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FACTORS INFLUENCING THE EFFECTIVENESS OF MALARIA CONTROL IN BIOKO ISLAND, EQUATORIAL GUINEA

IMMO KLEINSCHMIDT[*],
London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom, Telephone: +44 20 7612 7872, Fax: +44 20 7636 8739, Immo.Kleinschmidt@lshtm.ac.uk.

MIGUEL TORREZ,
Medical Care Development International, 8401 Colesville Rd., Suite 425, Silver Spring, MD 20910, Telephone: +1 (301) 562-1920, Fax: +1 (301) 562-1921, mitorrez@mixmail.com.

CHRIS SCHWABE,
Medical Care Development International, 8401 Colesville Rd., Suite 425, Silver Spring, MD 20910, Telephone: +1 (301) 562-1920, Fax: +1 (301) 562-1921, chris@schwabe.us.

LUIS BENAVENTE,
Medical Care Development International, 8401 Colesville Rd., Suite 425, Silver Spring, MD 20910, Telephone: +1 (301) 562-1920, Fax: +1 (301) 562-1921, lbenavente@mcd.org.

ISHEN SEOCHARAN,
Medical Research Council, 491 Ridge Rd., Over-port, Durban 4091, South Africa, Telephone: +27 31 203 4806, Fax: +27 31 203 4704, iseocharan@mrc.ac.za.

DAVID JITUBOH,
Medical Care Development International, 8401 Colesville Rd., Suite 425, Silver Spring, MD 20910, Telephone: +1 (301) 562-1920, Fax: +1 (301) 562-1921, teddyblaze@gmail.com.

GLORIA NSENG, and
Ministry of Health and Social Welfare, Malabo, Bioko, Equatorial Guinea, glorianseng@yahoo.es.

BRIAN SHARP
Medical Research Council, 491 Ridge Rd., Over-port, Durban 4091, South Africa, Telephone: +27 31 203 4806, Fax: +27 31 203 4704, sharpb@mrc.ac.za.

Abstract

The Bioko Island Malaria Control Project (BIMCP) has carried out intensive interventions since early 2004 to reduce malaria transmission through indoor residual spraying (IRS) and case management. Annual parasite prevalence surveys have been carried out to monitor the effectiveness of the program. Significant overall reductions in prevalence of infection have been observed, with 42% fewer infections occurring in 2006 compared with baseline. Nevertheless, there is evidence of considerable heterogeneity in impact of the intervention. Prevalence of infection was significantly associated with spray status of the child's house, spray coverage with effective insecticide of the neighborhood of the house, bed net use, and time elapsed since last spray. Careful scheduling of spray coverage is therefore essential to maximize the effectiveness of IRS and to ensure consistent reductions in parasite prevalence. This can only be achieved if

[*]Address correspondence: London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom. Immo.Kleinschmidt@lshtm.ac.uk.

comprehensive monitoring systems are in place for both the management and evaluation of the intervention.

INTRODUCTION

The effectiveness of large-scale malaria control interventions through vector control using indoor residual spraying (IRS) and case management based on definitive diagnosis and treatment with artemisinin combination therapy (ACT) has recently been documented.[1–4] Because additional similar interventions are currently being funded, it is important to use data from existing programs to identify factors that optimize IRS and that lead to rapid and sustained reductions in prevalence of infection.

The island of Bioko is situated in the Gulf of Guinea, about 40 miles from the coast of Cameroon. With a population of $\approx$ 250 000, the island has undergone radical economic change after the discovery of offshore oil in the 1990s. The Bioko Island Malaria Control Project (BIMCP) initiated an integrated malaria control intervention on Bioko from February 2004, with funding from a private-sector consortium led by Marathon Oil Company (Houston, TX) in partnership with the Government of Equatorial Guinea (EG). The measures consist of IRS, case management including definitive diagnosis and effective treatment with ACT, and intermittent preventive treatment of pregnant women (IPT).

