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Quantifying Effect of Geographic Location on Epidemiology of *Plasmodium vivax* Malaria

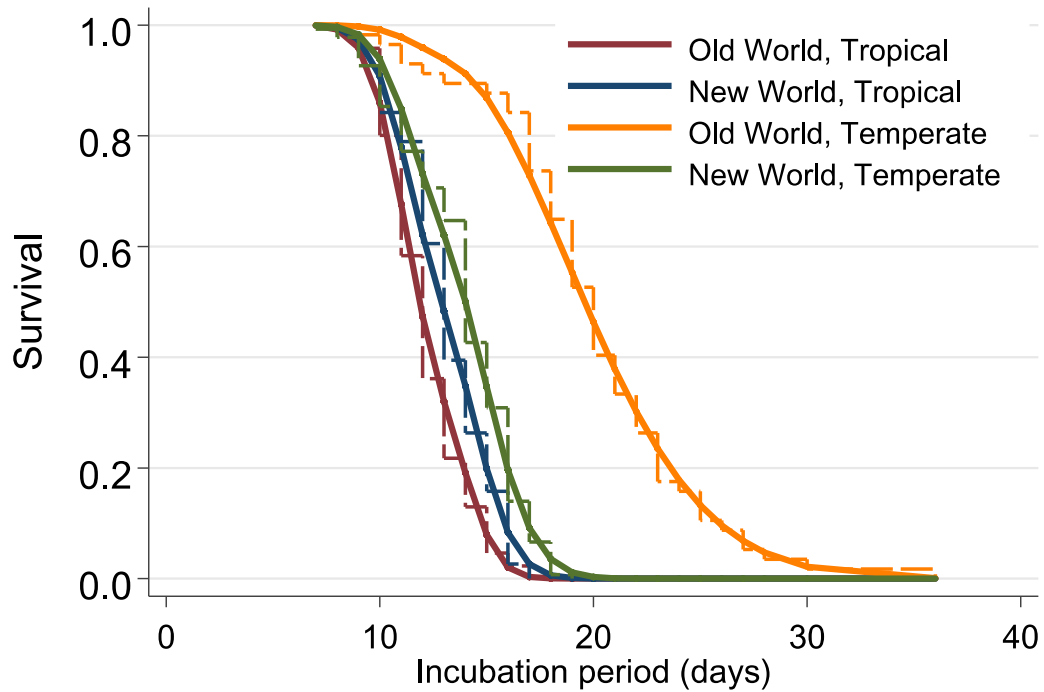
Technical Appendix

I. Detailed Methods

All models were adjusted for neurologic treatment, as a binary variable; the predicted survival times have all been made for a neurologic treatment-free population (baseline predictions, using the `-stpm2- predict -zeros-` option). Intra-class correlation among parasite strain effects was modeled using robust standard errors via Stata's `vce(cluster clustvar)` command (StataCorp, College Station, Texas, USA). The geographic regions were included in the time-to-relapse model as time-varying covariates due to extensive proportional hazard violations. The interaction between Old World, Temperate strains and neurologic treatment was significant and therefore included in the time-to-relapse model.

The proportional hazards assumption was tested using Schoenfeld residuals and by assessing the parallel nature of curves in log-log plots. Both the Akaike and Bayesian Information Criteria (AIC/BIC) were used to assess model parsimony and goodness-of-fit. Finally, for all models deviance residual plots were generated, and any significant outliers were identified and removed from the analysis. Goodness of fit was assessed by using a visual comparison of the fit models to Kaplan-Meier plots; the discriminatory power of the models was assessed with both Harrell's *c* statistic and Somer's *D* statistic, with bootstrapped errors. Statistical analysis was performed by using Stata 12.1; all tests were 2-tailed.

