Resurgence of malaria following discontinuation of indoor residual spraying of insecticide in a previously high transmission intensity area of Uganda

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Summary: IRS can be effective for reducing the burden of malaria but is difficult to maintain. In a historically high transmission intensity area of Uganda, discontinuation of IRS was associated with a rapid increase in malaria morbidity despite universal LLIN distribution.

ABSTRACT

Background

Indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs) are the primary tools for malaria prevention in Africa. It is not known whether reductions in malaria can be sustained after IRS is discontinued. The aim of this study was to assess changes in malaria morbidity in a historically high transmission area of Uganda where IRS was discontinued after a four-year period of effective control followed by a universal LLIN distribution campaign.

Methods

Individual-level malaria surveillance data were collected from one outpatient department and one inpatient setting in Apac District, Uganda from July 2009 through November 2015. Rounds of IRS were delivered approximately every six months from February 2010 through May 2014 followed by universal LLIN distribution in June 2014. Temporal changes in the malaria test positivity rate (TPR) were estimated during and after IRS using interrupted time series analyses, controlling for age, rainfall, and autocorrelation.

Results

Data include 65,421 outpatient visits and 13,955 pediatric inpatient admissions for which a diagnostic test for malaria was performed. In outpatients under five years, baseline TPR was 60-80% followed by a rapid and then sustained decrease to 15-30%. Over 4-18 months following discontinuation of IRS, absolute TPR values increased by an average of 3.29% per month (95% CI 2.01-4.57%), returning to baseline levels. Similar trends were seen in outpatients over five years of age and pediatric admissions.

Conclusions

Discontinuation of IRS in a historically high transmission intensity area was associated with a

rapid increase in malaria morbidity to pre-IRS levels.

INTRODUCTION

Malaria control activities in sub-Saharan Africa have increased approximately twentyfold over the last decade resulting in substantial reductions in the burden of malaria [1-3]. Despite these advances, the burden of malaria remains high with an estimated 215 million cases and 438,000 deaths in 2015, of which 88% of cases and 90% of deaths occurred in sub-Saharan Africa [4]. The primary interventions for the prevention of malaria include long-lasting insecticidal nets (LLINs) and indoor residual spraying of insecticide (IRS). LLINs have been shown to reduce malaria morbidity and mortality across a range of epidemiological settings, and the World Health Organization (WHO) recommends universal coverage of populations at risk [5, 6]. IRS has also been shown to be highly effective, but it is more resource-intensive to implement than distribution of LLINs and less than 10% of the population at risk in sub-Saharan Africa is currently protected by IRS [4, 7, 8].

Uganda is emblematic of countries with the highest burden of malaria in sub-Saharan Africa, where progress in reducing malaria morbidity and mortality has been slowest. LLINs have been the primary intervention for the prevention of malaria in Uganda and considerable effort has been made to achieving universal LLIN coverage, culminating in a universal LLIN distribution campaign conducted from 2013-14. After decades of inactivity, IRS was adopted as a key component of Uganda's malaria control strategy in 2006 with funding from the President's Malaria Initiative. Initial efforts focused on epidemic prone areas in the southwestern part of the country. However, in 2008 the IRS program was moved to ten districts in northern Uganda with high transmission intensity. The IRS program in northern Uganda achieved coverage levels consistently above 95% and resulted in marked reductions in the burden of malaria [9, 10]. In 2014, the IRS program was moved from the ten districts in the north, with hopes that gains would mainly be sustained following the universal LLIN distribution campaign.

This study utilizes data from an enhanced health facility-based malaria surveillance program established in an outpatient and inpatient setting in Apac District, one of the areas in northern Uganda where IRS was implemented, and later withdrawn. The study spans a 77-month period from July 2009 through November 2015, covering ten rounds of IRS before its discontinuation in May 2014, followed by universal distribution of LLINs in June 2014. Our primary objective was to evaluate trends in malaria morbidity before, during, and after the implementation of IRS.