The progress and effectiveness of the project are being monitored by entomological, clinical, and population-based indicators. Key among these is prevalence of infection with malarial parasites in children 2 to < 15 years of age. Annual parasitemia household surveys were conducted in March 2004, 2005, and 2006, respectively, at initially 16 and then at 18 sentinel sites. The number of children tested in each of the three surveys was 2440, 3086, and 5332, respectively.

Details of the intervention and the results of the first two annual parasite-prevalence surveys have previously been reported.[2] In this paper, we report on the change in prevalence observed during the third annual prevalence survey and its relationship to compliance with the intervention protocol. We believe that important lessons can be learned from this experience for IRS-based malaria control programs elsewhere.

METHODS

Interventions

All houses were sprayed once with the synthetic pyrethroid Deltamethrin (Bayer, Leverkusen, Germany) in 2004. Entomological monitoring carried out by the BIMCP led to the discovery of pyrethroid knock-down resistance (*kdr*)[5] in *Anopheles gambiae* populations after the first spray round, which was subsequently confirmed by Reimer and others.[6] From January 2005, the carbamate insecticide Ficam (Bayer) was therefore sprayed at 6-monthly intervals. The remaining stock of Deltamethrin was used up to spray a total of $\approx$ 17,000 structures in the Malabo area during the spray round conducted in the second half of 2005. By February 2006, a total of three spray rounds had been completed. Progress and efficiency of spray operations were continually monitored with the help of a computerized spray-management system developed for this purpose.[7] In total, $\approx$ 100,000 structures (rooms) were sprayed during each spray round.

Case management consisted of the introduction of oral artesunate in combination with sulfadoxine–pyrimethamine as the first-line treatment based on routine definitive diagnosis, the training of doctors and nurses in case management, and IPT. Adherence to all aspects of

the intervention was promoted through a concerted information, education, and communications (IEC) strategy, using mass media (radio, television, and printed materials) as well as community-based interpersonal communications techniques.

Prevalence surveys

For the 2004 and 2005 surveys, houses in rural sites were selected by systematic sampling from hand-drawn maps, and those in urban sites were selected by random sampling of coordinates using satellite images. For the 2006 survey, all households at each sentinel site were enumerated and their coordinates were taken using Dell Axim X50 (Dell, Round Rock, TX) personal digital assistants (PDAs) equipped with CompactFlash (NextWarehouse.com, Tustin, CA) global positioning system (GPS) devices. From the enumerated households that had at least one child of age 2 to < 15 years, a random selection was made. Written informed consent was sought from the responsible person at each selected household. Consenting householders were asked about attitudes to IRS, whether their house had been sprayed in the past year, and about illness history and health-seeking behavior. All children at participating households were tested for *Plasmodium falciparum* using ICT malaria rapid tests (R&R, Cape Town, South Africa). Children who tested positive for parasitemia were offered treatment at a local field-clinic set up for this purpose.

In the first two surveys, data from questionnaires were checked, entered, and verified using conventional data-entry methods. For the 2006 survey, PDA versions of the questionnaires were programmed using Visual CE 9 (Syware Inc., Cambridge, MA) so that data entry and error checking could be carried out during survey interviews. The survey program was piloted and further adapted during training of fieldworkers. Data files from the PDAs were uploaded daily into a Microsoft Access database and further checked for errors by running cross-tabulations.

Data derivation and statistical analysis

The following data were obtained directly from the household survey: status of infection with *P. falciparum* of each child, whether the child slept under a bednet the previous night, and whether the house had been sprayed in the last spray round.

Site-specific spray coverage was calculated from the survey responses as the proportion of householders who confirmed that their house was sprayed in 2005, as this was considered the least biased indicator of spray coverage. Based on the assumption that the presence of *kdr* in *A. gambiae* rendered pyrethroid insecticide only partially effective, effective spray coverage was calculated for each site, by multiplying the site-specific spray coverage by the proportion of structures that were sprayed with carbamate for that site in the last spray round as reported in the spray-management system.

