Dihydroartemisinin-piperaquine chemoprevention and malaria incidence after severe flooding: evaluation of a pragmatic intervention in rural Uganda

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Summary: Three rounds of chemoprevention with dihydroartemisinin-piperaquine delivered under pragmatic conditions reduced the incidence of malaria after severe flooding in western Uganda. These findings provide a proof-of-concept for the use of chemoprevention to reduce excess disease burden associated with severe flooding.

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ABSTRACT

Background

Malaria epidemics are a well-described phenomenon after extreme precipitation and flooding, which account for nearly half of global disasters over the past two decades. Yet few studies have examined mitigation measures to prevent post-flood malaria epidemics.

Methods

We conducted an evaluation of a malaria chemoprevention program implemented in response to severe flooding in western Uganda. Children ≤12 years of age from one village were eligible to receive 3 monthly rounds of dihydroartemisinin-piperaquine (DP). Two neighboring villages served as controls. Malaria cases were defined as individuals with a positive rapid diagnostic test result as recorded in health center registers. We performed a difference-in-differences analysis to estimate changes in the incidence and test positivity of malaria between intervention and control villages.

Results

A total of 554 children received at least one round of chemoprevention with 75% participating in at least two rounds. Compared to control villages, we estimated a 53.4% reduction (aRR 0.47, 95% CI 0.34 – 0.62, p<.01) in malaria incidence and a 30% decrease in the test positivity rate (aRR=0.70, CI 0.50 - 0.97, p=0.03) in the intervention village in the six months post-intervention. The impact was greatest among children receiving the intervention, but decreased incidence was also observed in older children and adults (aRR=0.57, CI 0.38-0.84, p<.01).

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Conclusions

Three rounds of chemoprevention with DP delivered under pragmatic conditions reduced the incidence of malaria after severe flooding in western Uganda. These findings provide a proof-of-concept for the use of malaria chemoprevention to reduce excess disease burden associated with severe flooding.

Keywords: malaria, Plasmodium, chemoprevention, mass drug administration, flooding

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BACKGROUND

The impact of climate change on the incidence of vector-borne diseases, including malaria, is an issue of substantial public health importance [1, 2]. In addition to rising surface temperatures, the manifold effects of global climate change also entail an increased frequency of weather extremes such as droughts and floods [3, 4]. Nearly half of global disasters over the past two decades were attributable to extreme precipitation and flooding, including 64% of events in the Africa region [5]. Populations in developing countries are particularly at risk of adverse health consequences from floods [6]. For many of the same reasons, these are also areas where malaria is endemic.

Unlike the immediate impacts of flooding, malaria epidemics emerge after the acute phase of the crisis has passed [7]. Heavy precipitation is thought to flush established larval habitats - an effect that can result in short-term reductions in disease transmission [8]. As floodwaters recede, however, malaria vectors rapidly re-establish breeding sites and a surge in disease may occur months after the disaster [9-11]. In a previous study, we observed a 30% increase in malaria test positivity and a 40% increase in malaria-related hospitalization after severe flooding in western Uganda [12]. While the peak risk was seen approximately three months after the flood, risk remained elevated for nearly a year. Even if temporary, the burden of increased malaria transmission is substantial, particularly among young children [13, 14]. Households also incur economic and opportunity costs due to care seeking [15, 16]. Despite these impacts, few studies have examined post-flood malaria mitigation measures.

Chemoprevention involves the administration of medication to prevent disease or infection. Malaria chemoprevention is increasingly used for disease control in malaria-endemic regions and can be delivered in various ways, including mass drug administration (MDA) and intermittent preventive treatment (IPT) of specific high-risk populations. In 2012, the World

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Health Organization (WHO) recommended the implementation of seasonal malaria chemoprevention (SMC) - essentially short periods of MDA - in areas where malaria transmission is highly seasonal [17]. SMC has been shown to be highly effective at both the individual and population level [18, 19] and is now implemented in 13 countries with more than 21 million children receiving at least one dose in 2019 [20].

Similar approaches applied to settings where transmission is perennial have demonstrated effectiveness [21]. More widespread adaptation of routine chemoprevention programs in young children is hampered by a rapid return to baseline levels of transmission as well as concerns about the emergence of artemisinin resistance and questions of sustainability. At present, it is unclear in what context various forms of chemoprophylaxis may be of most benefit in such settings [22]. Yet recent studies have demonstrated that more targeted uses of chemoprevention may offer opportunities to reduce excess disease transmission and limit morbidity and mortality in the short term [23, 24].