II. Models



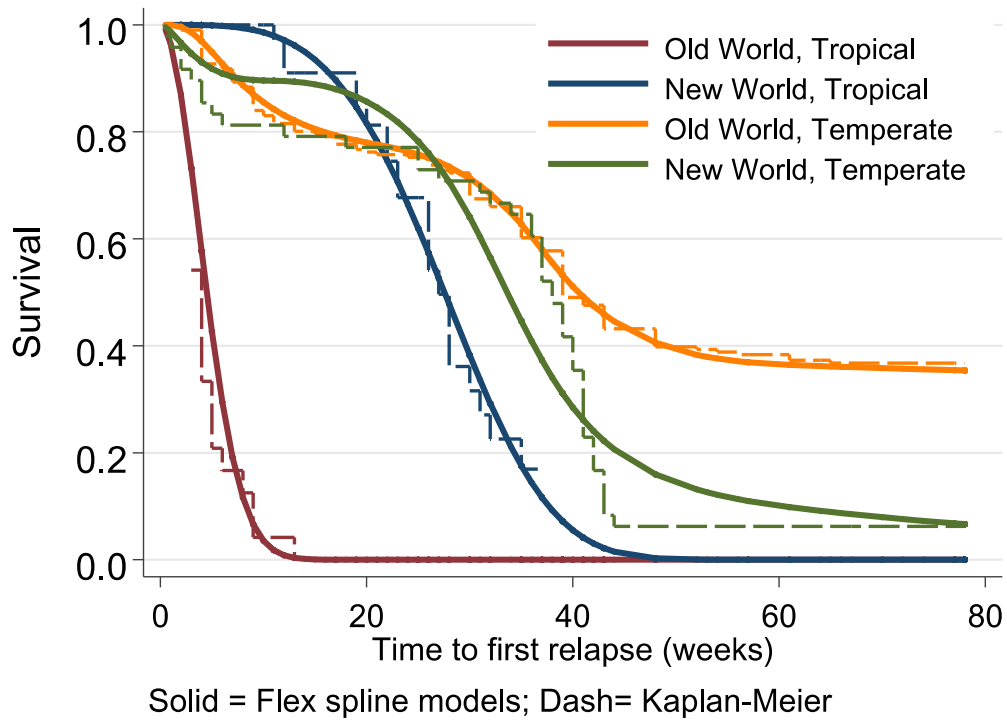
Technical Appendix Figure 1. Comparison of Kaplan-Meier estimates with Royston-Parmar flexible survival model, incubation period.

Technical Appendix Table 1. Royston-Parmar model, incubation period

Variable	Hazard ratio	95% CI	p value
Old World, Tropical	16.79	7.64–36.90	<0.001
New World, Tropical	10.77	4.60–25.24	<0.001
Old World, Temperate	Reference	–	–
New World, Temperate	7.30	3.82–13.96	<0.001
Neurotreatment	0.98	0.68–1.39	0.989

Harrell's c statistic = 0.67 [bootstrapped 95% CI: 0.64–0.71].

Somer's D statistic = 0.36 [bootstrapped 95% CI: 0.29–0.43].



Technical Appendix Figure 2. Comparison of Kaplan-Meier estimates with Royston-Parmar flexible survival model, time-to-first relapse.

