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FACULTY OF SCIENCES

Master of Statistics: Biostatistics

Masterproef

Statistical modelling of solicited symptoms in vaccine clinical trials

Promotor :
Prof. dr. Dan LIN

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Dr. EMMANUEL ARIS
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Bedilu Alamirie Ejigu

Master Thesis nominated to obtain the degree of Master of Statistics , specialization Biostatistics

Maastricht University

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UNIVERSITEIT VAN DE TOEKOMST

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Interuniversity Institute for Biostatistics and Statistics and Statistical Bioinformatics

Statistical Modeling of Solicited Symptoms in Vaccine Clinical Trials

By

Bedilu Alamirie Ejigu

Internal supervisor: prof.dr. Dan Lin
External supervisors: dr. Emmanuel Aris
dr. Fabian Tibaldi

Thesis submitted in partial fulfillment of the requirements for the Degree of Master of Science in Biostatistics of Hasselt University

September, 2011

Certification

I declare that this thesis was written by me under the guidance and counsel of my supervisors.

.....	Date.....
Bedilu Alamirie Ejigu	Student

We certify that this is the true thesis report written by Bedilu Alamirie Ejigu under our supervision and we thus permit its presentation for assessment.

.....	Date.....
prof.dr. Dan Lin	Internal Supervisor

.....	Date.....
dr. Emmanuel Aris	External Supervisor

.....	Date.....
dr. Fabian Tibaldi	External Supervisor

Dedication

I dedicate this thesis

to my lovely family, who scarified their life opportunities to educate me and provided me endlessly in both financial and moral support

And

to Vlaamse InterUniversitaire Raad (VLIR) for giving me the chance to study MSc. in biostatistics

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Last but not least, I wishes to express my love and gratitude to my beloved families; for their unlimited advice, pray and endless love, through my life.

Bedilu Alamirie Ejigu

September 10, 2011

Diepenbeek, Belgium

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Summary

In many clinical trials, in order to characterize the safety profile of a subject with a given treatment, multiple measurements are taken over time. Mostly, measurements taken from the same subject are not independent. Thus, in cases where the dependent variable is categorical, the use of logistic regression models assuming independence between observations taken from the same subject is not appropriate. In this report, marginal and random effect models that take the correlation among measurements of the same subject into account were fitted. The models were applied to data obtained from a phase-III clinical trial on a new meningococcal vaccine. The goal is to investigate whether children injected by the candidate vaccine have a lower or higher risk for the occurrence of specific adverse events than children injected with licensed vaccine, and if so, to quantify the difference. We extended the random intercept partial proportional odds model and generalized ordered logit model which assumes identical variability for different category levels by introducing category specific random terms. This is very appealing to study the association between different category levels. Since three outcomes (Pain, Redness, Irritability) are measured on the same child, in addition to analyzing a single outcome variable at a time, joint mixed models for a set of different outcomes were studied to see the association between outcomes. Further, whether the new vaccine has identical effect across different outcomes or not, were investigated based on the joint model and non-significant result was obtained.

In conclusion, in both marginal and random effects model, significant difference between the two vaccines were found for at least moderate and severe intensity levels of pain adverse event and all and at least moderate intensity levels of redness. For irritability adverse event, significant difference between the two vaccines were not observed.

Key word: Generalized estimating equations, Generalized linear mixed models, Generalized ordered logit models, Joint generalized mixed models, Meningococcal vaccine, Partial proportional odds models

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List of Abbreviations

AIC	Aikakes Information Criterion
d.f	Degrees of Freedom
GEE	Generalised Estimating Equations
GLMM	Generalized Linear Mixed Models
GOLM	Generalized Ordered Logit Models
ML	Maximum Likelihood
$logit(\mu_{ij})$	$log[\mu_{ij}/1-\mu_{ij}]$
ll	loglikelihood
OR	Odds Ratio
Parm	Parameters
POM	Proportional Odds Models
PPOM	Partial Proportional Odds Models
R^2_{ms}	Max-scaled R^2
Trt	Treatment
QIC	Quasi-Likelihood Information Criterion
$\chi^2_{(k)}$	Chi-square distribution with k degree of freedom
95%CI	95 percent Confidence Interval