Time elapsed since the last time the site was sprayed was calculated as follows: using the spray-management system, the median spray date was computed for each site for spray rounds 3 and 4, respectively. For sites that had not been sprayed in round 4 by February 15, 2006, the number of days elapsed between the median spray date of spray round 3 and February 15 was calculated for the site; for sites that had already been sprayed in round 4, the time interval between the median round 4 spray date for the site and February 15 was calculated. It was assumed that spraying after February 15 would have had no impact on prevalence of infection as measured in the survey, which started in late February.

Statistical analysis took account of the survey design using the Rao and Scott correction[8] as implemented in STATA,[9] thereby correcting standard errors for multistage sampling.[10] All analysis calculating results for all sites, or a subset of sites, was carried out assuming the

sentinel site to be the primary sampling unit (PSU); all calculations aimed at producing site-specific results assumed the household to be the PSU.

The following factors were investigated for their potential association with the infection status of children in March/April 2006: spray status of the house in which the child lived; whether the child had slept under a bednet the night before the survey; reported spray coverage for the neighborhood in which the child lived; the proportion of houses at the site sprayed with carbamate insecticide, as opposed to pyrethroid, in the second spray round of 2005; the time that had elapsed since the last time the site was sprayed; and the sentinel site-specific prevalence of infection in children 2 to < 15 years of age in the previous survey (March 2005).

Multivariable logistic regression models were used to assess the effects of each of these variables on the probability of infection of a child. Because the primary interest was on explaining the prevalence of malaria infection in 2006 relative to 2005, all models were specified to control for the prevalence of infection in 2005 by including the 2005 site-specific log-odds of infection in the model. We report the estimates made from two models: a "simple" model containing only one variable at a time together with the site specific prevalence in 2005, and a multiple-variable model containing all variables. However, the two variables—overall reported spray coverage and carbamate spray coverage—were not simultaneously entered into the multivariable model due to their strong correlation with each other.

Age-specific prevalence of infection for all sites combined was calculated for each of the three surveys and plotted (Fig. 1).

RESULTS

Average prevalence of infection with *P. falciparum* in children 2 to < 15 years of age at all sites combined reduced from 45% at baseline in 2004 to 32% in 2005 ($P < 0.001$) and to 26% in 2006 ($P < 0.03$), with substantial between-site variation. Prevalence of infection in 2006 ranged from 5% at the high-altitude site of Moka to 72% at Punta Europa (Table 1). There was also considerable inter-site variation in the explanatory variables that were investigated for their relationship with prevalence of infection.

There were substantial reductions in prevalence in all age groups after the first year, with more modest age-specific reductions after the second year (Figure 1). Although the protocol excluded children < 2 years old, a considerable number were tested, particularly in the 2005 survey. The data relating to this age group were therefore excluded from all analysis, except for the results shown in Figure 1, which are stratified by single year of age.

In the 2006 survey, 77% of householders reported that their house had been sprayed at least once during the previous year. Site-specific spray coverage of houses in the 2006 survey ranged from 58% to 87%. If houses sprayed with pyrethroid are excluded from the coverage numerator, then the proportion of houses sprayed with carbamates ranged from 46% to 87%.

About 26% of children surveyed slept under a bednet the night before the survey. This varied from > 40% in some urban sites in Malabo to 13% in the rural site of Basacato del Oeste and 11% at Moka.

The time interval from the previous spraying to February 15, 2006 (2 weeks before the start of the survey) averaged 153 days, ranging from 0 days for Bilelipa, which had just been sprayed in round 4, to > 190 days for Riaba and Luba.

In the simple model, controlling only for prevalence of infection of the neighborhood in which the child lived in 2005, malarial infection with *P. falciparum* in 2006 was significantly associated with spray status of the house, sleeping under a bednet, and duration since the last time the house was sprayed (Table 2).

Odds of infection in the simple model were significantly lower for children living in houses that had been sprayed (odds ratio = 0.69 relative to unsprayed houses, $P < 0.001$). Sleeping in houses that had been reported to have been sprayed prevented 21.5% of infections directly, compared with the number of infections that would have occurred if all children had slept in unsprayed houses. This figure does not include the number of infections averted in children who slept in unsprayed houses but who benefited from the mass effect of IRS.

