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Abstract. In addition to being effective, fast-acting, and well tolerated, artemisinin-based combination therapies (ACTs) are able to kill certain transmission stages of the malaria parasite. However, the population-level impacts of ACTs on reducing malaria transmission have been difficult to assess. In this study on the history of malaria control in Vietnam, we assemble annual reporting on malaria case counts, coverage with insecticide-treated nets (ITN) and indoor residual spraying (IRS), and drug purchases by provincial malaria control programs from 1991 to 2010 in Vietnam’s 20 southern provinces. We observe a significant negative association between artemisinin use and malaria incidence, with a 10% absolute increase in the purchase proportion of artemisinin-containing regimens being associated with a 29.1% (95% confidence interval: 14.8–41.0%) reduction in slide-confirmed malaria incidence, after accounting for changes in urbanization, ITN/IRS coverage, and two indicators of health system capacity. One budget-related indicator of health system capacity was found to have a smaller association with malaria incidence, and no other significant factors were found. Our findings suggest that including an artemisinin component in malaria drug regimens was strongly associated with reduced malaria incidence in southern Vietnam, whereas changes in urbanization and coverage with ITN or IRS were not.

INTRODUCTION

The most recent World Malaria Report from the World Health Organization (WHO) shows that between the years 2002 and 2012 malaria cases and deaths decreased by 10.4% and 28.4%, respectively, and widespread adoption of artemisinin-based combination therapies (ACTs) as first-line therapy for malaria is likely a significant contributor to these gains. 1–3 In comparison to other antimalarial drugs, artemisinin is associated with reduced treatment failure rates, 4 accelerated parasite clearance, 5 and reduced mortality. 6 Consequently, ACTs are the recommended treatment of both uncomplicated and severe malaria. 7 In addition to improving patient outcomes, artemisinin is also active against certain stages of gametocytes, the parasite sexual stage whose formless meshes are transformable to mosquitoes. 8 ACTs are therefore considered an important part of a concerted effort in many countries to achieve elimination through routine case management or mass drug administration strategies. 9

The relative contribution of ACTs to reducing malaria transmission is difficult to assess, particularly in the context of changing population coverage with insecticide-treated nets (ITN) and indoor residual spraying (IRS). Since approval by the WHO in the early 2000s, ACT scale-up has frequently occurred in parallel with other transmission-reducing interventions, making it difficult to isolate the impact of each intervention independently. 10–14 Although there have been few efforts to record changes in malaria incidence following ACT scale-up, select studies suggest that case management with ACT could play a critical role in reducing transmission of the parasite. A 1996 study of rapid replacement of mefloquine with ACTs in a refugee population in western Thailand reported a 47% reduction in Plasmodium falciparum infections over the 12-month follow-up. 15 This study design was expanded to include local populations in the same region and documented a 34% reduction in P. falciparum cases over 6 years following investment in early case detection and treatment with artemisinin-based therapies. 16 In Zanzibar, ACT introduction in 2003 was followed by no change in malaria admissions in 2004 and then a 68% reduction in 2005. 17 Although the reported associations between case management with ACTs and malaria incidence vary in magnitude and reference treatment regimen, these studies suggest an appreciable population-level effect that needs to be further explored in pre-elimination settings.

In contrast to many malaria-endemic countries, Vietnam’s centralized malaria control program enabled and documented a rapid shift from conventional drug regimens to those based on artemisinin. Vietnam was among the first countries to recommend first-line artemisinin use at a national level and annual records show a dramatic reduction in the burden of malaria during the years that artemisinin was introduced. 17,18 Province-level data on artemisinin scale-up and changes in malaria case numbers in Vietnam present a unique opportunity to examine the association between case management with ACT and malaria transmission. Here, we examine data on malaria cases, prevention measures, antimalarial treatment, and improvements in health system capacity for 20 southern Vietnamese provinces over 20 years to estimate the impact of ACTs on malaria incidence between 1991 and 2010. In addition to annual data on all antimalarial drug purchase requests, provincial malaria control programs report data on the quantity of pyrethroid-group insecticides used for twice-yearly indoor residual spraying and bed net impregnation, approximate population coverage of ITN and IRS, and several general measures of the province’s capacity to respond to high levels of malaria incidence. We show that artemisinin use is more strongly associated with a reduction in malaria incidence than other interventions including ITN and IRS.
MATERIALS AND METHODS