1 Introduction

1.1 Background

Pharmaceutical companies develop vaccines which contains an agent that resembles a disease-causing microorganism in order to improve immunity to a particular disease. When a company aims to bring a new vaccine product to market, the safety profile of the vaccine is assessed in different ways to ensure that it is safe. In most cases, the clinical safety evaluation of the vaccine is performed regarding two specific aspects (Bergsma *et al*, 2011). First, the occurrences of a certain number of local or general symptoms are checked pro actively via diary cards recording the occurrence or absence of the symptom during a certain number of days after the injection. These symptoms are usually called solicited symptoms. To properly assess the safety profile of the new vaccine, subjects injected with the vaccine are evaluated for different adverse event outcomes such as pain, redness and irritability over time.

In most cases, for ease of recording a standard intensity scale that expresses the level of adverse event is often used and contains a certain number of possible intensity of the symptom. Subjects are then asked to fill in their maximum daily intensity of each reported solicited symptom during the entire solicited symptom follow-up period in the diary card. Based on such scales, one can then establish the vaccine and outcome relationship and test whether subjects injected by the candidate vaccine have a lower or higher risk for the adverse event than subjects injected by the licensed vaccine.

This report will focus on the analysis of repeated categorical measurements concerning solicited symptoms coming from vaccine clinical trials. Specifically, the safety profile of a candidate vaccine for meningococcal disease which is a life-threatening illness caused by strain of bacteria called Neisseria meningitides will be assessed. Currently different vaccines such as Menactra, Menveo and Mencevax are available against Meningococcal infection(*http://www.fda.gov/BiologicsBloodVaccines/Vaccines/*).

The safety of the candidate vaccine for meningococcal disease is evaluated by comparing the level of redness, pain and irritability adverse events measured by ordinal scale at each followup day to the ones of a licensed vaccine. We will consider here a 4-day follow-up period, the day of vaccination being denoted as day 1 and taken as a reference day in further analysis. Analysis methods presented hereafter will take the ordinal and correlated nature of the data due to repeated measures from the same subject using

two model families: the marginal model family which is characterized by the specification of the mean function and the random effects family that focuses on the expectation conditional upon the random effects studied. The analysis will be done for primarily measured ordinal outcome as well as for the dichotomized outcome (Section 1.3). Generalized estimating equation (Liang and Zeger, 1986) from marginal models are usually preferred to evaluate the overall adverse events as a function of treatment group and visiting day. While, in a random effects approach (Berslow and Clayton, 1993), the response rates are modeled as a function of covariates and parameters specific to a subject. The two model families do not only differ in the questions they address, but also in the way they deal with the dependencies between the observations. This difference way of handling the within child association leads the two models families for different purpose as mentioned by different authors (Laird and Ware, 1982; Agresti, 2002; Fitzmaurice *et al*, 2004). As a result, interpretation of the regression model parameters are different. A brief review on these models will be presented in Sections 2.1 and 2.2. For the partial proportional odds random intercepts model which assume identical baseline variability within the subject being in different categories of the outcome, extensions that allow to have different random effect variability at each category proposed. The advantage of the extended model over the commonly used random effects model is that, it enables us to study the association between different category levels of the solicited symptoms (i.e. low, at least moderate and severe levels of intensity).

The three outcomes redness, pain and irritability are measured from the same child, to study the safety profile of the candidate vaccine. Thus, in addition to analyzing one single outcome variable at a time, joint mixed models (Fieuws and Verbeke, 2004) for a set of different outcomes are studied to see how the association between outcomes evolves over time. Moreover, in order to test whether the treatment effect is similar across different outcomes or not, the binary outcome joint model studied.

