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Analysis of Preventive Interventions for Malaria: Exploring Partial and Complete Protection and Total and Primary Intervention Effects

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Event dependence, the phenomenon in which future risk depends on past disease history, is not commonly accounted for in the statistical models used by malaria researchers. However, recently developed methods for the analysis of repeated events allow this to be done, while also accounting for heterogeneity in risk and nonsusceptible subgroups. Accounting for event dependence allows separation of the primary effect of an intervention from its total effect, which is composed of its primary effect on risk of disease and its secondary effect mediated by event dependence. To illustrate these methods and show the insights they can provide, we have reanalyzed 2 trials of seasonal malaria chemoprevention (SMC) in Boussé, Burkina Faso, and Kati, Mali, in 2008–2009, as well as a trial of intermittent preventive treatment of malaria in infants in Navrongo, Ghana, in 2000–2004. SMC completely protects a large fraction of recipients, while intermittent preventive treatment in infants provides modest partial protection, consistent with the rationale of these 2 different chemopreventive approaches. SMC has a primary effect that is substantially greater than the total effect previously estimated by trials, with the lower total effect mediated by negative event dependence. These methods contribute to an understanding of the mechanisms of protection from these interventions and could improve understanding of other tools to control malaria, including vaccines.

cure models; event dependence; heterogeneity; malaria; repeated events

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTi, intermittent preventive treatment in infants; SMC, seasonal malaria chemoprevention.

The transmission of many infectious diseases, including malaria, is highly heterogeneous (1–7). Under heterogeneous exposure, the clinical burden of malaria, which is the focus of this paper, may be concentrated disproportionately in certain subgroups within the population (1). Some individuals experience repeated episodes while others, despite exposure, experience only occasional episodes or escape disease altogether. Heterogeneity in the risk of disease may be further exaggerated by the presence of a subgroup within the population that is either unexposed, immune to disease, or does not report disease (i.e., is certain not to report illness) (3). Where such a nonsusceptible fraction, or "cured fraction," is present, accounting for this is important; otherwise, the risk for those truly susceptible may be underestimated (8). An important question regarding preventive interventions, such as chemoprophylaxis and vaccination, is whether they confer complete protection, that is, increase the nonsusceptible fraction (9). Consequently, presentation of vaccine trial results only in terms of reduction in incidence rates has been criticized (10, 11). Estimating both the overall reduction in incidence and exploring evidence for complete protection may give a better understanding of the effects of preventive interventions and their mode of action.

There is also a dynamic relationship between an individual's history of malarial disease and his/her future risk, known as event dependence. This could be mediated by posttreatment prophylaxis after treatment of malaria (12), loss of protection due to clearance of infection (13–15), development of

Table 1. Details of the Studies in Boussé, Burkina Faso (2008–2009), Kati, Mali (2008–2009), and Navrongo, Ghana (2000–2004)

First Author, Year (Reference No.)	Location	Study Dates, years	No. in Cohort	Person-Years at Risk[a]	Age at Enrollment, months	No. of Malaria Episodes[b]	Drug Used for Case Management
Konate, 2011 (22)	Boussé, Burkina Faso	2008–2009	2,989	2,423.70	3–59	1,496	Artemether-lumefantrine
Dicko, 2011 (23)	Kati, Mali	2008–2009	2,967	2,333.50	3–59	1,125	Artemether-lumefantrine
Chandramohan, 2005 (24)	Navrongo, Ghana	2000–2004	2,485	2,429.30	2–3	2,052	Chloroquine

[a] To avoid overestimation of the incidence rate in children who suffered multiple episodes of malaria, no deduction in person-time at risk was made after a malaria episode.
[b] To avoid counting the same episode twice, reports of malarial attacks within 7 days of a prior episode were not counted.

immunity (16–18), or changes in behavior, including use of protective measures. Accounting for event dependence is important; it allows separation of the primary effect of a protective intervention from its total effect, which is composed of primary and secondary effects. In this context, the primary effect refers to the ability of an intervention to directly reduce risk of malaria. Secondary effects occur if prevention of a particular episode influences the chances of subsequent episodes. If experiencing malaria reduces future risk (negative event dependence), for example, by inducing partial immunity, then when the total effect is measured, the primary benefit of prevention of malaria will be diluted because those who experience malaria will be at lower risk subsequently. If experiencing malaria increases future malaria risk (positive event dependence), prevention of malaria has a double benefit, by preventing both the index episode and the elevated future risk. Reduction of the total number of episodes (i.e., the total effect) is the usual endpoint of public health interest (8, 19). However, separation of primary and secondary effects is useful in understanding the mechanism by which a particular intervention protects against malaria. This type of secondary effect is distinct from those indirect effects mediated by reducing transmission, as has been shown, for example, with insecticide-treated nets.

