The short-term impact of a malaria elimination initiative in Southern Mozambique: Application of the synthetic control method to routine surveillance data

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Abstract

In public health epidemiology quasi-experimental methods are widely used to estimate the causal impacts of interventions. In this paper, we demonstrate the contribution the synthetic control method (SCM) can make in evaluating health interventions, when routine surveillance data are available and the validity of other quasi-experimental approaches may be in question. In our application we evaluate the short-term effects of a large-scale Mass Drug Administration (MDA) based malaria elimination initiative in Southern Mozambique. We apply the SCM to district level weekly malaria incidence data and compare the observed reduction in age group specific malaria incidence. Between August 2015 and April 2017, a total of 13,322 (78%) cases of malaria were averted relative to the synthetic control. During the peak malaria seasons, the elimination initiative resulted in an 87% reduction in year 1 (December 2015-April 2016), and 79% reduction in year 2 (December 2016-April 2017). Comparison with an interrupted time series approach shows the SCM accounts for pre-intervention trends in the data and post-intervention weather events influencing malaria cases. We conclude MDA brought about a drastic reduction in malaria burden and can be a useful addition to existing (or new) vector control strategies and tools in accelerating towards elimination.

1. Introduction

In 2019, the global burden of malaria was estimated as 229 million cases and 409,000 deaths, with over 90% of disease burden concentrated in Africa (World Health Organization, 2020). Despite this burden, progress is being made towards eliminating malaria (defined as the interruption of local transmission of a specific parasite species within an area) in several countries. Between 2000 and 2019, 21 countries achieved 3 consecutive years of zero local malaria cases and 10 of these countries were certified by the WHO as having achieved elimination (World Health Organization, 2020). However, none of these countries were in sub-Saharan Africa (SSA), where new and/or intensified strategies are needed to reach elimination.

In September 2015, WHO's Malaria Policy Advisory Committee recommended the use of Mass Drug Administration (MDA) in areas with universal coverage of vector control strategies (such as long-lasting insecticide treated nets (LLINs) and indoor residual spraying (IRS)), case management, and surveillance, for countries aiming to eliminate malaria including in SSA. With MDA, which can act either as treatment or preventive chemotherapy, a full therapeutic course of a safe and effective drug or combination of drugs is repeatedly distributed to the target population in endemic areas, irrespective of the presence of symptoms or actual infection (WHO Malaria Policy Advisory Committee and Secretariat, 2016). Concurrently, WHO also expressed the need for more research on the effectiveness

of MDA programs (World Health Organisation, 2015b) and more widely on malaria elimination initiatives (World Health Organisation, 2015a).

Randomized control trials (RCTs) are the gold standard for impact evaluations. However, the implementation of RCTs may imply financial, practical, and ethical challenges (Bothwell, Greene, Podolsky, & Jones, 2016; Osrin et al., 2009). Furthermore, RCTs have debatable usefulness in identifying intervention feasibility and implementation bottlenecks, which are particularly important in disease elimination contexts. Consequently, to maximize relevance for policy decision making, most malaria elimination initiatives are now conducted as operational research (World Health Organisation, 2014), with no randomization. This trade-off between practicality through operational research and impact evaluation can be resolved through the application of quasi-experimental approaches to non-randomized interventions. Quasi-experimental approaches are particularly useful when applied to data routinely collected as part of a surveillance system for notifiable diseases such as malaria; such data are systematically collected through existing platforms regardless of any interventions being planned, implemented or evaluated.

MDA alone or in combination with other intensified/modified strategies for malaria has been implemented in different contexts and its effectiveness evaluated using RCTs (Eisele et al., 2016; Michelle S. Hsiang et al., 2020; Landier et al., 2017; Morris et al., 2018; von Seidlein et al., 2019) and quasi-experimental studies (Fraser et al., 2020; Galatas, Saute, et al., 2020; M. S. Hsiang et al., 2013). The quasi-experimental evaluations listed have thus far mainly relied on interrupted time series (ITS) – a before and after study design, where time series data on the outcome is used to establish an underlying trend, which is 'interrupted' by an intervention at a specific point in time (Bernal, Cummins, & Gasparrini, 2016). The validity of this approach relies on the pre intervention trendline providing an unbiased representation of the counterfactual for a treated sample when projected into the post intervention period (Baicker & Svoronos, 2019).

Our aim is to demonstrate the applicability of the synthetic control method (SCM) for impact evaluation of MDA and other such interventions when routine disease surveillance data gathered in a consistent manner across multiple areas of a country are available, and evaluations are conducted outside of programme implementation. Our application provides evidence of the causal impact over two years of a recent large scale MDA malaria elimination initiative in Southern Mozambique. The elimination initiative has been described and evaluated by Galatas, Saute, et al. (2020) as part of programme implementation. SCM is a quasi-experimental approach widely used in quantitative social sciences, especially in economics (Billmeier & Nannicini, 2013; Cavallo, Galiani, Noy, & Pantano, 2013; DeAngelo & Hansen, 2014) and health economics (Kreif et al., 2016; Lépine, Lagarde, & Le Nestour, 2018). See A. Abadie (2020) for a review of other applications of SCM in economics. The only

application of SCM relating to malaria is by Barofsky, Anekwe, and Chase (2015) who evaluate the long-term economic consequences (schooling and employment) of the 1959–1960 malaria eradication campaign in Uganda. We are aware of only two applications of SCM in public health; an evaluation of a smoke free legislation in Thailand on neonatal and infant mortality (Radó, van Lenthe, Sheikh, & Been, 2020) and the impact of a decline in country democratic traits on universal health coverage (Wigley, Dieleman, Templin, Mumford, & Bollyky, 2020).

Our work differs from Galatas, Saute, et al. (2020) in several ways. First, we apply the SCM to routine surveillance data from the Ministry of Health (MoH) on weekly clinical malaria cases reported by health facilities to the National Malaria Control Program (NMCP), rather than data specifically gathered for the assessment (Galatas, Saute, et al., 2020). Second, our use of routine surveillance data and the SCM overcomes a threat to the validity of the ITS approach. As acknowledged by Galatas, Saute, et al. (2020) the lack of post-intervention counterfactual data in their application means the ITS model cannot control for the effects of irregular weather patterns, especially the El Niño and La Niña weather events that had a direct influence on post-intervention malaria incidence. Finally, our analysis focuses on the two-year MDA component -4 MDA rounds (phase 1 in Galatas, Saute, et al. (2020)) and does not include the phase 2 reactive focal MDA (rfMDA) pilot implemented after this. Consequently, we provide evidence of the heterogeneity in impact over years 1 and 2 of the MDA component unlike Galatas, Saute, et al. (2020) who evaluate the overall impact of the two-year MDA effort (phase 1).

2. Methods

2.1 Context and intervention

Mozambique is one of the 5 countries in the world with the highest malaria burden. According to the latest World Malaria Report (World Health Organization, 2020), in 2019 there were over 9 million estimated cases and more than 14,000 malaria-related deaths in Mozambique. As a member of the Elimination eight initiative, the country has increased its regional collaboration in order to accelerate progress towards elimination from the Southern African region. The Elimination Eight Initiative (E8) is a coalition of eight countries (Mozambique, Namibia, South Africa, Botswana, Angola, Zambia, Zimbabwe, Malawi) working across national borders to eliminate malaria from the southern Africa region by 2030. Cross-border collaboration is especially crucial for Mozambique, as it borders with six other malaria endemic countries, some of them already in pre-elimination stages. Renewed regional efforts began in 2015 with the establishment of an intergovernmental initiative among Mozambique, South Africa and Swaziland (MOSASWA) with the goal of accelerating the transition from pre-elimination to elimination in the latter two countries and from control to pre-elimination in the South of Mozambique by 2020.

In order to guide national strategies towards elimination for the South, a malaria elimination initiative was implemented in the district Magude, Maputo province, an area with a population of approximately 50,000 individuals (11,000 households) (Galatas, Nhacolo, et al., 2020). Magude was chosen because of its representativeness as a rural malaria endemic area (in 2014, the incident rate was 252 per 1,000 population), because of its international border with South Africa, and its proximity to the Manhiça Health Research Centre (CISM), the implementing organization.

The elimination initiative was implemented on top of existing standard of care for intermittent preventive treatment for pregnant women (IPTp), malaria case management and a mass LLIN distribution exercise conducted by NMCP across Mozambique in 2014 (Figure S1). This implies that any impact we observe in our analysis may be the cumulative effect of the intervention package, on top of these activities. Cross-sectional surveys by Galatas, Saute, et al. (2020) show 58.4% and 76.6% of individuals who reported having a fever in the preceding 30 days accessed care at a health facility. Between 69.0% and 75.0% of pregnant women in the second or third trimester found during the MDAs reported having attended at least one antenatal clinic visit of whom more than 90.0% reported receiving at least one dose of IPTp. LLIN usage was reported as 40.9% in 2015 and 64.4% in 2016.

Our analysis focuses on Phase 1 of the malaria elimination initiative in Magude (Figure S1). This phase was deployed over two years covering the start of rainy season and the peak of the malaria season. Year 1 represents August 2015-July 2016 and year 2 represents August 2016-June 2017. A summary of the intervention package is as follows (full details in Galatas, Saute, et al. (2020)):

(i) Comprehensive vector control through universal IRS, deployed between
   a. August-October of 2015 with an operational coverage of 94.4%
   b. September-November of 2016 with an operational coverage of 94.0%

(ii) Two rounds per year of population-wide MDA with Dihydroartemisinin-Piperaquine (DHA/PPQ)[1] at the start of each rainy reason.
   a. MDA1-November 2015 and MDA2- January 2016 - The effective MDA coverage in each round was 72.3% and 58.0%, respectively
   b. MDA3-December 2016 and MDA4- January 2017 - The effective MDA coverage in each round was 66.6% and 64.8%, respectively

   Each eligible and consenting participant was provided a full dose of DHA/PPQ to be take once a day for three consecutive days. Participants were observed taking the treatment only on day 1. Participants were provided instructions on how and when to take doses 2 and 3 which were

[1] DHA/PPQ is the drug recommended by the WHO for malaria elimination. Its efficacy has been demonstrated in several clinical trials Naing et al. (2013).

left with them. Exclusion criteria included infants under 6 months of age (or weighing <5kgs), severely ill individuals, women in the first trimester of pregnancy.

(iii) Community sensitization to maximize uptake and use of the interventions. 94.5% and 95.8% of household heads participating in MDA1 and MDA3 respectively, reported being recipients of messages from these activities.