The odds of infection of an individual child decreased on average by a factor of 0.97 ($P = 0.051$) for every 1% increase in spray coverage of the neighborhood in which the child lives, allowing for prevalence of neighborhood in 2005. In the simple model, carbamate spray coverage was not significantly associated with malarial infection.

However, according to the simple model the effect of delaying spraying was to significantly increase the probability of a child being infected (odds ratio, 1.1 per 30-day increase in the duration since the last spray round; $P = 0.01$).

Sleeping under a bednet was protective, significantly reducing prevalence of infection relative to not sleeping under a bednet (odds ratio = 0.57; $P < 0.001$, adjusting for the 2005 neighborhood prevalence of infection). Due to the low prevalence of bednet use, their impact was relatively small, averting directly only 8% of all infections that would have occurred if no children had slept under a bednet.

There was a mutually additive protective effect of spraying and sleeping under a bednet. Prevalence of infection was 34% (95% CI: 26–43%) in children who did not sleep under a bednet and whose house was not sprayed. Children whose house was sprayed but who did not sleep under a bednet had significantly lower prevalence of infection by comparison (prevalence = 26%; 95% CI: 19–34%; $P = 0.004$). Children who slept under a bednet but whose house was not sprayed benefited similarly (prevalence = 25%; 95% CI: 18–33%; $P = 0.032$). Children whose house was sprayed and who slept under a bednet had the lowest risk of infection (prevalence = 18%; 95% CI: 13–24%; $P < 0.001$).

Desire to have houses sprayed was uniformly high (mean, 92%; data not tabulated).

Spray status of the house, carbamate insecticide coverage of the neighborhood, sleeping under a bednet, prevalence of infection in 2005, and duration since the last spraying, each controlled for the effects of the others, were all independently associated with infection status in a multiple-variable logistic regression model (Table 2). Overall spray coverage was no longer significant in multiple-variable regression. The odds ratios for variables in the multiple-variable model, other than carbamate coverage, were very similar to the values that were obtained in the models adjusting only for prevalence of infection in 2005. Infection was significantly associated with site-specific prevalence of houses sprayed with effective insecticide (carbamate coverage) (odds ratio = 0.83 per 10% increase in coverage; $P = 0.018$) after adjusting for the other variables, indicating that the relationship between carbamate coverage and prevalence of infection was confounded by other factors in the simple model, as discussed below.

DISCUSSION

The results of the 2006 BIMCP parasite prevalence survey show a further reduction in prevalence of infection relative to baseline and relative to the 2005 survey. Overall prevalence of infection declined from 45% at baseline in 2004, to 32% after the first year of the intervention in 2005 (odds ratio = 0.57; P = 0.001), and subsequently to 26% in 2006 (odds ratio = 0.43 relative to baseline, P < 0.001). The number of infections prevented in 2006 as a proportion of the infections that occurred pre-intervention in 2004 is therefore 42%.

Although there was an overall reduction in prevalence of infection with malarial parasites in children 2 to < 15 years of age on Bioko, there were a small number of sites where parasitemia levels have remained persistently high. These were the sites of Punta Europa, Sacriba, and Santa Maria in the northwest sector of the island.

It is difficult to pin-point precisely the factors responsible for the persistence of high parasite prevalence in these sites, but our analysis shows that factors related to vector-control operations can explain some of the heterogeneity in impact. Reduction in prevalence was associated with effective spray coverage and inversely associated with the length of spraying intervals that exceeded the residual life of the insecticide Bendiocarb[10] in some sites.

The BIMCP has responded to this challenge by attempting to identify the factors that were associated with failure to reduce prevalence, as reported in this study, by a mass active-case detection and treatment campaign, and by increased entomological surveillance at high prevalence sites.