Recently, Cheung et al. (19) showed that the Andersen-Gill extension of the Cox regression model for repeated events estimates the total effect, and that frailty (heterogeneity) does not bias estimation of the total effect by the Andersen-Gill model. However, the Andersen-Gill model does not provide details about what constitutes the total effect. Although simple methods can be used to estimate the reduction in number of events or the increase in the proportion of the population free of disease due to an intervention, methods have been developed that allow these to be estimated jointly (8, 20, 21). Recently, a comprehensive analytical framework has been developed by Xu et al. (8, 21) to incorporate frailty, event dependence, and a nonsusceptible fraction in the analysis of repeated disease episodes.

To illustrate the application of these methods and to outline the insights they provide regarding the mechanism of intervention effects, we have reanalyzed data from 3 studies of malaria chemoprevention.

METHODS

Data

Data on clinical malaria incidence from 3 previously published studies (details shown in Tables 1 and 2) were used in this analysis.

First, data were used from 2,989 children under 5 years of age enrolled in a study of seasonal malaria chemoprevention (SMC) in Boussé, Burkina Faso (22). Children received sulfadoxine-pyrimethamine plus amodiaquine, or placebo, monthly for 3 months during the peak malaria transmission period. To focus on assessment of the intervention effect, we

Table 2. Incidence of Malaria in Boussé, Burkina Faso (2008–2009), Kati, Mali (2008–2009), and Navrongo, Ghana (2000–2004)

First Author, Year, Reference	Location	All Participants		Placebo Group		Intervention Group		No. of Malaria Episodes per Child			
		Incidence Rate[a,b]	95% CI	Incidence Rate[a,b]	95% CI	Incidence Rate[a,b]	95% CI	Mean	Median	Range	Variance
Konate, 2011 (22)	Boussé, Burkina Faso	617.2	586.7, 649.3	919.4	866.6, 975.4	324.2	293.9, 357.7	0.5	0	0–4	0.545
Dicko, 2011 (23)	Kati, Mali	482.1	454.7, 511.1	738.8	691.1, 789.9	226.6	200.9, 255.6	0.38	0	0–4	0.462
Chandramohan, 2005 (24)	Navrongo, Ghana	844.7	808.9, 882.1	986.1	931.9, 1,043.5	702.5	656.9, 751.3	0.83	1	0–7	0.98

Abbreviation: CI, confidence interval.
[a] Rate per 1,000 person-years.
[b] Analysis time was the time from enrollment until exit from follow-up, using time since enrollment as the timescale. Multiple episodes per child were included.

used data from the first 12 months of the study (i.e., the first wet season and following the dry season). Malaria transmission was high in this setting: 41.5% of the placebo group carried malarial parasites at the end of the rainy season (22).

Second, data were used from 2,967 children under 5 years of age enrolled in a parallel study of SMC to the one described above, conducted in Kati, Mali (23). Malaria transmission was moderate-high: 13.2% of the placebo group carried malaria infections at the end of the rainy season.

Third, data were used from 2,485 infants enrolled in a cluster-randomized trial of intermittent preventive treatment in infants (IPTi) in Navrongo, Ghana (24). Infants received sulfadoxine-pyrimethamine or placebo at 3, 4, 9, and 12 months of age alongside routine immunizations. As for the SMC studies, analysis was restricted to the year during which the intervention was given, between enrollment at 2–3 months and 14–15 months of age. Malaria transmission was high in this setting: 31.5% of children in the placebo group carried infections at 18 months of age.

Statistical analyses

Kaplan-Meier survival curves and cumulative hazard plots were calculated for each study. A simple approach to estimate the relative changes in the proportion with disease using the Kaplan-Meier survival estimate is given in the Web Appendix and Web Table 1, available at http://aje.oxfordjournals.org/. The user-written program `strmcure` (25) for Stata (StataCorp LP, College Station, Texas) can be used to implement a set of analytical models for analysis of repeated disease episodes (21, 25). In brief, this set of models incorporates a frailty term (a gamma-distributed random effect, as used in negative binomial regression for count data) to describe heterogeneity in disease hazard. For models allowing a nonsusceptible fraction, the proportion of the population not at risk is estimated by a logistic component, and susceptible individuals are assumed to have a proper survival distribution with an asymptote at 0 (i.e., all susceptible individuals would eventually experience disease). Parametric and zero-tail completion methods are available. The former extrapolates the tail of the hazard curve smoothly beyond the end of the follow-up period; the latter classifies all children who have not experienced malaria after the observed largest uncensored time to first event, as being nonsusceptible. The model parameters of interest are estimated by using the expectation-maximization algorithm, with their respective variance being estimated by using the Louis formula (26). The Breslow method was used for tied failure times. All analyses were undertaken in Stata release 13. Ninety-five percent confidence intervals were presented throughout. Protective efficacy of the interventions was calculated as (1 − hazard ratio) expressed as a percentage.