In May 2020, a severe flooding event occurred in Kasese District, a rural, malaria-endemic area of western Uganda. The event displaced more than 100,000 residents from their homes, particularly those along the Mubuku and Nyamwamba Rivers (**Figure 1**) [25]. We hypothesized that MDA with dihydroartemisinin-piperaquine (DP) which has a relatively simple dosing schedule, long post-treatment prophylaxis period, and established safety profile might serve as a valuable tool to mitigate a post-flood surge in malaria [26, 27]. To test this hypothesis, we carried out a pragmatic intervention aimed at reducing excess malaria incidence associated with flooding. Here we assess the impact of this program, comparing the intervention village to two neighboring villages where no intervention was deployed.

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METHODS:

Study Site

Izinga village is located in the Maliba sub-county of Kasese District (0.3006 N, 30.1059 E). Geographically, Izinga occupies an area of approximately 1.3 km^2 and is situated between the Mubuku River to the west and Kitajuka River to the east with the two rivers intersecting in both north and south (**Figure 2**). Compared to the surrounding terrain, the area is relatively flat and low-lying. According to the 2018 census conducted by community health workers (CHW), the village population is comprised of 188 households with 1,118 residents of whom 452 (38.1%) were reported to be children under 12 years of age. However, population projections available at the time of the flooding assumed a flat growth rate of 3.0% per year, which was likely an underestimate [28].

The climate in the Kasese District permits year-round malaria transmission with seasonal peaks in January and July following the end of the wet seasons. *P. falciparum* accounts for the overwhelming majority (>95%) of infections [29, 30]. The most recent malaria indicator surveys undertaken in the Mid-Western region (2014-15) and Tooro sub-national region (2018-19) which include the study area reported *P. falciparum* parasitemia rates (PfPR) of 17.4% and 7.3%, respectively [31, 32]. As part of an ongoing study of malaria, however, we had conducted a household survey of children 2 to 10 years of age in Izinga approximately two months prior to the flooding. In our survey, we identified *P. falciparum* parasitemia in 18 of 60 children using rapid diagnostic tests (RDT), resulting in a weighted estimate of $PfPR_{2-10}$ of 30.0% (95% CI 24.8 - 35.8%).

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Intervention

In response to the severe flooding that occurred on May 7, 2020, members of the Mbarara University of Science and Technology (MUST) - University of North Carolina at Chapel Hill (UNC) Research Collaboration coordinated with a local non-governmental organization (NGO) to plan and carry out a chemoprevention intervention in Izinga village, where the collaboration has a long-standing partnership. Based on previous work showing a transmission peak approximately 3-months post flooding, a written proposal to provide three rounds of monthly DP as chemoprevention to children 12 years of age and younger was submitted to and approved by the Kasese District Health Officer [12]. The NGO subsequently led community sensitization meetings to inform residents of the proposed activities in an effort to optimize engagement and participation.

The first round of chemoprevention was launched on June 10, 2020, approximately one month after the flood. CHWs led field staff to each household in their respective area of responsibility. When an eligible household (e.g., at least one child 12 years or younger in the home) was reached, field staff described the program objectives and activities to the adult caregiver, who was asked to provide verbal consent to participation. Staff administered a brief questionnaire that elicited responses about displacement due to the flooding, incident malaria cases since the flood, and bed net ownership and use in order to identify additional needs and guide future response. Eligible children were weighed to determine dosing using established guidelines [33]. Children weighing less than 5 kg were excluded from the intervention. Staff administered the first dose of DP (Duo-Cotecxin, Holly-Cotec Pharmaceuticals, Beijing, China) and children were observed for 15 minutes to monitor for adverse reactions including vomiting. If the child vomited, staff provided the caregiver with a replacement dose and instructions to re-administer the following day. Caregivers were

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provided with adequate tablets of DP and instructions to administer doses on Days 2 and 3. Similar programs were carried out starting July 16 and September 5, 2020 (**Figure 3**). CHWs monitored participants for adverse events following each round. Total costs of the program, including field staff, supplies, and medication were summarized.

