Using routine health data to evaluate the impact of indoor residual spraying on malaria transmission in Madagascar

Emily R Hilton,1,2 Saraha Rabeherisoa,2 Herizo Ramandimbiriajaona,2 Julie Rajaratnam,3 Allison Belemvire,4 Laurent Kapesa,5 Sarah Zohdy,6 Catherine Dentinger,6 Timothee Gandaho,7 Djenam Jacob,7 Sarah Burnett,8 Celestin Razafinjato2

ABSTRACT

Introduction Indoor residual spraying (IRS) and insecticide-treated bed nets (ITNs) are cornerstone malaria prevention methods in Madagascar. This retrospective observational study uses routine data to evaluate the impacts of IRS overall, sustained IRS exposure over multiple years and level of spray coverage (structures sprayed/found) in nine districts where non-pyrethroid IRS was deployed to complement standard pyrethroid ITNs from 2017 to 2020.

Methods Multilevel negative-binomial generalised linear models were fit to estimate the effects of IRS exposure overall, consecutive years of IRS exposure and spray coverage level on monthly all-ages population-adjusted malaria cases confirmed by rapid diagnostic test at the health facility level. The study period extended from July 2016 to June 2021. Facilities with missing data and non-geolocated communes were excluded. Facilities in IRS districts were matched with control facilities by propensity score analysis. Models were controlled for ITN survivorship, mass drug administration coverage, precipitation, enhanced vegetation index, seasonal effects and district. Predicted cases under a counterfactual no IRS scenario and number of cases averted by IRS were estimated using the fitted models.

Results Exposure to IRS overall reduced case incidence by an estimated 30.3% from 165.8 cases per 1000 population (95% CI=139.7 to 196.7) under a counterfactual no IRS scenario, to 114.3 (95% CI=96.5 to 135.3) over 12 months post-IRS campaign in nine districts. A third year of IRS reduced malaria cases 30.3% more than a first year (incidence rate ratio (IRR)=0.758, 95% CI=0.726 to 0.792, p<0.001) and 26.7% more than a second year (IRR=0.733, 95% CI=0.611 to 0.878, p=0.001). There was no significant difference between the first and second year (p>0.05). Coverage of 86%–90% was associated with a 19.7% reduction in incidence (IRR=0.803, 95% CI=0.690 to 0.934, p=0.005) compared with coverage ≤85%, although these results were not robust to sensitivity analysis.

Conclusion This study demonstrates that non-pyrethroid IRS appears to substantially reduce malaria incidence in Madagascar and that sustained implementation of IRS over three years confers additional benefits.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The use of non-pyrethroid insecticides for indoor residual spraying (IRS) in communities using pyrethroid-based insecticide-treated nets (ITNs) is associated with reduced malaria prevalence, and with reduced malaria incidence in some settings. To date, few studies have investigated the impact of high spray coverage and sustained IRS implementation over multiple years.

WHAT THIS STUDY ADDS

⇒ This study estimates the impact of IRS in a setting with heterogeneous malaria transmission and variation in intervention impact at the subnational level. Additionally, this study presents evidence of a benefit to continuing IRS implementation over multiple consecutive years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results reported here bolster the evidence around the effectiveness of non-pyrethroid insecticides for IRS while suggesting that policymakers should consider the benefits of sustaining IRS implementation over multiple years when undertaking decisions to move locations and/or withdraw IRS.