Data. The Institute for Malaria, Parasitology, and Entomology (IMPE) of southern Vietnam provided the data used in this analysis. Study provinces included An Giang, Bac Lieu, Ca Mau, Ben Tre, Binh Duong, Binh Phuoc, Ba Ria-Vung Tau, Can Tho, Hau Giang, Soc Trang, Dong Nai, Cong Thanh, Kien Giang, Lam Dong, Long An, Tay Ninh, Tien Giang, Ho Chi Minh City, Tra Vinh, and Vinh Long. As a result of shifting administrative borders during the reporting period, certain study provinces were combined into groups: Binh Duong/Binh Phuoc; Bac Lieu/Ca Mau; and Can Tho/Hau Giang/Soc Trang. Malaria is a notifiable disease in Vietnam, and IMPE uses a standardized hierarchical reporting system to collect data on interventions and cases. These reports include counts of suspected malaria cases, slide-positive smears, smears positive for *P. falciparum* parasites, smears positive for *Plasmodium vivax* parasites, the quantities of each drug type ordered by provincial malaria control programs, annual budgets, annual staff trainings, and the proportion of the population protected by ITNs or IRS. Records were translated into English and entered into an electronic database in collaboration with IMPE and the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam. Annual reports from 1991 to 2010 were analyzed for the southern provinces according to the 2010 provincial boundaries (Figure 1A). The data set is structured as a yearly panel series for 20 provinces in southern Vietnam over 20 years.

The primary covariate of interest is the proportion of antimalarial drug regimens ordered by a given province each year that contain artemisinin. This proportion measure serves as a proxy for the probability that the treatment received by a malaria patient included artemisinin. We hypothesize that replacing non-artemisinin-based therapies with ACTs may reduce malaria transmission. Data on antimalarial treatment requests by provincial governments were available in the form of number of tablets for oral regimens and number of tubes for injectable regimens for the years 1992, 1994, 1995, 1997–2007, 2009, and 2010. Purchase requests are submitted to the national government in Hanoi by each province for anticipated treatment needs each year. The artemisinin-based antimalarial treatments documented in the reports include: injectable artesunate (60 mg tube); artemisinin (250 mg tablet); artesunate (50 mg tablet); dihydroartemisinin-piperaquine (40 mg dihydroartemisinin, 320 mg piperaquine tablet); and CV8 (32 mg dihydroartemisinin, 320 mg piperaquine, 90 mg trimethoprim, 5 mg primaquine tablet). The non-artemisinin based antimalarial treatments include: quinine-sulfate (250 mg tablet); quinine hydrochloride (500 mg tube); mefloquine (250 mg tablet); sulfadoxine-pyrimethamine (500 mg sulfadoxine,

![Figure 1](image_url)  
**Figure 1.** Vietnamese provinces included in the study are hatched (Panel A). Exponential decrease in annual incidence of suspected malaria cases per 1,000 persons is observed in the changes from 1992 (Panel B) to 2000 (Panel C) and 2010 (Panel D). Note the use of a non-linear scale to accommodate the large dynamic range in incidence.
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Anopheles mosquitoes, the malaria vector. Yearly measurements from 1995 to 2007 were fit with a linear regression to impute missing values for this variable for the years 1991–1994 and 2008–2010 (Supplemental Figure 1).

Statistical analysis. Temporal trends of the primary covariates were evaluated for each province using non-parametric Spearman rank correlation tests to maximize power to detect changes over the study period and avoid misspecification. A simple linear regression of each covariate against time was fit to estimate the average annual change assuming a linear association. Significance thresholds for all tests were set to a 0.05 probability of type I error.

Annual malaria incidence was modeled with a Poisson regression model with the standard log link function. Generalized estimating equations (GEE) were used to measure population-averaged associations between covariates and malaria incidence after accounting for within-province correlation as a result of repeated observations over time. The working correlation structure between observations grouped in provinces was modeled as independent and standard errors were based on “sandwich” estimators robust to misclassification of within-group correlation structure and over-dispersion. To fit the regressions, the geepack package in the statistical computing environment R was used.

Predictors for four malaria incidence outcomes included 1) proportion of treatment regimens purchased that contained artemisinin, 2) the proportion of the population protected by either ITN or IRS, 3) the proportion of the population living in urban settings, 4) the number of staff trainings by provincial malaria control programs per 100 people, and 5) the discretionary malaria program budget per capita. Province population was used as an offset term to standardize annual malaria case counts and allow for the estimation of incidence rates. The impacts of intervention efforts on malaria transmission are assumed to occur within the year so associations between these predictors and the incidence response variables were measured in the same year.