Program Evaluation:

We selected two neighboring villages, Kakindo and Kanyamingo, as comparator villages to assess the effectiveness of the intervention in Izinga. These villages were selected due to their close proximity (**Figure 2**) and broadly similar demographic and geographic characteristics (**Table S1, Figure S1**). While these villages were also impacted by the flooding, no malaria-specific response was carried out until a government-led long-lasting insecticidal nets (LLIN) distribution campaign took place in mid-August 2020. To assess for changes in malaria incidence, we abstracted clinical information from registers at the five nearest health facilities and local CHWs conducting integrated community case management of malaria (ICCM), which would be expected to capture the vast majority of malaria care-seeking. For each patient presenting from one of three villages, we recorded the date of the visit, the age and sex of the patient, and the malaria RDT result. Data was collected from November 2019, a time period six months prior to the flood, through November 2020, approximately six months after the flood. All information was abstracted in and uploaded to a secure electronic database (e.g., REDCap) using smart phones with cellular internet connectivity [34].

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Statistical Analysis

The primary outcome of interest was the incidence of clinical malaria, defined as the number of individuals presenting to one of the catchment health facilities with a positive RDT result per village per week, using CHW census information to provide village-level population offsets. Our primary explanatory variable was calendar time, which we divided into "pre-intervention" and "post-intervention" periods. We first graphically depicted trends in the crude number of febrile illness visits (e.g., RDT negative) and malaria cases (e.g., RDT positive) over calendar time to examine patterns of care-seeking in relation to the flooding. We then compared malaria incidence before and after the flood by fitting generalized additive models (GAM) with a negative-binomial response using the mgcv package in R [35]. Incidence was modeled for each village and age category (e.g., <5 years, 5 to 12 years, ≥12 years). Effect size was estimated using a difference-in-differences approach averaging across the effect size of age groups within a village and the control villages. As a secondary outcome we examined the test-positivity rate (TPR), defined as the number of positive RDT results per 100 tests performed using similar models. The number of cases averted was calculated as the difference between the incidence in Izinga following the beginning of the intervention and the incidence without the intervention as derived from the two control villages (**Table S2, Figure S2**) Estimates were made using the predict.gam() function in the mgcv package.

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Ethical Approvals

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).

RESULTS

Over the course of the intervention, a total of 554 children at 157 unique households received at least one course of chemoprevention; a number that is approximately 20% higher than reported on the most recent CHW census. When a parent or guardian was able to be located, participation was high. Assuming that the actual eligible population was 554 children, rather than our initial estimate of 452 children, we achieved coverage rates of 79.8%, 76.9%, and 77.6% in each round respectively (**Figure 3**). No refusals were documented. More than 60% of participating children (n=335) completed all three rounds and nearly 75% of children (n=413) completed at least two rounds (**Table 1**).

The median age of participating children was 7 years (interquartile range [IQR] 3 – 10). Baseline LLIN ownership and reported use as assessed during the first visit was well below WHO targets, which may be partly due to the flood event occurring towards the end of a three-year distribution cycle [36]. More than half of participating households reported temporary displacement due to flooding, but generally for less than a week (3 days, IQR 2 – 5). Households that participated in at least two rounds of the intervention reported longer periods of displacement ($p<.01$) and more frequent malaria episodes ($p<.01$) compared to those who only participated in a single round. Of the 1,296 initial doses that were directly observed, the vast majority (1,227, 94.7%) were tolerated without immediate vomiting. No

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serious adverse events, including allergic reactions, were reported over the intervention period.

In the six-month period prior to flooding, the crude incidence of malaria was higher in Izinga when compared to Kanyamingo and Kakindo (**Table 2**), but was statistically similar in the adjusted model (aRR 1.17, 95% CI 0.84 – 1.48, p=.37; aRR 1.25, 95% CI 1.00 – 1.57, p=.13, respectively). After the flooding, we observed increases in the weekly incidence and TPR in all villages, but substantially larger increases in the two control villages compared to the intervention village (**Figure 4)**. The incidence peaked approximately 2-3 months after the flood and remained elevated above the study period's mean through the subsequent wet season in October. Using a difference-in-differences approach, the incidence of malaria following the intervention was significantly lower in the intervention village compared to the control villages (aRR 0.47, 95% CI 0.34 – 0.62, p<.01) representing an approximate 53% reduction. As expected, the greatest reductions in malaria incidence were observed in the target group, children age 12 years and younger (aRR 0.42, CI 0.29-0.60, p<0.01) with a smaller effect observed among older children and adults (aRR=0.57, CI 0.38-0.84, p<.01).

