## Title

Association between indoor residual spraying and pregnancy outcomes: a quasi-experimental study from Uganda



## Journal

International Journal of Epidemiology, 51(5)

## ISSN

0300-5771

## Authors

Roh, Michelle E
Mpimbaza, Arthur
Oundo, Brenda
et al.

## Publication Date

2022-10-13

## DOI

10.1093/ije/dyac043

Peer reviewed

International Journal of Epidemiology, 2022, 1489–1501
https://doi.org/10.1093/ije/dyac043
Advance Access Publication Date: 18 March 2022
Original article

Perinatal and Infant Health

# Association between indoor residual spraying and pregnancy outcomes: a quasi-experimental study from Uganda

**Michelle E Roh [1,2,*] Arthur Mpimbaza,[3] Brenda Oundo,[4] Amanda Irish,[1,2] Maxwell Murphy,[5] Sean L Wu,[5] Justin S White [1,6] Stephen Shiboski,[1] M Maria Glymour,[1] Roly Gosling,[1,2] Grant Dorsey[7] and Hugh Sturrock[1,2]**

[1]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA, [2]Malaria Elimination Initiative, Institute of Global Health Sciences, University of California, San Francisco, CA, USA, [3]Child Health and Development Centre, Makerere University, College of Health Sciences, Kampala, Uganda, [4]Infectious Diseases Research Collaboration, Kampala, Uganda, [5]Department of Biostatistics, University of California, Berkeley, CA, USA, [6]Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, CA, USA and [7]Division of HIV, Infectious Diseases, and Global Medicine, Department of Medicine, University of California, San Francisco, CA, USA

*Corresponding author. UCSF Malaria Elimination Initiative, Institute of Global Health Sciences, 550 16th Street, 3rd Floor, San Francisco, CA 94158, USA. E-mail: michelle.roh@ucsf.edu

Received 10 June 2021; Editorial decision 14 February 2022; Accepted 28 February 2022

## Abstract

**Background:** Malaria is a risk factor for adverse pregnancy outcomes. Indoor residual spraying with insecticide (IRS) reduces malaria infections, yet the effects of IRS on pregnancy outcomes are not well established. We evaluated the impact of a large-scale IRS campaign on pregnancy outcomes in Eastern Uganda.

**Methods:** Birth records ($n = 59\,992$) were obtained from routine surveillance data at 25 health facilities from five districts that were part of the IRS campaign and six neighbouring control districts ~27 months before and ~24 months after the start of the campaign (January 2013-May 2017). Campaign effects on low birthweight (LBW) and stillbirth incidence were estimated using the matrix completion method (MC-NNM), a machine-learning approach to estimating potential outcomes, and compared with the difference-in-differences (DiD) estimator. Subgroup analyses were conducted by HIV and gravidity.

**Results:** MC-NNM estimates indicated that the campaign was associated with a 33% reduction in LBW incidence: incidence rate ratio (IRR) = 0.67 [95% confidence interval (CI): 0.49–0.93)]. DiD estimates were similar to MC-NNM [IRR = 0.69 (0.47–1.01)], despite a parallel trends violation during the pre-IRS period. The campaign was not associated with substantial reductions in stillbirth incidence [$IRR_{MC\text{-}NNM} = 0.94$ (0.50–1.77)]. HIV

status modified the effects of the IRS campaign on LBW [$\beta_{IRSxHIV} = 0.42$ (0.05–0.78)], whereby HIV-negative women appeared to benefit from the campaign [IRR = 0.70 (0.61–0.81)], but not HIV-positive women [IRR = 1.12 (0.59–2.12)].

**Conclusions:** Our results support the effectiveness of the campaign in Eastern Uganda based on its benefit to LBW prevention, though HIV-positive women may require additional interventions. The IRS campaign was not associated with a substantively lower stillbirth incidence, warranting further research.

**Key words:** Malaria in pregnancy, indoor residual spraying, low birthweight, stillbirth, adverse pregnancy outcomes, *Plasmodium falciparum*, difference-in-differences, matrix completion method

**Key Messages**

- In 2014-15, the Ugandan Ministry of Health and their implementing partners initiated a population-level campaign of indoor residual spraying (IRS), a highly effective but underused malaria vector control tool recommended by the World Health Organization.
- Using a quasi-experimental study design, we estimated the IRS campaign was associated with a 33% reduction in low birthweight (LBW) incidence: incidence rate ratio (IRR) = 0.67 (95% CI: 0.49-0.93) in the 2 years following IRS initiation.
- Campaign effects on LBW were not uniform: benefits were not seen among HIV-positive women [IRR = 1.12 (95% CI: 0.59-2.12)], who represented 3.1% of the sample and for whom HIV-malaria co-infection can have more harmful effects than for HIV-negative women.
- Contrary to LBW estimates, the IRS campaign was not associated with a substantively lower stillbirth incidence in the 2 years following the initiation of the campaign [IRR = 0.94 (95% CI: 0.50-1.77)].

## Introduction

In sub-Saharan Africa, malaria in pregnancy is a major risk factor for adverse pregnancy outcomes. In 2020, an estimated 11.6 million pregnant women were exposed to the *Plasmodium falciparum* parasite, resulting in nearly 819 000 low birthweight (LBW) infants.[1] Indoor residual spraying of insecticide (IRS) is a WHO-recommended malaria vector control intervention, which involves the application of insecticide to household surfaces that serve as a resting place for mosquitoes.[1]

Despite its known benefits on malaria prevention,[2] particularly in areas where insecticide-treated net usage is low and pyrethroid resistance is high,[3] IRS is highly underused in sub-Saharan Africa.[4] In 2020, only 2.6% of people at risk for malaria in Africa were protected by IRS (a decline from a peak of 5.8% in 2010).[1] The primary barriers of IRS scale-up are concerns over its perceived harmful effects,[5] challenges in achieving high coverage and the need for insecticide resistance monitoring which may result in switching to more expensive, non-pyrethroid insecticides.[6] In contrast to insecticide-treated nets, IRS has the advantage of using non-pyrethroid insecticides (e.g. carbamates and organophosphates) which can help to slow the spread of pyrethroid resistance.[7] Whereas several studies have shown IRS to be highly effective in reducing malaria morbidity,[6,8,9] few studies have evaluated its indirect impact on overall health outcomes. Understanding the clinical implications of IRS, especially among pregnant women, has major policy implications for its scale-up, given that studies from non-malaria endemic areas have shown prenatal exposure to organophosphates and carbamate insecticides to be associated with adverse pregnancy outcomes.[10–12]

In 2014–15, the US President's Malaria Initiative, the Ugandan Ministry of Health and the UK Department for International Development launched the Uganda IRS Project, a population-level IRS campaign across 14 districts in Eastern Uganda. After its initiation, large reductions in malaria incidence were observed.[7,13] Small-scale pre-post studies in one of these districts (Tororo) found that among women concurrently receiving insecticide-treated nets and malaria chemoprevention, IRS could reduce LBW risk up to 92% among HIV-negative women and preterm delivery (a cause of LBW) by 65% among HIV-positive women.[14,15] However, these studies were conducted in only one district, with small sample sizes and prone to residual confounding as both studies lacked a contemporaneous control group.

