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The impact of stopping and starting indoor residual spraying on malaria burden in 14 districts of Uganda

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Abstract

The scale-up of malaria control efforts has led to marked reductions in malaria burden over the past twenty years, but progress has slowed. Implementation of indoor residual spraying (IRS) of insecticide, a proven vector control intervention, has been limited and difficult to sustain partly because questions remain on its added impact over widely accepted interventions such as bed nets. Using data from 14 enhanced surveillance health facilities in Uganda, a country with high bet net coverage yet high malaria burden, we estimate the impact of starting and stopping IRS. We show that stopping IRS resulted in a 5-fold increase in malaria incidence within 10 months, but reinstating IRS led to an over 5-fold decrease within 8 months. In areas where IRS was initiated and sustained, malaria incidence dropped by 85% after year 4. IRS could play a critical role in achieving global malaria targets, particularly in areas where progress has stalled.

Introduction

Over the past twenty years the scale-up of malaria control efforts has led to marked reductions in morbidity and mortality[1,2]. However, global progress has slowed in recent years, particularly in sub-Saharan Africa, which accounted for 93% of the world's 228 million cases in 2018[2]. Long-lasting insecticidal nets (LLINs) and indoor residual spraying of insecticide (IRS) are the primary vector control interventions used for the prevention of malaria. The World Health Organization recommends universal coverage of LLINs for at-risk populations in sub-Saharan Africa, where the proportion of households owning at least one LLIN is estimated to have increased from 47% in 2010 to 72% in 2018. Until recently, pyrethroids were the only class of insecticides approved for use in LLINs and, given the emergence of widespread pyrethroid resistance[3,4], there is concern that the effectiveness of LLINs may be diminishing. Unlike LLINs, IRS has the advantage of utilizing multiple different classes of insecticides and combing IRS with LLINs may improve malaria control and slow the spread of pyrethroid resistance. However, few controlled trials have evaluated the effect of adding IRS to communities using LLINs and the evidence is mixed, with a few studies showing benefits when IRS included 'non-pyrethroid-like' insecticides[5]. Other barriers to IRS delivery – including cost, logistics, and community acceptance – have limited its use[6], such that less than 5% of the population at risk in sub-Saharan Africa was protected by IRS in 2018, a decrease from over 10% coverage in 2010[2].

Uganda is illustrative of a country where the burden of malaria remains high and progress has slowed in recent years[2]. Malaria control efforts in Uganda have primarily focused on LLINs. In 2013-14 it became the first country to implement a universal LLIN distribution campaign, which was repeated in 2017-18. In 2018-19, Uganda had the highest coverage of LLINs in the world,

with 83% of households reported owning at least one LLIN[7]. In contrast to LLINs, the implementation of IRS in Uganda has been focal and limited. In 2006, IRS was reintroduced into Uganda for the first time since the 1960s. In 2007-09, the IRS program was shifted to 10 high burden districts in the north, leading to large reductions in malaria burden[8,9]. In 2014, the IRS program was relocated from these 10 northern districts to 14 districts in the eastern part of the country, where it has been sustained. The discontinuation of IRS in the 10 northern districts was followed by a marked resurgence in malaria cases[10,11], prompting the implementation of a single round of IRS in these 10 districts in 2017.

In this study, we used data from a network of health facility-based malaria surveillance sites to evaluate the impact of different IRS delivery scenarios in 14 districts in Uganda. This study had three objectives: (1) to estimate the impact of withdrawing IRS after five years of sustained use on the burden of malaria in three sites in Northern Uganda; (2) to estimate the impact of restarting IRS with a single round three to four years after IRS was discontinued on the burden of malaria in nine sites in Northern Uganda; and (3) to estimate the impact of five years of sustained IRS on the burden of malaria in five sites in Northern and Eastern Uganda.

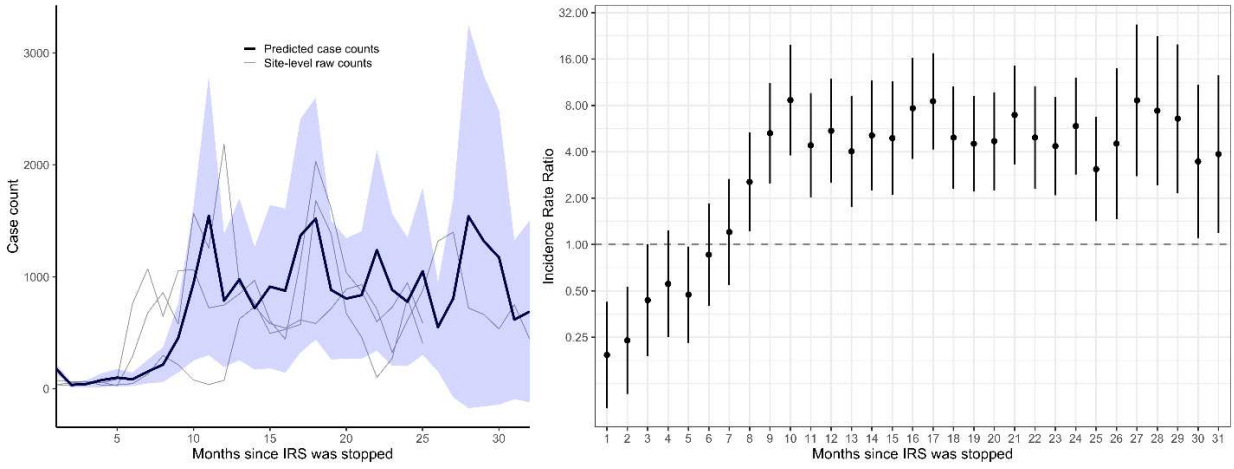
Results

Impact of withdrawing IRS after sustained use

Across the three sites included in the analysis, a total of 224,859 outpatient visits were observed (Table 1). During the baseline period, average monthly cases ranged from 104-272 and TPR ranged from 23.7%-25.9%. This increased to 491-751 and 52.3%-78.0% respectively, during the evaluation period (Supplementary Fig S1).

Monthly adjusted IRRs and 95% confidence intervals (CI) for the three sites combined are presented in Fig 1 and Supplementary Table S1. These results showed an initial reduction in malaria cases after the final round of IRS relative to the baseline period until (adjusted IRR in the first month after IRS = 0.19, 95% CI 0.09-0.42) about four to five months after the final IRS campaign when malaria cases began to increase. Over the 10-31 months after IRS was stopped, the number of malaria cases increased by over 5-fold relative to the baseline period (adjusted IRR = 5.24, 95% CI 3.67-7.50). This corresponds to predicted case counts of near zero immediately following final IRS campaign followed by an increase to about 1000 cases per month at each site (Fig 1). These results were consistent when considering only laboratory-confirmed cases unadjusted for testing rates (Supplementary Fig S2).

Fig 1. Adjusted IRR and predicted case counts from multilevel negative binomial model assessing the impact of withdrawing IRS after 5 years of sustained use. The blue shaded region represents the 95% confidence interval around the predicted case counts from the adjusted regression model. Vertical bars represent the 95% confidence interval around adjusted IRR.