Similar findings were observed with the TPR. Prior to flooding, the TPR was similar between the intervention and control villages (**Table 3**). In the post-flood period, however, the crude TPR was significantly lower in Izinga compared to Kanyamingo and Kakindo (**Figures S3-5**). In the difference-in-differences model, the adjusted risk ratio of a positive test was approximately 30% lower in the intervention compared to the control villages in the post-flood period (aRR=.70, CI 0.50 - 0.97, p=0.03).

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We estimate that the chemoprevention with DP averted 318 cases (95% CI 294 – 342), between June 1, 2020 and November 30, 2020 (**Figures 5 & S6**). While children under 12 years of age represent the largest share of averted cases (217, 68.2%), the model also predicted a substantial decrease in cases among individuals older than 12 years of age, who were not eligible for the intervention. Total program costs were $5,046 (**Table S3**) or $3.89 per course of DP delivered. Using the above estimate, these costs are $15.87 (95% CI $14.75 - $17.16) per case averted.

DISCUSSION

Three rounds of chemoprevention with DP targeted to children 12 years of age and younger resulted in substantial reductions in the incidence of malaria after severe flooding in western Uganda. The high rate of participation and low rate of adverse events suggests that the intervention was both feasible and broadly acceptable. Furthermore, the resources required to deliver the intervention were time-limited and relatively modest. Together, these findings - notable for the fact that they were obtained from a pragmatic intervention conducted in the context of a natural disaster amidst an ongoing global pandemic – provide a proof-of-concept for the use of malaria chemoprevention to reduce excess disease burden associated with severe flooding.

Our estimation of a 53% reduction in disease incidence in the six months of observation after flooding is somewhat less than that observed in clinical trials [21]. These differences may be attributable to difference in context and design, but may also have resulted from lower population coverage rates. While we were able to reach approximately 75% of eligible children each round, only 60% completed all three rounds. This suggests that a substantial proportion of children were at risk of infection for at least 30 days during the periods of peak transmission intensity. Modeling studies have shown that coverage is a critical component in

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determining the effect of MDA on percentage reduction in parasite prevalence [37]. The reduced effect may also be due to imperfect adherence to the full, three-day course of DP. Given logistical constraints, we were only able to observe the first dose and relied on caregivers to administer subsequent doses. Despite these issues, the observed effects are comparable with the findings from “real world” programs conducted in areas of seasonal transmission [18]. Similarly, our estimates of cost-effectiveness, both per course delivered and case averted, fall well within the range of previous estimates derived from SMC programs [38].

Our finding of sustained reductions in disease incidence and test positivity in the three months after the end of intervention is consistent with results from a study in Gambia using a pre-seasonal MDA approach [39]. These results suggest that the intervention was effective in reducing the parasite reservoir in the eligible population, which had a prolonged impact on local transmission even well after the last round of chemoprevention [40]. We also observed smaller, but significant reductions in malaria incidence among older children and adults who were not eligible to receive chemoprevention. The indirect effect on the larger population is likely due to the fact that school-aged children often represent a disproportionate burden of parasitemia and treatment resulted in a smaller parasite reservoir. Similar effects on the larger population have been observed in low transmission settings whereas more modest impacts were seen in high transmission settings when chemoprevention programs were implemented among school-aged children [41-43].

This study has a number of unique characteristics and strengths, the most remarkable of which is the context under which the study was conducted. While the circumstances imposed by the flooding and COVID-19 pandemic compressed our timelines, restricted access, and limited our ability to mobilize resources, they also allowed us to evaluate the

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program under the operational stresses expected to be encountered in disaster relief. The program also benefited from established partnerships with the affected communities that have been shown to be crucial factors associated with successful interventions in other settings [44].