2.2 Data

We use data extracted from Mozambique's *Boletim Epidemiológico Semanal (BES),* the epidemic disease reporting system used by the NMCP. It gathers data on weekly number of cases for several notifiable infectious diseases, including malaria. BES reports the number of confirmed (either by rapid diagnostic test or microscopy) malaria cases by week and age group (children under 5 years and those aged 5 and above). We use population estimates from the National Statistical Institute (INE) for the two age groups to create our primary outcome: weekly malaria incidence rate (cases per 1000 population at risk) for under 5 years (<5) and over 5 years (5+).

Our treatment group is the district of Magude, Maputo province. The control group consists of the other districts in Maputo province, as well as the districts from the neighbouring province, Gaza (Figure S2). We excluded Manhiça district from the analysis. Manhiça district also received the MDA in 2016-17 and because Manhiça is where most malaria research has been carried out over the past 20 years by CISM. The selection of control districts from locations around Magude is to ensure treatment and control groups have similar epidemiological characteristics. In addition, our analysis uses variables as predictors of malaria incidence: coverage of long-lasting insecticide treated bed nets (MISAU, 2016), average weekly temperature and weekly precipitation.

We retrieved weather data from all the National Oceanic and Atmospheric Administration (NOAA) weather stations in Mozambique and used a simple interpolation method (Hanigan, Hall, & Dear, 2006) to estimate local weather for each district. For each district centroid [2]on each date and for each weather indicator (temperature, precipitation), a weighted mean was calculated taking into consideration all NOAA weather stations in the country (a total of 27), with the weight being equivalent to 1 divided by the distance (in kilometres) from the district's centroid to each station. In other words, a station 5 kilometres from a district centroid would get a weight of 1/5 (0.2) whereas a station 100 kilometres from a district centroid would get a weight of 1/100 (0.01).

[2] The centroid is the location of the geographic centre of the district.

2.3 Estimating the effectiveness of the campaign in reducing malaria burden

In non-experimental settings where pre-intervention time series data is available for a group receiving the intervention, a common strategy in public health epidemiology has been to apply the ITS approach (Ashton et al., 2019; Derde et al., 2014; Lau et al., 2015; Ma, Cecil, Bottle, French, & Saxena, 2020). ITS involves a pre-post comparison while accounting for underlying trends in the outcome. By modelling the underlying pre-intervention trend, ITS can control for time-varying factors that are slow to change over time. In our application the ITS approach may not be internally valid as there were irregular rainfall patterns during the intervention period, with El Niño causing a very dry season in year 1 (2015-16) followed by La Niña in year 2 causing heavy rainfall in 2016-17 (Galatas, Saute, et al., 2020). In such situations the recommendation has been to apply approaches that involve a control group such as controlled ITS (CITS) or if only limited before-and-after data are available, a difference-in-differences (DD) approach (Bernal et al., 2016). These approaches estimate treatment effects in such settings by comparing changes in outcome pre- and -post intervention, for the treatment with that of control group. In these methods the purpose of the control is to exclude time-varying confounders, such as events occurring around the time of the intervention, as these are generally unpredictable based on modelling pre-intervention trends.

Both CITS and DD require the "parallel trends" assumption to hold for internal validity, wherein the pre-intervention difference in trends between intervention and control groups is constant over time, an assumption that does not hold in our dataset (Figure 1). Both graphs (Figure 1) indicate a relatively stable malaria trend in the control districts. However, Magude shows a downward trend in incidence over time, even prior to the elimination campaign. Accordingly, we employ the synthetic control method (SCM), which allows for greater flexibility in the estimation of the impact of the malaria elimination campaign by relaxing the parallel trends assumption (A. Abadie, 2020; A Abadie, Diamond, & Hainmueller, 2010, 2015).

The Synthetic Control Method

The basic premise of the SCM is that, when the units of observation in the data are a small number of aggregate entities (such as district level surveillance data in our case), a combination of untreated units often provides a more appropriate comparator than a single control unit (A. Abadie, 2020). In the SCM the selection of control units is based on a data driven procedure described below. Appling the SCM involves constructing a weighted combination of potential control districts, the "synthetic control", using the districts that best approximate the most relevant predictors of malaria incidence in Magude before the intervention. These must be predictors that are not affected by the elimination campaign, can include pre-intervention values of the outcome, and can be either time varying or time invariant (A Abadie et al., 2010).

Our data consists of districts $j = 1 \ldots, J+1$ with malaria outcomes for time periods $t = 1, \ldots., T$. For the sake of exposition, we assume the first unit is Magude $(j = 1)$ and exposed to the elimination campaign, leaving us with J control districts. In our application $J = 17, j = 1, \ldots.,17+1$ In the approach the intervention occurs at time-period $T_0 + 1$ such that time periods $1,2 \ldots., T_0$ are pre-elimination and $T_0 + 1, T_0 + 2, \ldots. T$ are intervention periods. We use time series data on weekly cases from October 2013 to April 2017 with the intervention beginning with IRS in August 2015.

Our primary interest is in the impact of the intervention during the two peak malaria seasons (December 2015/16 – April 2016/17). Malaria transmission is highly seasonal and highest in these months coinciding with the rainy season and is low outside these months (Galatas, Saute, et al., 2020; Zacarias & Andersson, 2011). This also avoids an overlap with the start of the rfMDA pilot in July 2017.

Two potential outcomes can be defined: First, the 'unobserved' counterfactual outcome Y_{jt}^N for Magude at time *t* if Magude had not been exposed to the elimination campaign; and second, Y_{jt}^I the outcome for Magude under the elimination campaign. Our aim was to estimate the effect of the campaign in Magude during the intervention periods. This effect is defined as the difference between the potential outcomes:$\alpha_{jt} = Y_{jt}^I - Y_{jt}^N$ for time-periods $T_0 + 1, T_0 + 2, \ldots T$ (August 2015 – April 2017). We apply the SCM to generate an estimate of Y_{jt}^N in the intervention period.

Following Abadie et al (2010) we assume a linear relationship between the outcome variable and predictors, to define the observed outcome as:

$$Y_{jt}^I = Y_{jt}^N + \alpha_{jt} D_{jt}$$
$$Y_{jt}^N = \delta_t + \lambda_t \mu_j + \theta_t Z_j + \epsilon_{jt}$$

Where δ_t represents a time fixed effect, μ_j is a vector of time-invariant unobserved predictor factors with time varying coefficients λ_t. Z_j is a vector of observed predictor variables, which in our case included pre-intervention - malaria incidence during the peak incidence months (January to March), precipitation, temperature, coverage of LLINs and precipitation in 2016 (post intervention). Since precipitation is unlikely to be affected by malaria incidence, we include precipitation in 2016 (post intervention) to capture the effects of the El Niño and La Niña events in Mozambique. D_{jt} is a binary indicator variable taking the value of 1 if the district is Magude (treated) and 0 for the control districts. The SCM as specified above allows the effect (λ_t) of the unobserved predictors μ_j to vary over time,

relaxing the parallel trend assumption of only time-varying unobservables in the CITS and DD approach.

We construct the synthetic control as a weighted combination of control districts that best approximate the pre-intervention characteristics of Magude. We estimate a vector $(J \times 1)$ of weights $W = (w_2, \ldots., w_{J+1})'$ such that each $w_j \geq 0$ and the weights, sum to 1 and w_j is the contribution of each control district to the formation of the synthetic control. The unobserved counterfactual for Magude is estimated as a weighted linear combination of control unit outcomes, $\hat{Y}_{1t}^N = \sum_2^{J+1} w_j Y_{jt}$. If the weighted values of the included predictor variables and pre-treatment outcomes for control districts are similar to those of Magude (i.e. $\sum_2^{J+1} w_j Z_j = Z_1$ and $\sum_2^{J+1} w_j Y_{jt} = Y_{1t}$) and if the outcomes are a linear combination of observed and unobserved predictor factors, then our estimated treatment effect $\hat{\alpha}_{1t}$ is an unbiased estimate of the true treatment effect α_{1t}.

To implement the SCM numerically, we estimate a vector of weights W^* to minimize the discrepancy in predictors between Magude and the synthetic control. This discrepancy is defined as a metric of distance $\sqrt{(X_1 - X_0 W)' V (X_1 - X_0 W)}$, where X_1 is a $k \times 1$ vector of predictor variables described earlier for Magude and X_0 is the corresponding vector of dimension $k \times j$ for control districts. The vector V is a $k \times k$ symmetric and positive semidefinite matrix which allows different weights to each of the predictor variables depending on their importance in generating the outcome. Both W and V were chosen to minimize the root mean squared prediction error (RMSPE) of pre-intervention outcomes (see A Abadie et al. (2015) for further details).

Valid implementation of the SCM requires that the synthetic control closely reproduce the pre-intervention predictors of malaria incidence in Magude. This can be evaluated by examining the RMSPE in the pre-intervention period. In the post-treatment period, the SCM provides the counterfactual situation for Magude, in the absence of the elimination campaign. The impact of the campaign is estimated by comparing the outcome trend of the synthetic control with Magude in the post-intervention period.

Compared to CITS, DD and other regression-based quasi-experimental methods, the SCM has several advantages: using a weighted average of control units, the SCM makes explicit the relative contribution of selected control districts to the counterfactual; the similarities between Magude and the synthetic control can be evaluated by comparing pre-intervention outcomes and predictors; the weights allocated to the control units are restricted to sum to one, providing a safeguard against extrapolation; and most importantly for our purposes, the SCM allows the effects of unobserved factors on malaria incidence to vary with time, relaxing the parallel trend assumption. To highlight the influence of pre-intervention

trends and post-intervention factors on the estimated counterfactual, we provide a visual comparison of SCM with an ITS model on our data.[3]

Statistical significance of estimated effects

A limitation of SCM is that it does not allow assessing the significance of the results using commonly used (large sample) inferential techniques since the number of control groups is small. Following the SCM literature (A. Abadie, 2020; A Abadie et al., 2010, 2015) we conducted inference using a set of placebo experiments, where we sequentially apply the SCM to each of the control units to generate a distribution of treatment effects. By construction, this approach provides exact inference irrespective of the number of control districts, however, the power of the test increases with the number of available control units. We compare the distribution of placebo effects to the treatment effect for Magude and calculate the p-value of the one-sided test as the proportion of placebo effects which were at least as extreme in value as the estimated effect for Magude. We note that, by construction, the smallest the p-value is likely to be when Magude has the largest treatment effect is 1/18=0.056. This method of inference is similar to permutation inference (Lehmann, 1997), where a test statistic is estimated by random permutations of assigning a particular unit to treatment or control. This approach does not generate confidence intervals and the interpretation is restricted to whether the estimated effect is large or not compared to the distribution of the placebo effects.

