Title

Modeling recurrent events: comparison of statistical models with continuous and discontinuous risk intervals on repeated malaria episodes data

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Background

Repetitive events data analysis is quite common in biomedicine. The literature review indicates that most statistical models used for such data are often based on time to the first event or consider events within subject as independent. Also, most applied analysis

data taking into account the non-independence of repeated events within subjects are done with continuous risk interval models which may not be relevant for infectious disease such as malaria.

Objectives

This work aimed to analyze repeated malaria episodes with continuous and discontinuous risk interval models in order to identify the best model estimating malaria risk respective to covariates, in endemic areas.

Methods

Data were collected from July 2005 to July 2007 in Bougala-Hameau, Sikasso, Mali. The study main objective was to compare malaria incidences within 3 different artemisinin based combination therapy (ACT) arms: artesunate/amodiaquine (AS+AQ), artesunate/sulfadoxine-pyrimethamine (AS+SP) and artemether-lumefantrine (AL). The AL arm and the age group ≥ 15 years old were used as reference groups in risk ratio (RR) computing.

We applied both continuous and discontinuous (14 days washout period after each episode treatment) time interval approaches to 4 different models to analyze the data using Stata®: the generalized estimating equation (**GEE**) using Poisson distribution, the extended Cox models (Andersen-Gill counting process –AG and Prentice-Williams-Peterson counting process-PWP-CP) and the frailty model. Models comparisons were based on the magnitude and confidence intervals of RR with respect to relevant covariates, power and goodness-of-fit criteria.

Result

The 780 subjects enrolled in the study, yield a total of 1650 malaria episodes, For the continuous interval analysis, the malaria episode RR for patients in the AS+AQ and AS+SP arms were respectively: 0.9098 (0.8592;0.9633) and 0.9256 (0.87580;0.9782) using the GEE model, 0.6114 (0.4948;0.7554) and 0.6053 (0.4957;0.7391) using Anderson-Gill model, 0.6137

(0.4967;0.7583) and 0.6053 (0.4958;0.7391) using PWP-CP model, 0.4428 (0.3159;0.6207) and 0.4215 (0.3052;0.5819) using Frailty model.

For the discontinuous interval analysis, the malaria episode RR for patients in the AS+AQ and AS+SP arms were respectively: 0.9098 (0.8592;0.9633) and 0.9256 (0.8758;0.9782) using the GEE model, 0.6111 (0.4946;0.7551) and 0.6051 (0.4955;0.7388) using Anderson-Gill model, 0.6135 (0.4965;0.7580) and 0.6051 (0.4955;0.7388) using PWP;CP model, 0.4421 (0.3153;0.6197) and 0.4211 (0.3049;0.5816) using Frailty model.

For the continuous risk interval, the malaria episodes RR for the patients in the age groups < 5 years using GEE, Anderson-Gill, PWP-CP and Frailty models were respectively: 2.0854 (1.3211;3.2919), 4.0168 (2.1656;7.4509), 4.0156 (2.1648;7.4487) and 10.2148 (3.9227;26.5997).

For the discontinuous risk interval, the malaria episodes RR for the patients in the age groups < 5 years using the GEE, Anderson-Gill,

PWP-CP and Frailty models were respectively: 2.0854(1.3211;3.2919), 4.0169(2.1655;7.4509), 4.0157(2.1649;7.4487) and 10.2113(3.9226; 26.5821).

Discussion and Conclusion

Discontinuous and continuous intervals models gave similar RRs estimated in all models. This may be due to the short washout period in relative to the long follow-up period of the study. Still, the discontinuous intervals models should be preferred because it is more appropriate in the epidemiological point of view to take into account the time a subject is not at risk to a disease in a given period of time.

Anderson-Gill, PWP-CP and Frailty models estimated RRs with higher magnitude compared to GEE Poisson family model which showed also an overdispersion sign and poor goodness-of-fit.

Key words

Repeated events, Malaria, Discontinuous interval, Risk ratio, clinical trials