As discussed above, the Andersen-Gill model estimates the total effect. The primary effect of the intervention can be estimated by stratification of risk sets according to event order (7, 19). In the stratified model, individuals yet to experience an event are compared between intervention and control groups (stratum 1), individuals with 1 prior event are compared between study groups (stratum 2), and so on. Consequently, the comparison is free of the impact of event dependence and therefore reveals the primary effect. Although the Andersen-Gill model estimates the total effect accurately without incorporating

Table 3. Details of Regression Models and the Insights They Provide

Model No.	Model Description	Estimate of Intervention Effect Obtained	Partial and Complete Protection Estimated Separately
	Models Exploring Event Dependence Only		
1	Andersen-Gill model (Cox model with robust standard error)	Total effect	No
2	Frailty model	Total effect	No
3	Frailty model, adjusted for posttreatment prophylaxis as a time-updated covariate	Total effect	No
4	Frailty model, adjusted for event dependence (by stratification on event order)	Primary effect	No
	Models Allowing for a Nonsusceptible Fraction		
5	Frailty model, extended to allow nonsusceptible fraction	Total effect	Yes
6	Frailty model, extended to allow nonsusceptible fraction and adjusted for posttreatment prophylaxis as a time-updated covariate	Total effect	Yes
7	Frailty model, extended to allow nonsusceptible fraction and adjusted for event dependence (by stratification on event order)	Primary effect	Yes
	Covariate-Adjusted Models, Allowing for Nonsusceptible Fraction (All Models Include Time-Constant Covariates in Both Logistic and Hazard Components)		
8	Frailty model, extended to allow nonsusceptible fraction	Total effect	Yes
9	Frailty model, extended to allow nonsusceptible fraction and adjusted for posttreatment prophylaxis as a time-updated covariate	Total effect	Yes
10	Frailty model, extended to allow nonsusceptible fraction and adjusted for event dependence (by stratification on event order)	Primary effect	Yes

a frailty term, the comprehensive analytical framework requires a frailty term so that no risk (nonsusceptible fraction) can be differentiated from low risk (frailty) and so that stratification models (to estimate the primary effect) work without bias due to frailty (in a trial, randomization prevents confounding by frailty only in the first event stratum). For completeness, the illustration below includes both the Andersen-Gill model and the frailty model to estimate the total effect.

As described above, one possible reason for event dependence in malaria is the period of posttreatment prophylaxis after experiencing a malaria episode. To explore this, we also fitted alternative models with a time-updated covariate indicating when children were protected by posttreatment prophylaxis, rather than stratifying on event number. We explored several options, but there was no significant (or important, in terms of magnitude) protection beyond 14 days, so a single indicator variable, identifying time spans within 14 days of a previous episode, was included as a covariate in the hazard component of models accounting for posttreatment prophylaxis.

Ten models were fitted to each data set (Table 3). The main effect of interest was the intervention group to which children were assigned at random. Comparison of models estimating the total effect (model 1 or model 2) with the model allowing for posttreatment prophylaxis (model 3) reveals the role played by posttreatment prophylaxis in the total effect. Estimates of the hazard ratio for posttreatment prophylaxis and the frailty are given in Web Tables 2 and 3. Comparison of models 1, 2, and 3 with the model estimating the primary effect by stratification on event order (model 4) allows separation of the primary effect of the intervention from its total effect. Models 5, 6, and 7 allow for a nonsusceptible subgroup, with the odds ratio reflecting the relative odds of being susceptible in the intervention group (i.e., the extent of complete protection) and the hazard ratio reflecting the protection due to the intervention among those who are susceptible (i.e., the extent of partial protection). Comparison of models 6 and 7 with model 5 allows investigation of the effect of accounting for posttreatment prophylaxis and event dependence. Models 8, 9, and 10 are analogous to models 5, 6, and 7 but also adjust for other covariates. In the covariate adjustment, time-constant covariates (e.g., sex) were included in both the logistic component (nonsusceptible fraction) and the hazard component (disease incidence among the susceptible subjects) of the models.