Our study also has important limitations, foremost of which is the quasi-experimental design and reliance on routine health facility data. While we attempted to select control villages with similar characteristics that were also impacted by the flooding, it is possible that there were differences between the populations that may have differentially affected malaria risk in pre-flood periods. The use of the difference-in-differences approach, however, does allow us to control for some of the variability in the analysis. To minimize the risk of bias in the outcome measures, we assessed our outcome similarly in both the intervention and control areas by abstracting cases of incident malaria cases from nearby health facilities and CHW records. However, we may still have missed individuals who sought care at unregistered private sector drug shops, traditional healers, or referral centers outside the catchment area. This is unlikely to have confounded our analysis unless there was a difference in care-seeking preferences between villages, but we cannot rule this out. Second, the relatively small geographic area and close proximity of the villages may have permitted spillover of the intervention effect into neighboring areas. We note, for example, that 554 children received at least one course of chemoprevention, a number that is approximately 20% higher than the eligible population of children from the most recent census. The discrepancy is likely due in part to more rapid than estimated population growth, but may also reflect children and caregivers from other villages – either by coincidence or purposefully - who were present on the days the intervention was delivered. Regardless, spillover of the intervention would be expected to bias the result towards the null, and we are reassured by the robustness of our findings. Lastly, the relatively short duration of follow-up limits our ability to assess long-term changes in disease incidence, including potential rebound effects.

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CONCLUSIONS

Three monthly rounds of chemoprevention with DP resulted in significant reductions in *P. falciparum* incidence after severe flooding in western Uganda. While these results are limited by the small scale of the program, the intervention appears to be feasible, acceptable, and effective even under challenging conditions. The application of focused chemoprevention strategies, typically limited to highly seasonal transmission settings, merits further investigation as a means of reducing excess morbidity and mortality associated with natural disasters and other time-limited crisis in areas of perennial transmission. Additional studies are needed to confirm our findings and refine criteria for use.

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DECLARATIONS

Author Contributions

Study conception and design: RMB, EX, RR, EB, RM, EMM. Funding: RMB. Study implementation: RMB, EX, EB, RM, MN, EMM. Data analysis: EX, BDH, VG, RMB. First draft of manuscript: EX, BDH, VG, ABM, RMB. Revisions: All.

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Conflicts of Interests

All authors have completed the ICMJE uniform disclosure form and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous three years except that noted in the funding section; no other relationships or activities that could appear to have influenced the submitted work. RMB reports donation of malaria RDTs for studies from SD Bioline. RR reports serving on Advisory Board of the Ugandan NGO for PHEALED. MN reports serving as Executive Director of NGO involved in study.

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Table 1: Characteristics of children and households participating in at least one round of chemoprevention with dihydroartemisinin-piperaquine (DP) stratified by the number of rounds completed.

	1 Round	2 Rounds	3 Rounds	*p*-value
Demographic Characteristics				
Children (n, %)	141 (25.5)	78 (14.1)	335 (60.5)	
Age (median, IQR)	6 (2-10)	8 (3-10)	7 (4-10)	**<.01**
LLIN Availability and Use				
Household has ≥1 LLIN	21 (67.7)	39 (50.0	113 (54.1)	.09
Median Number of LLIN in household	2 (0-3.5)	.5 (0-2)	1 (0-3)	**<.01**
Child slept under net previous night?	18 (58.1)	23 (61.5)	134 (64.7)	.48
Number of people sleeping under the LLIN	2 (0-2)	1 (0-3)	1 (0-2)	.30
Displacement				
Household displaced by flooding?	18 (58.1)	40 (51.3)	215 (64.2)	.10
Days displaced by flooding	2 (1-3)	4 (1-7)	3 (1-4)	**<.01**
Reported Malaria Episodes				
Child experienced a malaria episode	8 (5.71)	21 (36.8)	111 (33.1)	**<.01**
Did the child receive treatment?	8 (5.71)	21 (36.8)	102 (30.4)	.31

Abbreviations: IQR = interquartile range; LLIN = long-lasting insecticide-treated net; RDT = rapid diagnostic test

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Table 2: Malaria cases and incidence, defined as the number rapid diagnostic test confirmed cases per person year, in each village pre- and post-intervention

	Pre-Intervention				Post-Intervention			
Village	**Person-Year**	**Cases**	**Incidence**	***p*-value**	**Person-Year**	**Cases**	**Incidence**	***p*-value**
Izinga	645	210	0.33	0.025	602	260	0.43	<.001
Kakindo	580	141	0.24		541	489	0.90	
Kanyamingo	833	142	0.17		778	474	0.61	

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Table 3: Positive rapid diagnostic test results and test positivity (TPR) defined as the number of positive tests per 100 tests performed, in each village pre- and post-intervention

	Pre-Intervention				Post-Intervention			
Village	**Tests**	**Tests (+)**	**TPR**	***p*-value**	**Tests**	**Tests (+)**	**TPR**	***p*-value**
Izinga	427	210	0.49	0.62	478	260	0.54	<.001
Kakindo	303	141	0.47		830	489	0.59	
Kanyamingo	282	142	0.50		670	474	0.71	

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FIGURE LEGENDS

Figure 1: Immediate aftermath of flooding event in Izinga Village, western Uganda

Figure 2: Map of Izinga, the chemoprevention intervention village (green cross hatching) and immediate environs including Kakindo and Kanyamingo, the two non-intervention villages (red cross hatches) and neighboring health facilities (red crosses).