INTRODUCTION

Malaria prevalence worldwide has declined in recent decades, with significant contributions from the implementation of vector control interventions including indoor residual spraying (IRS).1 However, in recent years, progress has stalled and in some areas reversed.2 Malaria is among the top five causes of mortality in Madagascar,3 and in 2020, the country accounted for 1.5% of global malaria cases and 1.5% of global malaria deaths. From 2015 to 2020, Madagascar experienced an increase in malaria incidence and mortality greater than that observed in other countries of East and Southern Africa.2
IRS is an intervention that involves applying internal walls of homes with a residual insecticide that will kill mosquitoes and other insects that encounter the treated walls. From 1993 to 1998, widespread IRS campaigns using dichlorodiphenyltrichloroethane (DDT) carried out in the Central Highlands of Madagascar successfully reduced malaria prevalence and vector abundance in the sprayed areas. From 1999 to 2005, targeted DDT-based IRS operations continued in the Central Highlands. In 2005, the Malagasy National Malaria Control Programme (NMCP) replaced DDT with pyrethroid insecticides for IRS in the Highlands. Since 2008, the US President’s Malaria Initiative (PMI) has supported IRS campaigns in Madagascar, most recently through the PMI VectorLink Project (2017–2023) and its predecessor, the Africa Indoor Residual Spraying (AIRS) Programme (2014–2017). From 2008 to 2012, ‘generalised’ IRS spraying, meaning close to 100% of eligible structures are sprayed, was deployed in the pre-elimination Central Highlands area. In 2012, the strategy was shifted to ‘focussed’ spraying, which targeted areas in the Central Highlands with higher malaria case incidence, an approach that was sustained through 2015. Starting in 2014, the country shifted to a strategy of targeting high-transmission regions and deployed IRS in the east and southeast coastal districts. IRS has since been targeted to select high-burden areas based on epidemiological and entomological data, as well as other contextual factors such as the presence of environmentally protected areas and organic agriculture. Malaria vector resistance to pyrethroids has been detected in eastern and southeastern coastal regions, and from 2016 to 2020, non-pyrethroid insecticide products including pirimiphos-methyl and clothianidin were deployed. The 2018–2022 National Strategic Plan in Madagascar recommends rotation of insecticides every 2–3 years to manage insecticide resistance.

Although IRS is a widely used core vector control intervention that has been implemented to successfully reduce malaria incidence for decades, increasing resistance to pyrethroids presents a major challenge in global progress against malaria. The WHO Global Plan for Insecticide Resistance Management has encouraged the use of non-pyrethroid insecticides for IRS to reduce the spread of insecticide resistance, although rigorous evidence on the effectiveness of next-generation non-pyrethroid IRS products on real-world clinical outcomes is lacking. The WHO recommends that IRS structure coverage of at least 85% be achieved in order to attain a mass effect on local vector populations. Although there is a strong theoretical foundation for ensuring high coverage of IRS, to date, few reports have shown evidence for the relationship between level of coverage at the community level and reduction in malaria burden. Given the cost of IRS implementation, National Malaria Programs (NMPs) and donors often must make crucial targeting decisions for IRS campaigns, including whether to sustain implementation in the same place over several years or to rotate targeted geographies. This decision rests on two questions: (1) what is the impact of withdrawing IRS after one or multiple rounds of implementation? and (2) is there additional benefit to implementing IRS over multiple consecutive years in the same area? The impact of withdrawing IRS has been previously investigated.

Here we present an observational, retrospective analysis of the epidemiological impact of IRS in nine total districts of Madagascar where IRS was implemented from 2017 to 2020. This study has three objectives: (1) to estimate the overall impact of IRS campaigns on routinely reported malaria incidence; (2) to investigate the effect of implementing IRS over multiple consecutive years; and (3) to estimate the impact of high IRS coverage that meets the WHO 85% target. An additional aim of this work is to foster the use of routine malaria surveillance data for evidence-based decision-making.

**METHODS**

**Study setting**

Madagascar is a tropical island located in the southwest of the Indian Ocean, approximately 400 km off the western coast of Mozambique. The country is ecologically and climatically diverse, reflected in the highly heterogeneous nature of malaria transmission and seasonal malaria patterns across the island. Malaria has increased in all areas of Madagascar since 2011, with high endemicity observed chiefly in the eastern and western coastal regions, and lower transmission in the Central Highlands. IRS deployment from 2017 to 2020 took place in southeastern and southwestern districts (figure 1) in regions with primarily tropical climates, except for two districts (Betioqy Asimo and Ampanihy Ouest) located in a region where the climate is classed as subdesert. Malaria prevalence in children aged 6–59 months measured in the 2016 Malaria Indicator Survey (MIS) was found to be 14.9% in the tropical areas and 5% in the subdesert areas. The 2021 Demographic Health Survey (DHS) found that prevalence had increased to a range of 15.8%–27.2% prevalence in tropical regions where IRS was deployed, and decreased to 4.2% in the subdesert. The DHS reported that 69% of households nationally had access to at least one insecticide-treated bed net (ITN), a decrease from 80% reported by the 2016 MIS. Administratively, the country is divided into 23 regions and 114 districts, which are further subdivided into communes.