This report is organized as follows: Section 1.2 presents the objective of the thesis followed by Section 1.3 that describes the data set. Section 2 emphasizes on the statistical methodologies used to analyze repeated categorical data. A brief review of quasi-likelihood based marginal and likelihood based random effect models for binary and ordinal outcome variable with some terminologies used, will be presented under this section. Results for the considered case study are presented in Section 3. Finally, Section 4 summarizes results of the analysis and discuss some extensions of the models used.

1.2 Objective of the Thesis

The main goal of this thesis is, to use statistical techniques to investigate whether children injected by the candidate vaccine have a lower or higher risk for the occurrence of specific adverse events (Pain, Redness, Irritability) than children injected with licensed vaccine. And if there is a difference, to describe how does this difference between treatment groups develops over time, based on a case study from a phase-III clinical trial.

Moreover, instead of modeling one adverse event at a time, modeling jointly all the observed adverse event at a time is secondary objectives of the study. In general, we aim to analyze repeated categorical measurements concerning solicited symptoms coming from vaccine clinical trials and to evaluate statistical techniques for such type of data.

1.3 Case Study: Phase-III Clinical Trial

The data used in this report come from a phase III clinical trial evaluating the safety profile of a new vaccine for meningococcal infection. In the study, children with ages from 12 to 15 months are randomly assigned to the candidate and licensed vaccine with 3:1 ratio respectively. Children after recruitment in the study were injected with the vaccine at the upper left thigh at day 1, and the parents of the children were asked to fill in diary cards indicating whether or not their children experienced either pain, redness, or irritability during the follow-up period of 4 days (Bergsma *et al*, 2011). The level of solicited symptom (Pain, Redness, or Irritability) were measured using ordinal scale. Pain and redness were measured only at injection site. Table 1 below summarizes definition of solicited adverse event intensities.

For confidentiality reasons, only part of the data are used in this report. Further, only subjects with no missing values are taken into account here. The data used in this report were collected from 1880 children, of which 1381 (73.46%) were assigned to the active treatment group (candidate vaccine for meningococcal) and the remaining 499 (26.54%) were assigned to the control group (licensed vaccine). Data from different children were assumed to be independent, but due to repeated measurements (of same child) over time, correlation is expected to exist.

The primarily collected data consist of ordinal outcomes Y_{ij} for the observed solicited symptoms (Table 1) where Y_{ij} is the outcome for the i^{th} child (i=1,2,... 1880) at measurement day j (j=1,2..4). In order

Table 1: *Variable Description*

Adverse Event	Intensity	Description
Pain	0	Absent
	1	Minor reaction to touch
	2	Cries/protests on touch
	3	Cries when limb is moved/spontaneously painful
Redness	0	Absent
	1	Diameter of redness $\leq$10 mm
	2	Diameter of redness 10 - 30 mm
	3	Diameter of redness $\geq$30 mm
Irritability	0	Behavior as usual
	1	Crying more than usual/no effect on normal activities
	2	Crying more than usual/interferes with normal activities
	3	Crying that cannot be comforted/interferes with normal activities

to compare the effect of the treatment group at a certain level of intensity with the other level of intensity dichotomization will be done to the outcome variable Y_{ij} as follows.

- To model all observed symptom versus no symptom:

$$W_{ij} = \begin{cases} 1 & \text{if } Y_{ij} \geq 1, \\ 0 & \text{otherwise.} \end{cases}$$

- Observing at least moderate intensity levels of the symptom versus less than moderate levels:

$$X_{ij} = \begin{cases} 1 & \text{if } Y_{ij} \geq 2, \\ 0 & \text{otherwise.} \end{cases}$$

- Severe intensity level of the adverse event versus lower than severe adverse event:

$$Z_{ij} = \begin{cases} 1 & \text{if } Y_{ij} = 3, \\ 0 & \text{otherwise} \end{cases}$$