RESULTS

Malaria reduction in southern Vietnam. The total number of clinically diagnosed malaria cases in southern Vietnam decreased from 364,302 in 1992 to 73,146 cases in 2000 and 6,923 in 2010 (Figure 2). Severe cases declined even more steeply from 5,803 in 1992 to 239 in 2000 and 94 in 2010. A similar improvement in clinical outcome can be observed by the decrease in malaria deaths from 516 deaths in 1992 to 28 deaths in 2000 and 13 deaths in 2010. Due in part to increased access to ACTs, the case fatality ratio decreased by 85.9% (95% confidence interval [CI]: 75.6–91.8%) over the study period. The ratio of \( P. falciparum \) to \( P. vivax \) cases shifted from an average of 2:1 in the 1990s to 3:1 in the 2000s, although these changes were not uniform across the study provinces. See Supplemental Figure 2 for province-specific trends for the ratio of \( P. falciparum \) to \( P. vivax \) cases.

Temporal changes in antimalarial interventions. The percentage of purchased treatment regimens that contained artemisinin increased from 7.8% (province-specific range: 5.5–18.9%) in 1992 to 77.8% (province-specific range: 66.1–98.0%) in 2010 (Figure 2). Non-parametric Spearman rank correlation tests revealed this relationship to be strongly positive (\( r_s > 0.732 \)) and highly significant (\( P < 0.02 \)) in
This analysis examines the association between adoption of artemisinin-based therapies and malaria incidence using a

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Percent change in malaria incidence associated with a 10% increase in the listed covariate; with 95% confidence intervals in parentheses</th>
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<tbody>
<tr>
<td>Proportion of regimens containing artemisinin</td>
<td>Suspected malaria</td>
</tr>
<tr>
<td>−32.3*** (−40.6, −22.8)</td>
<td>−28.1*** (−39.5, −14.6)</td>
</tr>
<tr>
<td>Proportion of population covered by ITN or IRS</td>
<td>−12.5 (−29.0, +7.8)</td>
</tr>
<tr>
<td>Proportion of population living in urban settings</td>
<td>−5.1 (−22.7, +16.5)</td>
</tr>
</tbody>
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***P < 0.001.

ITN = insecticide-treated net; IRS = indoor residual spraying.
unique data set spanning two decades of malaria control
where artemisinin scale-up was programmatically independent of changes to other interventions including ITN and IRS. As a result of centralized intervention implementation and recordkeeping, these data present an opportunity to study the impact of interventions that are typically distributed by several regional programs in a less coordinated fashion. These data record a nearly 10-fold increase in proportion of drug purchases containing artemisinin and a remarkable 98% decrease in annual malaria incidence over this 20-year period in southern Vietnam. This expansive range allowed us to observe a significant, negative association between case management with artemisinin-based therapy and malaria incidence while controlling for other primary malaria interventions. Of the interventions tested, this association was found to be robust to different measures of malaria incidence. Although urbanization and increased ITN/IRS use are known to reduce the burden of malaria, they are not found to be drivers of the dramatic changes in incidence that were observed in southern Vietnam during the 1990s and early 2000s, one of the reasons being that changes in these two measures were small compared with changes in artemisinin use; in 2010, 63% of the population of southern Vietnam were still living in rural areas. Our results support the hypothesis that case management with artemisinin-based therapies should have a substantial impact on transmission in addition to improving patient outcomes.

As Vietnam invests in the goal of national malaria elimination, the choice of end-game tools and strategies becomes increasingly urgent.9 Our results measure the association between key interventions and incidence in a region leading the country toward elimination. Although China to the north has set a national malaria elimination goal by 2020, Cambodia and southern Laos, which border southern Vietnam are further from elimination.13 Border provinces of Vietnam must therefore maintain intervention coverage to avoid a resurgence of incidence as experienced in the 1980s following deterioration of regional health systems.17 Of importance, the maintenance of key interventions including ITN and IRS coverage and replacement of non-artemisinin regimens with ACTs was sufficient to prevent resurgence during this two-decade study period. After controlling for these key interventions, provincial discretionary malaria budget was also found to have a significantly protective association with incidence of clinically diagnosed malaria and suggests an independent protective role of health sector capacity building.