METHODS

Study site and vector control interventions

The study was conducted in Apac District, an area with historically high malaria transmission intensity; in 2002 the entomological inoculation rate was estimated to be over 1,500 infectious bites per person per year [11]. Malaria transmission is perennial in this area with peaks following the two annual rainy seasons. IRS was first implemented in Apac District in May 2008 with a single round of DDT followed by a 2nd round conducted in February 2010 using the pyrethroid alpha-cypermethrin. Due to concerns around the emergence of pyrethroid resistance [10], IRS was switched to the carbamate bendiocarb in August 2010 with repeated rounds of spraying approximately every six months through May 2014. For each round of IRS, the proportion of houses sprayed and population protected was over 90% (Table 1). A series of targeted LLIN distribution campaigns were conducted in the area between 2006 and 2010, followed by a universal coverage campaign carried out in June 2014 as part of a national program. According to a malaria indicator survey conducted in December 2014, 94% of households reported owning at least one LLIN and 77% of persons reported sleeping under an LLIN the prior evening in the mid-north region of Uganda, which includes Apac District [12].

Health facility-based surveillance

Enhanced malaria surveillance was conducted at one outpatient facility (Aduku Health Center) and one inpatient facility including children under 14 years of age (Apac Hospital) as previously described (Figure 1) [13, 14]. Briefly, data were collected on demographics, whether malaria was suspected (outpatient facility only), whether a laboratory test for malaria was performed, the type of laboratory test performed (microscopy or rapid diagnostic test [RDT]), and the laboratory test result. Additional training and support was provided to maximize the proportion of patients with suspected malaria who underwent diagnostic testing at the outpatient facility and among all children admitted at the inpatient facility. For inpatients, additional data were collected on disease severity. Patients with severe malaria were defined as having a positive diagnostic test and any of the following (based on available data): 1) severe anemia (hemoglobin < 5 g/dL), 2) coma, 3) jaundice, or 4) death during hospitalization. Patients with complicated malaria were defined as having a positive diagnostic test and any of the following: 1) any of the above criteria for severe malaria, 2) inability to breastfeed or drink, 3) convulsions, 4) lethargy, or 5) inability to sit up or stand.

Statistical analysis

Data were entered using Microsoft Access (Microsoft Corporation, Redmond, Washington, USA) and analyzed using STATA (STATA Corp., College Station, TX, USA). The primary outcome was the test positivity rate (TPR), defined as the proportion of patients tested for malaria (denominator) who tested positive (numerator). The period of observation extended from July 2009 through November 2015 for outpatient surveillance and from June 2011 through November 2015 for inpatient surveillance. The exposure variable of interest was time, evaluated as a categorical variable in relation to the timing of IRS, including a baseline period (July 2009 – August 2010), an initial period of effective IRS (September 2010 – February 2011), a sustained period of effective IRS (March 2011 – August 2014), which included the first 3 months after the last round of IRS was completed, and the 4-18 month period following IRS discontinuation (September 2014 – November 2015) when a resurgence of malaria was observed. Temporal changes in the monthly TPR over time periods of interest were estimated by interrupted time series using ordinary least-squares regression with Newey-West standard errors adjusted for estimates of monthly rainfall with a one month lag [15], method of laboratory testing (microscopy vs. RDT) and autocorrelation. Outpatient surveillance data were stratified for patients under five and five years or older. Among inpatients with laboratory confirmed malaria, the probabilities of having complicated malaria, severe malaria, or death with malaria were compared between the periods of effective IRS and 4-18 months after IRS was discontinued using logistic regression controlling for age, monthly rainfall with a one month lag, and autocorrelation by including a quadratic term for the day of observation.