2.4 Robustness tests

We conducted three types of robustness checks to validate our results. First, we conducted a form of "falsification exercise" where we investigated whether the observed reduction in malaria incidence was generated by the malaria elimination campaign or whether there were other structural factors that may have resulted in the observed reduction. Such factors may also influence other health outcomes such as diarrhoea in young children. We used data on diarrhoea cases amongst children 0-5 years taken from the same data source. However, these outcomes are only available for the district of Maputo province (which includes Magude district) up to December 2016. Nevertheless, this allows us to re-estimate the SCM using diarrhoea cases as the outcome and the same subset of control districts in Maputo province.

Second, following A. Abadie (2020) we performed a diagnostic check to assess the credibility of the synthetic control. In this exercise we backdated the intervention period to begin in Dec 2014. This is the "in-time placebo test" in Abadie et al. (2015) and similar to the "pre-program test" in Heckman and Hotz (1989). A credible synthetic control would be indicated by a lack of treatment effect prior to the

[3] The ITS model was estimated separately for the two age groups using a poisson distribution with three period autoregressive structure (based on an *actest*) and one-month lags for precipitation, LLIN coverage and temperature.

start of the actual intervention (August 2015) even when the estimator uses no information on the timing of the actual intervention.

Finally, to evaluate the robustness of our results to the choice of units contributing to the synthetic control we perform the leave-one-out test suggested in A. Abadie (2020). In this exercise, we re-estimate our main models (0-4 and 5+ years), taking out one-at-a-time, each of the districts that contribute to the synthetic control. A robust result would be indicated by the exclusion of donor unit not having a visually large impact on the result when plotted on an SCM graph.

3. Results

3.1 Characteristics of the synthetic control

Synthetic Magude for children below 5 years is a weighted average of Boane, Chicualacuala, Chigubo, Mablane, Matutuine and Xai-Xai districts; while for those 5 years and above it is a weighted average of Chigubo, Mablane, Namaacha and Xai-Xai districts. All other districts in the control pool obtain zero weights (Table S1). A comparison of predictors of weekly malaria incidence suggests small differences between synthetic Magude and Magude in predictor variables (Table 1). The weights chosen by the method indicate that the most important predictors (highest weights) were temperature and LLIN coverage, followed by post intervention precipitation, pre-intervention malaria incidence and pre-intervention precipitation. Characteristics that differ between real and synthetic Magude (for example, pre-intervention peak incidence), do so because those factors provide limited predictive power for future incidence.

Synthetic Magude closely reproduces the malaria trend in Magude in the pre-elimination period (Figure a and 2b). This good fit is also reflected in the pre-elimination RMSPE of 2.13 cases per week for the 0-4 years model and 1.65 cases per week for 5+ years. During the intervention period there is a clear difference in the trajectories indicating a reduction in malaria. In addition, the districts included in the construction of the synthetic control are close to Magude and all have the pre-intervention downward trend in malaria seen for Magude (Figures S3-S5).

3.2 Estimated treatment effects

Over the entire analysis period (August 2015 to April 2017), 78% of expected cases were averted.

August 2015- July 2016 (intervention year 1): The average treatment effect (ATE) (Table) was a reduction in weekly malaria incidence by 4 cases per 1000 in children (0-4 years) and by 2 cases per 1000 in those aged 5+ years. This translates to a reduction of 6,261 (77%) cases across both age groups.

During the peak malaria season 87% of cases were averted between December 2015 and April 2016.

August 2016-April 2017 (intervention year 2): There was a reduction of 5 cases per 1000 and 3 cases per 1000 amongst children (0-4 years) and those aged 5+ years, respectively. This indicates 7,061 (80%) cases were averted during this period across age groups.
During the peak malaria season 79% of cases were averted between December 2016 and April 2017.

Inference
If synthetic Magude had failed to fit malaria incidence for Magude in the weeks before the elimination campaign, we would interpret that much of the post-treatment gap between real and synthetic Magude was artificially created due to lack of fit. Similarly, placebo estimates of the treatment effect do not provide accurate estimates if their fit is poor prior to August 2015. A Abadie et al. (2010) propose excluding districts beyond a certain level of pre-August 2015 RMSPE. We apply a strict cut-off and include only those districts that we can fit almost as well as Magude in the period before August 2015, that is, those districts with pre-RMSPE not higher than 3 times the pre-RMSPE of Magude. We find one district (Massengena) had a RMSPE larger than this cut-off and eliminate it from the inference considerations.

The result for August 2015-July 2016 for 0-4 years is robust to placebo testing, as none of the placebo experiments for the control districts shows treatment effects larger than those for Magude; this is not the case for the 5+ age group (Figure 3 and 4). Between August 2016 and April 2017, the estimated treatment effect was larger, but these results were not robust to placebo tests. In terms of magnitude, the effect in Magude was only exceeded by two of the control districts.

3.3 Robustness of results

In our placebo test with diarrhoea outcomes the graphical representation of SCM (Figure 5) shows no divergence in the intervention period indicating our results are unlikely to be driven by other structural factors that may have resulted in the observed malaria reduction.

The “in-time” diagnostic check shows for both age groups the SCM closely tracks pre-intervention (October 2013-July 2015) weekly malaria cases for Magude (Figure). The absence of estimated effects prior to the intervention demonstrates the credibility of the synthetic control estimator (Abadie 2020). It indicates that the synthetic control can reproduce the trajectory of the outcome variable for the treated unit before the intervention occurs. In addition, the gap between Magude and synthetic Magude emerges only in August 2015 ie the actual intervention period. This is the case even when the intervention is backdated in the data and the estimator uses no information on the timing of the actual intervention.

The shape and direction of the gap in Figure are similar to that of Figures 4a and 4b, although of a somewhat lower magnitude (as in the example of Abadie 2020). Thus, our diagnostic check provides confirmation of the credibility of our synthetic control.

The leave-one-out test estimates of the synthetic control are all centred close-to or around the original synthetic control (ie using the full sample of control units) and indicate results in the same direction (Figure 7). Thus, our main conclusion of a reduction in malaria incidence is robust to the exclusion of any particular district.

4. Discussion

We demonstrated the use of the synthetic control method, to evaluate the short-term impact of a malaria elimination initiative in a district of Southern Mozambique. Results show that intensified vector control and MDA for two consecutive years dramatically reduces malaria burden but did not result in zero cases. Across age groups during the peak malaria season our estimates imply incidence declined by 87% and 79% in December 2015- April 2016 and December 2016- April 2017, respectively.

It is important to clarify that while elimination is defined as zero local cases, the BES data we use does not distinguish between local and imported cases. Therefore, the few non-zero cases could reflect sustained transmission from imported malaria cases. This is likely to be the case as Magude is characterized, on top of the normal movement of people across districts, by the migration of seasonal sugarcane workers.

Study usage data measured during MDA rounds 1 and 2 by looking at empty blister packs showed a clear decline from 73% to 62%. LLINs which were distributed to all households by MoH, also had similar usage (65%-70%, self-reported) (Galatas, Saute, et al., 2020). Assuming a constant impact of imported malaria, the larger decline during the malaria season in 2015-2016 is likely to be the combined effects of LLINs distributed in 2014, which has a life of three years, higher but declining MDA usage in the population at risk and the drought in Mozambique in 2016. In 2016-2017, a year with above average rainfall and with less effectiveness of LLINs, the decline in incidence was smaller. Our results may reflect bounds under two different circumstances given average usage and good coverage of IRS – the first (2015-2016) with optimal weather conditions for low malaria (drought) and high effectiveness of LLINs and the second (2016-2017) poor weather conditions (above average rainfall) and declining levels of effectiveness of LLINs.

Galatas, Saute, et al. (2020) report a 69% reduction in malaria cases immediately following the introduction of the intervention in August 2015 (level change), in contrast the SCM estimates a smaller

level change of 54% (also in August 2015). The authors do not report results by year or by malaria season but estimate 76% (95% CI 75.1–76.0) of malaria cases were averted between August 2015-August 2017. A visual inspection of their observed and counterfactual results (Figure S7) indicates a large proportion of the overall impact is seemingly generated during the malaria season in year 2 (December 2016- April 2017). The SCM estimates a 78% reduction in malaria cases between August 2015-April 2017, however placebo tests indicate this effect is not significant. The timeframe for this overall effect is shorter by three months, but this is unlikely to cause a big change in this result as May-July are not peak malaria months and generally have low number of cases. Considering the heterogeneity over two years, in contrast to the ITS results we find a much larger decline in incidence during the malaria season in year 1(89%) compared to the same period in year 2 (79%). A visual inspection of the counterfactuals indicates that with the use of controls to account for post-intervention time-varying factors, the SCM counterfactual estimates are lower in magnitude (Figures S6 and S7). It is possible that some of this variation is due to differences in the reported levels of malaria cases in the datasets. Galatas, Saute, et al. (2020) have higher levels of pre-intervention malaria cases. As part of programme implementation, they implemented an extensive and very detailed weekly rapid reporting system for malaria cases including community level reporting from health workers. While we used publicly available surveillance data from the Ministry of Health, which reports data at the health facility level and potentially underreports the true burden of malaria cases. However, any such underreporting in our data is likely to be consistent across intervention and control areas. In the absence of a control group, the ITS model does not control for the drought in 2016 and the excess rainfall in 2017 and projects the high pre-intervention malaria trend into the post-intervention period. As a result, it estimates a counterfactual peak of over 350 (2016) and 800 (2017) cases per week, the latter being higher than any pre-intervention peak in the data. In contrast, the SCM model with the use of a control group, removes the impact of not just the pre-intervention downward trend in our data but also of these post-intervention weather events, thus isolating the impact of the intervention, predicting a peak of 250 (2016) and 477 (2017) cases, respectively. To the extent that detailed data collection such as in Galatas, Saute, et al. (2020) are expensive and unlikely to be available when evaluations are conducted outside of programme implementation which must rely on available public data sources, our estimates provide a robust lower bound of the treatment effect.

A comparison of the SCM counterfactual to one from an ITS model on our data, highlights the importance of a control group and controlling for pre-intervention trends in the data (Figure S6). The ITS model generates similar counterfactuals to the SCM in 2016, a year when drought suppressed malaria cases on top of the projected downward pre-intervention trend. In 2017, the ITS model projects the expected upward trend in the counterfactual due to the excess rainfall but is lower in magnitude than the SCM. In this case, the upward impact of rainfall on malaria is countered by the downward pre-intervention trend in our data, which is projected into the post-intervention period.

