

## Web Appendix

### A simple approach to estimate the effect of an intervention on the risk of disease

A simple approach to calculation of the effect of an intervention (or risk factor) on the risk of disease is described below. Data from the study of seasonal malarial chemoprevention in Burkina Faso (1) are used to illustrate the approach (Web Table 1), showing that SMC approximately halves the risk of experiencing malaria compared with the placebo group.

The risk over the course of the study is estimated using the Kaplan-Meier failure function at the end of the follow-up period.  $P_v$  and  $P_u$  are the probabilities of failure for the intervention and control groups, with standard errors  $S_v$  and  $S_u$ , respectively (e.g., calculated by Greenwood's formula).

The risk ratio between the intervention and control groups  $RR=P_v/P_u$ . The protective efficacy of the intervention in terms of the risk of malaria (the relative change in the proportion who experience any malarial episode) can then be calculated as  $PE=100\times(1- RR)\%$  with 95% confidence interval  $100\times(1-RR\times EF)\%$  to  $100\times(1-RR/EF)\%$ , where EF is the error factor  $\exp(1.96\times \sqrt{[S_v^2/P_v^2 + S_u^2/P_u^2]})$ .

**Web Table 1. Example Calculation of the Effect of SMC on the Risk of Malaria in Boussé, Burkina Faso, 2008-2009**

	Failure function (P)	95% CI	SE (S)
Placebo (u)	0.538	0.517, 0.559	0.0108
SP-AQ (v)	0.241	0.221, 0.262	0.0105
SE of log RR (s)	0.0480		
Error Factor (EF)	1.099		
Risk ratio (RR)	0.447	0.407, 0.492	
Protective Efficacy (PE), %	55.3	50.8, 59.3	

### Reference

1. Konate AT, Yaro JB, Ouedraogo AZ, Diarra A, Gansane A, Soulama I, Kangoye DT, Kabore Y, Ouedraogo E, Ouedraogo A, et al: **Intermittent Preventive Treatment of Malaria Provides Substantial Protection against Malaria in Children Already Protected by an Insecticide-Treated Bednet in Burkina Faso: A Randomised, Double-Blind, Placebo-Controlled Trial.** *PLoS Med* 2011, **8**:e1000408.

**Web Table 2. Additional Regression Output: Frailty and Hazards Ratios for Posttreatment Prophylaxis – Boussé, Burkina Faso, and Kati, Mali, 2008-2009.**

<b>Model No. (Boussé, Burkina Faso)</b>	<b>Frailty</b>	<b>HR for PTP</b>	<b>95% CI</b>	<b>HR for SMC</b>	<b>95% CI</b>	<b>OR for SMC</b>	<b>95% CI</b>
1. SMC, AG model	-	-		0.36	0.32, 0.40	-	
2. SMC, frailty	1.02	-		0.36	0.32, 0.40	-	
3. SMC, frailty, PTP as TUC	1.17	0.12	0.07, 0.20	0.33	0.30, 0.38	-	
4. SMC, frailty, adjusted for event dependence	16.9 <sup>b</sup>	-		0.15	0.13, 0.18	-	
5. SMC, frailty, nonsusceptible fraction	1.00	-		0.85	0.76, 0.96	0.24	0.21, 0.26
6. SMC, frailty, nonsusceptible fraction, PTP as TUC	1.00	0.06	0.04, 0.11	0.81	0.72, 0.91	0.24	0.21, 0.26
7. SMC, frailty, nonsusceptible fraction, event dependence	2.07	-		0.40	0.33, 0.49	0.25	0.22, 0.27
8. SMC, frailty, nonsusceptible fraction, covariates <sup>a</sup>	1.00	-		0.86	0.76, 0.97	0.22	0.20, 0.25
9. SMC, frailty, nonsusceptible fraction, PTP as TUC, covariates <sup>a</sup>	1.00	0.06	0.04, 0.11	0.81	0.72, 0.92	0.22	0.20, 0.25
10. SMC, frailty, nonsusceptible fraction, covariates <sup>a</sup> , adjusted for event dependence	1.94	-		0.43	0.36, 0.51	0.23	0.21, 0.26

  