Figure 3: Timeline of events including flooding, each round of chemoprevention (blue) including number of children receiving chemoprevention and estimated proportion of coverage, and period of clinic surveillance.

*Figure created with BioRender.com. *Pre-flood survey was conducted in Izinga village as part of unrelated, ongoing study of malaria transmission in the area.*

Figure 4: Number of positive tests for a given week (histogram) and the smoothed weekly incidence of malaria (black line with 95% CI given by shaded area) in each village. Solid vertical line represents date of flood, while dotted vertical lines show dates of each round of chemoprevention in Izinga village. Similar results shown in villages when stratified by eligibility (i.e., age ≤12 years) for the intervention in Figures 4B and 4C.

Figure 5: Model predictions for the incidence of malaria in Izinga with and without intervention, stratified by age group.

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Figure 1

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Figure 2

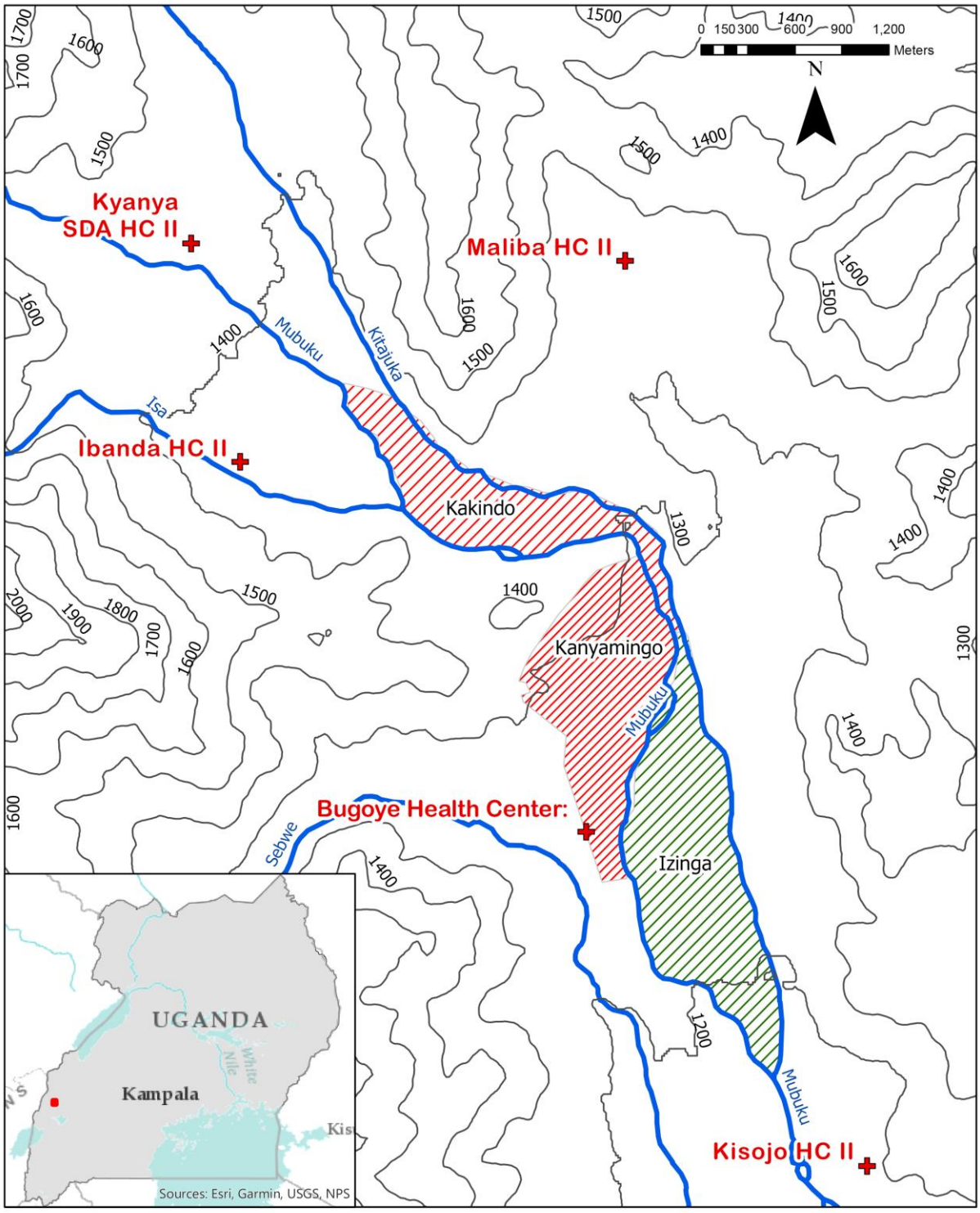

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Figure 3

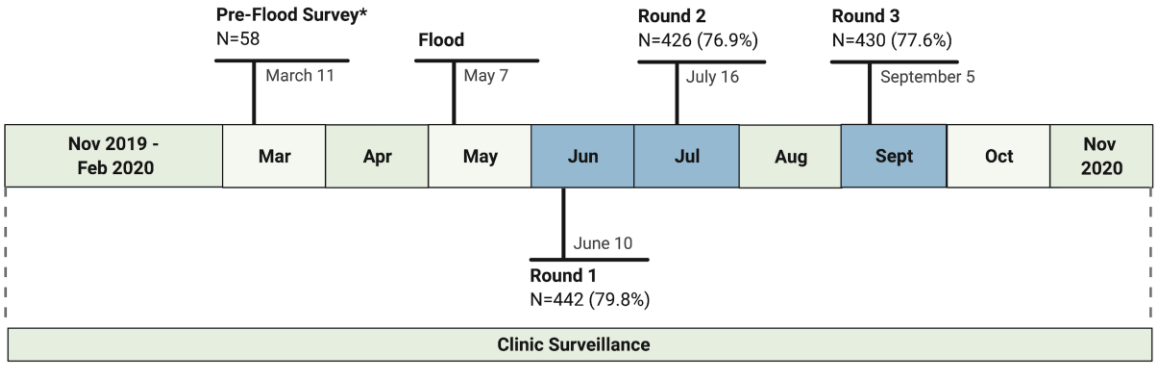

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Figure 4

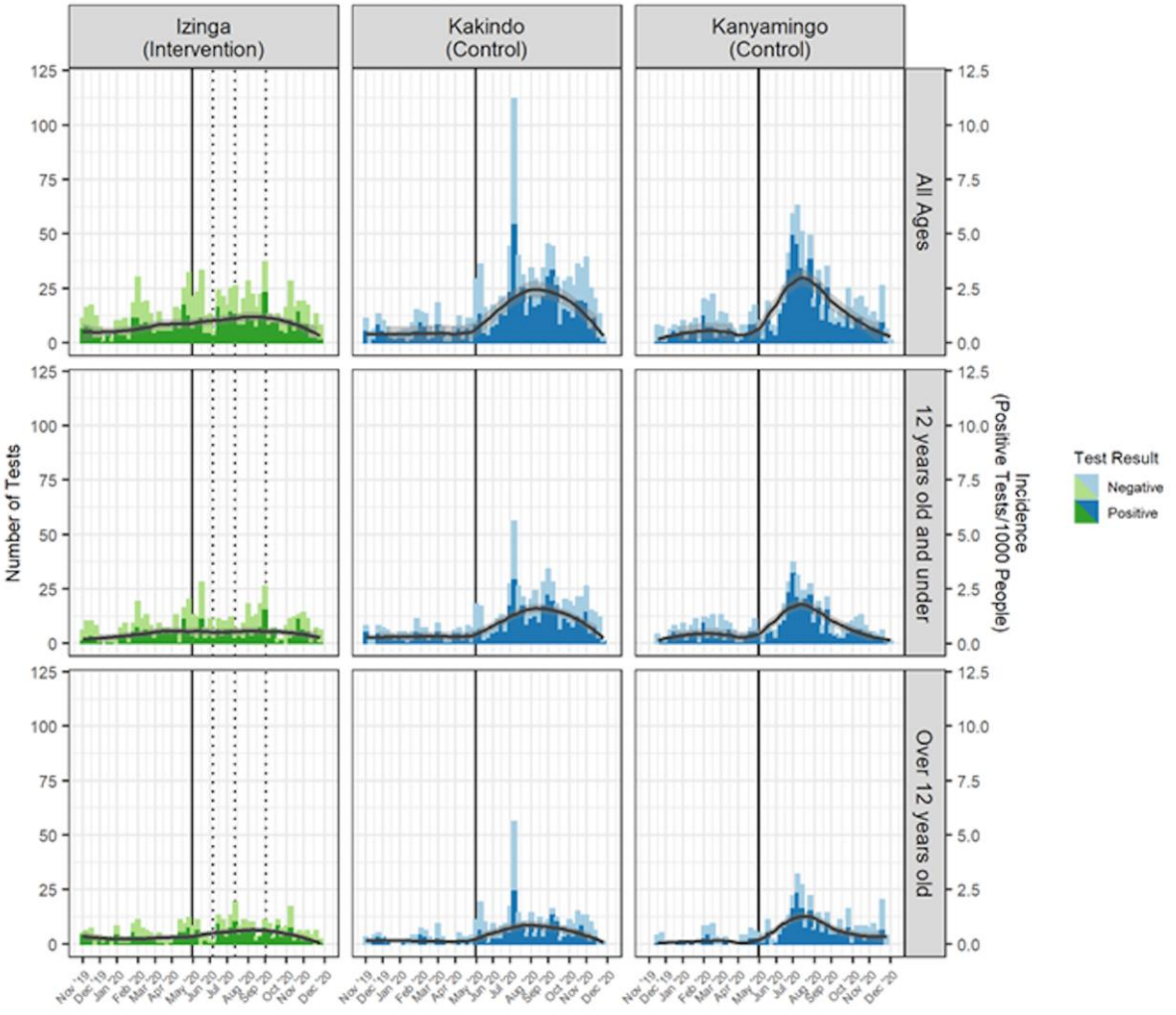

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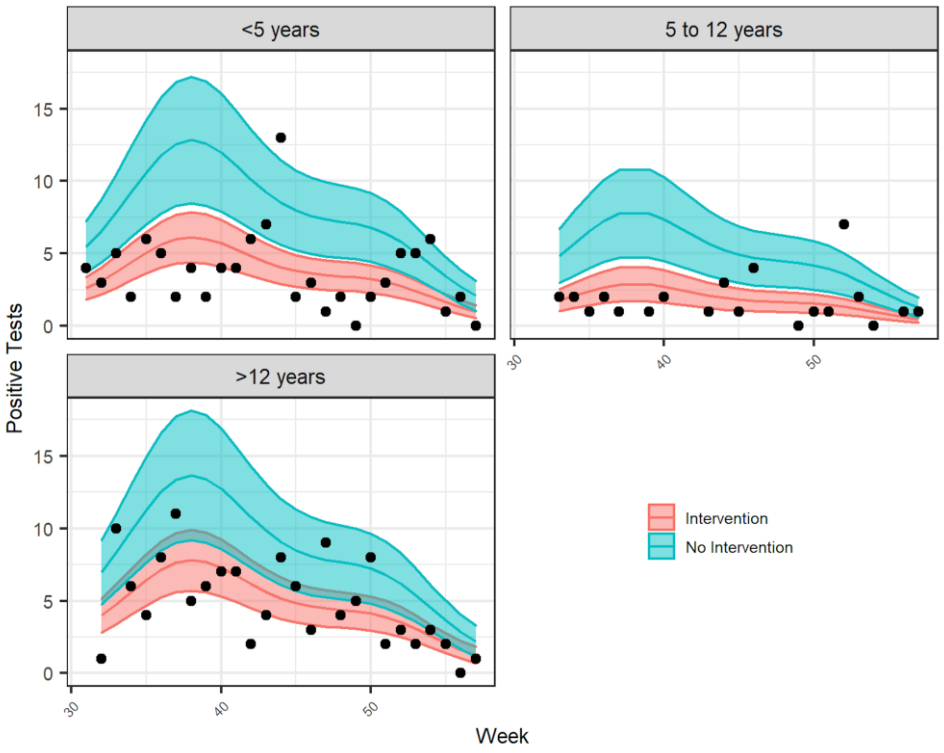
Figure 5



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