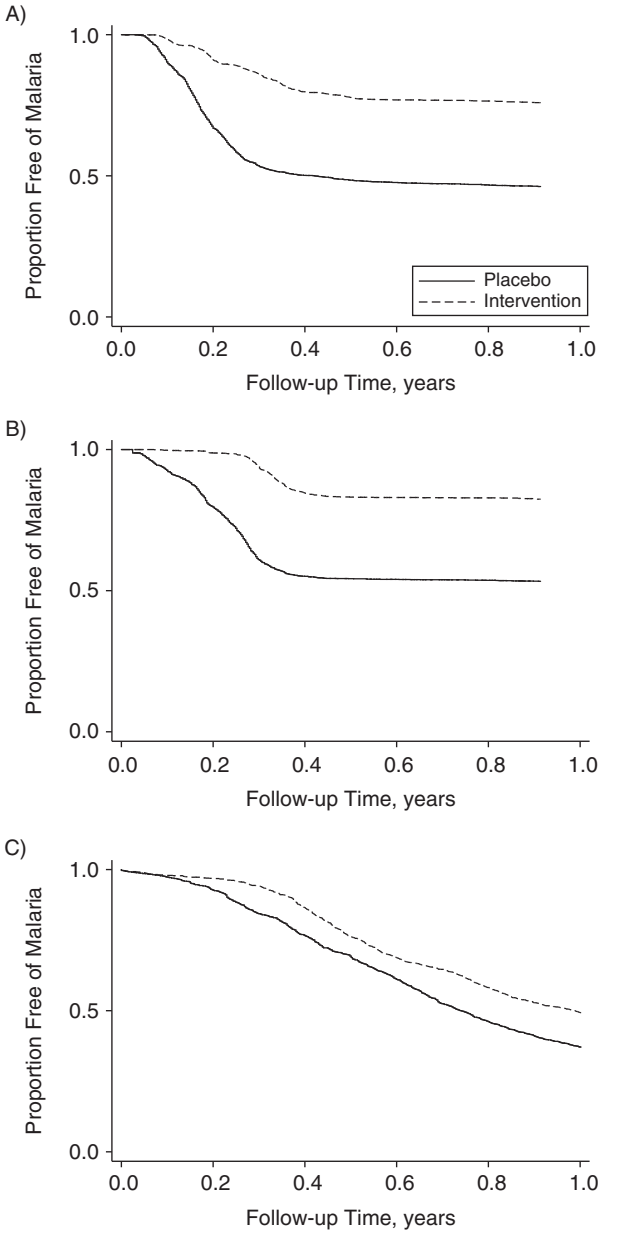

Figure 1. Kaplan-Meier survival plots for data from A) Boussé, Burkina Faso, 2008–2009; B) Kati, Mali, 2008–2009; and C) Navrongo, Ghana, 2000–2004.

RESULTS

SMC studies in Boussé, Burkina Faso, and Kati, Mali

In Boussé, during the first year of the study, 1,496 malaria episodes were observed, and incidence was estimated at 919.4 episodes and 324.2 episodes per 1,000 person-years in the placebo and SMC groups, respectively. In Kati, 1,125 malaria episodes were documented, and incidence was estimated at 738.8 episodes and 226.6 episodes per 1,000 person-years in the placebo and SMC groups, respectively.

In both sites, inspection of the survival curves shows a leveling off in both groups (Figure 1A and 1B), compatible with either the remainder of the population's being nonsusceptible or the cessation of malaria transmission. Because the cumulative hazards also flatten (Figure 2A and 2B), some of the subgroup without malaria may in fact be susceptible, and the leveling off of the survival function may be due in part to the seasonal drop in malaria incidence at the end of the rainy season (22, 23). Overall, about two-thirds of the children remained free of malaria, the majority in the SMC group.

In Boussé, the estimated total effect (overall reduction in incidence) from SMC was 64% (hazard ratio (HR) = 0.36, 95% confidence interval (CI): 0.32, 0.40) as shown in models 1 and 2 (Table 4). Models 1 and 2 give identical estimates,

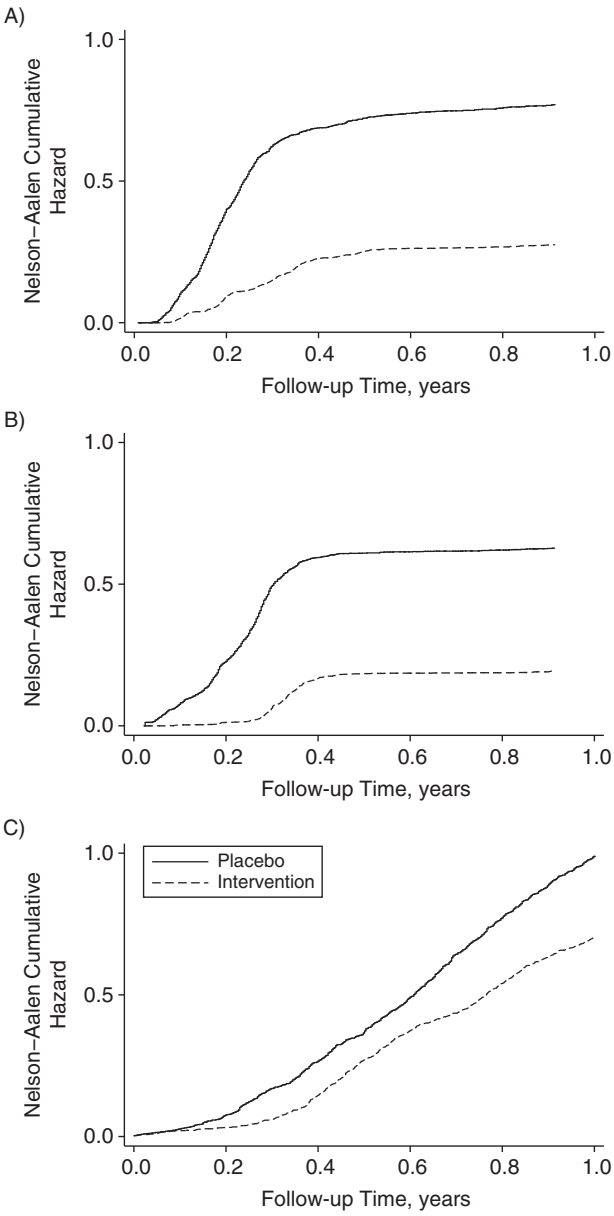

Figure 2. Nelson-Aalen cumulative hazard plots for data from A) Boussé, Burkina Faso, 2008–2009; B) Kati, Mali, 2008–2009; and C) Navrongo, Ghana, 2000–2004.