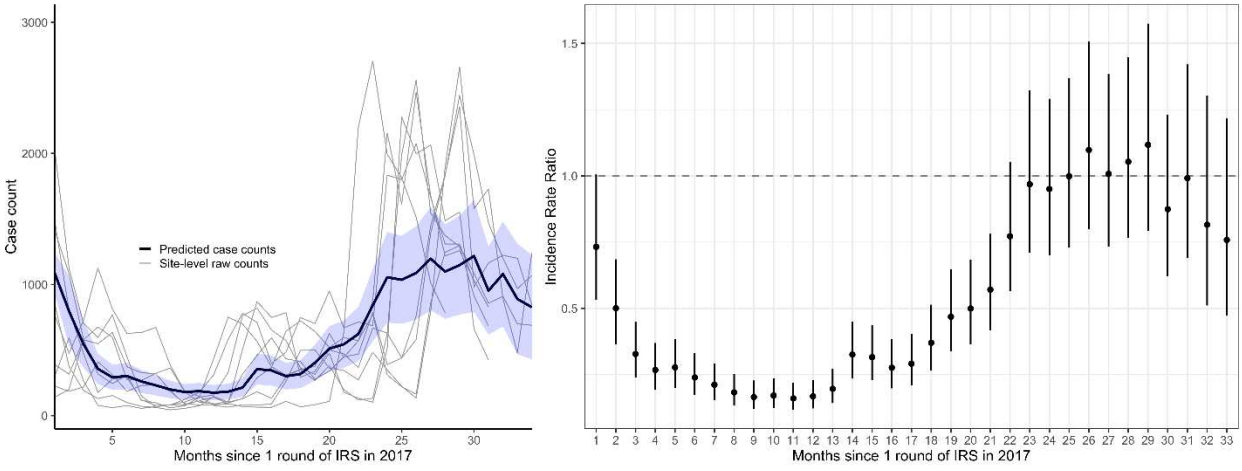
Impact of restarting IRS with a single round

A total of 858,380 outpatient visits were recorded across the analysis period for the nine sites. (Table 2). Mean monthly malaria cases ranged from 643-1,569 and the TPR ranged from 56.5%-

84.7% during the baseline period. These ranges were 501-762 and 48.5%-72.0% respectively during the evaluation period. Temporal trends of laboratory-confirmed malaria cases over time for the individual health facilities are presented in Supplementary Fig S3.

Monthly adjusted IRRs and 95% CI for the nine sites combined are presented in Fig 2 and Supplementary Table S2. The single round of IRS led to a reduction in malaria cases until approximately 23 months post-IRS. Over the 8-12 months after the single round of IRS, malaria cases decreased by over 5-fold relative to the baseline period (adjusted IRR = 0.17, 95% CI 0.15-0.20). After 23 months following the single round of IRS, malaria cases returned to a level similar to the baseline period before the single round of IRS (adjusted IRR for months 23-31 = 1.06, 95% CI 0.92-1.21). These results were consistent when considering only laboratory-confirmed cases unadjusted for testing rates (Supplementary Fig S4).

Fig 2. Adjusted IRR and predicted case counts from multilevel negative binomial model assessing the impact of restarting IRS with a single round. The blue shaded region represents the 95% CI around the predicted case counts from the adjusted regression model. Vertical bars represent the 95% CI around adjusted IRR.



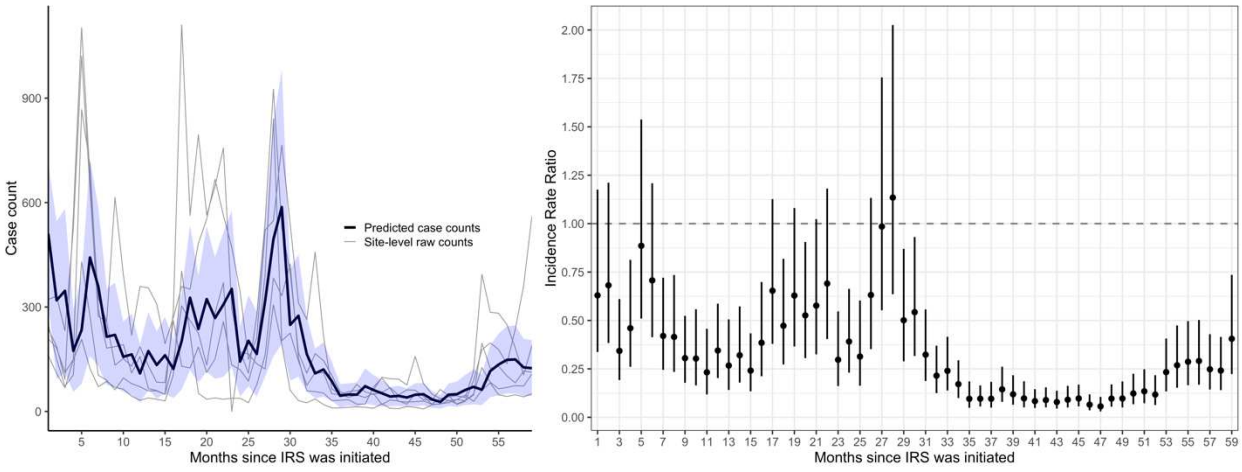
Impact of initiating and sustaining IRS

In total, 574,587 outpatient visits were observed across the five sites included in the analysis. (Table 3). During the baseline period, average monthly malaria cases adjusted for testing rates

ranged from 286-657 and the TPR ranged from 25.4%-67.0%. This range decreased to 85-289 for malaria cases and 13.8%-45.3% for the TPR during the evaluation period. Temporal trends of laboratory-confirmed malaria cases over time for the individual health facilities are presented in Supplementary Fig S5.

Monthly adjusted IRRs and 95% CI for the five sites combined are presented in Fig 3 and Supplementary Table S3. There was a modest overall reduction in malaria case counts in the first three years after IRS was initiated relative to the baseline period, with some peaks in case counts returning to near baseline levels just prior to when rounds of IRS were administered. However, after the third year of sustained use, malaria case counts dropped substantially and remained low relative to the period before IRS was initiated. In the 4th and 5th year after IRS was initiated and sustained, malaria cases dropped by 85% (adjusted IRR = 0.15, 95% CI 0.12-0.18). These results were consistent when considering only laboratory-confirmed cases unadjusted for testing rates (Supplementary Fig S6).

Fig 3. Adjusted IRR and predicted case counts from multilevel negative binomial model assessing the impact of initiating and sustaining IRS. The blue shaded region represents the 95% CI around the predicted case counts from the adjusted regression model. Vertical bars represent the 95% CI around adjusted IRR.