The simple logistic regression model revealed that infection status was marginally negatively associated with overall site-specific spray coverage of the neighborhood; however, in the multiple-variable model, overall spray coverage was no longer significant because it was obviously strongly correlated with other factors, in particular with spray status of the individual house. By contrast, carbamate spray coverage was not significant in the simple model, but it was significantly associated with infection status once confounding had been controlled for in the multiple variable model. This finding is most likely a result of pyrethroids having become partially ineffective in some areas due to the presence of *kdr* resistance in one of the vector species. Any beneficial effect of carbamates over pyrethroids would be limited to localities where the spray interval did not exceed the residual life of the carbamate, which may explain why the effect of carbamate coverage in the model would have to be controlled for the interval between spray rounds.

Spraying an individual house offered protection from infection to its occupants, and high spray coverage in an area was of benefit to the whole community, including those whose houses were not sprayed, due to the neighborhood effect of IRS. The multiple-variable model showed that high spray coverage of the neighborhood with effective insecticide, in this case carbamate, provided a protective effect in addition to the individual benefit derived from living in a house that had been sprayed. Achieving high levels of spray coverage in IRS programs therefore has the dual benefit of protecting children living in sprayed houses directly as well as indirectly offering a level of protection to those living in unsprayed houses. However, sleeping in a sprayed house or a neighborhood of high spray coverage reduces the risk of infection but does not guarantee protection. Spray operations should therefore aim at universal coverage wherever possible.

The relatively short residual life of Bendiocarb[11] necessitates careful scheduling and monitoring of spray intervals because the 6-month period between spray rounds has to be adhered to for all individual spray localities. Our analysis implies that, on average, the odds

of infection with *P. falciparum* increased by 15% for each month that spraying was delayed (Table 2), although it is possible that this increase accelerates once spray intervals are well in excess of the residual life of the product. The BIMCP's computerized spray-management system had previously been used to monitor spray progress but not to implement detailed spray planning. In response to the analysis reported here, the spray-information system has been used to schedule the spraying of each spray locality in future spray rounds to occur before the 6-month anniversary of its previous spray date. The system thereby proved an invaluable tool for optimizing IRS, ensuring as much as possible uninterrupted residual insecticide on walls.

The odds of infection with *P. falciparum* were associated with the neighborhood odds of infection measured 12 months earlier. Although this is not surprising, it should not be forgotten when planning malaria-control strategies because it implies that additional effort may be needed to achieve a satisfactory impact in high-prevalence areas.

Although bednet programs are not a component of the BIMCP, their use in the presence of IRS has evidently had a beneficial effect, even though the overall impact of bednets was small compared with the impact of IRS because of the relatively low prevalence of bednet use (26%) compared with IRS coverage (77%). Notably, the protective effects of bednet use and IRS were additive, i.e. sleeping under a bednet provided additional protection even if the house had been sprayed, and *vice versa*. Most vector-control malaria programs use either bednets or IRS; our results show that even in well-functioning IRS programs potential benefits can be derived from additionally promoting bednet use.

Overall prevalence of infection in children who lived in an unsprayed house and who did not sleep under a bednet was 34%. Because this is significantly lower than overall prevalence at baseline before spraying started in 2004 ($P = 0.0072$), it is reasonable to conclude that all children benefited from the mass effect of IRS, even if their house was not sprayed.

For an IRS program to be successful, it is vital to maintain a high level of public support, as this determines ultimately the ceiling of spray coverage that can be achieved. In the BIMCP, 92% of respondents expressed a desire to have their house sprayed, which was a cornerstone of the accomplishment of this project. To this end, the BIMCP developed a number of IEC strategies, so that the public remained aware of the health benefits from IRS, and that these far outweighed the inconvenience caused by having one's house sprayed twice a year.

The results of the third annual household survey conducted by the BIMCP demonstrate its success in further reducing overall prevalence of malaria infection through a combination of vector-control, case-management, and IEC measures. The analysis shows that success in reducing prevalence was linked to adequate adherence to intervention measures and inversely to pre-existing prevalence of infection. Comprehensive monitoring is therefore essential for both the management and evaluation of the intervention. Monitoring should include not only impact measures such as prevalence of infection but also intervention-compliance indicators, such as spray coverage and spray intervals, as well as household-level information, such as spray status of a dwelling and bednet use. We believe that analysis of these indicators, as presented in this study, provides useful guidance for similar interventions that are currently being initiated elsewhere.