RESULTS

Characteristics of the study population

Over the 77-month observation period, there were 126,260 outpatient encounters of which 53.6% were suspected of having malaria. Among patients with suspected malaria, 96.7% underwent laboratory testing. Laboratory testing was exclusively based on microscopy until 2012 when RDTs became available at the health center. Initially RDT use was low, but increased to 29.4% during the 4-18 month period after IRS was discontinued. Following the implementation of IRS there was a shift to an older age range among patients suspected and tested for malaria that then returned to baseline after IRS was discontinued (Table 2).

Over the 54-month inpatient observation period, 14,595 children were admitted to the hospital of which 95.6% underwent diagnostic testing for malaria. Among children tested for malaria, the proportion of testing based on RDTs was only 1.6% during the period of effective IRS, increasing to 33.0% during the 4-18 month period after IRS was discontinued. The age distribution of children admitted to the hospital was similar during the period before and after IRS was discontinued (Table 2).

Temporal changes in malaria morbidity in relation to IRS

For the outpatient surveillance data, the baseline period, which included the one round of IRS with alpha-cypermethrin, which was not associated with a significant change in the TPR. During this period monthly TPRs ranged from 59-82% in patients under five years and 30-54% for patients five years and older (Figure 2). Following the first round of IRS with bendiocarb, there was a marked decrease in the TPR. From September 2010 – February 2011, there was an absolute decrease in the TPR of 5.84% per month ($p<0.0001$) reaching 20% in patients under five years and 3.06% per month ($p=0.001$) reaching 14% in patients five years and older (Figure

2, Table 3). Rounds of IRS with bendiocarb were repeated approximately every six months through May 2014 with a sustained reduction in TPR up to three months following the discontinuation of IRS. However, even during this sustained reduction there were unexplained short periods where the TPRs “spiked” above what were predicted (e.g. July-November 2013). From March 2011 – August 2014, there was an absolute decrease in the TPR of 0.40% per month ($p=0.002$) reaching as low as 10% in patients under five years and 0.41% per month ($p<0.0001$) reaching 4% in patients five years and older (Figure 2, Table 3). A universal LLIN distribution campaign was conducted the month following the last round of IRS. During the 4-18 months after IRS was discontinued there was a significant increase in the TPR, returning to baseline levels. From September 2014 – November 2015, there was an absolute increase in the TPR of 3.29% per month ($p<0.0001$) reaching as high as 79% in patients under five years and 2.78% per month ($p<0.0001$) reaching 65% in patients five years and older (Figure 2, Table 3). Of note, monthly estimates of rainfall with a one month lag time were controlled for in all analyses and there was no significant difference in average monthly rainfall in 2015 (mean 106.1mm) compared to each of the proceeding 4 years (range 97.6-111.6mm, $p>0.74$ for all pair-wise comparisons).

Inpatient surveillance began in June 2011, when the 3rd round of IRS with bendiocarb was being administered. During the sustained period of effective IRS monthly TPRs among all children admitted to the hospital ranged from 17-86%, with an average of 56%. During the 4-18 months after IRS was discontinued, there was an absolute increase in the TPR of 5.66% per month ($p<0.0001$) reaching 100% in August 2015 (Figure 2, Table 3). Despite the marked increase in TPR following discontinuation of IRS, there was no evidence for worsening of disease severity.

Comparing the 4-18 month period after IRS was discontinued to the sustained period of effective IRS, the probabilities of having complicated malaria (24.5% vs. 27.2%) and severe malaria (1.9% vs. 5.6%) were lower ($p<0.0001$ for both comparisons) and there was no significant change in the probability of death with malaria during hospitalization (0.3% vs. 0.5%, $p=0.42$).

DISCUSSION

In a district of Uganda with historically high malaria transmission intensity, the implementation of IRS with the carbamate bendiocarb was associated with a rapid decline in the malaria TPR among outpatients, followed by a sustained decline over a four-year period. Immediately following the discontinuation of IRS, a universal LLIN distribution campaign was conducted with the hopes that gains achieved by IRS would be maintained. However, TPRs began to rise four months after IRS was discontinued, reaching pre-IRS levels within 18 months. Similar trends were seen following discontinuation of IRS among children admitted to the district hospital, although there was no evidence of worsening in disease severity.