Discussion

Uganda has been exceptionally successful in scaling-up coverage of LLINs. Following the mass distribution campaigns to deliver free LLINs in 2013-14 and 2017-18, 90% and 83% of households respectively reported ownership of at least one LLIN[7,12]. However, despite this success, the burden of malaria remains high in much of the country. Uganda had the 3rd highest number of malaria cases reported in 2018, with reported case incidence increasing since 2014[2]. If Uganda is to achieve the goals established by the World Health Organization's Global Technical Strategy for malaria including reducing malaria case incidence by at least 90% by 2030 as compared with 2015[13], additional malaria control measures will be needed. This report highlights the critical role of IRS in substantially reducing the burden of malaria in areas where transmission remains high despite deployment of LLINs. Withdrawing IRS after five years of sustained use in three districts in northern Uganda resulted in a more than 5-fold increase in malaria cases within 10 months. Re-starting IRS with a single round in nine districts in Northern Uganda approximately three years after IRS had been stopped led to a transient but important (more than a 5-fold) decrease in malaria cases within 8-12 months, returning to pre-IRS levels after 23 months. Initiating and sustaining IRS in five districts in Eastern Uganda led to a gradual reduction in malaria cases reaching almost a 7-fold reduction after 4-5 years.

Robust evidence supports the widespread use of LLINs for malaria control. In a systematic review of clinical trials conducted between 1987 and 2001, insecticide treated nets reduced all cause child mortality by 17% and the incidence of uncomplicated *P. falciparum* malaria by almost half [14]. However, there is concern that the effectiveness of LLINs may be diminishing due to widespread resistance to pyrethroids which until recently were the only class of insecticides

183 approved for LLINs. Similar to many other African countries, high-level resistance to
184 pyrethroids among the principle *Anopheles* vectors has been reported recently throughout
185 Uganda[15-17]. In addition, behavioral changes in vector biting activity following the introduction
186 of LLINs have been reported which could present new challenges for malaria control[18-20].
187 Finally, the effectiveness of LLINs may be further compromised by poor adherence and waning
188 coverage in the setting of free distribution campaigns done intermittently. In Uganda, less than
189 18% of households reported adequate coverage (defined as at least one LLIN per 2 residents)
190 three years after the 2013-14 distribution campaign[21] and adequate coverage decreased from 71%
191 to 51% between 6 and 18 months following the 2017-18 distribution campaign[22]. Although the
192 World Health Organization recommends mass distribution campaigns every three years,
193 mounting evidence suggests that LLINs should be distributed more frequently to sustain high
194 coverage[23-29].
195
196 Given concerns about the current effectiveness of pyrethroid-based LLINs and the persistently
197 high burden of malaria despite aggressive scale up of LLINs in countries like Uganda, additional
198 malaria control measures are needed. IRS is an attractive option. Historically, IRS programs
199 were used to dramatically reduce and even eliminate malaria in many parts of the world. Thus, it
200 is surprising that the evidence base from contemporary controlled trials on the impact of adding
201 IRS to LLINs for vector control is limited. A recent systematic review of cluster randomized
202 controlled trials conducted in sub-Saharan Africa since 2008, reported that adding IRS using a
203 "pyrethroid-like" insecticide to LLINs did not provide any benefits, while adding IRS with a
204 "non-pyrethroid-like" insecticide produced mixed results[5]. Among the four trials comparing IRS
205 plus LLINs with LLINs alone, three evaluated IRS with a carbamate (bendiocarb) and one

206 evaluated a long-lasting organophosphate, pirimiphos-methyl (Actellic 300CS®)[30-33]. Only two
207 trials (both using bendiocarb) assessed malaria incidence; one from Sudan found a 35%
208 reduction when adding IRS to LLINs[31], while another from Benin found no benefit of adding
209 IRS [30]. All four trials assessed parasite prevalence, with an overall non-significant trend towards
210 a lower prevalence when adding IRS to LLINs (RR=0.67, 95% CI 0.35-1.28)[5]. However, when
211 the analyses were restricted to include only the two studies with LLIN usage over 50%, adding
212 IRS reduced parasite prevalence by over 50% (RR=0.47, 95% CI 0.33-0.67)[5]. Of note, none of
213 the trials that evaluated the impact of adding IRS with a "non-pyrethroid-like" insecticide
214 assessed outcomes beyond two years. More recently, a number of observational studies have
215 reported benefits of using IRS with pirimiphos-methyl (Actellic 300CS®). In the Mopti Region
216 of Mali, delivery of a single round of IRS with Actellic 300CS® was associated with a 42%
217 decrease in the peak incidence of laboratory confirmed malaria cases reported at public health
218 facilities[34]. In the Koulikoro Region of Mali, villages that received a single round of IRS with
219 Actellic 300CS® combined with LLINs observed a greater than 50% decrease in the incidence
220 of malaria compared to villages that only received LLINs[35]. In the Northern Region of Ghana,
221 districts that received IRS with Actellic 300CS® reported 26-58% fewer cases of laboratory
222 confirmed malaria cases reported at public health facilities over a two-year period, compared to
223 districts that did not receive IRS[36]. In Northern Zambia, implementation of IRS with Actellic
224 300CS® targeting only high burden areas over a three year period was associated with a 25%
225 decline in parasite prevalence during the rainy season, but no decline during the dry season[37]. In
226 Western Kenya, the introduction of a single round of IRS with Actellic 300CS® was associated
227 with a 44-65% decrease in district level malaria case counts over a 10 month period compared to
228 pre-IRS levels[38]. In addition, several recent reports have documented dramatic resurgences

following the withdrawal of IRS with bendiocarb in Benin[39], and the withdrawal of IRS with Actellic 300CS® in Mali and Ghana[34,36].

The results from this study provides additional support for the critical role IRS can play in reducing the burden of malaria in African countries with high LLINs coverage. We analyzed a large, rigorously collected dataset, which is a strength of study. Data were collected over nearly seven years through an enhanced health facility-based surveillance system covering 14 districts in Uganda where IRS was being withdrawn, re-started, and initiated. This enhanced surveillance system facilitated laboratory testing and provided prospectively collected, individual-level data, allowing for analyses of quantitative changes in laboratory-confirmed cases of malaria over time, controlling for temporal changes in rainfall, seasonal effects, diagnostic practices, and health seeking behavior. Previous work by our group documented a marked decrease in malaria test positivity rates after four years of sustained IRS with bendiocarb in one district of Northern Uganda followed by a rapid resurgence over an 18-month period after IRS was withdrawn[11]. In this study we expand on these findings by including data from three districts and covering a 31-month period following the withdrawal of IRS. We were able to quantify more than a 5-fold increase in malaria cases which was sustained over the 10-31 months following the withdrawal of IRS. This marked resurgence occurred despite the fact the first universal LLIN distribution campaign was timed to occur right after IRS was withdrawn. Given the dramatic nature of the resurgence, the Ugandan government was able to procure funding for a single round of IRS with Actellic 300CS® approximately three years after IRS was withdrawn in 10 districts of Northern Uganda. In this study, we assessed the impact of this single round in nine of these districts. This single round was associated with over a 5-fold decrease in malaria cases after 8-12 months, with

