.37, 2.30)	0.45 (0.13, 1.50)
T3	0.24 (0.06, 0.92)	0.72 (0.22, 2.29)	1.18 (0.23, 6.05)
Mean age of children in the home (Ref: Under 5 years old)			
5 years or older	2.54 (1.08, 5.94)	0.65 (0.23, 1.81)	1.32 (0.41, 4.31)

Note: Adjusted results from multivariable multinomial regression models estimating relative risk ratios (RRR). The reference group for the model is households with neither malaria nor pneumonia ($n = 305$). Bolded values indicate estimates where the confidence interval does not cross the null.

Abbreviation: NE: not estimable.

4 | Discussion

In a longitudinal cohort of households in rural western Uganda, we found that the incidence of malaria and pneumonia—leading causes of child mortality—demonstrated considerable spatial heterogeneity within a relatively small geographic area. Despite the furthest distance between households being just 5 km, the 8-month incidence of malaria was approximate 7-fold higher in Kasanzi compared to Bunyangoni (0.225 vs. 0.033 cases per person-year) with similar trends for pneumonia. Disproportionate transmission in Kasanzi also impacted the number of within household co-occurrences. Together, these findings suggest that fine-scale environmental and social factors, such as elevation and SES, may be related to focal, yet distinct transmission dynamics, highlighting the need for targeted interventions. While other studies have looked at similar issues in larger areas (e.g., administrative regions), ours is one of the few to do so on a fine geographic scale [32–34]. Our focus on contrasts between neighbouring communities shows that even in areas that might appear similar, disease prevalence can vary dramatically and that special attention needs to be paid to individual communities facing higher disease burdens rather than universal, “one-size fits all” approaches.

Elevation was highly associated with malaria and pneumonia co-occurrence, with more cases identified at higher elevations,

despite elevation typically being inversely related with malaria [35]. At our site, however, elevation is also associated with reduced access to and utilization of health services, though it is important to note that all households in this study were within the habitable range for mosquito populations [36, 37]. We believe that elevation might serve as a proxy for access to health care services. Kasanzi has a higher median elevation than the other two communities, with steeper roads that become difficult to pass in the rainy season when roads become muddy, as compared to Bunyangoni and Rwakingi 1A, which are at lower elevations with flatter roads. Furthermore, the health facility nearest Kasanzi is only a level II health facility, providing fewer services as compared to Bugoye Health Center, a level III facility, which is more centrally located to Bunyangoni and Rwakingi 1A. These issues may have had a greater relative impact on disease transmission than elevation alone.

While the estimates for the RRR for SES were small and imprecise, the proportion of households experiencing disease co-occurrence was not evenly distributed even within Kasanzi. Households in Kasanzi in the highest SES tertile were far less likely to have a co-occurrence (4.2%) compared to the middle (24.0%) and lowest (36.0%) SES tertiles, respectively. This provides some evidence for a more complex relationship between SES and disease incidence. Therefore, it appears that the

combination of SES and environmental factors may contribute to a higher disease burden, though more research is needed with a larger sample size to investigate this association more fully. Though previous studies have linked all three diseases to lower SES, there were still key differences in disease burden among the area in the lowest quintiles of SES [9, 38]. Even in poor communities, there are differences by SES, with the poorest households still being less likely to access healthcare services than less poor homes in rural Tanzania [39]. Therefore, even though most participants living in the study would likely be considered part of the lowest SES quintile across Uganda, they are not all at the same level.

Kasanzi was selected for this study based on high malaria transmission, likely driven by its proximity to several rivers and a spillway in combination with a low SES. While not surprising that malaria incidence was high, it was a surprise that the incidence of pneumonia and diarrhoea was also high in Kasanzi. Previous research shows that these diseases do co-occur with similar patterns of increased cases of malaria among children with severe pneumonia and vice versa, accounting for up to one fifth of children, from a meta-analysis of studies conducted across malaria-endemic areas [4]. Studies looking at severe pneumonia have found a concurrent malaria or diarrhoea infection of 2.88 and 3.41 times higher than children with non-severe pneumonia [40]. This pattern indicates the importance of understanding and preventing co-infections.

While malaria, a vector-borne disease, is highly tied to the environment through the necessity for stagnant water for mosquito breeding sites, the parametrized distance to the nearest river in the study did not result in a significant association with co-occurrence of diseases [41]. This is likely because proximity to standing water is not important for the mechanism of pneumonia. In contrast, proximity to standing water, which may be contaminated and result in cases of diarrhoea, or the location of water used for drinking, which could also serve as a mosquito breeding site, could result in greater co-occurrence of malaria and diarrhoea [42, 43]. Therefore, there is a potential for greater environmental influence in the patterns of disease co-occurrence that could not be assessed in this analysis resulting from similar spatial patterning of different environmentally linked risk factors which may further explain the concentration of cases in Kasanzi.