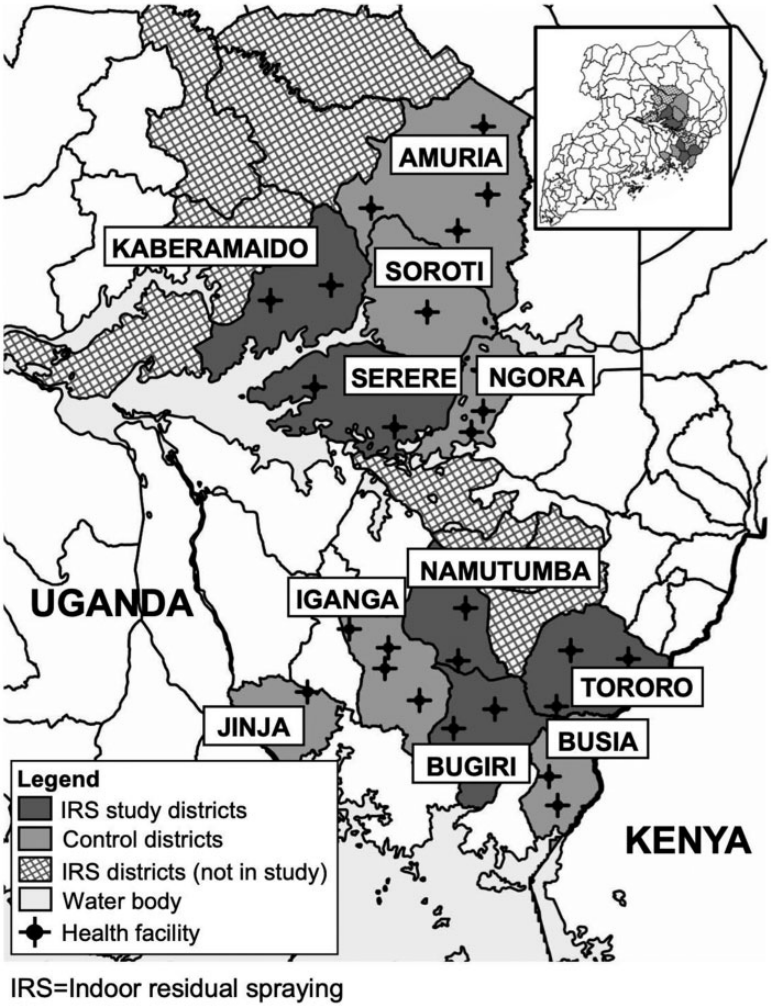


**Figure 1** Location of study districts and health facilities

The present study aimed to quantify the impact of the Uganda IRS Project on birth outcomes. We overcome limitations of prior studies by evaluating more districts and using contemporaneous data from neighbouring control districts to generate more plausible counterfactual control groups.

## Methods

### Study setting

This study used data from 25 health facilities located in five of the 14 districts included in the Uganda IRS Project (Tororo, Kaberamaido, Serere, Bugiri and Namutumba) and six control districts. Campaign study districts were selected based on budget, feasibility and geographical representativeness of the original 14 districts included in the IRS campaign (Figure 1). Timing of the IRS campaign was staggered across districts, such that the first round of IRS was initiated in December 2014 in Tororo and Kaberamaido, in April 2015 in Serere and in May 2015 in Bugiri and Namutumba. Bendiocarb (carbamate insecticide) was used at the start of the campaign and repeated approximately biannually (Supplementary Table S1, available as Supplementary data at *IJE* online). In 2016-17, the formulation changed to Actellic 300CS®, a longer-lasting organophosphate insecticide, and repeated approximately annually. Overall, IRS coverage was ≥92% across all rounds, with a few exceptions—coverage in the first round of IRS in Kaberamaido was 71% and 85% in Tororo (Supplementary Table S1).[16,17] Six neighbouring districts not part of the Uganda IRS Project (Amuria, Busia, Iganga, Jinja, Ngora and Soroti) were selected based on convenience sampling to generate the control group.

### Study design

To evaluate the impact of the campaign on birth outcomes, our initial analysis was based on the standard difference-in-differences (DiD) approach comparing the average pre-post

changes in birth outcomes in the IRS group with average pre-post changes in the control group.[18] The main outcome model for a DiD estimator with multiple units and time periods[18] is as follows:

$$Y_{it} = \beta_0 + \beta_1 T_{it} + \beta_2 X_{it} + \beta_3 \alpha_i + \beta_4 \gamma_t + \varepsilon_{it}$$

where $Y_{it}$ is the outcome for unit $i$ at time $t$; $T_{it}$ is a treatment indicator variable that equals 1 if unit $i$ is treated at time $t$ and 0 otherwise; $X_{it}$ is a vector of measured unit- and time-varying covariates; and $\alpha_i$ and $\gamma_t$ are unit- and time-fixed effects. $\beta_1$ is the key parameter in this model which estimates the treatment effect of the campaign on birth outcomes. Valid causal inference from DiD relies on the parallel trends assumption which assumes that the average trend of the treated and control groups would have been parallel in the absence of IRS.[18] If this assumption is met, DiD can estimate unbiased intervention effects in the presence of group-varying, but time-invariant confounders (e.g. baseline differences in malaria transmission intensity) and time-varying causes of the outcome that are stable across units (e.g. changes in the scale-up of other interventions over time which affected groups similarly).[18] Though this assumption cannot be formally tested (given that the potential outcomes of the IRS group in absence of IRS during the post-IRS period are not directly observed), parallel trends can be tested during the pre-IRS period. If 'pre-trends' differ between IRS and control groups, this suggests that the trend of the control group would not be a suitable estimate of the expected trend of the IRS group in absence of the campaign, resulting in biased DiD estimates.

We also conducted an alternative, machine-learning approach to estimating potential outcomes which does not rely on the parallel trends assumption, i.e. the matrix completion method with nuclear norm minimization (MC-NNM).[19] This method is similar in principle to DiD[18] in that it uses a regression-based approach, but the aim of MC-NNM is not to estimate the treatment effect directly, but to estimate the unobserved potential outcomes for each group and time period [similar to the synthetic control method (SCM)[20,21])] The MC-NNM outcome model is defined for unit $i$ at time $t$ as:

$$Y(0)_{it} = L_{it} + \beta X_{it} + \alpha_i + \gamma_t + \varepsilon_{it}$$

where $Y(0)$ is a matrix that contains the potential outcomes for units and time periods had the IRS campaign never occurred, and the terms $\beta X_{it}$, $\alpha_i$ and $\gamma_t$ are interpreted similarly to the DiD estimator. In the $Y(0)$ matrix, only the outcomes for treated units during the campaign period are missing. To recover these values, MC-NNM assumes that the $Y(0)$ can be approximated by matrix $L$, a simplified (lower-rank) matrix representation of the $Y(0)$ matrix. To estimate values of matrix $L$, MC-NNM uses matrix factorization methods[22–24] first to decompose $Y(0)$ as a product of two matrices: $UV^T$, where $U$ contains factor loadings (i.e. unit-specific intercepts) and $V$ contains time-varying factors.[25,26] The rationale for decomposing the $Y(0)$ matrix is that it may identify important relationships between units and time periods that cannot be adequately modelled through group- and time-fixed effects (e.g. effects of unmeasured time-varying causes of the outcome that differ between units). As these group- and time-varying factors are not directly observed, they are considered latent factors that are revealed through matrix decomposition. To reduce the complexity of the $Y(0)$ matrix and thus estimate matrix $L$, MC-NNM uses nuclear norm regularization, a machine-learning approach to retain the latent factors that explain the most variability in the outcomes.