<b>Model No. (Kati, Mali)</b>	<b>Frailty</b>	<b>HR for PTP</b>	<b>95% CI</b>	<b>HR for SMC</b>	<b>95% CI</b>	<b>OR for SMC</b>	<b>95% CI</b>
1. SMC, AG model	-	-		0.31	0.26, 0.35	-	
2. SMC, frailty	1.32	-		0.30	0.26, 0.35	-	
3. SMC, frailty, PTP as TUC	2.00	0.06	0.03, 0.13	0.28	0.24, 0.33	-	
4. SMC, frailty, adjusted for event dependence	606.0 <sup>b</sup>	-		0.05	0.04, 0.07	-	
5. SMC, frailty, nonsusceptible fraction	1.00	-		0.78	0.67, 0.89	0.26	0.23, 0.29
6. SMC, frailty, nonsusceptible fraction, PTP as TUC	1.00	0.04	0.02, 0.07	0.73	0.64, 0.85	0.26	0.23, 0.30
7. SMC, frailty, nonsusceptible fraction, adjusted for event dependence	2.39	-		0.16	0.12, 0.20	0.26	0.23, 0.30
8. SMC, frailty, nonsusceptible fraction, covariates <sup>a</sup>	1.00	-		0.76	0.66, 0.88	0.22	0.20, 0.25
9. SMC, frailty, nonsusceptible fraction, PTP as TUC, covariates <sup>a</sup>	1.00	0.04	0.02, 0.07	0.71	0.62, 0.82	0.23	0.20, 0.26
10. SMC, frailty, nonsusceptible fraction, covariates <sup>a</sup> , adjusted for event dependence	2.26	-		0.15	0.11, 0.20	0.23	0.20, 0.26

HR, hazard ratio; OR, odds ratio; PTP, posttreatment prophylaxis; SMC, seasonal malarial chemoprevention; TUC, time-updated covariate.

<sup>a</sup> Covariates: sex, village of residence, age group, weight for age category. HR for PTP indicates reduction in hazard within 14 days of a prior malarial episode. For ease of interpretation, HR and OR are also shown for seasonal malarial chemoprevention, as shown in Table 3. Event dependence: the primary effect is estimated by stratifying on event order. The odds ratio is the relative change in the odds of being susceptible due to the intervention.

<sup>b</sup> Frailty estimates from model 4 for both data sets are very large, i.e., 16.9 and 606.0, respectively, mainly because of the low frequency of malarial episodes across the event strata. Therefore, the estimated frailty distribution is highly skewed to the right by a small number of subjects with more than one event, for whom the frailty tends to attain a very large value due to the low background incidence rate that becomes smaller as event stratum increases.

**Web Table 3. Additional Regression Output: Frailty and Hazard Ratios for Posttreatment Prophylaxis – Navrongo, Ghana, 2000-2004**

Model No. (Navrongo, Ghana)	Frailty	HR for PTP	95% CI	HR for IPTi	95% CI	OR for IPTi	95% CI
1. IPTi, AG model	-	-		0.71	0.65, 0.78		
2. IPTi, frailty	1.20	-		0.71	0.65, 0.78		
3. IPTi, frailty, PTP as TUC	1.32	0.25	0.17, 0.38	0.70	0.64, 0.78		
4. IPTi, frailty, adjusted for event dependence	1.07	-		0.73	0.66, 0.80		
5. IPTi, frailty, nonsusceptible fraction	1.00	-		0.84	0.77, 0.92	0.69	0.64, 0.74
6. IPTi, frailty, nonsusceptible fraction, PTP as TUC	1.00	0.17	0.12, 0.25	0.84	0.77, 0.92	0.69	0.64, 0.74
7. IPTi, frailty, nonsusceptible fraction, adjusted for event dependence	1.01	-		0.79	0.73, 0.87	0.69	0.64, 0.74
8. IPTi, frailty, nonsusceptible fraction, covariates <sup>a</sup>	1.00	-		0.84	0.77, 0.92	0.68	0.64, 0.74
9. IPTi, frailty, nonsusceptible fraction, PTP as TUC, covariates <sup>a</sup>	1.00	0.17	0.12, 0.25	0.83	0.76, 0.91	0.68	0.64, 0.74
10. IPTi, frailty, nonsusceptible fraction, covariates <sup>a</sup> , adjusted for event dependence	1.01	-		0.78	0.71, 0.85	0.68	0.63, 0.73

HR, hazard ratio; IPTi, intermittent preventive treatment in infants; OR, odds ratio; PTP, posttreatment prophylaxis; TUC, time-updated covariate.

<sup>a</sup> Covariates: sex, place of residence, season of birth. HR for PTP indicates reduction in hazard within 14 days of a prior malarial episode. For ease of interpretation, HR and OR are also shown for intermittent preventive treatment in infants, as shown in Table 4. Event dependence: the primary effect is estimated by stratifying on event order. The odds ratio is the relative change in the odds of being susceptible due to the intervention.