LLINs and IRS are the most widely used interventions for the prevention of malaria in Africa and the WHO recommends universal access to either of these measures [4]. The benefits of LLINs have been well-established in randomized controlled trials, with use of LLINs associated with reductions in the incidence of malaria of 50% and child mortality of 20% [5]. It has been estimated that the incidence of malaria decreased by 40% across sub-Saharan Africa between 2000 and 2015, and that LLINs were responsible for 68% of cases averted [1]. In Uganda, the proportion of households with at least one LLIN increased from 47% to 90% between 2009-2014, and the average number of LLINs per household increased from 0.8 to 2.5 [12].

Historically, IRS has played a major role in the elimination of malaria in several countries outside of Africa and in greatly reducing the burden of malaria in parts of Africa with low or seasonal transmission [16, 17]. Although the effectiveness of IRS has been well-established through historical and operational evidence, high-quality data from randomized controlled trials on the impact of IRS in stable transmission settings is limited [18]. Recent cluster randomized trials from Africa comparing IRS combined with LLINs versus either intervention alone have provided mixed results [19-21]. Adding IRS to LLINs appears to be most effective in areas where LLIN coverage is low, pyrethroid resistance is high, and/or when using IRS with non-pyrethroid based insecticides [22].

In our study, the benefits of IRS with bendiocarb were clear as evidenced by the dramatic decline in malaria morbidity after its initiation followed by an equally dramatic increase shortly after IRS was discontinued. The resurgence of malaria occurred despite universal LLIN distribution immediately following discontinuation of IRS. These findings raise questions about whether the LLINs were used properly, or if insecticide resistance may have limited their effectiveness. The recent spread of pyrethroid resistance, the only class of insecticides currently available for LLINs, is of concern. The emergence of high-level pyrethroid resistance among the primary vectors, *An. gambiae* s.s. and *An. arabiensis*, has been reported in Uganda and other parts of Africa [23, 24]. Also of concern are putative changes in vector behavior and shifts in the relative abundance of vector species, which may increase exposure risk during the early evening hours while people are outside of their bed nets and unprotected by LLINs [25]. One reassuring finding from our study was the lack of an increased risk of severe or complicated malaria among pediatric inpatients during the resurgence of malaria following discontinuation of IRS. However, following the discontinuation of IRS, the TPR among outpatients 5 years and older increased to levels higher than those observed before the initiation of effective IRS, suggesting a loss of some immunity against uncomplicated malaria.

In the last decade, the WHO has reaffirmed the importance of IRS as a primary intervention for reducing malaria transmission in Africa. IRS coverage increased from less than 2% in 2006 to 11% in 2010. However, the spread of pyrethroid resistance has led many control programs to replace pyrethroids with more expensive alternatives such as carbamates or organophosphates, leading to downscaling of IRS programs. This has resulted in a reported 53% decrease in the number of houses sprayed between years of peak coverage and 2015 across 18 countries in Africa supported by the U.S. President's Malaria Initiative [26]. Historically most malaria resurgences have been linked to weakening of control programs. In a systematic review of 75 malaria resurgence events in 61 countries occurring from the 1930s through the 2000s, withdrawal of IRS was a major contributing factor, but this was felt to be primarily due to resource constraints or complacency rather than insecticide resistance [27]. In a cross-case study review, premature reductions of coverage or withdrawal of IRS were linked to malaria resurgence in Cape Verde, Sri Lanka, and Turkey [28]. Contemporary data from Africa on the impact of discontinuing IRS is limited given that this has been a recent phenomenon. In the high transmission region of Northeastern Zambia, but not in the rest of the country where transmission is lower, a resurgence of malaria cases was reported following disruption of IRS [29]; in two districts of Tanzania an increase in parasite prevalence was reported following the discontinuation of IRS after four years despite distribution of LLINs [26]; and in Benin an increase in entomological measures of transmission was reported following the discontinuation of IRS after three years despite distribution of LLINs [30]. In contrast, following a 3-year experimental program of IRS in South Pare, Tanzania, which ended in 1959, the expected resurgence of malaria was delayed for several years which was attributed to changes brought about in the original vector mosquito populations and a program to increase the use of antimalarial drugs [31].