Acknowledgments

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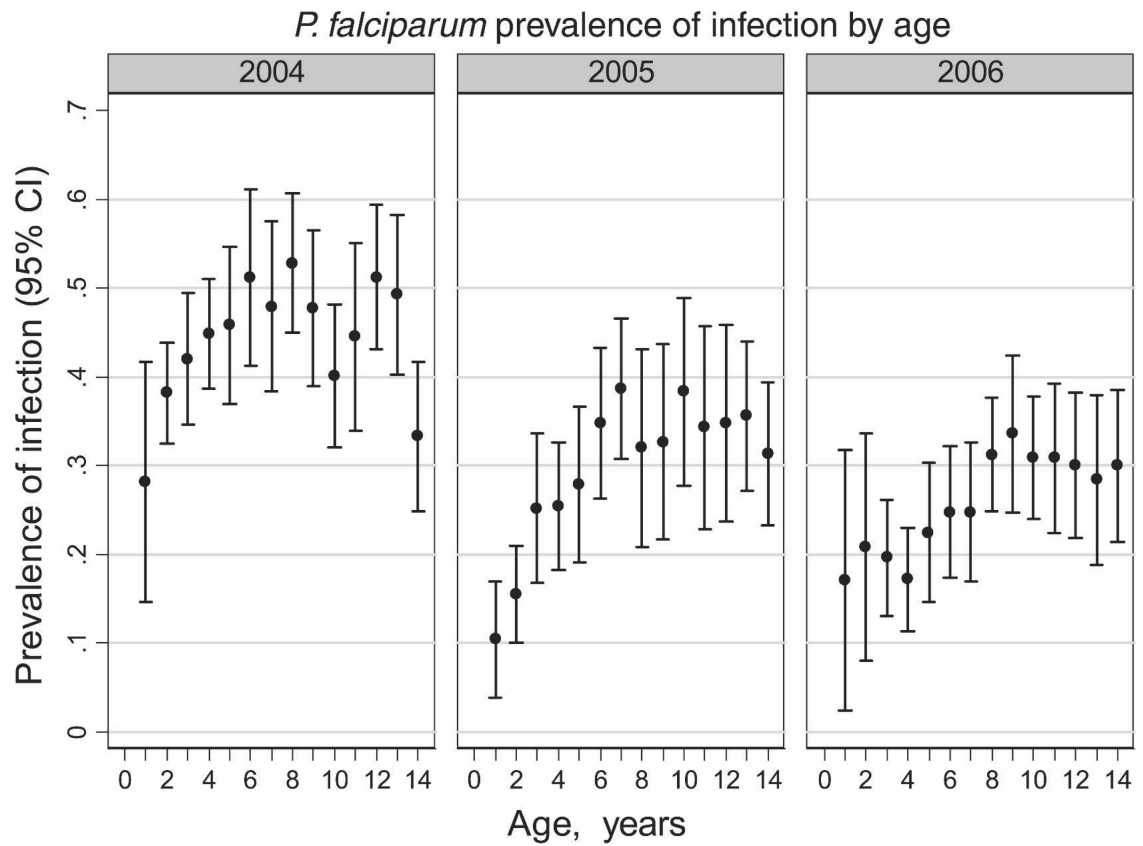
FIGURE 1.
Age-specific prevalence of infection with *P. falciparum* in children 2 to < 15 years of age on Bioko Island, by survey.

TABLE 1

Prevalence of infection with *P. falciparum* (estimated from surveys in 2005 and 2006) and vector control measures, by sentinel site