**Intervention**

From 2014 through 2020, PMI VectorLink/AIRS deployed annual IRS campaigns in 14 total districts of Madagascar. Due to concerns around health management information system (HMIS) data quality prior to 2016, five districts where IRS was deployed from 2014 to 2016 were excluded from this study, leaving nine study districts. Between three and five study districts were targeted for IRS each year. Each study district received between one and three consecutive years of IRS implementation with pirimiphos-methyl (Actellic 300CS),
clothianidin (SumiShield 50WG), or a combination of clothianidin and deltamethrin (Fludora Fusion) (figure 1). IRS coverage was reported at the commune level (the administrative level below district). IRS campaigns took place from July to September in 2017 and 2018 and from October to December in 2019 and 2020. Of the nine study districts that received at least one year of IRS implementation from 2017 to 2020, six received a second consecutive year and three received a third year.23–27

Study design
This study is a retrospective, observational evaluation of the epidemiological impact of IRS campaigns that took place from 2017 to 2020 in nine districts of Madagascar. The evaluation period encompassed July 2016 through June 2021. The primary outcome was confirmed outpatient malaria cases among all ages, standardised per health facility catchment population as reported to the HMIS. Case confirmation was done by rapid diagnostic testing (RDT). Exposure was defined at the commune level (administrative level below district) by IRS status (whether IRS was conducted within the commune) and by level of spray coverage achieved. Further details on IRS exposure definitions are provided in the following sections. The evaluation used a ‘transmission year’ defined as starting in July and extending to June of the following year to account for seasonal malaria transmission.

Primary outcome
The primary outcome was monthly RDT-confirmed outpatient malaria cases among all ages, standardised per health facility catchment population. Malaria case data were extracted from the Madagascar HMIS for all health facilities in the country. In 2017, Madagascar’s HMIS transitioned to the District Health Information Systems (DHIS2) platform from a previous database based in Microsoft Access. Data from January 2016 onward were available in DHIS2. The final dataset used in this study was accessed from DHIS2 on 12 October 2021, for the period July 2016–June 2021, including malaria cases confirmed by RDT and health facility catchment populations. Microscopy testing and unconfirmed cases are not reported in DHIS2. Facility catchment populations are defined based on the most recent census conducted in 2018 and projected forward and backward assuming a 2.9% annual growth rate.28

Health facilities were excluded from analysis according to the following criteria: private health facilities and hospitals; facilities missing catchment population data; facilities in communes missing geocoordinates, which did not allow them to be linked to climate data; and facilities missing RDT-confirmed case data for an entire year. Anomalous values were identified by visual inspection of time-series plots for each health facility and comparing against outpatient totals. One value determined to be anomalous for being greater than 4 standard deviations (SD) from the mean was excluded.

Potential confounding variables
To account for the potential impact of other malaria control interventions on the outcome, indicators of access to ITNs and mass drug administration (MDA) coverage were included in the analysis. Mass distribution of standard pyrethroid ITNs took place in October and November 2015 in 92 districts and in August 2018 in 106 districts. Both distributions included all nine IRS study districts. ITN survivorship was included as a covariate to control for the time since the most recent ITN campaign, based on durability monitoring conducted by the PMI VectorLink Project and the Institut Pasteur de Madagascar.29,30 Durability monitoring using standard protocols31,32 found that net survivorship declined exponentially after both distributions during
the 36-month monitoring period. Net survivorship was averaged at each follow-up time point (3–6 months, 12 months and 24 months post-distribution in 2015; 12 months, 24 months and 36 months post-distribution in 2018) and applied monthly to districts based on the time since the previous ITN campaign. Net survivorship was set to zero for districts that were not included in the ITN campaigns.