Similar to SCM, MC-NNM generates a 'synthetic control', but unlike SCM, the control generated by MC-NNM is not based on weights that are assumed to be time-invariant.[19] The main identifying assumptions of MC-NNM are that: (i) the errors are exogenous and have conditional mean zero:

$$E[\varepsilon_{it}|L_{it},\ X_{it},\ \alpha_i,\ \gamma_t] = 0$$

and (ii) counterfactual outcomes are conditionally independent of treatment assignment, given observed covariates and model specification:

$$Y(0)_{it},\ Y(1)_{it}\ \ D_{it}|L_{it},\ X_{it},\ \alpha_i,\ \gamma_t$$

where $D_{it}$ represents the observed treatment for unit $i$ at time $t$.[19,25,26] To estimate the average treatment effect of the treated (ATT), observed outcomes of the treated group are compared with the MC-NNM-generated synthetic control. The full methodological details of MC-NNM are found elsewhere[19,25] and a brief overview is provided in the Supplementary Methods (available as Supplementary data at *IJE* online).

## Data source

Birth records were collected from routine surveillance data from 11 health facilities in IRS districts and 14 in control districts (Figure 2). Due to budgetary limitations and heterogeneity in data quality, not all health facilities were sampled from each district. To select study health facilities, we generated a list of all known non-referral public health facilities with a maternity ward. Facilities were excluded if they averaged <200 births per year and were <5 km away from a neighbouring district (to mitigate treatment misclassification). From this list, three health facilities were

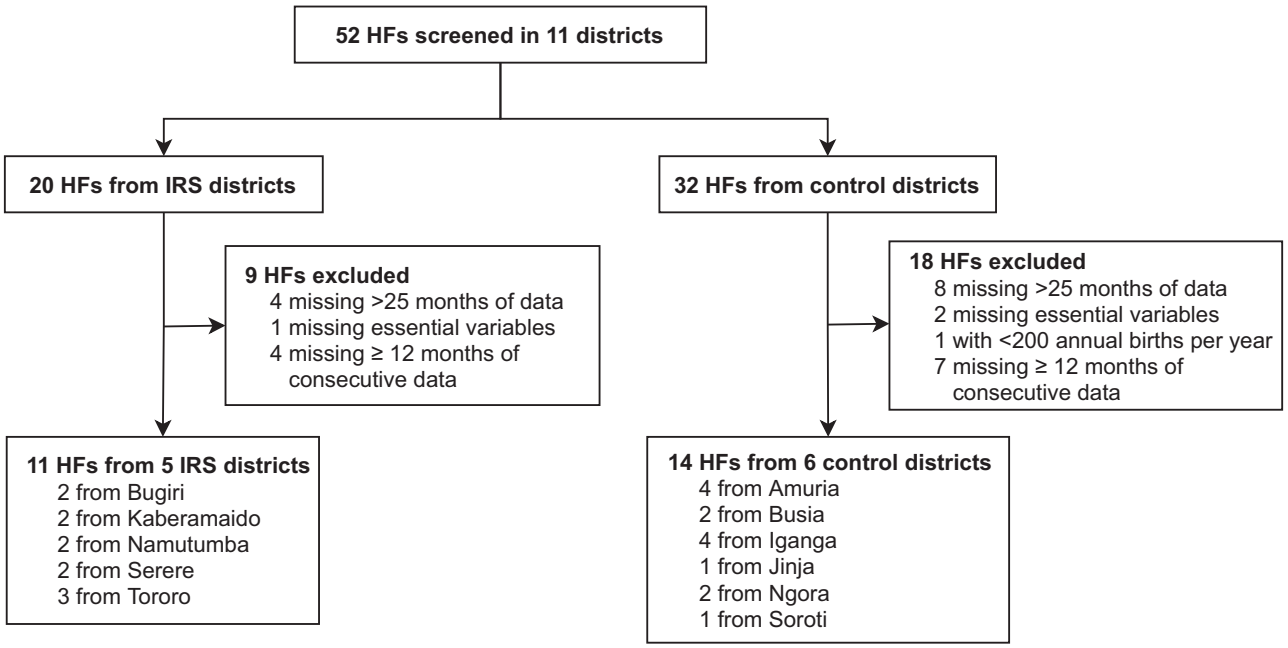


**Figure 2** Flow diagram of the selection of health facilities

randomly sampled from each district. Health facility registries were screened to determine data quality. Those with low-quality data (defined as either missing complete months of data for >25 months during study period or missing covariates and/or outcome data for >30% of records) were excluded, and the next eligible health facility was sampled until at least three were sampled per district. If three health facilities could not be reached, health facilities from neighbouring districts with the same exposure status were sampled.

Of the 52 health facilities that were screened, data were collected from 36 health facilities. Of the 16 that were excluded, 12 were missing >25 months of data, three were missing birthweight values for >30% of records and one had a delivery rate of <200 births per year (found post-screening). Post-data collection, we found 11 health facilities had ≥12 months of consecutively missing data. These health facilities were excluded from the final analyses, as trends could not be accurately modelled for these units. The final analytical sample included data from 25 health facilities.

From each health facility, individual-level birth records from all singleton deliveries from January 2013 to May 2017 were collected from the Integrated Maternity Registry of the Health Management Information System (HMIS).[27] The registry is managed by trained nurses and midwives and includes data on delivery outcomes (e.g. delivery date, birthweight and stillbirth) and maternal characteristics (e.g. age, gravidity and HIV status based on HIV diagnosis and/or receipt of antiretrovirals). For the primary analysis, data were aggregated to the health facility-month—a total of 1247 observations. Outcome data were missing for 5.9% of observations (Supplementary Figure S1, available as Supplementary data at *IJE* online).

## Measurements

### Treatment variable

Treatment was defined as a binary variable where treatment = 1 in the post-IRS campaign period for treated districts and otherwise 0. Because IRS effects are expected to be dose-dependent, campaign effects were separately estimated for the first and second year following IRS campaign initiation.

### Outcomes

The study outcomes were incidence of LBW (defined as birthweight <2500 g)[28] among live, singleton deliveries, and stillbirth incidence.

## Statistical analysis plan

### Difference-in-differences

DiD analyses were implemented using negative binomial regression to model the number of LBW and stillborn infants per health facility-month. Models included the post-IRS treatment variable, month- and health facility-fixed effects, and time-varying characteristics (e.g. mean maternal age, proportion of primigravidae, proportion of

HIV-positive women). The log number of deliveries per health facility-month was included as an offset term, and robust standard errors were used to account for correlated outcomes.