252 malaria cases returning to pre-IRS levels after almost 2 years. These data suggest that IRS with
253 longer-acting formulations such as Actellic 300CS® administered every 2 years may be a cost-
254 effective strategy for mitigating the risk of resurgence following sustained IRS and/or enabling
255 countries to expand coverage when resources are limited. This study also evaluated the impact of
256 five years of sustained IRS in 5 districts of Eastern Uganda, starting first with bendiocarb and
257 then switching to Actellic 300CS® after 18 months. Rounds of IRS were initially associated with
258 marked decreases in malaria cases followed by peaks before subsequent rounds until the 4th and
259 5th years after IRS was initiated when there was a sustained decrease of almost 7-fold compared
260 to pre-IRS level. Given the before-and-after nature of our study design, it is not clear whether the
261 maximum sustained benefits of IRS seen after 4-5 years were due to the cumulative effect of
262 multiple rounds of IRS, the switch from bendiocarb to Actellic 300CS®, the second universal
263 LLIN distribution campaign which occurred in this area in 2017, and/or other factors.
264
265 This study had several limitations. First, we used an observational study design, with measures
266 of impact based on comparisons made before-and-after key changes in IRS policy. Although
267 cluster randomized controlled trials are the gold standard study design for estimating the impact
268 of IRS, it could be argued that withholding IRS would be unethical, given what is known about
269 its impact in Uganda. Second, our estimates of impact could have been confounded by secular
270 trends in factors not accounted for in our analyses. However, we feel that our overall conclusions
271 are robust given the large amount of data available from multiple sites over an extended period
272 with multiple complementary objectives providing consistent findings. Third, we could not
273 assess the impact of IRS independent of LLIN use and did not have access to measures of IRS or
274 LLIN coverage from our study populations. However, we were able to provide a “real world”

assessment of IRS in a setting where LLIN use is strongly supported by repeated universal distribution campaigns that are becoming increasingly common in sub-Saharan Africa. Finally, our study outcome was limited to case counts of laboratory confirmed malaria captured at health facilities. Thus, we were unable to measure the impact of IRS on other important indicators such as measures of transmission intensity, parasite prevalence, or mortality.

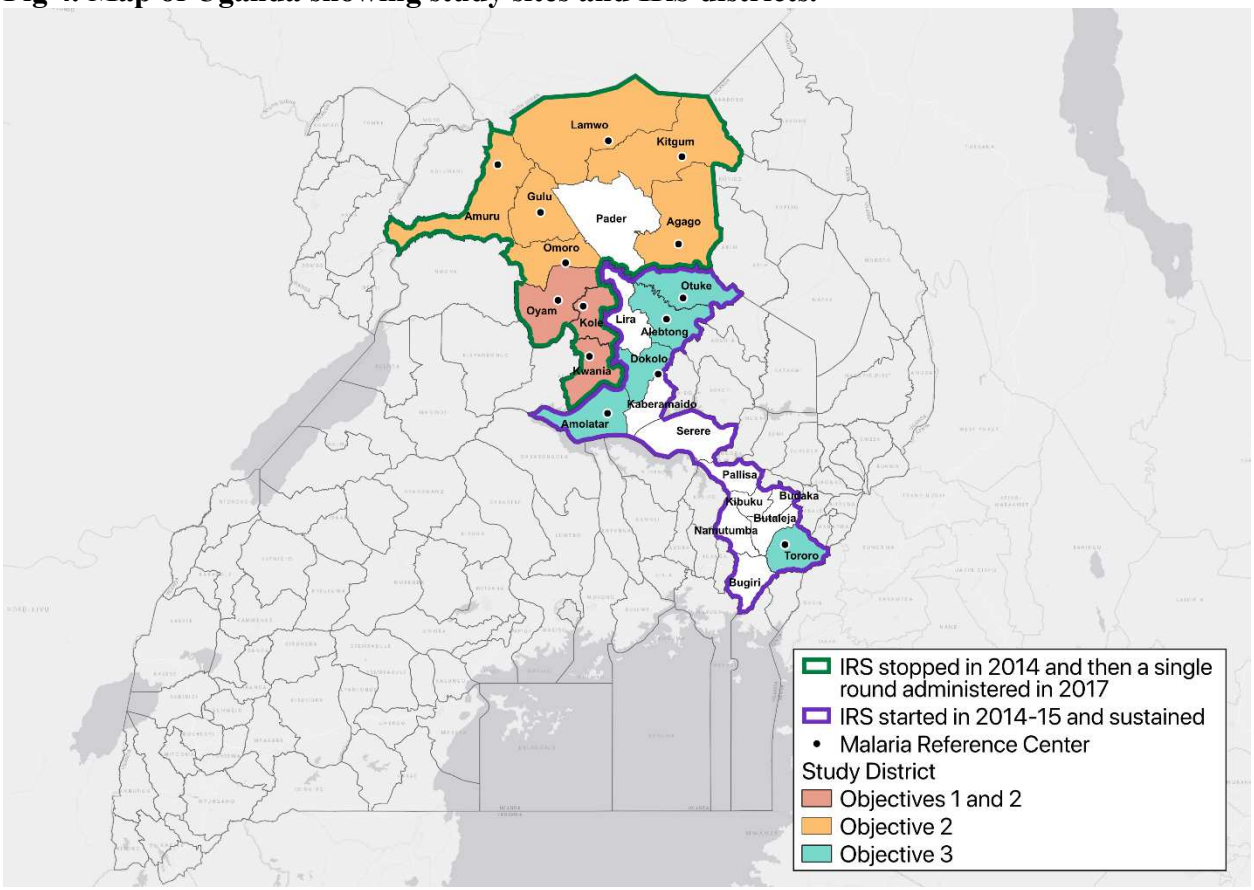
There is a growing body of evidence that combining LLINs with IRS using "non-pyrethroid-like" insecticides, especially the long acting organophosphate Actellic 300CS®, is highly effective at reducing the burden of malaria in Uganda, and elsewhere in Africa. Despite these encouraging findings, IRS coverage in Africa has been moving in the wrong direction. The proportion of those at risk protected by IRS in Africa peaked at just over 10% in 2010. However, the spread of pyrethroid resistance has led many control programs to switch to more expensive formulations resulting in a 53% decrease in the number of houses sprayed between years of peak coverage and 2015 across 18 countries supported by the U.S. President's Malaria Initiative[40] and an overall reduction in the proportion protected by IRS in Africa to less than 5% in 2018[2]. Given the lack of recent progress in reducing the global burden of malaria coupled with challenges in funding, renewed commitments are needed to address the "high burden to high impact" approach now being advocated by the World Health Organization[2]. IRS is a widely available tool that could be scaled up, however demands currently exceed the availability of resources. Additional work is needed to optimize the use of IRS, prevent further spread of insecticide resistance, and better evaluate the cost effectiveness of IRS in the context of other control interventions.

Methods

Study sites and vector control interventions

This study utilized data from 14 health facilities located in 14 districts in Northern and Eastern Uganda (Fig 4) which were part of a larger comprehensive malaria surveillance network called the Uganda Malaria Surveillance Program (UMSP). Between 2007 and 2009, IRS was implemented in 10 high burden districts in northern Uganda. DDT or pyrethroids were initially used but in 2010 the insecticide was changed to a carbamate (bendiocarb) due to concern regarding the spread of pyrethroid resistance. Rounds of bendiocarb were repeated approximately every 6 months until 2014 when the IRS program was discontinued, so that resources could be shifted to other high burden districts. In 2017, these 10 districts in northern Uganda received a single round of the organophosphate pirimiphos-methyl (Actellic 300CS®) following reports of malaria resurgence after IRS has been discontinued in 2014. Between 2014 and 2015, IRS with bendiocarb was implemented in 14 districts in the Northern and Eastern part of the country. Rounds of bendiocarb were repeated approximately every six months until 2016 when the formulation was changed to Actellic 300CS®, which continues to be administered once a year.