Our finding of an immediate decline in malaria cases following MDA is consistent with those obtained in two cluster randomized controlled trials (RCT) estimating the effectiveness of MDA with DHA/PPQ in Zambia (Eisele et al., 2016) and South East Asia (von Seidlein et al., 2019). In both studies, MDA resulted in a rapid decline in the number of malaria cases (59% over 9 months since implementation of the MDA (von Seidlein et al., 2019) and 70% over a 5 month follow up in low transmission areas and 58% in high transmission areas (Eisele et al., 2016))). They are also similar to the predictions of a consensus study that put together 4 models focusing on the impact of MDA with a drug having similar characteristics as DHA/PPQ (Brady et al., 2017). The consensus study predicted an immediate decline in malaria prevalence after MDA, but also that the decline would be transient if no other long-term intervention is implemented such as LLINs. While our results from the second year indicate two other districts had larger declines in incidence that year, it is important to emphasize that to break transmission and achieve elimination, sustained low levels of incidence are required. In the absence of MDA, this cannot be guaranteed by just LLINs and IRS as reflected the historic trends we see for the region.

We have demonstrated how routine epidemic surveillance data gathered under most NMCPs around the world can be combined with the SCM to evaluate the impact of such large-scale programs. The SCM is a robust method for evaluating interventions when data collection for evaluation is not built into the implementation or when the evaluators are not the implementers of the interventions, and when data are available at a large scale as routinely collected. The approach is also applicable for the evaluation of unplanned interventions or 'natural shocks', which definition cannot be randomised (A Abadie et al., 2015; Alberto Abadie & Gardeazabal, 2003). Given the focus over the last decade on malaria elimination with both large- and small-scale campaigns across the globe, this approach offers a rigorous and inexpensive alternative to randomized-control trials. To the extent that observational data is widely (and often publicly) available, that true experimental approaches may not always be feasible, and that the internal validity requirements of methods such as the ITS may not always hold, approaches like the SCM are an excellent alternative for the evaluation of malaria elimination initiatives. They can also be used for the evaluation of any non-randomised intervention and for diseases beyond malaria when a (good) national routine surveillance system is in place.

Our analysis has limitations. First, we rely on surveillance malaria cases reported at the health facility level, which is likely to be an incomplete proxy for malaria infection incidence, missing asymptomatic infections. It may also under-represent the symptomatic cases as health-seeking behaviour has been described to be suboptimal in Mozambique with care sought for only 60% of children with a history of fever(Cassy et al., 2019). On the other hand, awareness-raising associated with the campaign may have increased health-seeking behaviour, thereby resulting in our underestimation of the campaign's true effect. Second, the health facility registries from which we gathered data are themselves imperfect; we

have no mechanisms by which to validate the entirety of the data. Still, BES data offers the best country-wide comparison of malaria trends at a granular level (weekly and by district). Third, the external validity of our results may be limited by the implementation of the programme in a single district in Southern Mozambique and the malaria trends specific to the region. Finally, long-term transmission modelling is required to evaluate whether and when the combination of interventions evaluated may lead to elimination.

Despite these limitations, our study demonstrates the utility of the SCM for the estimation of similar initiatives' effectiveness when surveillance data are available and when evaluations may need to be conducted outside of programme implementation. This study also provides important evidence that MDA leads to a large reduction in malaria burden but additional methods to improve uptake and usage as well as maintaining high coverage of existing (or new) vector control strategies and tools (e.g., a safe and efficacious vaccine) are likely to be required to reach a goal of sustained zero local cases. Researchers, policymakers and those actively engaged in or planning health interventions and disease control/elimination initiatives, should include SCM in their evaluation toolkit for malaria and other public health interventions.

Figures and Tables

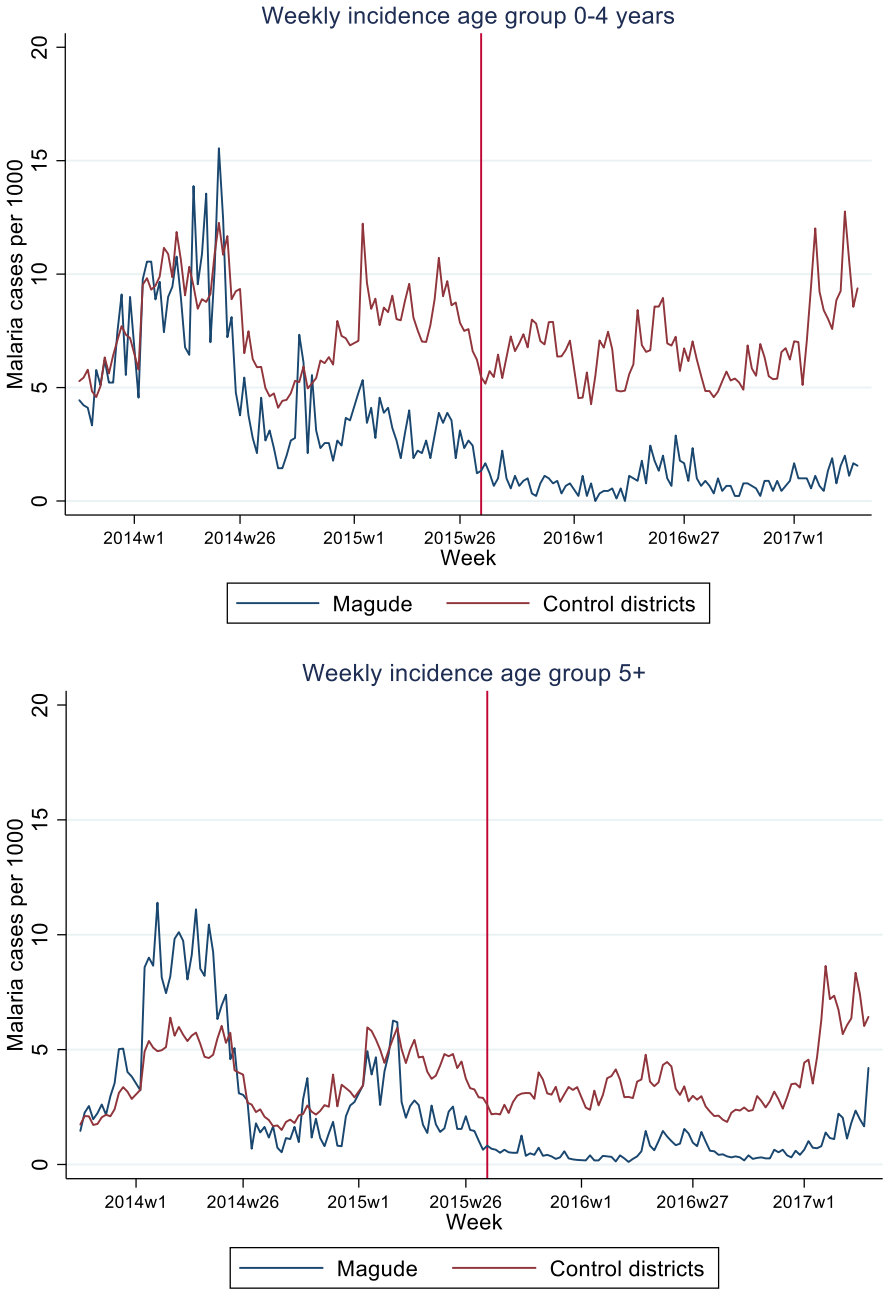


Figure 1: Trends in weekly incidence by age group

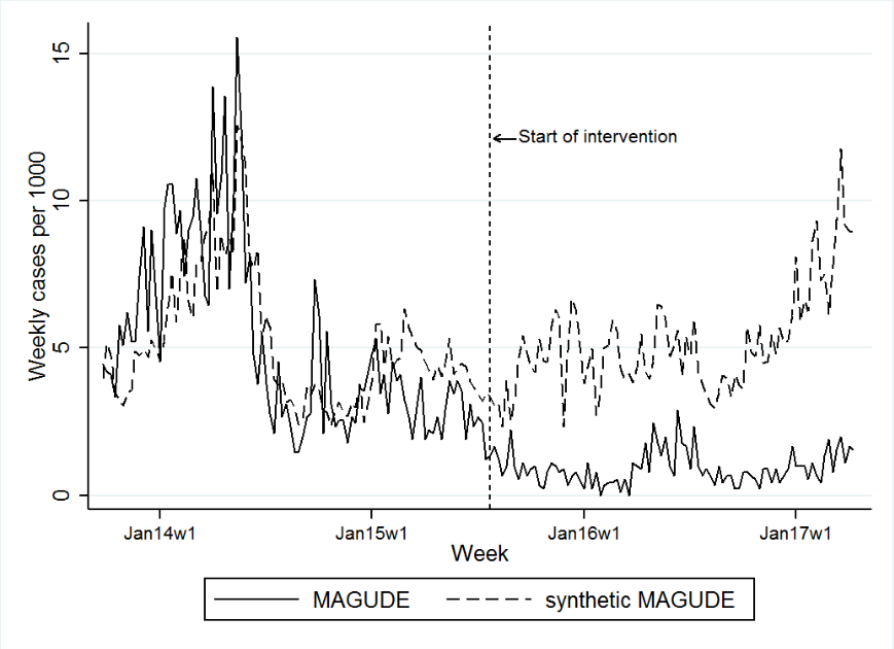


Figure 2a: Trends in malaria incidence: Magude versus synthetic Magude ages 0-4 years