These findings support the need for CHWs and the importance of maintaining care within communities. While all communities would benefit from the presence of CHWs, limited funding has traditionally been a challenge to maintaining CHW activities and supplies [44]. Given the clear disparity in disease incidence across villages, irrespective of the causes, surveillance data can be used to help target the limited funding available to communities with higher disease transmission and lower access to care. While prevention of disease through identification and management of specific causes would be ideal, the clear spatial patterns of disease do allow for more targeted responses and more focused action.

Our study benefitted from high participation rates, comprehensive surveillance reporting, and household coordinates enabling

integration of environmental data. However, the study also has important limitations, foremost of which was the relatively small sample size and limited duration of follow up. While there were over 391 households in the study, this was insufficient when stratifying by village when using co-occurrence as outcome. We therefore had to rely on infection data that was not time bound in the multivariable models. Further, having just three villages limits our ability to understand the greater landscape to assess how Kasanzi relates to other villages. Given most of the cases occur in Kasanzi and that village and elevation are highly correlated, we are unable to completely disentangle the effects of village and elevation. There may be other ecological factors that are contributing to the effect seen in Kasanzi that are not represented in our data, which may result in residual spatial confounding.

Secondly, due to challenges linking individuals in the household data to surveillance data, we used household as the unit of observation. This makes it difficult to identify potential temporal and biological (e.g., malaria infection resulting in increased susceptibility to respiratory disease) associations within an individual and reduced the overall power of the study. We also could not capture care seeking at more distant, often private clinics, which may have affected our outcome measurement. There are likely important differences in populations seeking care at private vs. public health facilities and those who have differing levels of access to health care. Lastly, we were surprised by how few diarrhoea cases were identified given the proportion of households without piped water sources. It is possible that diarrhoea was underreported as it is more easily treated with home management than malaria and pneumonia. In general, it is likely that cases for all three diseases are undercounts due to the use of passive surveillance data, the lack of data on private health facilities, and possible misclassification due to a lack of laboratory confirmation for pneumonia and diarrhoea cases. However, possible misclassification may similarly lead to an overcount of cases.

5 | Conclusions

In this longitudinal cohort study, we found considerable fine-scale heterogeneity in the incidence of malaria and pneumonia, with disease burden concentrated in one village despite its proximity to lower-burden villages. Our findings suggest that environmental factors like elevation may play an important role in shaping transmission dynamics. These results highlight the importance of localized, community-specific strategies to effectively target areas of highest disease burden.

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Disclosure

These results have previously been presented at the annual meeting for the Society of Epidemiologic Research (SER) in Boston, MA (June 2025).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

In accordance with institutional regulations, deidentified individual data that supports the results will be shared provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes a data use/sharing agreement with UNC. The Principal Investigator should submit a request to the UNC Industry Contracting team (ospcontracting@unc.edu) to initiate the data use/sharing agreement.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** tmi70188-sup-0001-supinfo.docx. *Heat Map of the Spatial Distribution of Individual Diseases.* Heat maps were created using household GPS coordinates aggregated to a spatial resolution of 0.03 km² per grid cell. All boxes include at a minimum three households. The top row of heat maps shows the absolute number of cases for each disease in the area, not the number of households with a case. The bottom row maps the risk of disease as the number of households with a case (binary) over the total number of households in the grid square. Grey boxes represent areas where there are no households enrolled in the study. The community in the top left corner of each pane is Kasanzi, Bunyangoni is the large area in the lower middle, conjoined the Rwakingi 1A, which continues down towards the bottom righthand corner. Please note that graphs have different colour scales to enable visualization to differences for diseases of lower-case counts. **Table S1:** Description of temporal characteristics of disease co-occurrence. **Figure S2:** Heat map of the spatial distribution of disease co-occurrence. Heat maps were created using household GPS coordinates aggregated to a spatial resolution of 0.03 km² per grid cell. All boxes include at a minimum three households. The top row of heat maps shows the absolute number of cases for each co-occurrence of disease in the grid cell, not the number of households with a case. The bottom row maps the risk of disease co-occurrence as the number of households with at least one instance of the given co-occurrence (binary) over the total number of households in the grid square. Grey boxes represent areas where there are no households enrolled in the study. The community in the top left corner of each pane is Kasanzi, Bunyangoni is the large area in the lower middle, conjoined to Rwakingi 1A, which continues down towards the bottom righthand corner. Please note that graphs have different colour scales to enable visualization to differences for diseases of lower-case counts.