Fig 4. Map of Uganda showing study sites and IRS districts.



Universal LLIN distribution campaigns were conducted in 2013-14 and 2017-18, where LLINs were distributed free-of-charge by the Uganda Ministry of Health targeting 1 LLIN for every two household residents.

Health-facility based surveillance

Enhanced malaria surveillance was established by UMSP in 2006, as previously described [41]. UMSP operates Malaria Reference Centers (MRCs) at 70 level III/IV public health facilities across Uganda. At each MRC, individual-level data from standardized registers for all patients presenting to the outpatient departments are entered into an Access database by on-site data entry officers. Variables include patient demographics, results of laboratory testing for malaria (rapid

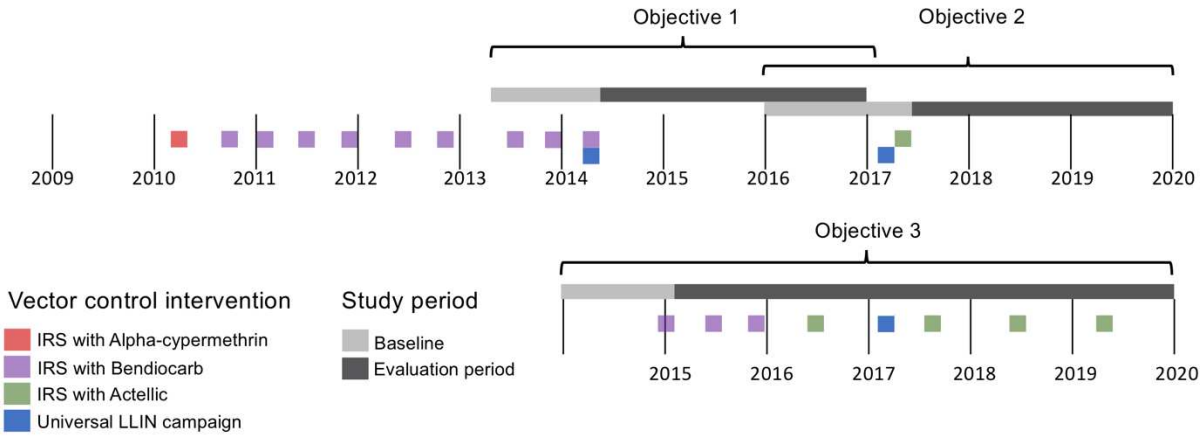
diagnostic test [RDT] or microscopy), diagnoses given, and treatments prescribed. Emphasis is placed on ensuring that patients with suspected malaria undergo testing, by either RDT or microscopy.

This study utilized data from 14 MRCs located in districts that either previously had IRS or have ongoing IRS campaigns. We estimated the impact of withdrawing IRS using data from three sites in Northern Uganda that had at least six months of data preceding the final round of IRS administered in 2014. To estimate the impact of restarting IRS with a single round administered in 2017, we used data from nine sites in Northern Uganda. To estimate the impact of sustained IRS over five years, we used data from five sites in Eastern Uganda where IRS had been implemented since 2014-15.

Measures

Exposure. The exposure was specified as an indicator variable for each month since IRS was withdrawn or initiated relative to a baseline period (Fig 5 and Supplementary Fig S7). We also fit separate models with categorical exposure variables divided into distinct periods of months. To determine the impact of withdrawing IRS after at least five years of sustained use, the baseline period was defined as the final year of sustained IRS use, and the evaluation period lasted through 2016, prior to when an additional round of IRS was implemented. In order to determine the impact of restarting IRS with a single round of IRS, the baseline period was defined as one year prior to the single round of IRS and the evaluation period went through December 2019. To determine the impact of initiating and sustaining IRS, the baseline period was the year prior to IRS initiation, and the evaluation period lasted through December 2019.

Fig 5. Timeline summarizing the dates of IRS campaigns, baseline and evaluation periods. Objective 1 is to assess the impact of withdrawing IRS after five years of sustained use; Objective 2 is to assess the impact of restarting IRS with a single round; and Objective 3 is to assess the impact of initiating and sustaining IRS.



Outcome. The primary outcome was the monthly count of laboratory-confirmed malaria cases at each MRC. The case count was corrected for testing rates by multiplying the number of individuals with suspected malaria but not tested each month by the test positivity rate (the number who tested positive divided by the total number tested) for that month and adding the result to the number of laboratory-confirmed positive cases. As a sensitivity analysis, we re-specified the models including only laboratory-confirmed case counts as the outcome.

Covariates. We adjusted for time-varying variables that impact malaria burden and malaria case detection at the health facility. These variables included average rainfall at the health facility lagged by 1 month, indicator variables for month of the year (to adjust for seasonal effects), the proportion of tests that were RDTs in that month (vs. microscopy), and the number of individuals who attended the health facility but were not suspected of having malaria in that month (to adjust for care-seeking behaviors).

Statistical analysis

For each objective, we specified mixed effects negative binomial regression models with random intercepts for health facility. Coefficients for the exposure variable were exponentiated to represent the incidence rate ratio (IRR) comparing the incidence of malaria in the month of interest relative to the baseline period. This method assumes that the underlying population has remained constant over the study period.

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Author Contributions

JFN, AE, GD, and IRB conceived of the study. JFN led the data collection activities with support from JIN, AM, MK, AS, JK, EA, SG, CE, SGS, CMS, and MRK. AE and IRB led the data analysis with support from GD. AE and JFN drafted the manuscript with support from GD, SGS, and IRB. All authors contributed to interpretation of the results and edited the manuscripts. All authors read and approved the final manuscript.

Competing Interests

The authors declare no competing interests.

Materials and Correspondence

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Table 1. Summary statistics from health-facility based surveillance sites where IRS was stopped after sustained use.

MRC (District)	Time period	Number of months included	Total outpatient visits, n	Suspected malaria cases, n (% of total)	Tested for malaria, n (% of suspected)	RDT performed (versus microscopy), n (% of tested)	Confirmed malaria cases, n (% of tested)	Confirmed cases adjusted for testing rate, n	Mean monthly confirmed cases adjusted for testing rate, n
Aboke HCIV (Kole)	Baseline	9	14,015	3,766 (26.9)	3,735 (99.2)	2,450 (65.6)	923 (24.7)	932	104
	Evaluation	25	46,850	21,245 (45.3)	18,185 (85.6)	17,210 (94.6)	14,200 (78.0)	16,699	668
Aduku HCIV (Kwania)	Baseline	13	24,164	13,742 (56.9)	13,719 (99.8)	1,049 (7.6)	3,254 (23.7)	3,529	272
	Evaluation	32	57,470	30,035 (52.2)	25,896 (86.2)	10,731 (41.4)	13,537 (52.3)	15,717	491
Anyeke HCIV (Oyam)	Baseline	8	15,859	3,514 (22.2)	2,627 (74.8)	2,604 (99.1)	680 (25.9)	918	115
	Evaluation	25	66,501	28,755 (43.2)	20,659 (71.8)	16,147 (78.2)	13,559 (65.6)	18,774	751

Table 2. Summary statistics from health-facility based surveillance sites that received a single round of IRS.