To test whether pre-IRS trends differed between IRS and control groups, an interaction term between an IRS indicator variable and a linear time trend ($\beta_{IRS \times month}$) were included in models using pre-campaign data (January 2013-November 2014). Models included the same covariates as primary DiD analyses, but the post-IRS treatment variable was replaced with an indicator variable denoting whether the health facility was located in an IRS campaign district.

### Matrix completion with nuclear norm minimization

MC-NNM analyses were used to estimate the number of LBW and stillbirth deliveries per health facility-month that would have been expected in absence of IRS. For MC-NNM analyses, we modelled the outcome as incidence of birth outcomes per 100 deliveries. Alternative specifications of the outcome were considered, including modelling the outcome as counts and log-transforming the outcome and adding a value of one to account for zero cases (to make estimates comparable to DiD analyses). Findings from these alternative specifications did not substantively change the magnitude or direction of the effect estimates (Supplementary Figure S2, available as Supplementary data at *IJE* online). Covariates included the number of deliveries per health facility-month and those included in DiD analyses. Incidence rate ratios (IRRs) were estimated by dividing the averaged observed outcome in the IRS group by the averaged outcome generated by the MC-NNM synthetic control at each month and IRRs were averaged across the overall 2-year, first year and second year post-campaign period; 95% confidence intervals were obtained using 1000 block-bootstrapped percentiles to account for clustered observations at the health facility-level. Analyses were performed using the gsynth package in R.[29]

### Subgroup analyses

In areas of high *Plasmodium falciparum* transmission, HIV-positive and primigravid women have less parity-specific immunity to malaria, increasing their risk of adverse pregnancy outcomes.[30] To investigate whether the IRS campaign differentially affected birth outcomes for HIV-positive women and primigravidae, DiD analyses were performed using individual-level data. Poisson regression with robust standard errors was used to estimate the campaign's effect on LBW and stillbirth risk. To test whether campaign effects differed for each subgroup, models included a two-way interaction term between the post-IRS treatment variable and subgroup ($\beta_{IRS \times subgroup}$). Stratified analyses were conducted separately for each subgroup regardless of whether *P*-values ($P_{IRS \times subgroup}$) indicated evidence of a statistical interaction.

Testing of pre-IRS parallel trends was conducted using a three-way interaction term ($\beta_{month \times IRS \times subgroup}$). If the *P*-value of the interaction term was $<0.05$, unit-specific linear time trends ($\beta_{health\ facility \times time}$) were included in standard DiD estimators. This approach allows group pre-trends to vary, but assumes the rate of change would have been parallel.[18,31] MC-NNM analyses were not separately performed for subgroups as the small sample size and rarity of the outcome would not allow accurate predictions using aggregated data. All analyses were conducted using Stata 16.1 (StataCorp LLC) and in R (version 3.5.3).

### Sensitivity analyses

Though individual-level data were available, the primary analyses were conducted using group-level data aggregated to the health facility-month to ensure DiD estimates were comparable to MC-NNM (which requires group-level data). A major limitation of using group-level data is its susceptibility to ecological fallacy bias.[32] Sensitivity analyses were performed by conducting DiD using individual-level confounder and outcome data to estimate the campaign's effect on LBW and stillbirth risk (Supplementary Figure S3, available as Supplementary data at *IJE* online). DiD estimators used Poisson regression with robust standard errors to model outcomes using the same parameters as the primary DiD analyses, except that time-varying covariates (i.e. maternal age at delivery, gravidity and HIV status) were modelled at the individual-level.

Valid estimates from MC-NNM rely on the assumption that MC-NNM adequately modelled all time-varying factors that differ across units (i.e. effects estimated by MC-NNM were due to the IRS campaign and not through other interventions that occurred during the same period). To test the robustness of our effect estimates, we conducted placebo tests that falsely reassigned treated periods 3 and 6 months prior to the true start date of the campaign. Details and results of the placebo tests are provided in Supplementary Table S2 (available as Supplementary data at *IJE* online).

## Results

### Study population

The final sample size included data from 59 992 singleton deliveries recorded between January 2013 and May 2017, ~27 months before and ~24 months after IRS initiation. Approximately 3.4% of deliveries were stillbirths ($n = 2045$). Of the 57 947 live births, 2871 (5.0%) were LBW.

**Table 1** Maternal characteristics and delivery outcomes in study health facilities recorded between January 2013 and May 2017. Summary statistics are provided as monthly means (standard deviation) per health facility averaged across IRS and non-IRS (control) groups and pre- and post-IRS periods

| | No IRS (control) | | | IRS | | |
|---|---|---|---|---|---|---|
| | Pre-IRS[a] | Year 1 | Year 2 | Pre-IRS | Year 1 | Year 2 |
| Total number of deliveries | 13 065 | 7701 | 9811 | 12 615 | 7100 | 9700 |
| Number of months of observation | 26.5 | 12 | 12 | 23, 27, 28[b] | 12 | 12 |
| Maternal age in years per HF-month, mean (SD) | 24.7 (1.3) | 24.4 (1.1) | 24.3 (1.1) | 24.6 (1.2) | 24.4 (1.0) | 24.5 (1.1) |
| % of primigravidae women per HF-month, mean (SD) | 18.5 (11.9) | 21.6 (11.1) | 22.5 (11.0) | 19.6 (10.8) | 21.9 (9.3) | 24.6 (9.0) |
| % of HIV-positive women per HF-month, mean (SD) | 3.2 (3.4) | 2.9 (2.7) | 3.4 (3.0) | 2.6 (4.3) | 2.6 (2.9) | 3.1 (3.2) |
| **Delivery outcomes** | | | | | | |
| Number of deliveries per HF-month, mean (SD) | 40.0 (17.8) | 50.0 (23.5) | 47.9 (24.7) | 45.7 (24.7) | 55.5 (27.7) | 60.1 (32.0) |
| LBW incidence per 100 deliveries per HF-month, mean (SD) | 3.3 (4.0) | 3.2 (3.4) | 4.2 (4.6) | 4.9 (6.5) | 3.7 (5.4) | 3.9 (5.1) |
| Stillbirth incidence per 100 deliveries per HF-month (SD) | 2.8 (4.3) | 2.8 (4.1) | 3.3 (5.0) | 2.8 (3.3) | 2.7 (3.7) | 3.2 (3.8) |

HF, health facility; IRS, indoor residual spraying; LBW, low birthweight; SD, standard deviation.

[a]Due to the staggered adoption of IRS, the post-IRS period for the control group in this table was defined as the mid-point between the earliest and latest date of the first round of IRS (14 February 2015).

[b]Pre-IRS months of observation were 23 months for districts that initiated IRS in December 2014 (Kaberamaido and Tororo), 27 months for districts that started IRS in April 2015 (Serere) and 28 months for districts that started IRS in May 2015 (Bugiri and Namutum).