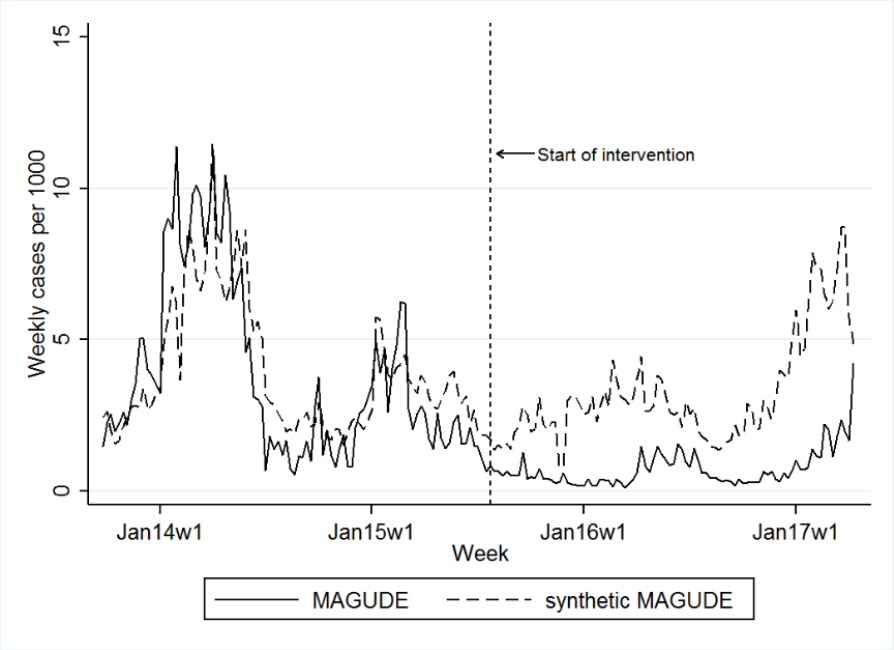
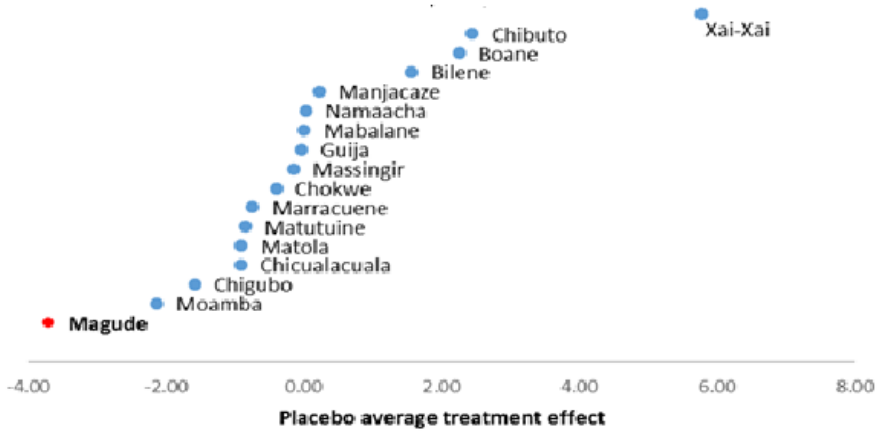


Figure 2b :Trends in malaria incidence: Magude versus synthetic Magude ages 5+ years



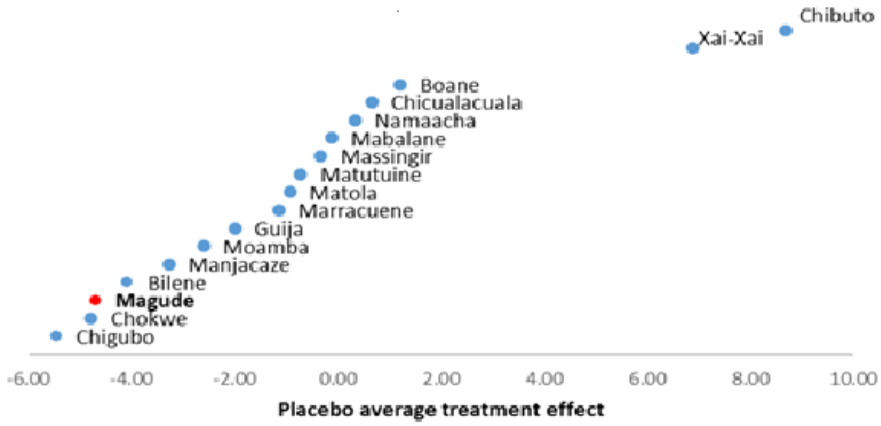


Figure 3: Placebo average treatment effect 0-4 years

Notes: Top panel August 2015-July 2016. Lower panel August 2016-April 2017. Panels indicates the distribution of treatment effects from the placebo experiment sequentially applying the SCM to each of the control units to generate a distribution of treatment effects

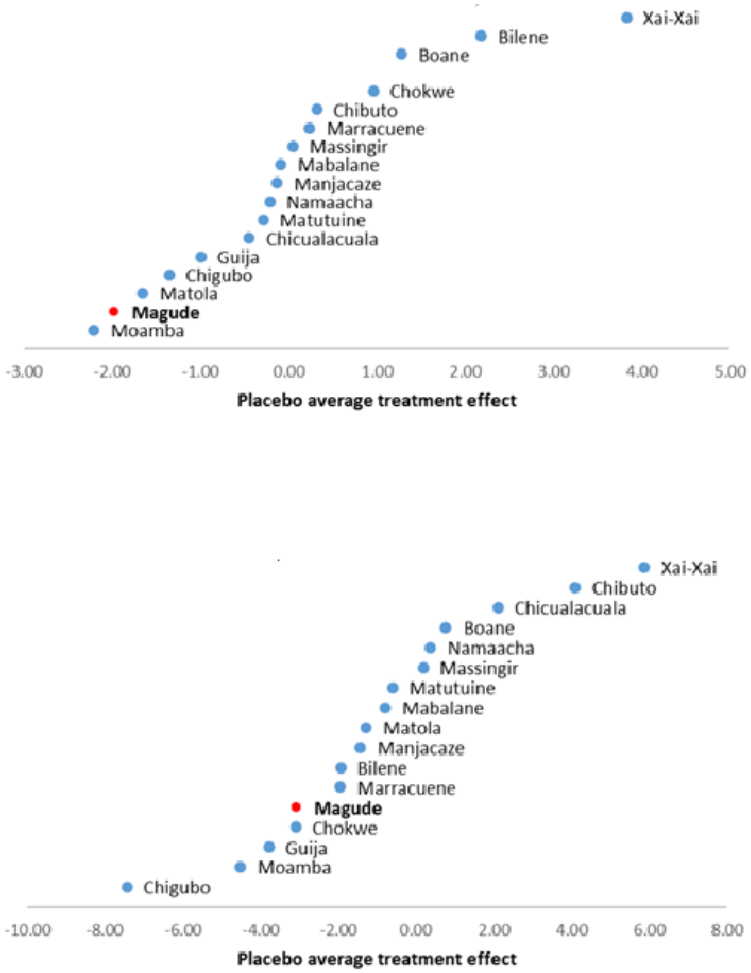


Figure 4: Placebo average treatment effect 5+ years

Notes: Top panel August 2015-July 2016. Lower panel August 2016-April 2017. Panels indicates the distribution of treatment effects from the placebo experiment sequentially applying the SCM to each of the control units to generate a distribution of treatment effects

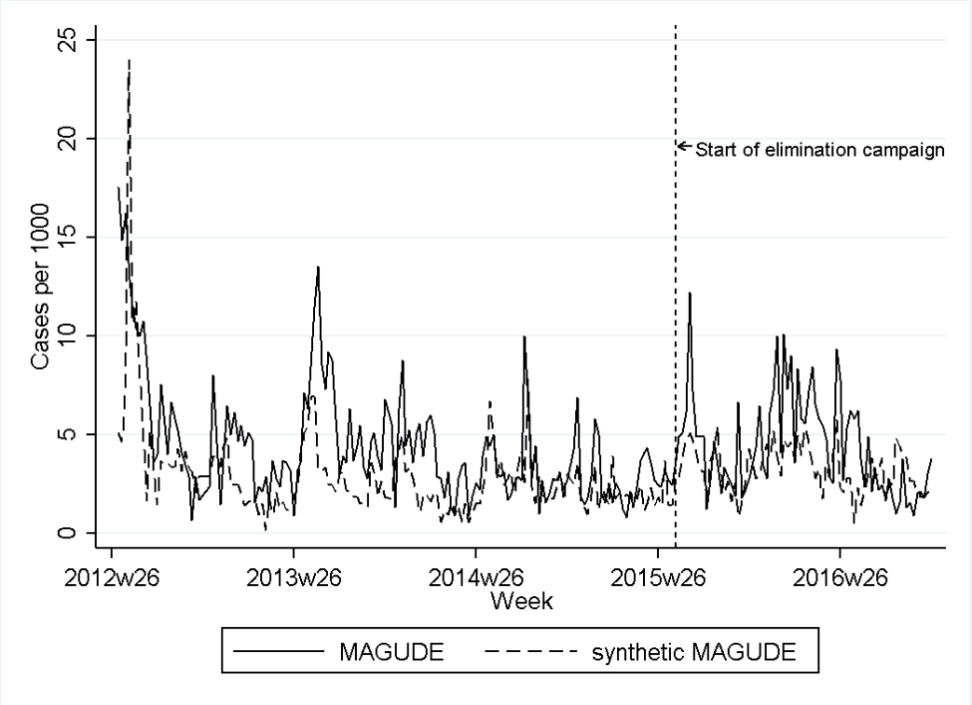
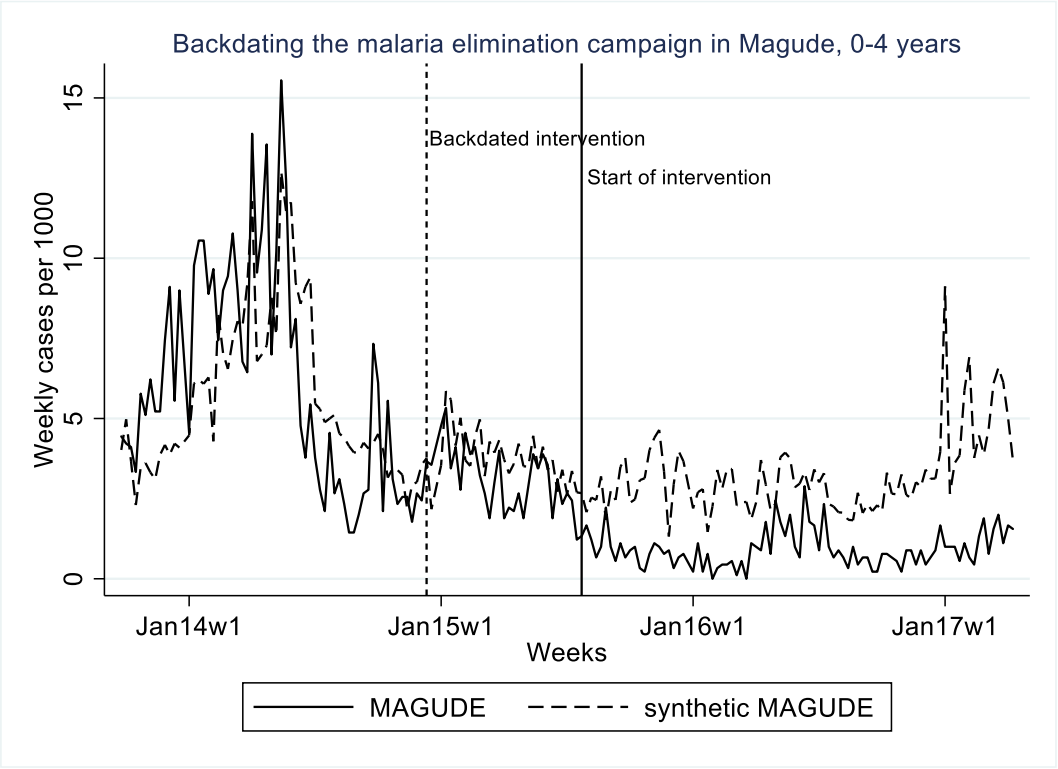