Two rounds of MDA with dihydroartemisinin–piperaquine took place in 11 districts in March and June 2021. Of the 11 districts where MDA took place, only one district, Ampanihy Ouest, had also received IRS implementation (in 2019). MDA coverage data at the district level were provided by the Madagascar NMCP. Coverage was calculated as the number of treated inhabitants divided by total population and included in analysis as a continuous covariate.

Monthly precipitation data were pulled from the Climate Hazards Group InfraRed Precipitation with Station dataset33 and enhanced vegetation index (EVI) data were pulled from the Famine Early Warning Systems Network.34 Commune-level shapefiles were used to access monthly averages from these spatial datasets, which were matched by name to commune-level data from the HMIS. To account for varying climate and transmission patterns across Madagascar, precipitation and EVI lags were calculated using Pearson correlation tests with malaria cases, with districts grouped into the eight malaria transmission ecozones identified by Howes et al.35 The selected lagged values were then scaled to have a mean of zero and an SD of one.

Analytical approach
Matching intervention and control groups
Selection of control groups was done using propensity score matching, a method for obtaining intervention and control groups with similar covariate distributions.36 Matching was performed at the health facility level, and all health facilities in non-IRS districts meeting the inclusion criteria described above were eligible to be matched as controls. For each facility, EVI, precipitation, ITN survival and RDT-confirmed malaria case incidence per 1000 population were averaged over a 12-month baseline period (July 2016–June 2017) before IRS had been deployed in any of the study IRS districts. Propensity scores were obtained via logistic regression where the previously described variables were included as covariates and the outcome variable was a binary variable for which facilities that would receive IRS were assigned a one and facilities that would not were assigned a zero.

IRS and control facilities were matched based on their propensity scores using nearest neighbour matching with a one to four ratio (each IRS facility was matched to four control facilities) and without replacement (each control facility could only be matched with one IRS facility). Diagnosis of the quality of matches was done by comparing covariate distributions in control and IRS groups. The standard mean difference for each covariate was assessed against a threshold of 0.25, and density plots and distribution plots of propensity scores were examined.37

Model development
Different models were developed to respond to each study question and estimate the effect of IRS exposure on the outcome variable. The models differed primarily according to their exposure variables as described in the sections below. For each study question, a negative binomial generalised linear multilevel mixed-effects model with a log link was specified, with the following basic formulation:

\[
y_{ij} \sim \text{Negative binomial}(\lambda_{ij}, N_{ij})
\]

\[
\log(\hat{y}_{ij}) = \log(N_{ij}) + X_{ij}\beta + Z_{ij}\gamma
\]

Where \(y_{ij}\) is malaria cases at the \(i^{th}\) month in the \(j^{th}\) cluster; \(N_{ij}\) is the population, treated as ancillary parameter; \(X_{ij}\) is the \(p \times 1\) row vector of \(p\) fixed-effects predictor covariates; and \(\beta\) is the \(p \times 1\) column vector of the fixed-effects regression coefficients. The \(q \times 1\) vector of \(q\) random-effects covariates is given by \(Z_{ij}\), and their coefficients by \(\gamma_{j}\), where the \(j\) subscript indexes the random-effects grouping variables.

The following variables were included as fixed predictors (\(X_{ij}\)): ITN survival, MDA coverage, precipitation, EVI, district (categorical) and transmission year (categorical). Seasonal effects of malaria were also included as fixed effects, and modelled by including cosine and sine functions for the first harmonic with a period of 12 months and an interaction with year and district to allow flexibility of the sinusoidal curve by district and year as:

\[
\sin (\frac{2\pi t}{12}) \times \text{year}_{ij} + \cos (\frac{2\pi t}{12}) \times \text{district}_{ij}
\]

Where \(t_{ij}\) is the month of the year (from 1 to 12), \(T\) is the harmonic period (12), and \(\text{year}_{ij}\) and \(\text{district}_{ij}\) are dummy variables for the year and district.38

The variables of interest for modelling IRS exposure were included as fixed predictors and were specified differently in each model to respond to each study question. These are described in detail in the following sections and a sample table is provided in the online supplemental material 2.