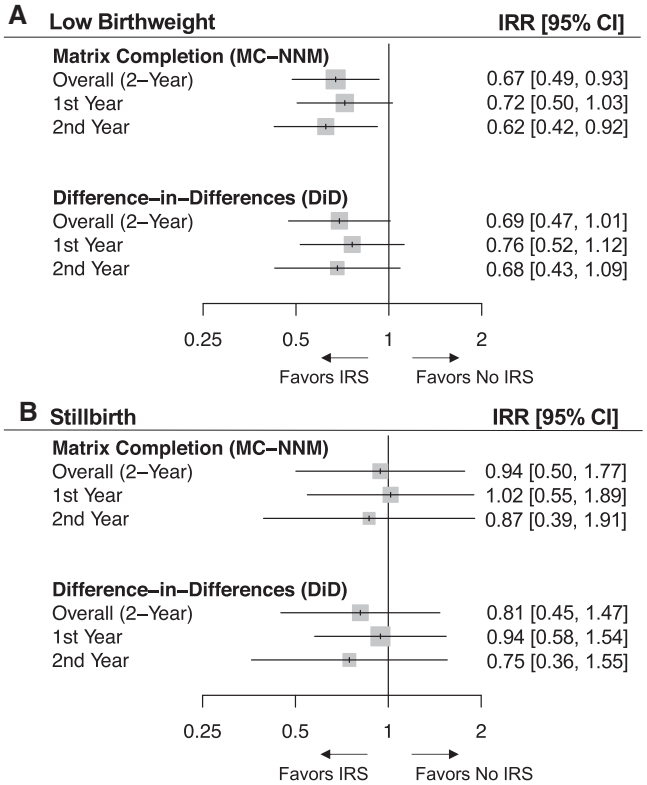


**Figure 3** Overall, first- and second-year impact of the Uganda IRS Project on low birthweight incidence (A) and stillbirth incidence (B), estimated by the matrix completion method and difference-in-differences models. Average treatment effects on the treated are reported as incidence rate ratios

The demographic characteristics and delivery outcomes of the study population are presented in Table 1. Mean maternal age was similar between IRS and control groups and across pre- and post-IRS periods. The mean proportion of primigravidae was lower during the pre-IRS period, but this finding was consistent across both IRS and control

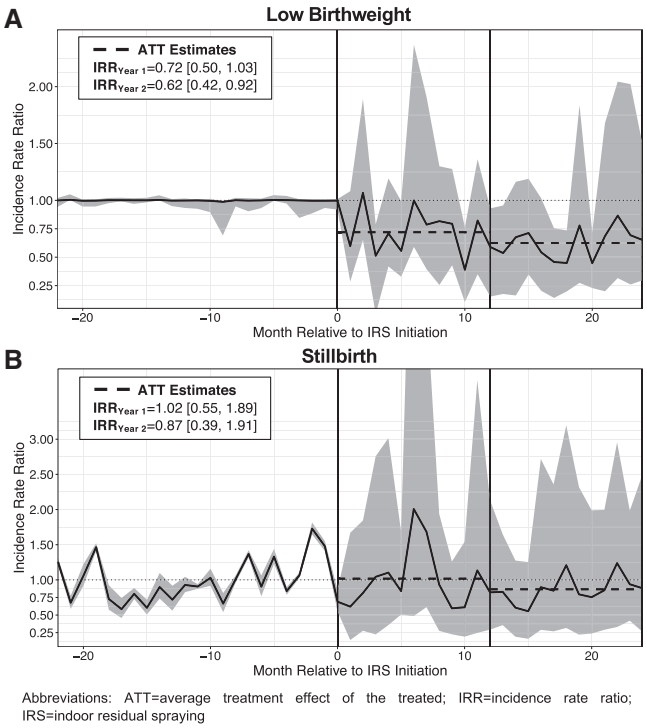


**Figure 4** Month-by-month estimates of the average treatment effect of the treated (ATT) on low birthweight (A) and stillbirth incidence (B). Results are reported as incidence rate ratios estimated using the matrix completion method. The vertical solid lines indicate time points (in months) 0, 12 and 24 after the start of the Uganda IRS campaign. Thick horizontal dashed lines represent the average treatment effect estimated during Years 1 and 2 post-IRS initiation. The horizontal dotted line denotes a reference line when incidence rate ratio = 0

groups. Mean prevalence of HIV was higher in the control group compared with the IRS group, but this finding was consistent across pre- and post-IRS periods.

### Impact of IRS on birth outcomes

Figure 3 presents MC-NNM and DiD estimates of the IRS campaign's effect on birth outcomes. Over a 2-year period, the campaign was associated with a 33% reduction in LBW incidence [$IRR_{MC\text{-}NNM} = 0.67$ (95% CI: 0.49-0.93)]. Reductions were seen in the first- and second-year post-IRS campaign, though associations were slightly larger in second year [$IRR_{Year\ 1} = 0.72$ (95% CI: 0.50-1.03) versus $IRR_{Year\ 2} = 0.62$ (95% CI: 0.420-.92)]. The MC-NNM-generated synthetic control appeared to be a good fit to the observed outcomes during the pre-campaign period (Figure 4A; Supplementary Figure S4, available as Supplementary data at *IJE* online). MC-NNM estimates were similar to DiD [$IRR_{DiD} = 0.69$ (95% CI: 0.47-1.01)], though DiD analyses were subject to a parallel trends violation ($\beta_{IRS\ x\ month} = 0.03$; $P = 0.006$) (Supplementary Figure S5, available as Supplementary data at *IJE* online).

MC-NNM estimates indicated the campaign was not associated with substantively lower stillbirth incidence [$IRR_{MC\text{-}NNM} = 0.94$ [95% CI: 0.50-1.77)]. Though the campaign appeared to be associated with a lower stillbirth incidence in the second-year post-IRS campaign [IRR = 0.87 (95% CI: 0.39-1.91)], confidence intervals were too wide to provide reliable estimates. Unlike the MC-NNM synthetic control for LBW, the MC-NNM synthetic control did not appear to be a suitable control group (Figure 4B; Supplementary Figure S4). There did not appear to be a violation in the parallel trends assumption during the pre-IRS period ($\beta_{IRS\ x\ month} = -0.02$; $P = 0.49$) (Supplementary Figure S5) though DiD estimates for the 2-year impact were further from the null [IRR = 0.81 (95% CI: 0.45-1.47)]. However, both MC-NNM and DiD estimates exhibited wide confidence intervals.

### Subgroup analyses

Of the 59 992 deliveries, 1814 (3.0%) were among HIV-positive women and 13 306 (22.2%) were among primigravidae. HIV status appeared to modify the relationship between the IRS campaign and LBW risk [$\beta_{IRS\ x\ HIV} = 0.42$ (95% CI: 0.05-0.78); $p_{IRS\ x\ HIV} = 0.025$], such that the campaign appeared to benefit HIV-negative women [$RR_{HIV-} = 0.70$ (95% CI: 0.61-0.81)], but not HIV-positive women [$RR_{HIV+} = 1.12$ (95% CI: 0.59-2.12)] (Figure 5A). There was insufficient evidence to suggest HIV status modified the relationship between the IRS campaign and stillbirth risk [$\beta_{IRS\ x\ HIV} = -0.34$ (95% CI: -1.06-0.40); $p_{IRS\ x\ HIV} = 0.37$]. However, subgroup analyses showed the campaign was associated with lower LBW and stillbirth risk for HIV-negative women, whereas confidence intervals around effect estimates