because the Andersen-Gill model estimates the total effect without bias, even without incorporating a frailty term, as discussed above. The confidence intervals are also the same in the context of a randomized trial because the frailty level is independent of the study group, and therefore adjustment for frailty does not induce colinearity that reduces precision. Accounting for posttreatment prophylaxis slightly increased the estimate of the total effect (HR = 0.33, 95% CI: 0.30, 0.38) in model 3 (Table 4). Stratification on event order (and therefore estimating the primary effect of SMC) indicates a much greater primary protective effect of SMC than its total effect (HR = 0.15, 95% CI: 0.13, 0.18) (PE = 85%, 95% CI: 82, 87) as shown in model 4 (Table 4).

When allowing for a nonsusceptible fraction to investigate partial and complete protection in Boussé, we found that children given SMC had a much lower odds of being susceptible (odds ratio = 0.24, 95% CI: 0.21, 0.26) (Table 4). In other words, more children given SMC were completely protected. The estimated susceptible fraction from model 5 was 56.3% in the placebo group and 23.4% in children given SMC. Having accounted for nonsusceptible children, we saw a more modest total effect among the remaining susceptible children (HR = 0.85, 95% CI: 0.76, 0.96) in model 5 (Table 4) (i.e., protective efficacy of 15%, compared with protective efficacy of 64% when nonsusceptible children were ignored). Thus, part of the protective effect of SMC appears to be provision of complete protection to some children. Accounting for posttreatment prophylaxis in addition to a nonsusceptible subgroup slightly reduced the hazard ratio to 0.81 (95% CI: 0.72, 0.91) in model 6 (Table 4). When accounting for event dependence and a nonsusceptible fraction, we estimated the primary effect among susceptible children to be 60% (HR = 0.40, 95% CI: 0.33, 0.49) in model 7 (Table 4). Further adjustment for covariates (sex, village of residence, age group, weight-for-age category) only slightly changed these estimates in models 8, 9, and 10 (Table 4).

Similar results were observed in Kati, Mali. The estimated total effect of SMC was a reduction in incidence of about 70% (HR = 0.31, 95% CI: 0.26, 0.35 and HR = 0.30, 95% CI: 0.26, 0.35) as shown in models 1 and 2 (Table 4). Accounting for posttreatment prophylaxis slightly increased the estimate of the total effect (HR = 0.28, 95% CI: 0.24, 0.33) in model 3 (Table 4). Accounting for event dependence reduced the hazard ratio substantially (HR = 0.05, 95% CI: 0.04, 0.07), again indicating that the primary protective effect of SMC was much larger than its total effect (95% vs. 70%). The estimated susceptible fraction from model 5 was 44.1% in the placebo group and 16.9% in children given SMC (odds ratio = 0.26, 95% CI: 0.23, 0.29). Having accounted for nonsusceptible children, the estimated total effect of SMC was then a 22% reduction in incidence among those susceptible (HR = 0.78, 95% CI: 0.67, 0.89) in model 5 (Table 4) (compared with the protective efficacy of 70% ignoring those nonsusceptible). Accounting for posttreatment prophylaxis in addition to a nonsusceptible subgroup slightly reduced the hazard ratio to 0.73 (95% CI: 0.64, 0.85) in model 6 (Table 4). When accounting for event dependence and a nonsusceptible fraction, we estimated the primary protective effect among the susceptible fraction to be 84% (HR = 0.16, 95% CI: 0.12, 0.20) in model 7 (Table 4). Further adjustment for covariates (sex, village of residence, age group, weight-for-age category) only slightly changed these estimates in models 8, 9, and 10 (Table 4).

Navrongo IPTi study, Ghana

There were 2,052 malaria episodes in 2,429.3 person-years of follow-up; incidence was 986.1 cases and 702.5 cases per 1,000 person-years in the placebo and IPTi groups, respectively. The survival curves indicate that approximately half the children experienced malaria by the end of the period observed, with slightly more remaining free of malaria in the

Table 4. Output From Regression Models in SMC Studies in Boussé, Burkina Faso, and Kati, Mali, 2008–2009