Figure 5:Trends in diarrhoea cases: Synthetic Magude versus real Magude



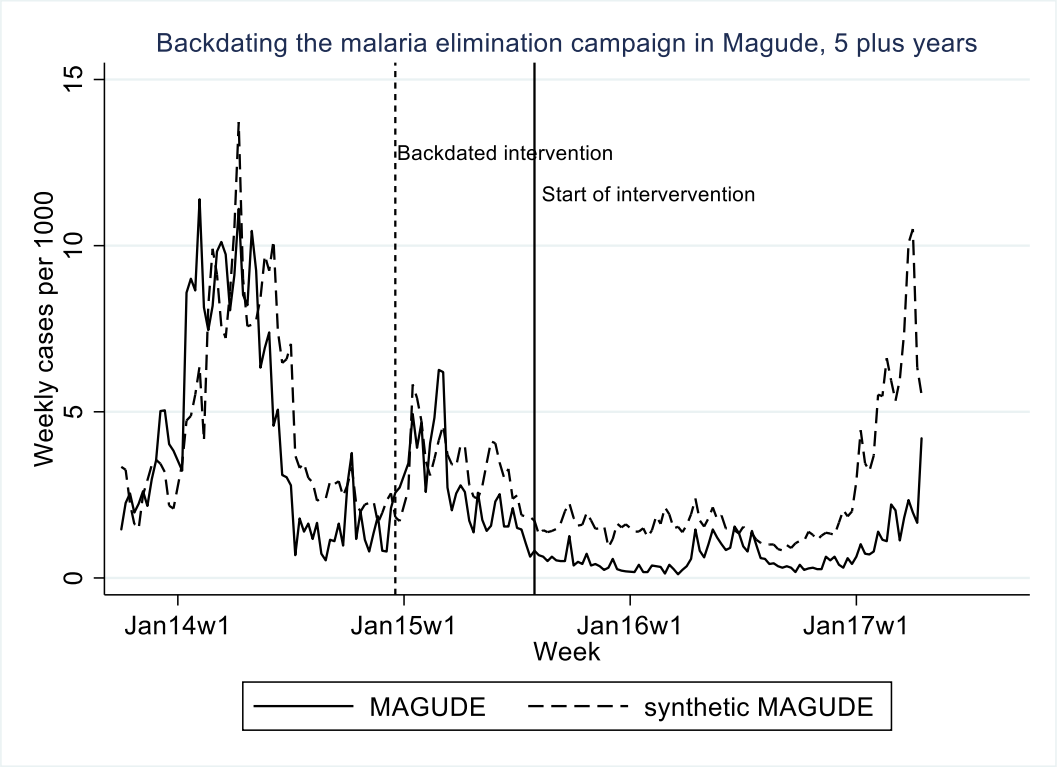


Figure 6:In-time placebo test for 0-4 years and 5+ years

Notes: In this robustness test, the intervention is backdated to December 2014. An absence of estimated effects prior to the actual intervention demonstrates the credibility of the synthetic control estimator

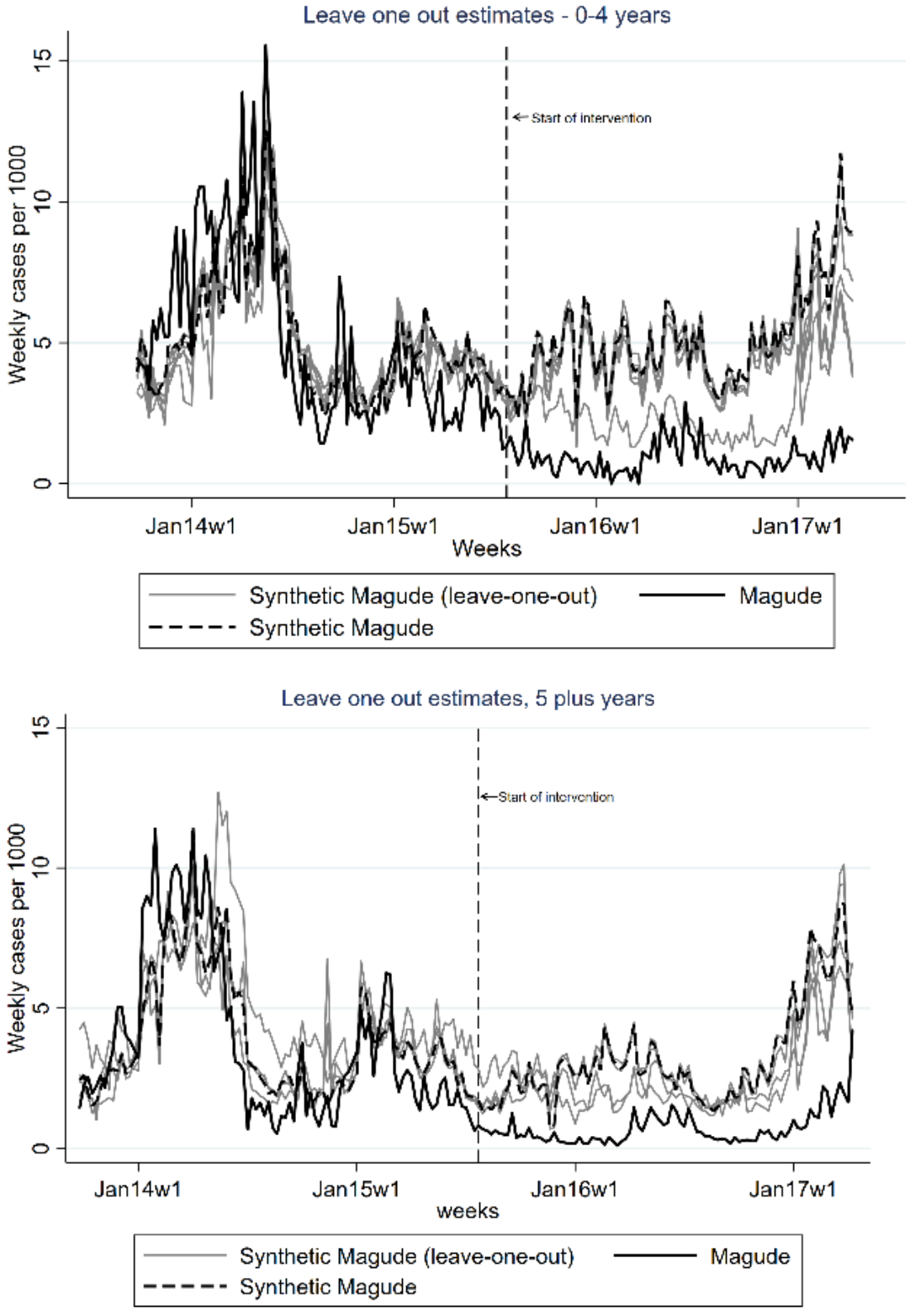


Figure 7: Leave-one-out test for 0-4 years and 5+ years

Notes: Test to evaluate the robustness of results to choice of units contributing to the synthetic control, the SCM is re-estimated taking out one-at-a-time, each of the countries that contribute to the synthetic control. Results centred close-to or around the original synthetic control (ie using the full sample of control units) and indicate results in the same direction.

Table 1: Predictor means

	Age 0-4 years		Age 5 + years	
	Magude	Synthetic Magude	Magude	Synthetic Magude
Incidence (Jan–Mar 2014)	8.87	6.93	8.53	6.29
Incidence (Jan-Mar 2015)	3.65	5.1	4.02	4.12
LLIN coverage	24.82	24.77	24.83	25.22
Precipitation (pre-intervention period)	1.71	1.74	1.71	1.71
Temperature (pre-intervention period)	24.52	24.51	24.52	24.49
Precipitation (post-intervention period)	1.84	1.84	1.84	1.83

Note: Incidence is averaged over the periods Jan 15-Mar 15, Jan 14-Mar 14, LLIN coverage/Precipitation/ Temperature (pre-intervention period) are averaged over the entire pre-intervention period, Precipitation (post-intervention period) is averaged over 2016.

Table 2: Average treatment effect and number of cases averted

	Weekly reduction in malaria incidence per 1000		**Number of cases averted (% reduction)**
	Age 0-4 years model	Age 5+ years model	All ages
Aug 2015- July 2016 (intervention year 1)	-3.64	-1.94	6,261 (77%)*****
Aug 2016 – April 2017 (intervention year 2)	-5.07	-3.21	7,061 (80%)*****
Total (Aug 2015-Apr 2017)			13,322 (78%)**
Peak malaria season (Dec 2015-Apr 2016)			3,214 (87%)**
Peak malaria season (Dec 2016-Apr 2017)			5,251 (79%)**

Note: * Number of cases averted calculated from the age group specific SCM model. **Totals for the entire analysis period and peak malaria season are calculated by summing age group specific SCM model estimates.

References

Abadie, A. (2020). Using Synthetic Controls: Feasibility, Data Requirements, and Methodological Aspects. *Journal of Economic Literature, Forthcoming*.

Abadie, A., Diamond, A., & Hainmueller, J. (2010). Synthetic Control Methods for Comparative Case Studies: Estimating the Effect of California's Tobacco Control Program. *Journal of the American Statistical Association, 105*(490).

Abadie, A., Diamond, A., & Hainmueller, J. (2015). Comparative Politics and the Synthetic Control Method. *American Journal of Political Science, 59*(2), 495–510.