Cluster identification for matched IRS facilities with comparator facilities and transmission year was included as random-effects (\(Z_{ij}\)) variables.

Study question 1: overall impact of IRS
To estimate the overall impact of IRS exposure on all-ages RDT-confirmed malaria incidence, the model dataset included all health facilities in IRS districts and their comparator facilities selected through propensity score matching.

IRS exposure was modelled using two binary dummy variables that indicated the first 6-months and the 7th–12th months since the most recent IRS campaign. For the ‘IRS exposure 0–6 months’ variable, commune-months within the first 6 months post-IRS were assigned a one and all others were assigned a zero. Similarly, for the
Study question 2: impact of multiple years of exposure to IRS
To estimate the impact of sustained exposure to IRS over multiple years, three binary IRS exposure variables were applied to the commune-spray-year. A spray-year was defined as the 12 months following the start of IRS implementation. These variables indicated the 12 months following an IRS campaign and whether that campaign was a first, second or third consecutive year of IRS implementation. In districts where 13 months passed between the 2018 and 2019 IRS campaigns, the 13th month was also assigned a ‘1’ for the IRS status variable 7–12 months, to reflect the sustained IRS implementation in those districts.

To quantify the model results in a more meaningful measure of overall impact of IRS, the number of malaria cases averted by IRS was estimated. The final fitted model was used to predict malaria cases under a counterfactual scenario of no IRS and compared against predicted cases under observed conditions. This step also allowed the inference of findings for areas missing RDT-confirmed case data and to generate district-specific results. The counterfactual prediction dataset was created by duplicating the model-fitting dataset and setting all IRS exposure variables to zero. The variables in the prediction dataset under observed conditions were unchanged. Both prediction datasets included facility-months missing RDT-confirmed case data, which had previously been excluded from model fitting. Monthly malaria case counts in each of the nine IRS districts were estimated using the fitted model and the prediction datasets. Uncertainty intervals were generated by simulating from the fixed (betas and associated variance–covariance matrix) and random (predicted random effect and associated standard error [SE]) parts of the model to generate 1000 linear predictions per facility-month for both the observed and counterfactual scenarios. Cases averted by IRS were calculated by subtracting predicted cases under observed conditions from predicted cases under the no IRS counterfactual scenario. The mean of these 1000 simulations was the resulting point estimate, and the 2.5th and 97.5th percentiles were the lower and upper bounds of the uncertainty intervals.86

Study question 3: impact of level of IRS coverage
To estimate the impact of level of spray coverage, the modelling dataset included only data from the nine IRS districts, during the 12 months following an IRS campaign. Two models were developed with structures similar to those described above and with differences as follows: IRS exposure, defined as spray coverage (the number of structures sprayed out of structures found), was applied to the level of commune-spray-year. Spray coverage was first modelled as a categorical dummy variable with four coverage bins: <85%, 85%–90%, 91%–95% and 96%–100%, to determine if significant benefit is detected at the WHO-recommended 85% threshold or at a higher level of coverage. Second, a sensitivity analysis was conducted with spray coverage modelled as a continuous covariate to examine a potential linear relationship with the outcome variable. These models did not include a covariate for MDA coverage, as this intervention did not take place in any of the IRS districts in the same year as an IRS campaign. Clusters of matched IRS and comparator facilities were not included as random effects, as the modelling datasets did not include any comparator data. Communes were instead included as random effects.

Data were cleaned, transformed and joined in R V.4.1.1 and Alteryx Designer x64 V.2021.1 (Alteryx, Colorado, USA). Model fitting and simulations were run in Stata/SE V.17.0 (StataCorp, Texas, USA). Data visualisations were created in Tableau V.2021.2.4 (Tableau Software, Washington, USA).

As the team of coauthors involved an international partnership, an author reflexivity statement was elaborated using guidance for promoting equitable authorship in publications,41 42 and is available in the online supplemental material 1.