Model No.	Model Description	Effect Estimated	PE, %	95% CI	HR	95% CI	OR[a]	95% CI
		Boussé, Burkina Faso						
1	SMC, Andersen-Gill model	Total	64	60, 68	0.36	0.32, 0.40		
2	SMC, frailty	Total	64	60, 68	0.36	0.32, 0.40		
3	SMC, frailty, PTP as TUC	Total	67	62, 70	0.33	0.30, 0.38		
4	SMC, frailty, adjusted for event dependence[b]	Primary	85	82, 87	0.15	0.13, 0.18		
5	SMC, frailty, nonsusceptible fraction	Total	15	4, 24	0.85	0.76, 0.96	0.24	0.21, 0.26
6	SMC, frailty, nonsusceptible fraction, PTP as TUC	Total	19	9, 28	0.81	0.72, 0.91	0.24	0.21, 0.26
7	SMC, frailty, nonsusceptible fraction, adjusted for event dependence[b]	Primary	60	51, 67	0.40	0.33, 0.49	0.25	0.22, 0.27
8	SMC, frailty, nonsusceptible fraction, covariates[c]	Total	14	3, 24	0.86	0.76, 0.97	0.22	0.20, 0.25
9	SMC, frailty, nonsusceptible fraction, PTP as TUC, covariates[c]	Total	19	8, 28	0.81	0.72, 0.92	0.22	0.20, 0.25
10	SMC, frailty, nonsusceptible fraction, covariates[c], adjusted for event dependence[b]	Primary	57	49, 64	0.43	0.36, 0.51	0.23	0.21, 0.26
		Kati, Mali						
1	SMC, Andersen-Gill model	Total	69	65, 74	0.31	0.26, 0.35		
2	SMC, frailty	Total	70	65, 74	0.30	0.26, 0.35		
3	SMC, frailty, PTP as TUC	Total	72	67, 76	0.28	0.24, 0.33		
4	SMC, frailty, adjusted for event dependence[b]	Primary	95	93, 96	0.05	0.04, 0.07		
5	SMC, frailty, nonsusceptible fraction	Total	22	11, 33	0.78	0.67, 0.89	0.26	0.23, 0.29
6	SMC, frailty, nonsusceptible fraction, PTP as TUC	Total	27	15, 36	0.73	0.64, 0.85	0.26	0.23, 0.30
7	SMC, frailty, nonsusceptible fraction, adjusted for event dependence[b]	Primary	84	80, 88	0.16	0.12, 0.20	0.26	0.23, 0.30
8	SMC, frailty, nonsusceptible fraction, covariates[c]	Total	24	12, 34	0.76	0.66, 0.88	0.22	0.20, 0.25
9	SMC, frailty, nonsusceptible fraction, PTP as TUC, covariates[c]	Total	29	18, 38	0.71	0.62, 0.82	0.23	0.20, 0.26
10	SMC, frailty, nonsusceptible fraction, covariates[c], adjusted for event dependence[b]	Primary	85	80, 89	0.15	0.11, 0.20	0.23	0.20, 0.26

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; PE, protective efficacy; PTP, posttreatment prophylaxis; SMC, seasonal malaria chemoprevention; TUC, time-updated covariate.

[a] The odds ratio is the relative change in the odds of being susceptible due to the intervention.

[b] Event dependence occurs when the primary effect is estimated by stratifying on event order.

[c] Covariates consist of sex, village of residence, age group, and weight-for-age category.

IPTi group (Figure 1C). As the survival curves do not clearly level off, estimation of the nonsusceptible fraction may not be robust. We, therefore, undertook a sensitivity analysis using the Weibull parametric tail completion method (discussed below). The cumulative hazard plot deviated slightly from a linear pattern over time, possibly reflecting the seasonal patterns in malaria incidence in Navrongo (Figure 2C).

The estimated total effect of IPTi was modest: a 29% reduction in incidence over the first year of the study in the Andersen-Gill and frailty models (HR = 0.71, 95% CI: 0.65, 0.78) in models 1 and 2 (Table 5). Accounting for posttreatment prophylaxis made only a very small difference to this estimate in model 3 (Table 5). Adjusting for event dependence (and thus estimating the primary effect) also made only minor changes (HR = 0.73, 95% CI: 0.66, 0.80) in model 4 (Table 5).

In the main analysis that used the zero-tail completion method to estimate a nonsusceptible fraction, the odds of being susceptible to malaria were lower in the intervention group (odds ratio = 0.69, 95% CI: 0.64, 0.74). Having allowed for a nonsusceptible fraction, we found evidence that a modest total effect among the susceptible fraction remains (HR = 0.84, 95% CI: 0.77, 0.92) in model 5 (Table 5). Accounting for posttreatment prophylaxis did not alter these estimates (model 6). Estimating the primary effect by adjusting for event dependence did not make major changes (HR = 0.79, 95% CI: 0.73, 0.87) in model 7 (Table 5). Adjustment for covariates (sex, place of residence, season of birth) made only minor changes to these estimates (models 8, 9, and 10) (Table 5).