Future analyses may consider applying these methods to provinces throughout Vietnam to increase generalizability and power to detect possible effects of other drivers of malaria case reductions. In particular, the effect of improved case management on malaria incidence is expected to be largest in settings like our study where transmission intensity is low, the proportion of malaria infections that develop symptoms is large, and treatment access is high.25

### Table 2

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<tr>
<th>Percent change in malaria incidence associated with a 10% increase in the listed covariate; with 95% confidence intervals in parentheses</th>
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<td><strong>Suspected malaria</strong></td>
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<td>Proportion of regimens containing artemisinin</td>
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<tr>
<td>Proportion of population living in urban settings</td>
</tr>
<tr>
<td>Discretionary budget per capita</td>
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<tr>
<td>Number of staff trained per capita</td>
</tr>
</tbody>
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* $P < 0.05$  
** $P < 0.005$  
*** $P < 0.001$

ITN = insecticide-treated net; IRS = indoor residual spraying.
The primary covariate of interest, the proportion of purchased treatment regimens containing artemisinin, was used as a proxy for the proportion of patients who would be treated with an artemisinin-based drug. However, drug regimens were sometimes distributed for purposes other than clinical treatment, including stand-by treatment and prophylaxis of high-risk populations during outbreaks. In the first years following artemisinin introduction in Vietnam in 1989 and 1990, the usage of artemisinins may have been higher than suggested by the purchase proportions in these data (Thuan PD, Thanh NV, Hien TT, personal communication). High malaria incidence during this decade necessitated large-volume purchases of chloroquine and primaquine for *P. vivax* treatment, but low rates of blood-slide confirmation would lead the vast majority of clinical cases to be treated with the most efficacious treatment available at that time, namely, artemisinin.

An important covariate that was omitted from the models was lagged malaria incidence, as it would be expected that incidence in the year \( t - 1 \) would affect incidence in the year \( t \). We omitted this variable for two reasons. First, it would be reasonable to assume that malaria case numbers at the end of a calendar year would not have a strong effect on malaria case numbers recorded in the middle of the following year in an area with strong seasonality, especially after a 4–5 month period of low or zero malaria transmission. Second, an attempt to decompose the correlation between lagged incidence and current incidence into the direct effect and the indirect effect through the intermediate variable of drug purchase patterns may require more temporally resolved data. A dynamic malaria transmission model should be considered to test for these potentially causal relationships. Future analyses of this kind should aim to assemble case data sets with aggregation at the level of week or month as this will allow for a more detailed analysis of potentially lagged effects. An additional benefit of using more temporally resolved data will be improved data quality for the ITN/IRS measures and an understanding of whether ITN/IRS campaigns are followed by long-term or short-term decreased incidence in Vietnam.

As discussed previously, artemisinin is believed to reduce population-level malaria incidence through rapid parasite clearance, low treatment failure rate, and some pharmacological activity against the transmission stages of the parasite, gametocytes. Gametocidal activity of artemisinin has been shown to be more powerful in clearing *P. falciparum* parasites than *P. vivax* parasites. Additionally, *P. vivax* infections tend to produce gametocytes before patients present symptoms, whereas *P. falciparum* infections tend to yield both symptoms and gametocytes around the same time. Therefore, case management with artemisinin is expected to have a larger impact on *P. falciparum* transmission than *P. vivax* transmission because treatment may more effectively clear infection before patients are infectious. Previous studies have considered slide-confirmed *P. vivax* infections as a quasi control in expectation that *P. falciparum* transmission would be more sensitive to increasing use of artemisinin in case management. However, we found that the associations between artemisinin use and incidence of slide-confirmed infections with either parasite species were not significantly different. This null finding could result from a lack of statistical power to detect a potentially small difference in artemisinin potency against *P. falciparum* compared with *P. vivax*.

These results support the hypothesis that artemisinin scale-up may be a powerful strategy for not only patient care but also transmission reduction. However, evidence of slower parasite clearance rates in the Greater Mekong Subregion may threaten the individual and population-level potency of artemisinin-based therapies. It is crucial to understand the true population-level impact of artemisinin drugs, properly manage their distribution, and prepare strategies to prevent and contain resistance. Results from Thailand, Zanzibar, and now Vietnam support the hypothesis that case management with artemisinin-based combination therapies is likely to be strongly associated with reduced malaria transmission.

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Note: Supplemental tables, figures and data are available at www.ajtmh.org.

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