MRC (District)	Time period	Number of months included	Total outpatient visits, n	Suspected malaria cases, n (% of total)	Tested for malaria, n (% of suspected)	RDT performed (versus microscopy), n (% of tested)	Confirmed malaria cases, n (% of tested)	Confirmed cases adjusted for testing rate, n	Mean monthly confirmed cases adjusted for testing rate, n
Aboke HCIV (Kole)	Baseline	14	21,186	11,752 (55.5)	9,613 (81.8)	9,079 (94.5)	7,297 (75.9)	9,006	643
	Evaluation	34	54,826	30,973 (56.5)	30,674 (99.0)	29,064 (94.8)	22,097 (72.0)	22,308	656
Aduku HCIV (Kwania)	Baseline	17	35,017	20,645 (59.0)	17,156 (83.1)	7,938 (46.3)	9,699 (56.5)	11,465	674
	Evaluation	31	65,379	32,260 (49.3)	31,337 (97.1)	20,385 (65.1)	15,201 (48.5)	15,534	501
Anyeke HCIV (Oyam)	Baseline	14	35,378	18,445 (52.1)	12,997 (70.5)	9,151 (70.4)	8,967 (69.0)	12,595	900
	Evaluation	34	70,149	33,618 (47.9)	32,522 (96.7)	31,208 (96.0)	21,799 (67.0)	22,375	658
Awach HCIV (Gulu)	Baseline	17	36,923	21,920 (59.4)	17,927 (82.0)	17,736 (98.7)	13,663 (76.0)	16,749	985
	Evaluation	30	69,375	36,760 (53.0)	35,189 (95.7)	34,070 (96.8)	21,879 (62.2)	22,851	762
Lalogi HCIV (Omoro)	Baseline	17	54,436	32,642 (60.0)	31,545 (96.6)	31,490 (99.8)	23,106 (73.2)	23,948	1,409
	Evaluation	31	72,449	41,846 (57.8)	41,668 (99.6)	40,804 (97.9)	22,986 (55.2)	23,060	744
Patongo HCIII (Agago)	Baseline	14	24,686	15,453 (62.6)	15,122 (97.9)	14,758 (97.6)	11,313 (74.8)	11,487	821
	Evaluation	34	54,486	34,482 (63.3)	33,797 (98.0)	32,176 (95.2)	17,231 (51.0)	17,440	513
Atiak HCIV (Amuru)	Baseline	14	38,916	25,929 (66.6)	22,418 (86.5)	22,335 (99.6)	18,978 (84.7)	21,966	1,569
	Evaluation	34	60,750	31,650 (52.1)	30,754 (97.2)	30,541 (99.3)	19,766 (64.3)	20,325	598
Padibe HCIV (Lamwo)	Baseline	20	29,740	20,589 (69.0)	20,427 (99.2)	20,420 (99.9)	17,031 (83.4)	17,161	858
	Evaluation	28	50,117	26,883 (53.6)	26,831 (99.8)	25,956 (96.7)	15,199 (56.6)	15,224	544
Namokora HCIV (Kitgum)	Baseline	17	27,802	22,597 (81.3)	19,990 (88.5)	18,909 (94.6)	12,294 (61.5)	14,401	847
	Evaluation	31	56,765	40,185 (70.8)	39,966 (99.5)	38,468 (96.3)	21,958 (54.9)	22,063	712

Table 3. Summary statistics from health-facility based surveillance sites where IRS was initiated and sustained.

MRC (District)	Time period	Number of months included	Total outpatient visits, n	Suspected malaria cases, n (%)	Tested for malaria, n (%)	RDT performed (versus microscopy), n (% of tested)	Confirmed malaria cases, n (%)	Confirmed malaria cases adjusted for testing rate, n	Mean monthly confirmed cases adjusted for testing rate, n
Nagongera HCIV (Tororo	Baseline	13	22,859	14,676 (64.2)	14,516 (98.9)	799 (5.5)	3,682 (25.4)	3,722	286
	Evaluation	59	97,012	36,308 (37.4)	36,069 (99.3)	13,129 (36.4)	4,984 (13.8)	5,022	85
Amolatar HCIV (Amolatar)	Baseline	12	19,552	8,547 (43.7)	6,512 (76.2)	5,923 (91.0)	3,701 (56.8)	4,845	404
	Evaluation	59	89,779	24,889 (27.8)	21,849 (87.9)	19,459 (89.1)	4,822 (22.1)	5,854	99
Dokolo HCIV (Dokolo)	Baseline	12	25,570	12,854 (50.3)	8,875 (69.0)	8,212 (92.5)	5,211 (58.7)	7,889	657
	Evaluation	59	129,245	46,428 (35.9)	44,972 (96.9)	42,259 (94.0)	10,210 (22.7)	10,761	183
Orum HCIV (Otuke)	Baseline	11	16,120	9,324 (57.8)	8,929 (95.8)	3,990 (44.7)	5,974 (66.9)	6,236	567
	Evaluation	59	65,036	37,430 (57.6)	36,371 (97.2)	19,536 (53.7)	16,481 (45.3)	17,069	289
Alebtong HCIV (Alebtong)	Baseline	8	15,359	6,694 (43.6)	4,789 (71.5)	4,620 (96.5)	3,209 (67.0)	4,317	540
	Evaluation	59	94,055	40,821 (43.0)	36,211 (88.7)	32,327 (89.3)	12,037 (33.2)	13,869	235