Models with a nonsusceptible fraction, estimated using the Weibull tail completion method (Table 6), gave very different estimates for the hazard ratio and the odds ratio, as compared with those based on the zero-tail completion method. Figure 2C shows that the cumulative hazard was increasing with the follow-up time. Thus, the models with a nonsusceptible fraction based on the zero-tail completion method, which assumes 0 hazard after the observed largest uncensored time to first event time, are not robust in this situation. The disagreement

Table 5. Output From Regression Models in IPTi Study in Navrongo, Ghana, 2000–2004

Model No.	Model Description	Effect Estimated	PE, %	95% CI	HR	95% CI	OR[a]	95% CI
1	IPTi, Andersen-Gill model	Total	29	22, 35	0.71	0.65, 0.78		
2	IPTi, frailty	Total	29	22, 35	0.71	0.65, 0.78		
3	IPTi, frailty, PTP as TUC	Total	30	22, 36	0.70	0.64, 0.78		
4	IPTi, frailty, adjusted for event dependence[b]	Primary	27	20, 34	0.73	0.66, 0.80		
5	IPTi, frailty, nonsusceptible fraction	Total	16	8, 23	0.84	0.77, 0.92	0.69	0.64, 0.74
6	IPTi, frailty, nonsusceptible fraction, PTP as TUC	Total	16	8, 23	0.84	0.77, 0.92	0.69	0.64, 0.74
7	IPTi, frailty, nonsusceptible fraction, adjusted for event dependence[b]	Primary	21	13, 27	0.79	0.73, 0.87	0.69	0.64, 0.74
8	IPTi, frailty, nonsusceptible fraction, covariates[c]	Total	16	8, 23	0.84	0.77, 0.92	0.68	0.64, 0.74
9	IPTi, frailty, nonsusceptible fraction, PTP as TUC, covariates[c]	Total	17	9, 24	0.83	0.76, 0.91	0.68	0.64, 0.74
10	IPTi, frailty, nonsusceptible fraction, covariates[c], adjusted for event dependence[b]	Primary	22	15, 29	0.78	0.71, 0.85	0.68	0.63, 0.73

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTi, intermittent preventive treatment in infants; OR, odds ratio; PE, protective efficacy; PTP, posttreatment prophylaxis; TUC, time-updated covariate.

[a] The odds ratio is the relative change in the odds of being susceptible due to the intervention.

[b] Event dependence occurs when the primary effect is estimated by stratifying on event order.

[c] Covariates consist of sex, place of residence, and season of birth.

between these analyses highlights the fact that this particular data set does not allow reliable estimation of a nonsusceptible fraction.

DISCUSSION

We have applied regression methods for analysis of recurrent events that consider individual-level heterogeneity in risk (frailty), nonsusceptible subgroups within the population, and event dependence to data from 3 studies of malaria chemoprevention.

SMC consists of monthly treatment courses of antimalarial drugs given "during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk" (27, p. 1). For children in whom this is achieved, complete protection is biologically plausible. In both study sites, there was a large reduction, relative to the placebo group, in the estimated susceptible fraction in the SMC group (56% vs. 23% in Burkina Faso; 44% vs. 17% in Mali). Having accounted for this, we found that the total protective effect of SMC among children not completely protected was then more modest—around 15% in Burkina Faso and 22% in Mali. Comparing this with the estimates of the total protective effect obtained if a nonsusceptible fraction is not accounted for (64% and 70%) suggests that a large

Table 6. Sensitivity Analysis of the Tail Completion Method for Data From the IPTi Study in Navrongo, Ghana, 2000–2004

Model No.	Model Description	Effect Estimated	Zero Tail Completion				Weibull Tail Completion			
			HR	95% CI	OR[a]	95% CI	HR	95% CI	OR[a]	95% CI
5	IPTi, frailty, nonsusceptible fraction	Total	0.84	0.77, 0.92	0.69	0.64, 0.74	0.65	0.58, 0.74	10.2	9.41, 11.0
7	IPTi, frailty, nonsusceptible fraction, adjusted for event dependence[b]	Primary	0.79	0.73, 0.87	0.69	0.64, 0.74	0.66	0.60, 0.73	3.32	3.32[c]
8	IPTi, frailty, nonsusceptible fraction, covariates[d]	Total	0.84	0.77, 0.92	0.68	0.64, 0.74	0.71	0.64, 0.78	1.29	1.28, 1.29
10	IPTi, frailty, nonsusceptible fraction, covariates[d], adjusted for event dependence[b]	Primary	0.78	0.71, 0.85	0.68	0.63, 0.73	0.72	0.66, 0.79[e]	1.23	1.22, 1.24[e]

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTi, intermittent preventive treatment in infants; OR, odds ratio.

[a] The odds ratio is the relative change in the odds of being susceptible due to the intervention.

[b] Event dependence occurs when the primary effect is estimated by stratifying on event order.

[c] Standard error not estimated; CI is not presented.

[d] Covariates consist of sex, place of residence, and season of birth.

[e] Model did not fully converge.

part of the benefit of SMC occurs by providing complete protection to many children.