Our study had several limitations. Most importantly were the observational study design and the lack of a control group. Thus, we are unable to exclude the possibility that factors other than the discontinuation of IRS contributed to the resurgence of malaria seen. For example, adherence to LLINs was not measured, therefore although LLIN coverage was reportedly high, it is unknown whether they were sufficient numbers of LLINs and they were being used properly. In addition, the availability of ACTs was not measured and stock outs could have contributed to the resurgence. Another potential limitation was use of the TPR as our outcome measure, which is a surrogate measure of malaria incidence and can be influenced by factors such as health facility attendance, selection bias for those referred for testing, and the accuracy of laboratory testing. Despite these limitations, it is likely that the observed changes in malaria morbidity were related to starting and stopping effective IRS given the longitudinal nature of the data, the magnitude of changes, and the consistency with which data was collected over an extended period of time. It should also be pointed out that our study area bordered several districts where IRS was not implemented (Figure 1), which may have contributed to the rapid resurgence of malaria.

Uganda and other countries in Africa are now facing difficult decisions about the role of IRS when demands exceed the availability of resources. Current funding levels are insufficient to achieve full IRS coverage in Uganda and current gains in malaria may not be sustained if control measures are withdrawn. In addition, the emergence of pyrethroid resistance has required countries to consider alternative classes of insecticide, which can be considerably more expensive. There is an urgent need to better define when IRS should be maintained, changed to different formulations, or can be safely discontinued or scaled back. This will require effective surveillance systems to monitor trends in disease burden and insecticide resistance. In this area of historically highly intense transmission the reductions in malaria achieved through effective IRS could not be maintained by a LLIN distribution campaign alone. Additional interventions are needed to supplement LLINs, ensure LLINs are being used properly and prevent stock outs of ACTs when IRS is withdrawn from areas where malaria transmission was historically high.

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Conflict of interest

We declare no competing interests. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The authors had the final responsibility for the decision to submit for publication.

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Table 1. Details of indoor residual spraying of insecticide in Apac District

Formulation of insecticide	Dates of Spraying	Percentage of households sprayed	Percentage of population protected
DDT	March – May 2008	92.4%	91.0%
alpha-cypermethrin	February 23rd – March 31st 2010	99.9%	99.9%
bendiocarb	August 23rd – September 21st 2010	99.5%	99.5%
bendiocarb	January 5th – January 30th 2011	99.6%	99.6%
bendiocarb	May 23rd – June 20th 2011	97.6%	97.8%
bendiocarb	November 9th – December 10th 2011	93.1%	94.0%
bendiocarb	April 23rd – June 2nd 2012	90.3%	90.4%
bendiocarb	October 22nd – November 30th 2012	92.3%	93.2%
bendiocarb	April 2nd – May 25th 2013	97.5%	96.6%
bendiocarb	November 4th – December 7th 2013	92.7%	93.5%
bendiocarb	April 22nd – May 23rd 2014	92.6%	91.3%

Table 2. Characteristics of study populations from outpatient and inpatient surveillance