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Figures

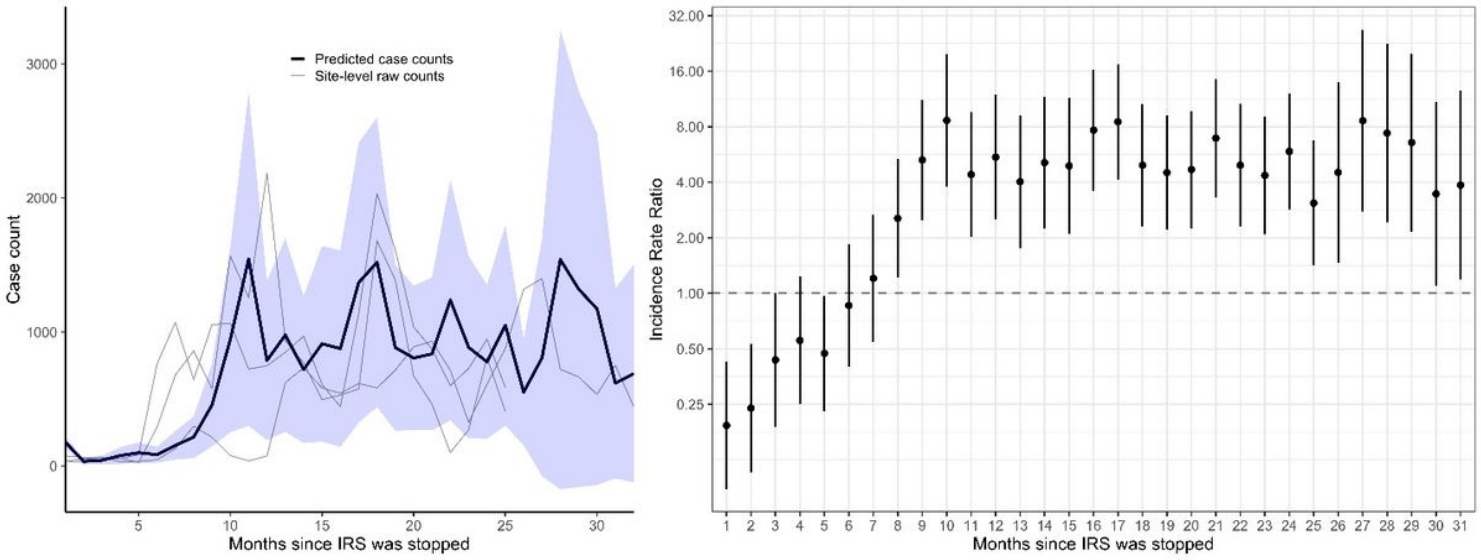

Figure 1

Adjusted IRR and predicted case counts from multilevel negative binomial model assessing the impact of withdrawing IRS after 5 years of sustained use. The blue shaded region represents the 95% confidence interval around the predicted case counts from the adjusted regression model. Vertical bars represent the 95% confidence interval around adjusted IRR.

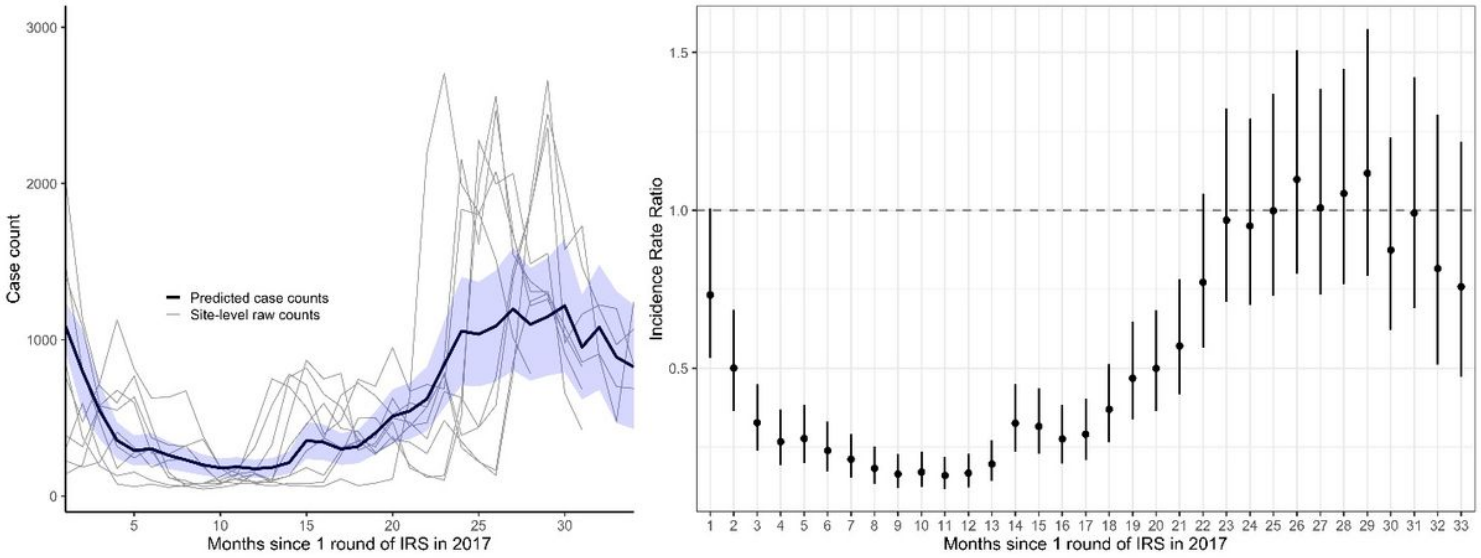

Figure 2

Adjusted IRR and predicted case counts from multilevel negative binomial model assessing the impact of restarting IRS with a single round. The blue shaded region represents the 95% CI around the predicted case counts from the adjusted regression model. Vertical bars represent the 95% CI around adjusted IRR.

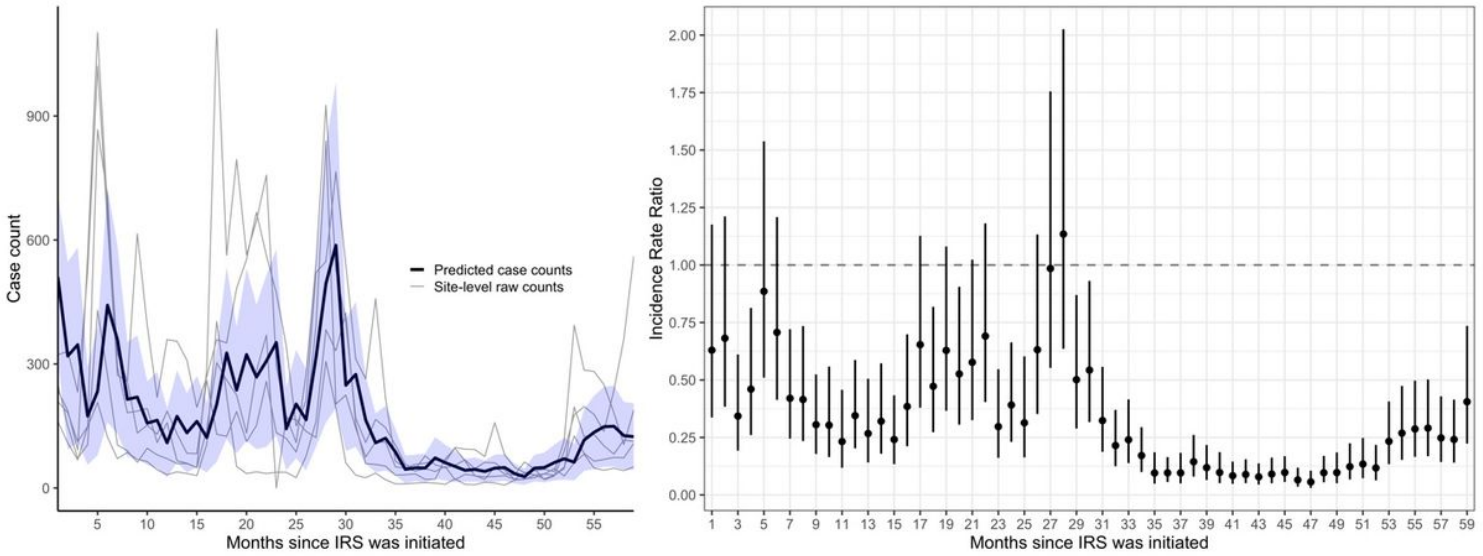

Figure 3

Adjusted IRR and predicted case counts from multilevel negative binomial model assessing the impact of initiating and sustaining IRS. The blue shaded region represents the 95% CI around the predicted case counts from the adjusted regression model. Vertical bars represent the 95% CI around adjusted IRR.