There were also substantial differences between the total and primary effects of SMC. The rate ratio was further from 1 when models were stratified on event order, in addition to allowing for a nonsusceptible fraction: The estimated primary protective effect, among those individuals who were not completely protected, was 60% in Burkina Faso and 84% in Mali, which is substantially higher than the total protective effect (allowing for a nonsusceptible subgroup) of 15% and 22%. This suggests a strong degree of negative event dependence; that is, experiencing malaria reduces future risk. Although SMC dramatically reduces disease episodes among people with the same prior disease experience (primary effect), the total benefit is slightly diluted by the fact that those children who do experience malaria will be at reduced risk subsequently (secondary effect). This secondary effect could be mediated by faster acquisition of immunity in children who experience malaria, or equivalently, slower acquisition of immunity in children who are protected, leading to increased future risk (the "rebound effect"). In support of this, children who did not receive SMC had a slightly lower incidence than did SMC recipients in the subsequent year, although this was outweighed about 10-fold by the protection during the intervention period (28, 29).

It is important to examine whether survival curves and/or cumulative hazard curves are leveling off before one interprets estimates of the nonsusceptible (completely protected) fraction. For SMC, flattening off of the survival curve with increasing time may reflect the exhaustion of the susceptible population, leaving a completely protected subgroup, but could also be caused by disappearance of mosquitoes at the onset of the dry season. If the former, disease cases would continue to occur in the susceptible population, and this will be apparent from the cumulative hazard plot. If exposure has stopped because of the seasonality of malaria transmission, it may not be possible to interpret the estimated nonsusceptible fraction as completely protected.

The rationale of IPTi is to allow immunity to malaria to develop naturally while limiting the clinical consequences, by providing alternating intervals of protection and exposure during infancy (30, 31). Without considering a nonsusceptible fraction, we found that analysis of the Navrongo trial shows that IPTi reduced the hazard of malaria by about 30%. The primary and total benefits of IPTi appeared to be similar in this context, which may be because this intervention was delivered only in the first year of life, when acquisition of immunity is only just beginning to develop, and therefore prevention of malaria does not have major effects on subsequent risk. Long-term follow-up of children given continuous chemoprophylaxis or placebo in the first year of life did not find large differences in subsequent malaria risk (32), and the differences would be likely to be smaller for IPTi and would be smaller in the shorter period observed in this study.

In the IPTi trial, results were unstable because the survival curves did not level off. Although the Weibull tail completion is more robust than the zero-tail completion in these circumstances, it is still an extrapolation of the past hazard pattern to the future. On the basis of Figure 2C, it appears that the follow-up time has been too short to know whether the extrapolation is reasonable. Cheung et al. (19) previously studied the Navrongo data with a longer follow-up time, up to 23 months, and the zero-tail completion and the parametric tail completion by Weibull distribution (for models without covariates) agreed well. In the present study, the intention was to focus on the intervention period (when IPTi drugs were administered and therefore when assessment of complete protection would be biologically meaningful) but, because the intervention period was short, doing so reduces follow-up time, making it difficult to estimate reliably the nonsusceptible fraction.

A limitation of this study is that we have not considered estimation of time-varying intervention effects and duration of protection, which may be of particular interest in vaccine studies. Nonproportionality of hazards may exist because of faster acquisition of immunity in the control group and also because of waning of the intervention effect. However, even if hazards are not proportional, the estimated hazard ratio from those models without a cured fraction is practically useful, as it represents the average of the covariate effect over the study period (33). For models with a cured fraction, the impact of the violation of the proportional hazards assumption on the parameter estimation warrants further investigation but is beyond the scope of the current paper.

There are no established statistical methods for evaluating the goodness-of-fit of recurrent events survival models, and this is a topic of further research. Whether the aim of analysis should be to fit the data well or to estimate the parameter of interest depends on the research question (34). In this study, we focused on obtaining parameter estimates for intervention effects, assuming different biologically plausible mechanisms rather than formally identifying which model fits the data better. However, if the goal were to develop a prognostic model, then model fit is of primary importance. We did not attempt to estimate formally the degree of event dependence or the secondary effect, because this requires strong parametric assumptions about the event dependence in the hazard function (35); instead, we made an informal comparison between the primary and total effects.

These methods allow simultaneous investigation of partial and complete protections and primary and total intervention effects. As discussed above and in the Web Appendix, simple methods are available to describe efficacy in terms of the number of events or in terms of the proportion completely free of disease. For estimation of the total effect, the Andersen-Gill model is not inferior to the frailty model in randomized trials and is superior in nonrandomized studies. Unless it is desired to quantify the degree of heterogeneity in the population, the frailty model is mainly a building block of the more complex models described above. When the aims of analysis are simple, simple models such as the Andersen-Gill model can be used more widely than they are at present.

Application of the more sophisticated approaches described in this paper to data from studies of other interventions has the potential to improve understanding of the mechanism of protective interventions against malaria and other infectious diseases. Particularly relevant in the near future will be analysis of studies of malaria vaccines, for which the ability to disentangle the different possible benefits of vaccination (partial and complete protection, primary and total effect) would be a major asset.

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