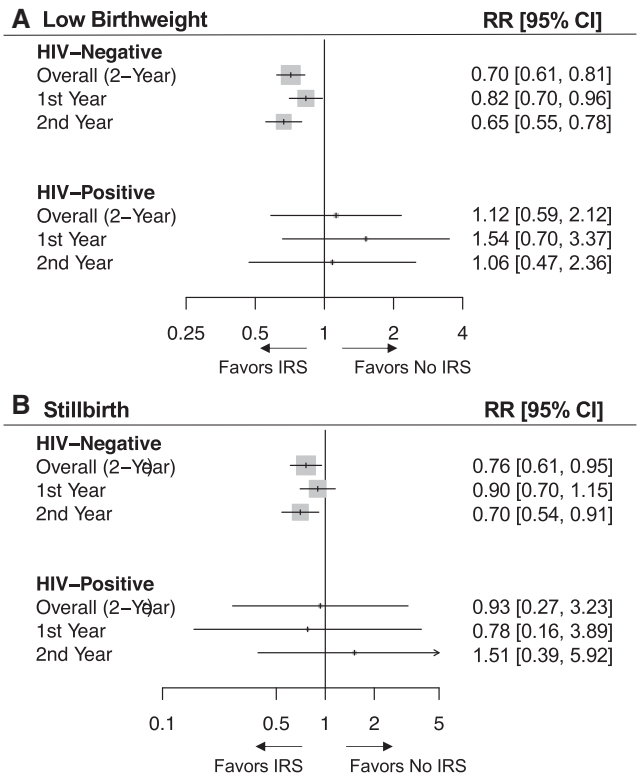


**Figure 5** Results of subgroup analyses by HIV. Average treatment effects on the treated were estimated using difference-in-differences models using individual-level data. Results are provided as the overall-, first- and second-year impact of the Uganda IRS Project on low birthweight (A) and stillbirth incidence (B)

among HIV-positive women were too wide to provide reliable estimates (Figure 5B).

Gravidity did not appear to modify the effect of the campaign on LBW risk [$\beta_{IRS \times Primigravidae} = 0.06$ (95% CI: −0.09-0.22); $P = 0.43$] (Figure 6A) or stillbirth risk [$\beta_{IRS \times Primigravidae} = 0.09$ (95% CI: −0.18-0.37); $P = 0.52$] (Figure 6B). However, subgroup analyses indicated a protective effect of the campaign on stillbirth risk among multigravidae [RR = 0.68 (95% CI: 0.53–0.88)].

### Sensiivity analyses

Using individual-level covariate and outcome data, we found that the direction and magnitude of DiD effect estimates estimating the campaign's effect on LBW and stillbirth risk did not substantively differ from DiD estimates using group-level incidence data (Supplementary Figure S3). Placebo tests, falsifying the treatment period to 3 and 6 months prior to the true start of the campaign date, found little evidence of campaign effects on LBW incidence during the 'placebo' periods (Supplementary Table S2). In contrast, campaign effects on stillbirth incidence were observed 3 months prior to the actual start of the campaign, suggesting other factors were affecting stillbirth rates around the same time as the campaign.

## Discussion

Between 2014 and 2015, the Ugandan Ministry of Health and implementing partners began a large-scale IRS campaign in a highly malaria-endemic region of Eastern Uganda. Using a novel application of matrix completion methods to estimating potential outcomes, our study found the campaign was associated with a 33% reduction in LBW incidence in the 2 years following IRS initiation. Subgroup analyses indicated that the IRS campaign was associated with reductions in LBW and stillbirth risk among HIV-negative women, but not among HIV-positive women. Gravidity did not appear to modify the effects of the campaign, though subgroup analyses suggest that multigravidae, but not primigravidae, may have had a lower stillbirth risk after the campaign. However, stillbirth estimates should be interpreted with caution as placebo tests from our sensitivity analyses suggest other concurrent interventions may explain these effects.

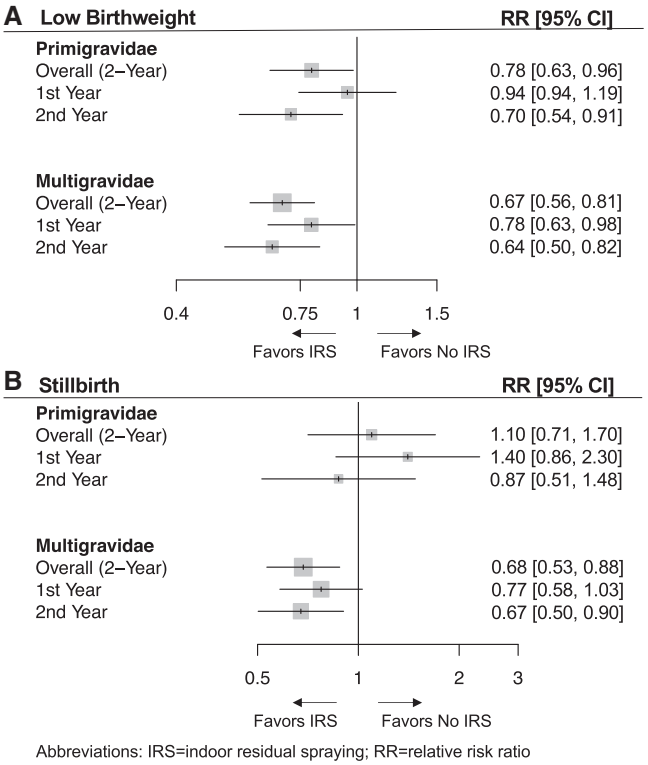


**Figure 6** Results of subgroup analyses by gravidity. Average treatment effects on the treated group were estimated using difference-in-differences models based on individual-level data. Results are provided as the overall-, first, and second-year impact of the Uganda IRS Project on low birthweight (A) and stillbirth incidence (B)

Though malaria is a known cause of stillbirth,[33] it was not clear whether the campaign lowered stillbirth incidence. A plausible reason for this finding may be that the MC-NNM synthetic control was not a suitable control to estimate the true treatment effect of the campaign as shown by our sensitivity analyses. However, several other reasons may explain this result. First, malaria is a cause of antepartum, but not intrapartum, stillbirths[34] and our inability to distinguish between the two may explain the attenuated effects and wide confidence intervals. Second, it is possible that organophosphate and carbamate exposure may increase stillbirth risk,[35] which may have counteracted the benefits of IRS on malaria prevention. However, more research is needed to confirm these findings.

Though the effects of IRS on stillbirth remain unclear, our LBW findings are consistent with the current literature on the benefits of IRS,[8,36] and more broadly, the benefits of malaria prevention on LBW.[37,38] A previous meta-analysis of 25 African countries[37] found that full malaria prevention with insecticide-treated nets and/or malaria chemoprevention was associated with a 21% reduction in LBW risk, similar to the benefits seen with IRS in this study (33%). Our findings differ from studies linking prenatal exposure to organophosphates and carbamate insecticides to increased LBW risk,[10–12] but these studies were mainly conducted in non-malaria-endemic settings and, in this setting, the benefits of preventing LBW likely counteracted the potential adverse consequences of prenatal pesticide exposure. However, to fully understand the clinical implications of IRS, further research is needed on other downstream health outcomes across a range of malaria endemicities to determine at which point, if any, the harm outweighs the benefit.