	(a) Prevalence of infection in 2006, % [95% CI][*]	(b) Prevalence of infection in 2005, % [95% CI][†]	(c) Reporting that house was sprayed in 2005, % [95% CI][*]	(d) Proportion of houses sprayed with carbamate insecticide, %[‡]	(e) Reporting that child slept under a bednet, % [95% CI][*]	(f) Time interval between survey and last spray round, days[§]
Bakake Grande	16 [12–22]	24 [17–34]	78 [70–85]	78	21 [14–30]	173
Baney	10 [7.8–14]	20 [14–29]	85 [80–90]	85	23 [17–30]	154
Basacato del Oeste	28 [21–37]	44 [36–54]	69 [57–78]	69	13 [7–25]	161
Batete	12 [8–19]	15 [10–23]	80 [69–88]	80	18 [10–29]	189
Bilelipa	30 [20–42]	50 [39–61]	70 [56–81]	70	18 [9–31]	0
Campo Yaounde	26 [21–32]	15 [10–21]	76 [68–82]	58	46 [38–55]	180
Central	18 [14–23]	22 [16–30]	75 [68–81]	46	28 [21–36]	104
Ela Nguema	29 [24–35]	30 [23–39]	70 [63–77]	59	15 [10–21]	167
Luba	33 [27–38]	38 [30–47]	77 [70–83]	77	22 [15–30]	195
Moka	5 [2–11]	2 [1–6]	76 [63–85]	76	11 [5–23]	183
Musola	24 [18–31]	13 [7–21]	80 [71–87]	80	9 [5–17]	180
Punta Europa	72 [63–79]	73 [63–82]	58 [45–71]	47	16 [7–30]	189
Rebola	10 [7–14]	21 [16–28]	81 [75-87]	81	21 [15–28]	138
Riaba	43 [35–52]	54 [46–62]	85 [75–92]	85	20 [12–31]	194
Sacriba	54 [44–62]	57 [49–64]	73 [63–82]	73	23 [15–34]	148
Sampaka	29 [23–36]	37 [28–46]	87 [80–92]	74	33 [25–41]	114
Santa Maria	44 [39–49]	51 [42–59]	72 [66–78]	60	34 [28–42]	119
Semu	24 [19–29]	35 [28–43]	80 [73–86]	70	45 [37–54]	156
All sites (*n*)	26 [20–33] (5332)	32 [24–41] (3086)	77 [74–80] (2142)	71 [64–77] (2142)	26 [24–28] (5811)	153 [129–176]

[*] Data obtained from 2006 household survey.

[†] Data obtained from 2005 household survey.

[‡] Column (c) multiplied by proportion carbamate spray in second round of 2005; obtained from spray management system database.

[§] Number of days between February 15, 2006, and median spray date of preceding spray round, calculated from spray management system.

TABLE 2

Association between infection with *P. falciparum* in March 2006 and factors related to IRS, bednet use, and prevalence in 2005

	Simple model: Controlling only for log-odds of neighbourhood prevalence of infection in 2005*		Multiple variable model: All variables controlled for each other	
	Odds ratio [95% CI]	*P* value	Odds ratio [95% CI]	*P* value
Log-odds of prevalence of neighborhood in 2005, per unit log-odds in 2005	2.17 [1.56–3.04]	< 0.001	2.25 [1.74–2.90]	< 0.001
House sprayed, relative to not sprayed	0.69 [0.58–0.83]	< 0.001	0.73 [0.61–0.88]	0.002
Slept under a bednet previous night, relative to not sleeping under a bednet	0.57 [0.47–0.69]	< 0.001	0.57 [0.48–0.67]	< 0.001
Time since last sprayed, per day	1.0033[†] [1.0009–1.0058]	0.01	1.0047[‡] [1.0013–1.0082]	0.01
Reported spray coverage of neighborhood, per percent coverage	0.973 [0.947–1.000]	0.051	(Not significant in multiple variable model)	
Carbamate coverage of neighborhood, per percent coverage	0.987 [0.970–1.005]	0.146	0.981[§] [0.967–0.996]	0.018

[*] All odds ratios estimated from models that included the variable of interest and the log-odds of neighborhood prevalence in 2005, apart from the odds ratio for log-odds of prevalence in 2005, which was estimated from a model with no other co-variates.

[†] Equivalent to an odds ratio of 1.10 per 30-day delay.

[‡] Equivalent to an odds ratio of 1.15 per 30-day delay.

[§] Equivalent to an odds ratio of 0.83 per 10% increase in coverage.