Abadie, A., & Gardeazabal, J. (2003). The Economic Costs of Conflict: A Case Study of the Basque Country. *American Economic Review, 93*(1), 113-132. doi:10.1257/000282803321455188

Ashton, R. A., Bennett, A., Al-Mafazy, A.-W., Abass, A. K., Msellem, M. I., McElroy, P., . . . Bhattarai, A. (2019). Use of Routine Health Information System Data to Evaluate Impact of Malaria Control Interventions in Zanzibar, Tanzania from 2000 to 2015. *EClinicalMedicine, 12*, 11-19. doi:10.1016/j.eclinm.2019.05.011

Baicker, K., & Svoronos, T. (2019). *Testing the validity of the interupted time series design*. Retrieved from http://www.nber.org/papers/w26080.pdf

Barofsky, J., Anekwe, T. D., & Chase, C. (2015). Malaria eradication and economic outcomes in sub-Saharan Africa: Evidence from Uganda. *J Health Econ, 44*, 118-136. doi:10.1016/j.jhealeco.2015.08.002

Bernal, J. L., Cummins, S., & Gasparrini, A. (2016). Interrupted time series regression for the evaluation of public health interventions: a tutorial. *International Journal of Epidemiology, 46*(1), 348-355. doi:10.1093/ije/dyw098

Billmeier, A., & Nannicini, T. (2013). Assessing Economic Liberalization Episodes: A Synthetic Control Approach. *The Review of Economics and Statistics, 95*(3), 983-1001. doi:10.1162/REST_a_00324

Bothwell, L. E., Greene, J. A., Podolsky, S. H., & Jones, D. S. (2016). Assessing the Gold Standard — Lessons from the History of RCTs. *New England Journal of Medicine, 374*(22), 2175-2181. doi:10.1056/NEJMms1604593

Brady, O. J., Slater, H. C., Pemberton-Ross, P., Wenger, E., Maude, R. J., Ghani, A. C., . . . Okell, L. C. (2017). Role of mass drug administration in elimination of Plasmodium falciparum malaria: a consensus modelling study. *Lancet Glob Health*. doi:10.1016/S2214-109X(17)30220-6

Cassy, A., Saifodine, A., Candrinho, B., Martins, M. d. R., da Cunha, S., Pereira, F. M., & Samo Gudo, E. (2019). Care-seeking behaviour and treatment practices for malaria in children under 5 years in Mozambique: a secondary analysis of 2011 DHS and 2015 IMASIDA datasets. *Malar J, 18*(1), 115. doi:10.1186/s12936-019-2751-9

Cavallo, E., Galiani, S., Noy, I., & Pantano, J. (2013). Catastrophic Natural Disasters and Economic Growth. *The Review of Economics and Statistics, 95*(5), 1549-1561. doi:10.1162/REST_a_00413

DeAngelo, G., & Hansen, B. (2014). Life and Death in the Fast Lane: Police Enforcement and Traffic Fatalities. *American Economic Journal: Economic Policy, 6*(2), 231-257. doi:10.1257/pol.6.2.231

Derde, L. P. G., Cooper, B. S., Goossens, H., Malhotra-Kumar, S., Willems, R. J. L., Gniadkowski, M., . . . Bonten, M. J. M. (2014). Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis, 14*(1), 31-39. doi:10.1016/s1473-3099(13)70295-0

Eisele, T. P., Bennett, A., Silumbe, K., Finn, T. P., Chalwe, V., Kamuliwo, M., . . . Miller, J. M. (2016). Short-term Impact of Mass Drug Administration With Dihydroartemisinin Plus Piperaquine on Malaria in Southern Province Zambia: A Cluster-Randomized Controlled Trial. *J Infect Dis, 214*(12), 1831-1839. doi:10.1093/infdis/jiw416

Fraser, M., Miller, J. M., Silumbe, K., Hainsworth, M., Mudenda, M., Hamainza, B., . . . Guinovart, C. (2020). Evaluating the impact of programmatic mass drug administration for malaria in Zambia using routine incidence data. *J Infect Dis*. doi:10.1093/infdis/jiaa434

Galatas, B., Nhacolo, A., Marti, H., Munguambe, H., Jamise, E., Guinovart, C., . . . Sacoor, C. (2020). Demographic and health community-based surveys to inform a malaria elimination project in Magude district, southern Mozambique. *BMJ Open, 10*(5), e033985. doi:10.1136/bmjopen-2019-033985

Galatas, B., Saute, F., Marti-Soler, H., Guinovart, C., Nhamussua, L., Simone, W., . . . Aide, P. (2020). A multiphase program for malaria elimination in southern Mozambique (the Magude project): A before-after study. *PLoS Med, 17*(8), e1003227. doi:10.1371/journal.pmed.1003227

Hanigan, I., Hall, G., & Dear, K. B. G. (2006). A comparison of methods for calculating population exposure estimates of daily weather for health research. *International Journal of Health Geographics, 5*(1), 38. doi:10.1186/1476-072X-5-38

Heckman, J. J., & Hotz, V. J. (1989). Choosing Among Alternative Nonexperimental Methods for Estimating the Impact of Social Programs: The Case of Manpower Training. *Journal of the American Statistical Association, 84*(408), 862-874. doi:10.2307/2290059

Hsiang, M. S., Hwang, J., Tao, A. R., Liu, Y., Bennett, A., Shanks, G. D., . . . Gao, Q. (2013). Mass drug administration for the control and elimination of Plasmodium vivax malaria: an ecological study from Jiangsu province, China. *Malar J, 12*, 383. doi:10.1186/1475-2875-12-383

Hsiang, M. S., Ntuku, H., Roberts, K. W., Dufour, M.-S. K., Whittemore, B., Tambo, M., . . . Gosling, R. (2020). Effectiveness of reactive focal mass drug administration and reactive focal vector control to reduce malaria transmission in the low malaria-endemic setting of Namibia: a cluster-randomised controlled, open-label, two-by-two factorial design trial. *The Lancet, 395*(10233), 1361-1373. doi:10.1016/S0140-6736(20)30470-0

Kreif, N., Grieve, R., Hangartner, D., Turner, A. J., Nikolova, S., & Sutton, M. (2016). Examination of the Synthetic Control Method for Evaluating Health Policies with Multiple Treated Units. *Health Economics, 25*(12), 1514-1528. doi:https://doi.org/10.1002/hec.3258

Landier, J., Kajeechiwa, L., Thwin, M. M., Parker, D. M., Chaumeau, V., Wiladphaingern, J., . . . Nosten, F. H. (2017). Safety and effectiveness of mass drug administration to accelerate elimination of artemisinin-resistant falciparum malaria: A pilot trial in four villages of Eastern Myanmar. *Wellcome Open Res, 2*, 81. doi:10.12688/wellcomeopenres.12240.1

Lau, W. C. Y., Murray, M., El-Turki, A., Saxena, S., Ladhani, S., Long, P., . . . Hsia, Y. (2015). Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. *Vaccine, 33*(39), 5072-5079. doi:https://doi.org/10.1016/j.vaccine.2015.08.022

Lehmann, E. L. (1997). Testing statistical hypotheses: The story of a book. *Statistical Science, 12*(1), 48-52.

Lépine, A., Lagarde, M., & Le Nestour, A. (2018). How effective and fair is user fee removal? Evidence from Zambia using a pooled synthetic control. *Health Economics, 27*(3), 493-508. doi:https://doi.org/10.1002/hec.3589

Ma, R., Cecil, E., Bottle, A., French, R., & Saxena, S. (2020). Impact of a pay-for-performance scheme for long-acting reversible contraceptive (LARC) advice on contraceptive uptake and abortion in British primary care: An interrupted time series study. *PLOS Medicine, 17*(9), e1003333. doi:10.1371/journal.pmed.1003333

MISAU. (2016). *Relatório anual 2015. Programa Nacional de Controlo da Malária 2015.* . Retrieved from

Morris, U., Msellem, M. I., Mkali, H., Islam, A., Aydin-Schmidt, B., Jovel, I., . . . Björkman, A. (2018). A cluster randomised controlled trial of two rounds of mass drug administration in Zanzibar, a malaria pre-elimination setting—high coverage and safety, but no significant impact on transmission. *BMC Medicine, 16*(1), 215. doi:10.1186/s12916-018-1202-8

Naing, C., Racloz, V., Whittaker, M. A., Aung, K., Reid, S. A., Mak, J. W., & Tanner, M. (2013). Efficacy and safety of dihydroartemisinin-piperaquine for treatment of Plasmodium vivax malaria in endemic countries: meta-analysis of randomized controlled studies. *PloS one, 8*(12), e78819-e78819. doi:10.1371/journal.pone.0078819

Osrin, D., Azad, K., Fernandez, A., Manandhar, D. S., Mwansambo, C. W., Tripathy, P., & Costello, A. M. (2009). Ethical challenges in cluster randomized controlled trials: experiences from public health interventions in Africa and Asia. *Bull World Health Organ, 87*(10), 772-779. doi:10.2471/blt.08.051060

Radó, M. K., van Lenthe, F. J., Sheikh, A., & Been, J. V. (2020). Investigating the effects of comprehensive smoke-free legislation on neonatal and infant mortality in Thailand using the synthetic control method. *EClinicalMedicine, 27*. doi:10.1016/j.eclinm.2020.100560

von Seidlein, L., Peto, T. J., Landier, J., Nguyen, T. N., Tripura, R., Phommasone, K., . . . White, N. J. (2019). The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial. *PLoS Med, 16*(2), e1002745. doi:10.1371/journal.pmed.1002745

WHO Malaria Policy Advisory Committee and Secretariat. (2016). Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015). *Malar J, 15*(1), 117. doi:10.1186/s12936-016-1169-x

Wigley, S., Dieleman, J. L., Templin, T., Mumford, J. E., & Bollyky, T. J. (2020). Autocratisation and universal health coverage: synthetic control study. *BMJ (Clinical research ed.), 371*, m4040-m4040. doi:10.1136/bmj.m4040

World Health Organisation. (2014). Planning meeting for operational research on malaria elimination.Meeting report.

World Health Organisation. (2015a). Global technical strategy for malaria 2016–2030.