In this setting and potentially other malaria-endemic regions of sub-Saharan Africa, investment in IRS may lower rates of LBW, a condition which imposes major financial burden on families and health systems.[39,40] In resource-limited settings, LBW contributes to 60–80% of all neonatal deaths[40,41] and among surviving infants, LBW increases the risk of respiratory and diarrhoeal disease,[40] impaired growth and cognitive development,[42–44] diabetes,[45] and cardiovascular disease.[46] These factors should be taken into account when determining the cost-effectiveness of IRS and decision for its use. Coincidentally, the President's Malaria Initiative has been conducting large-scale IRS campaigns in 13 other African countries.[47] Evaluation of these campaigns should consider the indirect effects of IRS, which may justify its continued use. However, its initiation should be carefully considered, as withdrawal of IRS after a sustained period can result in rapid malaria resurgence.[6,7,48]

Our study had limitations and should be interpreted with caution. First, control units were selected based on convenience sampling and it is plausible that these units did not accurately represent the unobserved potential outcome of the treated group. Second, our results may have limited generalizability to the following groups: (i) the other nine IRS districts excluded from this study; (ii) home-based births, which in Uganda comprise approximately 30% of deliveries[49];and (iii) the catchment areas of health facilities that were excluded due to low-quality data. Exclusion of these health facilities could have affected the internal validity of our estimates, had LBW and stillbirth trends within these health facilities systematically differed from health facilities with higher-quality data and between treated and control groups. Fourth, variables in our dataset may have been measured with error. For example, exposure to the IRS campaign may have been misclassified for women delivering at health facilities outside their district of residence. Though we aimed to minimize this bias by selecting health facilities >5 km away from a neighbouring district, this type of non-differential misclassification error may have biased our estimates toward the null. Furthermore in 2014, around the time of the IRS campaign, the format of the birth registry was changed to improve accurate reporting of gravidity, likely explaining the change in the proportion of primigravidae before and after IRS. Improvements in reporting of gravidity or other covariates may have resulted in non-differential misclassification error, which could have underestimated true differences in our subgroup analyses. Fifth, individual-level IRS coverage data were unavailable and thus effects estimated in this study can only be interpreted as the intervention effects of the Uganda IRS Project, rather than on an individual exposure level. Sixth, due to our limited sample size, effect modification by insecticide type (i.e. organophosphates versus carbamates) was not evaluated as part of our study. Seventh, outcomes ascertained in this study were only among women who made it to delivery and excluded women who experienced fetal loss. Though it is difficult to predict the direction of this bias, as IRS may have affected fetal loss both favourably through malaria prevention and potentially adversely through insecticide exposure, it is unlikely that this type of collider bias would explain away the LBW estimates observed in this study. However, future studies assessing the effects of IRS on early fetal loss are needed. Last, we cannot rule out that our estimates were subject to other forms of bias or a chance finding.

## Conclusion

Despite these limitations, our study demonstrated that in an area of intense malaria transmission, a high-coverage IRS campaign appeared to substantially reduce LBW incidence. Campaign effects were similar in magnitude to receiving full malaria prevention during pregnancy. Clear benefits of the IRS campaign on LBW were observed among infants born to HIV-negative women. However, similar effects of the campaign were not observed among HIV-positive women, confirming the need for additional tools for LBW prevention in this subgroup.[50] Our study provides important evidence highlighting the benefits of the Uganda IRS Project on LBW prevention, warranting its continued implementation in Eastern Uganda. However, future studies are needed to understand the effects of the campaign on other health outcomes, including its effects on stillbirth.

## Ethics approval

Study approvals were granted by the Uganda National Council for Science and Technology (HS-2503), the Makerere University College of Health Sciences (2018–126) and the University of California, San Francisco (17–22660).

## Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

## Supplementary data

Supplementary data are available at *IJE* online.

## Author contributions

M.E.R., A.M., G.D. and H.S. conceived and designed the study. M.E.R., A.M. and B.O. implemented the study. M.E.R. and A.I. analysed the data. M.E.R. wrote the first draft of the manuscript, with significant contributions in the interpretation of the findings from A.M., J.S.W., S.S., M.M.G., R.G., G.D. and H.S. M.M. and S.L.W. helped to draft and revise the important statistical aspects of the study. All authors reviewed and approved the final version of the manuscript.

## Funding

This research was supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development under a Ruth L. Kirschstein National Research Service Award (F31 HD096861) and the National Institutes of Health, University of California, San Francisco-Gladstone Institute of Virology & Immunology Center for AIDS Research (P30-AI027763).

## Acknowledgements

We thank: the women whose data contributed to the findings of this manuscript; the dedicated study staff, researchers and members of the Infectious Disease Research Collaboration in Uganda who were involved in collecting registry data; the Ugandan Ministry of Health

who approved of the collection of these data; and Joshua Wei who provided input in the statistical analysis of the study.

## Conflict of interest

None declared.