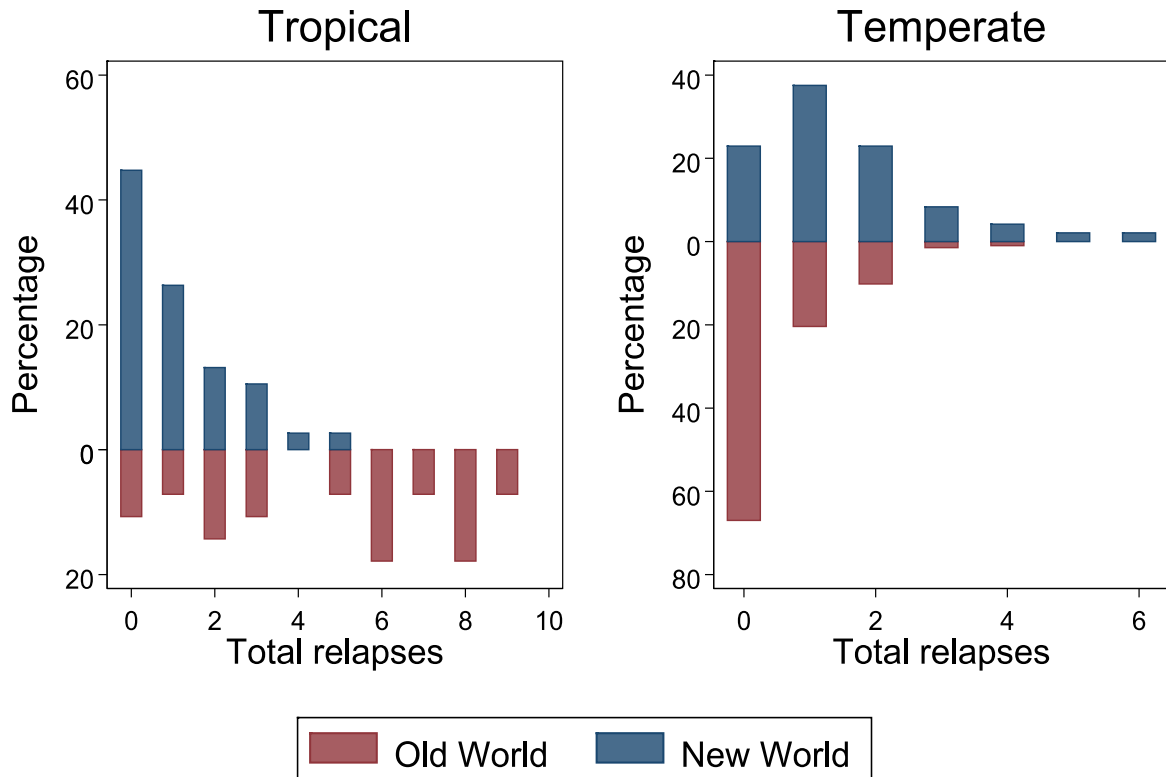
Technical Appendix Table 2. Royston-Parmar model, time-to-first relapse

Variable	HR	95% CI	P value
Old World, Tropical	39.60	9.17–170.91	<0.001
New World, Tropical	0.93	0.36–2.42	0.888
Old World, Temperate	3.15	2.18– 4.56	<0.001
New World, Temperate	Reference	–	–
Neurologic treatment	1.16	0.20–6.74	0.870
Old World, Temperate x neurologic treatment (interaction term)	0.15	0.024–0.92	0.040

Harrell’s c statistic = 0.85 [bootstrapped 95% CI: 0.76–0.93].

Somer’s D 0.69 [bootstrapped 95% CI: 0.54–0.84]

III. Distribution of Relapses



Technical Appendix Figure 3. Comparison of the distribution of total individual relapses within 48 weeks, by region.

IV. Primary Literature References

Technical Appendix Table 3. Primary literature references

Strain	Place, date of origin	Reference(s)
Chesson	Papua New Guinea, circa 1944	(1-8)
Hlebnikovo	Moscow Oblast, 1948	(9)
Holland	Netherlands, circa 1928	(10,11)
Korea	North Korea, 1953	(9)
Leninabad	Tajikistan, 1950	(9)
Madagascar	Madagascar, 1925	(11-13)
McCoy	Florida, USA, 1931	(14)
Moscow	Moscow, 1950	(9)
NICA	Nicaragua, circa 1970	(15)
Nahicevan	Azerbaijan, 1937	(9)
Naro-Fominsk	Moscow Oblast, 1946	(9)
Panama	Panama, circa 1970	(15)
Rjazan	Ryazan, Russia circa 1945	(9)
St. Elizabeth	South Carolina, USA, 1937	(3,7,16-20)
Salvador I	El Salvador, circa 1970	(15)
Salvador II	El Salvador, circa 1970	(15)
South Vietnam	Southern Vietnam, circa 1972	(21)
Vietnam (North)	Northern Vietnam, 1954	(9)
Volgograd	Volgograd, Russia, 1945	(9)
West Pakistan	Pakistan, 1968	(22)
<i>P. vivax multinucleatum</i>	Central China, 1965	(23)

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