World Health Organisation. (2015b). *Mass drug administration, mass screening and treatment and focal screening and treatment for malaria, Evidence Review Group meeting report*. Retrieved from

World Health Organization. (2020). *World Malaria Report 2020*. Retrieved from Geneva, Switzerland: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020/

Zacarias, O. P., & Andersson, M. (2011). Spatial and temporal patterns of malaria incidence in Mozambique. *Malar J, 10*(1), 189. doi:10.1186/1475-2875-10-189

Supplementary Material for "The short-term impact of a malaria elimination initiative in Southern Mozambique: Application of the synthetic control method to routine surveillance data"

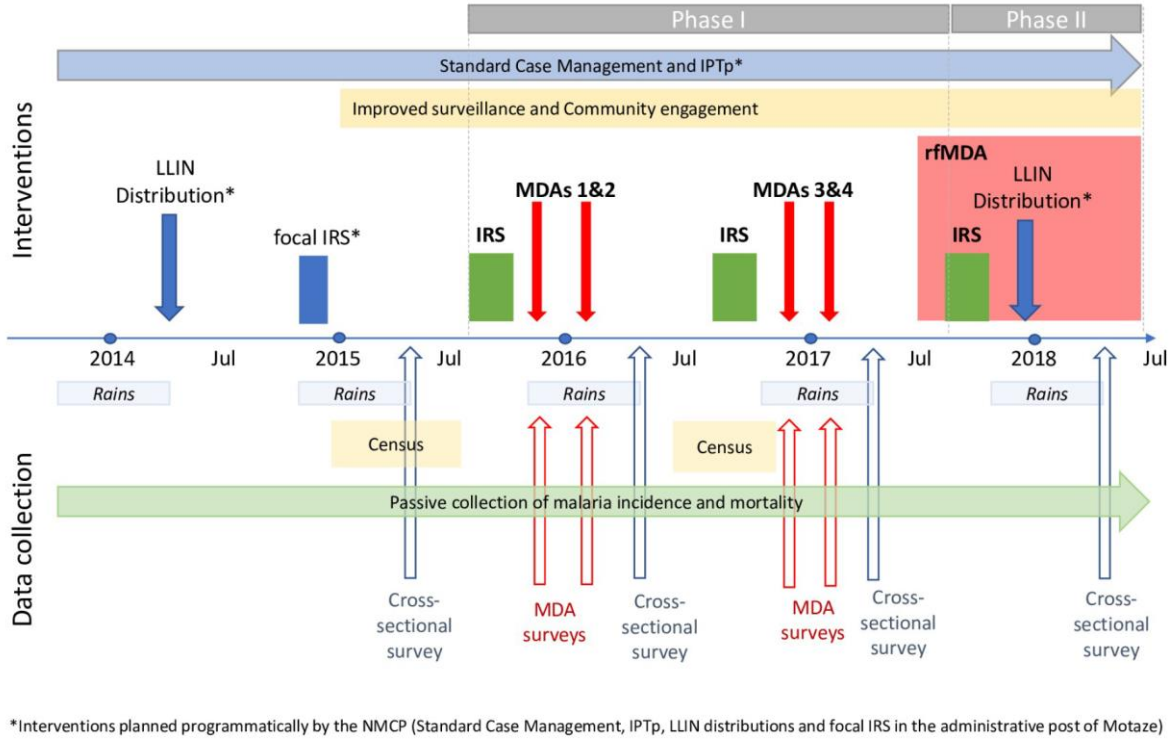


Figure S 1: Intervention package timelines. Source (Galatas, Saute, et al., 2020 (Galatas, Saute, et al., 2020))

Notes: IPTp, intermittent preventive treatment for pregnant women; IRS, indoor residual spraying; LLIN, long-lasting insecticidal net; MDA, mass drug administration; NMCP, National Malaria Control Program; rfMDA, reactive focal mass drug administration

Figure S2: Map of Mozambique showing treatment and control districts

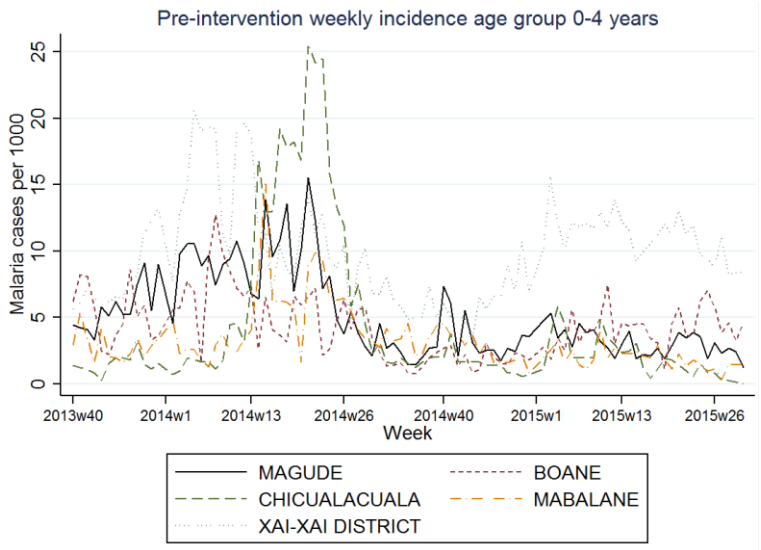


Figure S 3:Pre-intervention malaria incidence 0-4 years in control districts selected for synthetic Magude

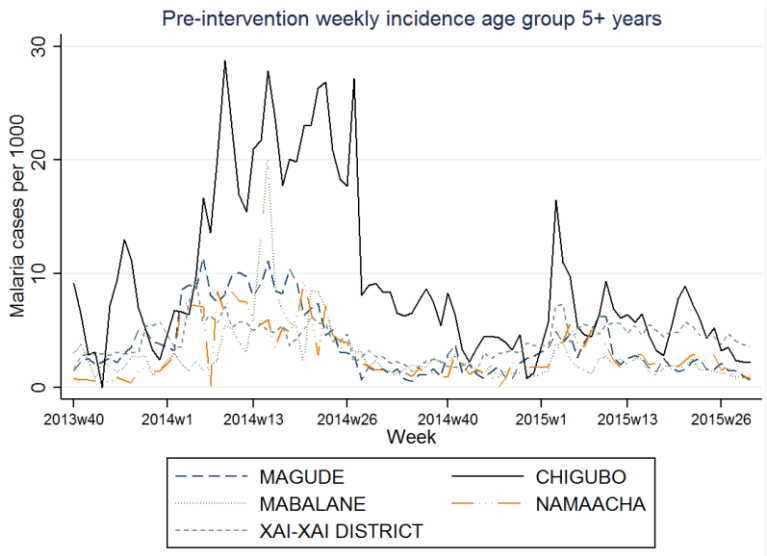


Figure S 4: Pre-intervention malaria incidence 5+ years in control districts selected for synthetic Magude

Figure S 5: Map of Mozambique with control districts contributing to Synthetic Magude

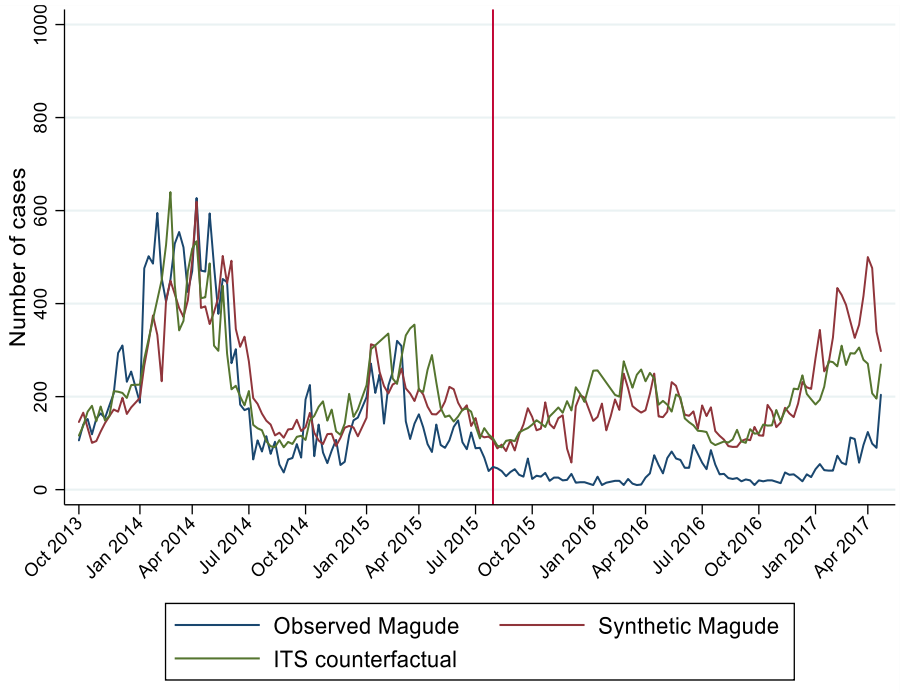


Figure S 6: SCM and ITS estimates of counterfactual cases and observed cases in Magude.

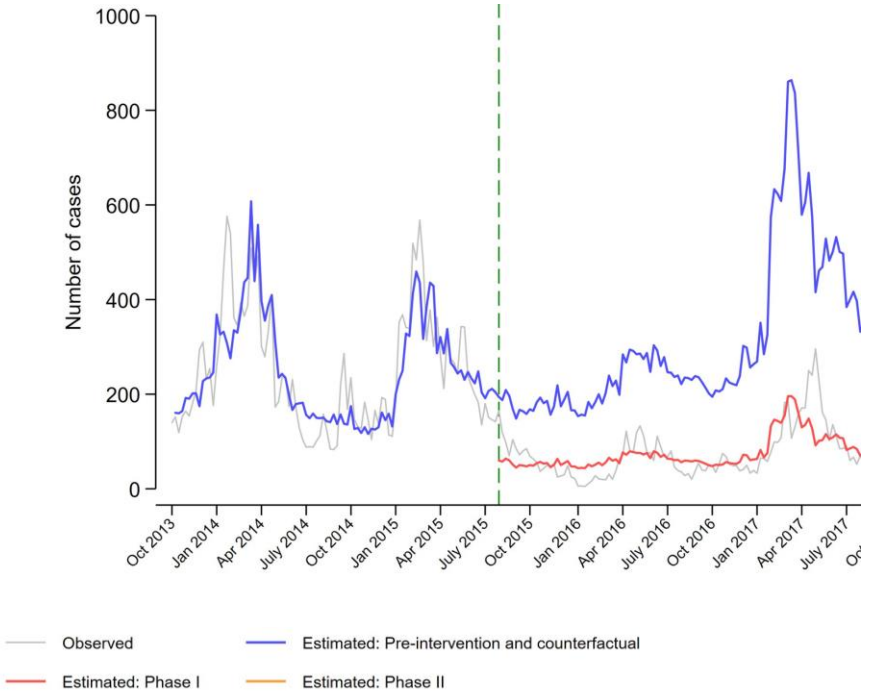


Figure S 7: ITS estimates of counterfactual cases (and observed cases) in Magude (Source Galatas et al 2020)

Table S1:Synthetic Weights for Magude

	Age 0-4 years	**Age 5 + years**
Bilene	0	0
Boane	0.22	0
Chibuto	0	0
Chicualacuala	0.19	0
Chigubo	0.01	0.1
Chokwe	0	0
Guija	0	0
Mabalane	0.27	0.26
Manjacaze	0	0
Marracuene	0	0
Massagena	0	0
Massingir	0	0
Matola	0	0
Matutuine	0.07	0
Moamba	0	0
Namaacha	0	0.35
Xai-Xai	0.24	0.29

Galatas, B., Saute, F., Marti-Soler, H., Guinovart, C., Nhamussua, L., Simone, W., . . . Aide, P. (2020). A multiphase program for malaria elimination in southern Mozambique (the Magude project): A before-after study. *PLoS Med, 17*(8), e1003227. doi:10.1371/journal.pmed.1003227