## References


1. World Health Organization. *World Malaria Report 2021*. Geneva: WHO,, 2020.
2. Bhatt S, Weiss D, Cameron E *et al.* The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. *Nature* 2015;**526**:207–11.
3. Sherrard-Smith E, Griffin JT, Winskill P *et al.* Systematic review of indoor residual spray efficacy and effectiveness against Plasmodium falciparum in Africa. *Nat Commun* 2018;**9**:13.
4. World Health Organization. *Guidelines for Malaria Vector Control*. Geneva: World Health Organization, 2019.
5. Wadunde I, Mpimbaza A, Musoke D *et al.* Factors associated with willingness to take up indoor residual spraying to prevent malaria in Tororo district, Uganda: a cross-sectional study. *Malar J* 2018;**17**:5.
6. Raouf S, Mpimbaza A, Kigozi R *et al.* Resurgence of malaria following discontinuation of indoor residual spraying of insecticide in an area of Uganda with previously high-transmission intensity. *Clin Infect Dis* 2017;**65**:453–60.
7. Namuganga JF, Epstein A, Nankabirwa JI *et al.* The impact of stopping and starting indoor residual spraying on malaria burden in Uganda. *Nat Commun* 2021;**12**:9.
8. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. *Cochrane Database Syst Rev* 2010;CD006657.
9. Eisele TP, Larsen D, Steketee RW. Protective efficacy of interventions for preventing malaria mortality in children in *Plasmodium falciparum*-endemic areas. *Int J Epidemiol* 2010;**39**:i88–101.
10. Rauch SA, Braun JM, Barr DB *et al.* Associations of prenatal exposure to organophosphate pesticide metabolites with gestational age and birth weight. *Environ Health Perspect* 2012;**120**: 1055–60.
11. Rowe C, Gunier R, Bradman A *et al.* Residential proximity to organophosphate and carbamate pesticide use during pregnancy, poverty during childhood, and cognitive functioning in 10-year-old children. *Environ Res* 2016;**150**:128–37.
12. Harley KG, Engel SM, Vedar MG *et al.* Prenatal exposure to organophosphorous pesticides and fetal growth: pooled results from four longitudinal birth cohort studies. *Environ Health Perspect* 2016;**124**:1084–92.
13. Katureebe A, Zinszer K, Arinaitwe E *et al.* Measures of malaria burden after long-lasting insecticidal net distribution and indoor residual spraying at three sites in Uganda: a prospective observational study. *PLoS Med* 2016;**13**:e1002167.
14. Muhindo MK, Kakuru A, Natureeba P *et al.* Reductions in malaria in pregnancy and adverse birth outcomes following indoor residual spraying of insecticide in Uganda. *Malar J* 2016;**15**:437.
15. Roh ME, Shiboski S, Natureeba P *et al.* Protective effect of indoor residual spraying of insecticide on preterm birth among pregnant women with HIV in Uganda: a secondary data analysis. *J Infect Dis* 2017;**216**:1541–49.
16. US Agency for International Development, Centers for Disease Prevention and Control, US Department of Health and Human Services, US State Department. *President's Malaria Initiative: Uganda Malaria Operational Plan FY 2017*. 2018. https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-2018/fy-2018-uganda-malaria-operational-plan.pdf (28 April 2020, date last accessed).
17. US Agency for International Development, Centers for Disease Prevention and Control, US Department of Health and Human Services, US State Department. *President's Malaria Initiative: Uganda Malaria Operational Plan FY 2018*. 2019. https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-2018/fy-2018-uganda-malaria-operational-plan.pdf (28 April 2020, date last accessed).
18. Wing C, Simon K, Bello-Gomez RA. Designing difference in difference studies: best practices for public health policy research. *Annu Rev Public Health* 2018;**39**:453–69.
19. Athey S, Bayati M, Doudchenko N, Imbens G, Khosravi K. Matrix completion methods for causal panel data models. *J Am Stat Assoc* 2021;**116**:1716–30.
20. Abadie A, Diamond A, Hainmueller J. Synthetic control methods for comparative case studies: estimating the effect of California's tobacco control program. *J Am Stat Assoc* 2010;**105**:493–505.
21. Bouttell J, Craig P, Lewsey J, Robinson M, Popham F. Synthetic control methodology as a tool for evaluating population-level health interventions. *J Epidemiol Community Health* 2018;**72**:673–78.
22. Candès EJ, Recht B. Exact matrix completion via convex optimization. *Found Comput Math* 2009;**9**:717–72.
23. Candes EJ, Plan Y. Matrix completion with noise. *Proc IEEE* 2010;**98**:925–36.
24. Mazumder R, Hastie T, Tibshirani R. Spectral regularization algorithms for learning large incomplete matrices. *J Mach Learn Res* 2010;**11**:2287–322.
25. Liu L, Wang Y, Xu Y, A practical guide to counterfactual estimators for causal inference with time-series cross-sectional data. *arXiv* 2021; doi:210700856v1, preprint: not peer reviewed.
26. Poulos J, Albanese A, Mercatanti A, Li F, Retrospective causal inference via matrix completion, with an evaluation of the effect of European integration on cross-border employment. *arXiv* 2021; doi: 210600788, preprint: not peer reviewed.
27. Uganda Ministry of Health, CDC Uganda, AFENET. *Uganda Ministry of Health Health Management Information System*. https://hmis2.health.go.ug/#/ (date last accessed).
28. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems: Tenth Revision*. 2nd ed. Geneva: World Health Organization, 2004.
29. Xu Y. Generalized synthetic control method: Causal inference with interactive fixed effects models. *Polit Anal* 2017;**25**:57–76.
30. Fried M, Duffy PE. Malaria during pregnancy. *Cold Spring Harb Perspect Med* 2017;**7**:a025551.
31. Angrist JD, Pischke J-S. *Mastering 'Metrics': The Path from Cause to Effect*. Princeton, NJ: Princeton University Press, 2014.
32. Greenland S. Ecological versus individual-level sources of bias in ecological estimates of contextual health effects. *Int J Epidemiol* 2001;**30**:1343–50.

33. Moore KA, Simpson JA, Scoullar MJ, McGready R, Fowkes FJ. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. *Lancet Glob Health* 2017;**5**:1101–12.
34. Moore KA, Fowkes FJ, Wiladphaingern J *et al.* Mediation of the effect of malaria in pregnancy on stillbirth and neonatal death in an area of low transmission: observational data analysis. *BMC Med* 2017;**15**:98.
35. Bell EM, Hertz-Picciotto I, Beaumont JJ. A case-control study of pesticides and fetal death due to congenital anomalies. *Epidemiology* 2001;**12**:148–56.
36. Steinhardt LC, Yeka A, Nasr S *et al.* The effect of indoor residual spraying on malaria and anemia in a high-transmission area of northern Uganda. *Am J Trop Med* 2013;**88**:855–61.
37. Eisele TP, Larsen DA, Anglewicz PA *et al.* Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect Dis* 2012;**12**:942–49.
38. Cates JE, Westreich D, Unger HW *et al.*; Maternal Malaria and Malnutrition (M3) Initiative. Intermittent preventive therapy in pregnancy and incidence of low birth weight in malaria-endemic countries. *Am J Public Health* 2018;**108**:399–406.
39. Tongo O, Orimadegun A, Ajayi S, Akinyinka O. The economic burden of preterm/very low birth weight care in Nigeria. *J Trop Pediatr* 2009;**55**:262–64.
40. Sicuri E, Bardají A, Sigauque B *et al.* Costs associated with low birth weight in a rural area of Southern Mozambique. *PLoS One* 2011;**6**:e28744.
41. World Health Organization. Care of the Preterm and Low-Birth-Weight Newborn. *Maternal, Newborn, Child and Adolescent Health*. 2018. https://www.who.int/maternal_child_adolescent/newborns/prematurity/en/ (date last accessed).
42. McCormick MC, Brooks-Gunn J, Workman-Daniels K, Turner J, Peckham GJ. The health and developmental status of very low—birth-weight children at school age. *JAMA* 1992;**267**:2204–08.
43. Kirk CM, Uwamungu JC, Wilson K *et al.* Health, nutrition, and development of children born preterm and low birth weight in rural Rwanda: a cross-sectional study. *BMC Pediatr* 2017;**17**:191.
44. Larroque B, Bertrais S, Czernichow P, Léger J. School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. *Pediatrics* 2001;**108**:111–15.
45. Mi D, Fang H, Zhao Y, Zhong L. Birth weight and type 2 diabetes: a meta-analysis. *Exp Ther Med* 2017;**14**:5313–20.
46. Risnes KR, Vatten LJ, Baker JL *et al.* Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol* 2011;**40**:647–61.
47. PMI VectorLink Project. *Annual Report: October 1, 2018-September 30, 2019*. Rockville, MD: .PMI VectorLink Project, 2019.
48. Masaninga F, Chanda E, Chanda-Kapata P *et al.* Review of the malaria epidemiology and trends in Zambia. *Asian Pac J Trop Biomed* 2013;**3**:89–94.
49. Uganda Bureau of Statistics (UBOS), ICF. *Uganda Demographic Health Survey 2016*. Kampala, and Rockville, MD: UBOS, 2018.
50. Ter Kuile FO, Taylor SM. Gilding the lily? Enhancing antenatal malaria prevention in HIV-infected women. *J Infect Dis* 2017; **216**:4–6.