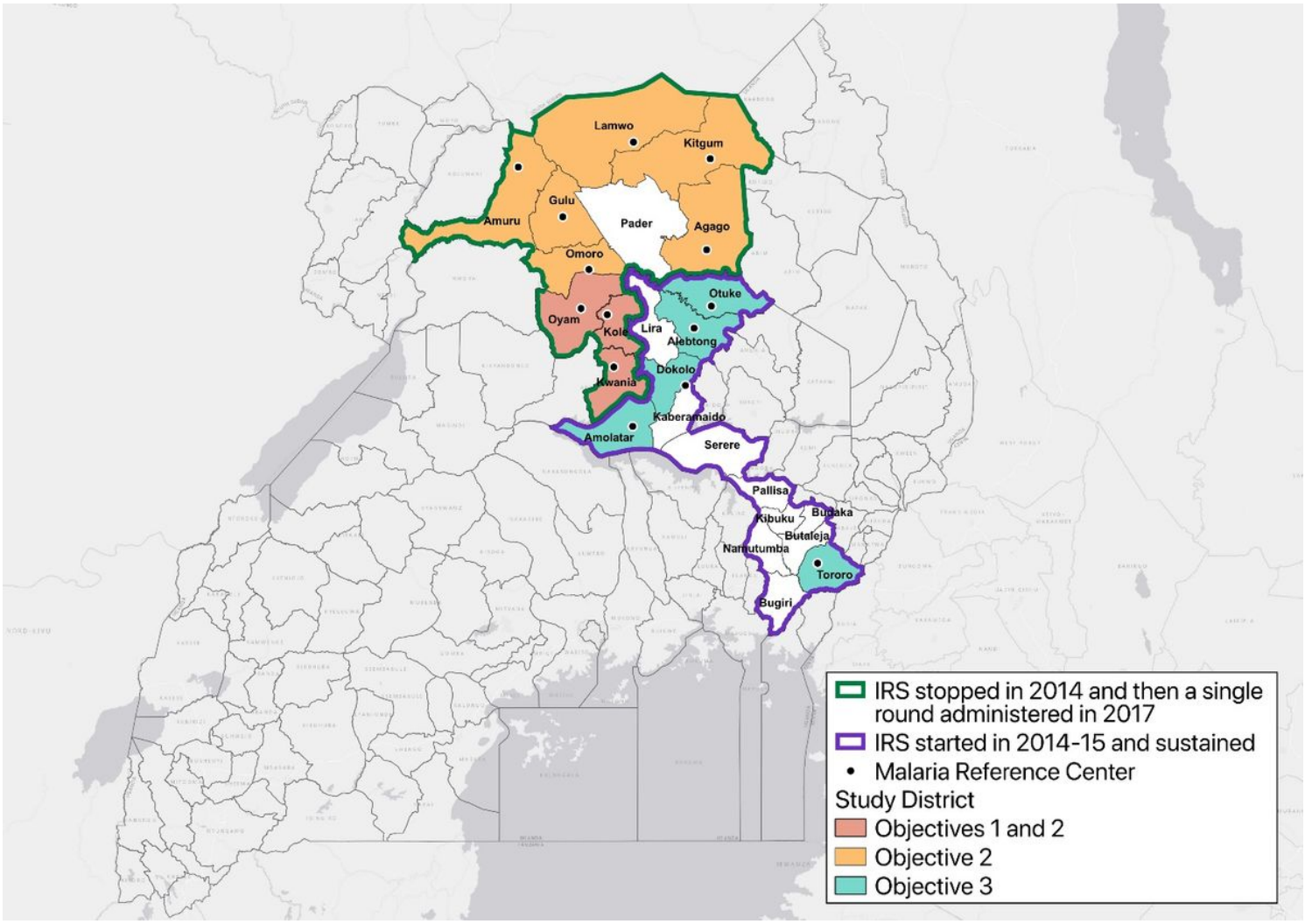

Figure 4

Map of Uganda showing study sites and IRS districts.

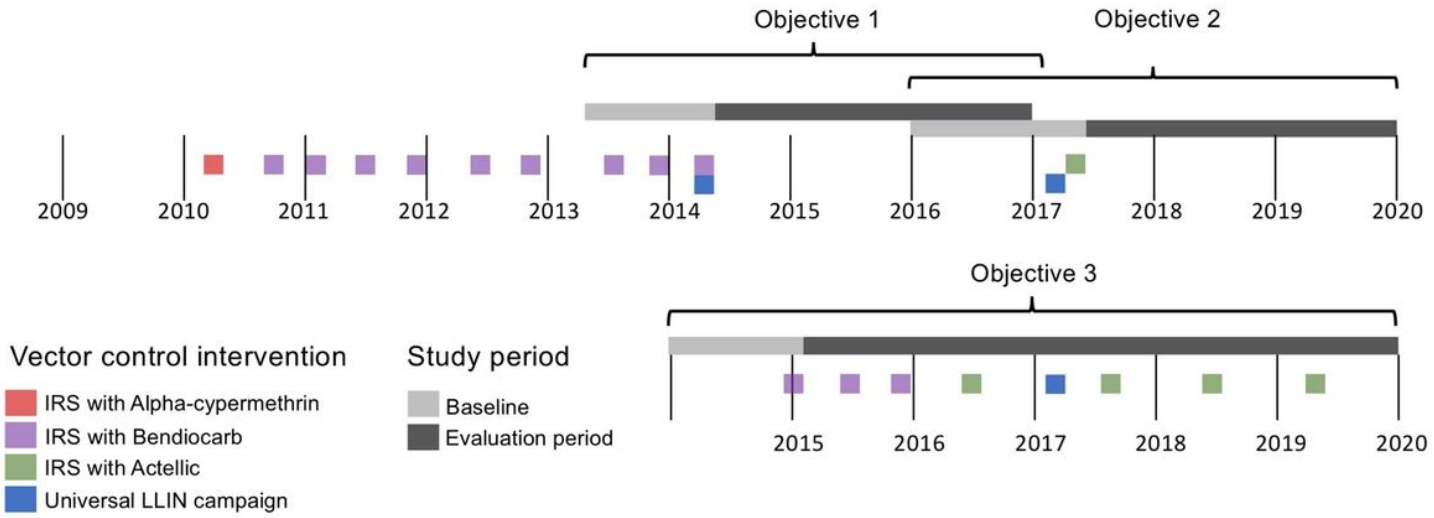

Figure 5

Timeline summarizing the dates of IRS campaigns, baseline 357 and evaluation periods. Objective 1 is to assess the impact of withdrawing IRS after five years of sustained use; Objective 2 is to assess the impact of restarting IRS with a single round; and Objective 3 is to assess the impact of initiating and sustaining IRS.

Supplementary Files

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- IRSprojectsupplements.pdf