Characteristic	Time categories			
	Baseline Jul 2009 – Aug 2010	Initial period of effective IRS Sep 2010 – Feb 2011	Sustained period of effective IRS Mar 2011 – Aug 2014	4-18 months after IRS discontinued Sep 2014 – Nov 2015
Outpatient surveillance (Aduku Health Center IV)				
Total number of patient encounters [a]	25,945	8,840	67,575	23,900
Malaria suspected (% total)	14 718 (56.7%)	5 034 (57.0%)	37 003 (54.8%)	10 879 (45.5%)
Malaria laboratory testing done (% suspected)	14 104 (95.8%)	4 994 (99.2%)	36 888 (99.7%)	9 435 (86.7%)
Microscopy performed (% total tested) [b]	14 104 (100%)	4 994 (100%)	35 373 (95.9%)	6 656 (70.6%)
Mean age in years if tested (SD)	15.6 (18.0)	21.3 (19.0)	19.9 (18.7)	15.8 (17.6)
Age < 5 years (% total tested)	6 577 (46.6%)	1 370 (27.4%)	11 223 (30.4%)	3 430 (36.4%)
Tested positive for malaria (% total tested)	7 899 (56.0%)	1 643 (32.9%)	8 418 (22.8%)	4 569 (48.4%)
Inpatient surveillance (Apac Hospital) [c]				
Total number of children age ≤ 13 years admitted [a]			8,604	5,991
Malaria laboratory testing done (% total admitted)			8,345 (97.0%)	5,610 (93.6%)
Microscopy performed (% total tested) [b]			8,210 (98.4%)	3,756 (67.0%)
Mean age in years if tested (SD)	Prior to implementation		3.2 (2.8)	3.6 (2.9)
Tested positive for parasites (% total tested)	of inpatient surveillance		4,650 (55.7%)	4,683 (83.5%)
Complicated malaria (% laboratory confirmed cases)			1,264 (27.2%)	1,146 (24.5%)
Severe malaria (% laboratory confirmed cases)			261 (5.6%)	90 (1.9%)
Death with malaria (% laboratory confirmed cases)			42 (0.5%)	17 (0.3%)

[a] Excludes patients with no age recorded
[b] RDT performed if microscopy not done
[c] Inpatient surveillance began June 2011

Table 3. Temporal changes in malaria test positivity rates in relation to IRS

Patient population	Age group	Estimated average monthly change in absolute value of TPR: Initial period of effective IRS Sep 2010 – Feb 2011 Δ TPR (95% CI) [a]	p-value	Sustained period of effective IRS Mar 2011 – Aug 2014 Δ TPR (95% CI) [a]	p-value	4-18 months after IRS discontinued Sep 2014 – Nov 2015 Δ TPR (95% CI) [a]	p-value
Outpatient surveillance	< 5 years	- 5.84% (-7.44 to -4.24%)	<0.001	- 0.40% (-0.64 to -0.16%)	0.002	3.29% (2.01 to 4.57%)	<0.001
	≥ 5 years	- 3.06% (-4.89 to -1.24%)	0.001	- 0.41% (-0.61 to -0.21%)	<0.001	2.78% (2.01 to 3.54%)	<0.001
Inpatient surveillance [b]	≤ 13 years	N/A		N/A		5.66% (3.22 to 8.10%)	<0.001

[a] Adjusted for rainfall with a one month lag and proportion of laboratory testing based on microscopy vs. RDT
[b] Inpatient surveillance began June 2011

Figure Legends

Figure 1.

Map of Uganda with study district (solid red) and other nine districts where IRS was discontinued (red dots). Expanded view of study district with location of outpatient (Aduku HC IV) and inpatient (Apac Hospital) health facilities were surveillance data collected.

Figure 2.

Temporal changes in malaria test positivity rates in relation to IRS. Vertical dashed lines separate the study period into the following 4 categories: a baseline period (July 2009 – August 2010), an initial period of effective IRS (September 2010 – February 2011), a sustained period of effective IRS (March 2011 – August 2014), which included the first 3 months after the last round of IRS was completed, and the 4-18 month period following IRS discontinuation (September 2014 – November 2015) when a resurgence of malaria was observed. Pink bars show the timing of indoor residual spraying (IRS) with a single round of alpha-cypermethrin, yellow bars the timing of IRS with nine rounds of bendiocarb, and blue bars the mass deployment of long-lasting insecticidal nets.