Data sources
Routinely collected data on IRS implementation and coverage were sourced from the PMI AIRS and the PMI VectorLink Projects. Malaria case data and health facility populations were extracted from the Madagascar HMIS. ITN and MDA campaign data and administrative shapefiles were provided by the Madagascar NMCP.

Patient and public involvement
Patients and the public were not involved in this research study.

RESULTS
A total of 2547 public health facilities were identified in the Madagascar HMIS during the study period (July 2016–June 2021), of which 2171 met the eligibility criteria for inclusion in this study. Of these, 214 facilities (9.8%) were in IRS districts. After matching based on propensity scores, 848 control facilities from 76 districts were retained for inclusion in modelling for study questions 1 and 2. Only the 214 facilities in IRS districts were included in modelling for study question 3 (further
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details on facility inclusion in the analysis dataset can be found in the online supplemental material 2).

Epidemiological curves showing the average monthly incidence of RDT-confirmed malaria cases of facilities in IRS districts and their matched comparator facilities are shown in figure 2. In the final analysis dataset, a total of 3,412,689 RDT-confirmed malaria cases were reported during the study period, of which 775,547 (22.7%) were reported from facilities in IRS districts. A wide range of case incidence was observed throughout the study period. Among IRS districts, district-level annual incidence ranged from 8.6 to 435.1 confirmed cases per 1000 population.

Summary characteristics and IRS campaign results as well as the final lags for rainfall and EVI included in modelling for each malaria transmission ecozone are available in the online supplemental material 2.

Study question 1: overall impact of IRS

The first 6 months following an IRS campaign were associated with an estimated 43.3% reduction in malaria incidence (incidence rate ratio (IRR)=0.567, 95% CI=0.531 to 0.605; p<0.001); and the 7th–12th months post-IRS showed a 24.8% reduction in incidence (IRR=0.752, 95% CI=0.802; p<0.001) (figure 3A).

An estimated 116,323 (95% CI=40,152 to 196,764) cases of malaria were averted between July 2016 and June 2021 by IRS campaigns in the nine study districts. Malaria incidence was reduced by an estimated 30.3% from 165.8 (95% CI=139.7 to 196.7) cases per 1000 population under a counterfactual no IRS scenario, to 114.3 (95% CI=96.5 to 135.3) under observed conditions, over the 12 months following an IRS campaign in the nine spray districts. The estimated incidence of cases averted per 1000 population was highest in Sakaraha following the 2020 campaign (56.52, 95% CI=11.29 to 105.72) and lowest in Mananjary following the 2017 IRS campaign (5.26, 95% CI=0.52 to 10.07). Estimated incidence of cases averted was not significant in Iakora (245.88, 95% CI=−46.86 to 567.69) following the 2020 IRS campaign. A map of estimated cases averted per 1000 population for each district where IRS campaigns were implemented is shown in figure 4 along with graphs of modelled case incidence under observed and counterfactual scenarios. The full model regression results are available in the online supplemental material 2.

Study question 2: impact of multiple years of exposure to IRS

A single year of IRS exposure was associated with a 37.0% reduction in malaria case incidence (IRR=0.630, 95% CI=0.594 to 0.668, p<0.001), and a second year of IRS was associated with a 40.2% reduction in incidence (IRR=0.598, 95% CI=0.555 to 0.644, p<0.001) compared with no IRS. Compared with the first year of IRS, a second year was not associated with a significantly different reduction in incidence (IRR=0.943, 95% CI=0.801 to 1.110).

Figure 2  Monthly incidence per 1000 population of routinely reported malaria cases confirmed by rapid diagnostic test from July 2016 to June 2021. Case incidence reported by health facilities in the nine study districts treated with indoor residual spraying (IRS) is plotted with matched control facilities. The dates of IRS campaigns are indicated by vertical dashed lines. Red lines represent facilities in IRS districts and black lines represent matched control facilities.
CI=0.866 to 1.023, p=0.170). IRS in year 3 continued to reduce case rates compared with no spray (IRR=0.423, 95% CI=0.355 to 0.504, p<0.001), and produced a significantly greater effect than both year 1 and year 2. The year 3 per cent reduction in cases was 30.9% greater than the effect in year 1 (IRR=0.578, 95% CI=0.578 to 0.825, p<0.001) and 26.7% greater than in year 2 (IRR=0.733, 95% CI=0.611 to 0.878, p=0.001) (figure 3B). The full model regression results are available in the online supplemental material 2.

**Study question 3: impact of level of IRS coverage**

In 2019 and 2020, all communes achieved spray coverage at or above 85%. From 2017 to 2018, 22 of 300 total communes (7.3%) achieved coverage at or below the 85% target threshold set by the WHO. Low coverage was generally attributable to accessibility challenges in remote areas and refusals.23–27 Twenty-two communes (7.3%) achieved coverage between 86% and 90%; 86 communes (28.7%) achieved coverage from 91% to 95%; and 170 communes (56.7%) achieved coverage higher than 95% (table 1).

When modelled as a categorical variable, IRS coverage between 86% and 90% was associated with a 19.7% reduction in incidence (IRS=0.803, 95% CI=0.690 to 0.934, p=0.005) compared with spray coverage at or below 85%. IRS coverage in categories higher than 90% was associated with smaller and non-significant (p>0.05) reductions in incidence compared with coverage at or below 85%. When modelled as a continuous covariate, IRS coverage was significantly associated with a 1.0% increase in malaria incidence with every 1% increase in coverage (IRR=1.010, 95% CI=1.003 to 1.016, p=0.003). Full model regression results are available in the online supplemental material 2.

**DISCUSSION**

This study presents evidence of the impact of IRS on reduction of malaria burden in Madagascar. The results demonstrate a consistent overall association between implementation of IRS and reduced RDT-confirmed all-ages routinely reported malaria incidence. As expected, the observed effect decreased (while remaining significant) from the first 6 months post-IRS to the 7th through 12th months post-IRS, as the residual efficacy of IRS insecticides waned.39

In one district, Iakora, IRS did not appear to significantly reduce case incidence compared with if it had not been deployed. Iakora, which received a single IRS campaign in 2020, had the least amount of data (6 out of 11 health facilities and 55% of facility-months) eligible for inclusion in the analysis, which may have affected the model’s ability to detect a significant IRS impact.

A third consecutive year of exposure to IRS produced significantly greater impact than the first or second year. Sustained implementation of IRS in Eastern Uganda was also associated with a significant and sustained reduction in malaria after 4–5 years,17 though there is recent preliminary evidence of a resurgence in the sixth and seventh years of implementation in the same area, which coincided with a shift in insecticide formulation from pirimiphos-methyl to clothianidin.43 These results suggest that policymakers should consider sustaining implementation of IRS for at least 3 years in target geographies, and give further weight to the tradeoff between the increased benefits of continued IRS versus the potential for a resurgence in malaria cases if IRS is withdrawn, as has been observed in Mali and Uganda.16 45

The results of investigating the impact of level of IRS coverage were not robust to sensitivity analysis. The extreme skewness in the data (87.9% of communes achieved coverage greater than 90% across all spray campaigns) and lack of variation in coverage levels likely hindered this analysis. Additional studies should be undertaken in contexts where there is greater variation in IRS coverage. The results of such a study would be particularly relevant to NMPs seeking to save costs if levels of coverage below 85% (WHO guideline target) are found to achieve similar impact as high coverage. High IRS coverage (>80%) in Bioko Island, Equatorial Guinea was demonstrated to offer community protection to individuals in sprayed and unsprayed houses, compared with individuals in communities with <20%...
coverage, although differences in effect at other levels have not been previously investigated.

The IRS interventions in this study were implemented in communities where mass ITN distributions also took place. Although there is evidence of the individual efficacy of both interventions, few studies have evaluated their joint effect, and the evidence of their combined effectiveness remains inconclusive. The WHO has recognised the need to close this evidence gap. This study suggests a significant benefit of non-pyrethroid IRS implementation in the presence of standard pyrethroid ITNs on malaria case incidence in Madagascar.

**Table 1** Number and percentage of communes that achieved each indoor residual spraying coverage threshold in campaigns that took place from 2017 to 2020.

<table>
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<tr>
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<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
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<tr>
<td>≤85% coverage</td>
<td>4 (6.0%)</td>
<td>18 (21.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>22 (7.3%)</td>
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<tr>
<td>86%–90%</td>
<td>6 (9.0%)</td>
<td>12 (14.1%)</td>
<td>4 (5.0%)</td>
<td>0 (0.0%)</td>
<td>22 (7.3%)</td>
</tr>
<tr>
<td>91%–95%</td>
<td>27 (40.3%)</td>
<td>30 (35.3%)</td>
<td>24 (30.0%)</td>
<td>5 (7.4%)</td>
<td>86 (28.7%)</td>
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<tr>
<td>96%–100%</td>
<td>30 (44.8%)</td>
<td>25 (29.4%)</td>
<td>52 (65.0%)</td>
<td>63 (92.6%)</td>
<td>170 (56.7%)</td>
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<tr>
<td>Total</td>
<td>67 (100.0%)</td>
<td>85 (100.0%)</td>
<td>80 (100.0%)</td>
<td>68 (100.0%)</td>
<td>300 (100.0%)</td>
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</table>
Important limitations of this study include its observational design and reliance on routine passive surveillance data, which were used to generate the primary outcome variable. These data do not account for care-seeking challenges such as patient access to healthcare, which are likely disproportionately present in rural areas, nor potential differential data reporting consistency among health facilities. It has been estimated that as many as four out of every five malaria cases go uncounted in Madagascar,8 which would mean that the true malaria cases were undercounted and likely an underestimated number of cases averted at the community level.

However, the availability of routine surveillance data for all years and districts allows us to estimate district-level impact at a much lower cost than collecting data through a survey. Conducted routinely, this type of study is ideal for informing national policy decisions, such as the targeting of a survey. Conducted routinely, this type of study is ideal for informing national policy decisions, such as the targeting of vector control interventions in line with the WHO strategy for subnational targeting.47

The selection of appropriate controls conducted via propensity score matching represents another limitation related to the observational nature of this study. Although covariate distributional balance between matched IRS and control facilities was ensured, this method cannot truly replicate the benefits of a controlled randomised experiment, nor can it account for the influence of unobserved covariates on the outcome measure.

With regard to the impact of IRS coverage on malaria incidence, potential biases include bias of IRS teams to report high coverage, although internal post-spray data quality audits performed within 90 days of spray completion help ensure accurate coverage reporting.25–27 Additionally, there is potential correlation between low spray coverage and difficult-to-access areas where there may also be less access to healthcare and less likelihood of obtaining RDT confirmation of cases. These potential biases would be expected to influence our findings toward the null effect of no impact of level of IRS coverage on malaria incidence.

CONCLUSION
The results presented here, interpreted with the limitations described above, suggest a positive public health impact of IRS that bolsters the evidence base around effectiveness of non-pyrethroid insecticides. These results suggest that sustained non-pyrethroid IRS implementation for 3 years may confer additional vector control benefits. This work highlights the value of routine surveillance data for evaluating intervention impact, which empowers evidence-based decision-making as NMPs seek to implement targeted vector control at subnational levels.

Author affiliations
1PMI VectorLink Project, PATH, Seattle, Washington, USA
2Programme National de Lutte Contre le Paludisme, Ministère de la Santé Publique, Antananarivo, Madagascar
3Center for Digital and Data Excellence, PATH, Seattle, Washington, USA
4US Agency for International Development, US President’s Malaria Initiative, Washington, District of Columbia, USA
5US Agency for International Development, US President’s Malaria Initiative, Antananarivo, Madagascar
6Entomology Branch, US Centers for Disease Control and Prevention, US President’s Malaria Initiative, Atlanta, Georgia, USA
7PMI VectorLink Project, Abt Associates, Rockville, Maryland, USA
8PMI VectorLink Project, PATH, Washington, District of Columbia, USA

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ORCID iD
Emily R Hilton http://orcid.org/0000-0001-9319-5203

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