At the time of vaccine injection (first day), 67.3%, 57.7%, and 41.3% of the children, who enrolled for the candidate vaccine showed all intensity levels of symptom for pain, redness, and irritability, respectively (Table 10, Figure 1). The respective observed percentages treated by the licensed vaccine are 66.7%, 62.1%, and 44.3%, respectively. In both, groups of children, assigned to the candidate and licensed vaccine, the proportions of observing those symptoms seem to decrease over time and at the last occasion (day 4) 7.4%, 17.1%, and 17.8% of children in the candidate vaccine and 9.8%, 23.0%, and 23.0% of the

children for control group showed pain, redness, and irritability. Figure 1 shows the overall percentage of observing those solicited symptoms at each visiting day by treatment group. For example, at first day, the percentage of children who showed pain symptoms of any intensity level seems to be similar in both treatment groups (Figure 1, left top panel). The graphical exploration reveals that the new vaccine for

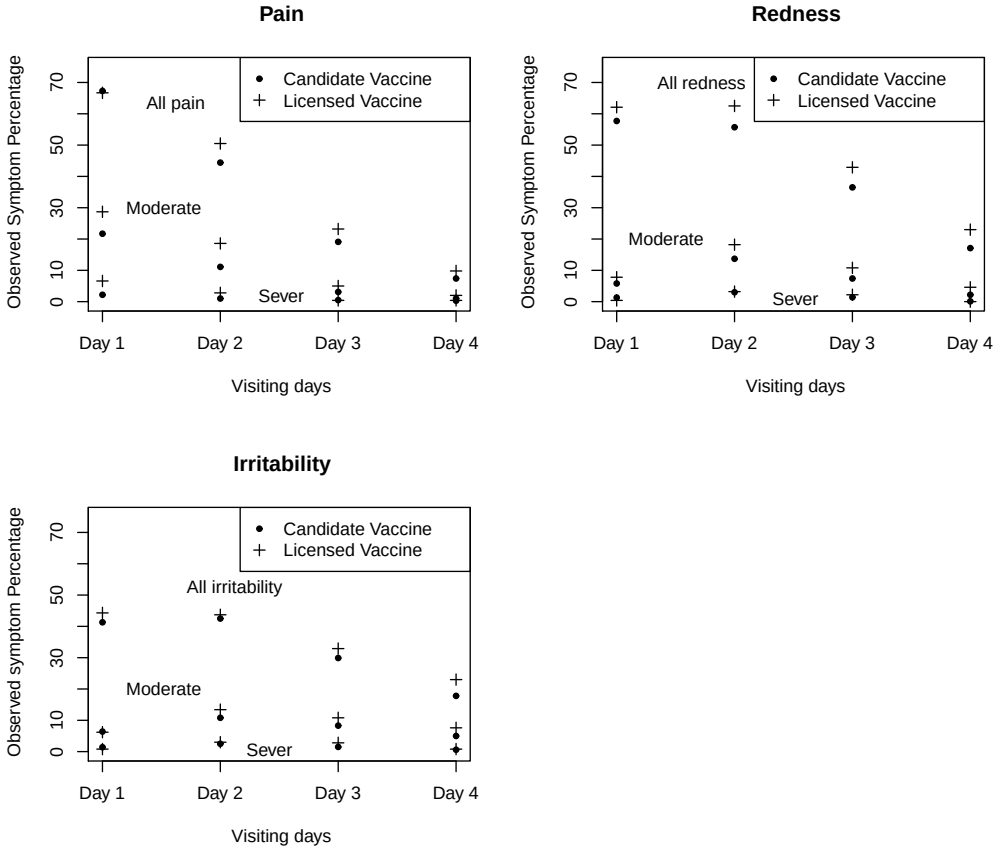

Figure 1: *Percentage of observed solicited symptoms by treatment group at each day*

meningococcal disease seems to somewhat results in slightly less occurrence of adverse events as compared with the licensed vaccine. However, statistical testing taking in to account the repeated nature of the data is needed to confirm this observation. Several models handling the correlated nature of the data are explained in the next Section.

2 Statistical Methodology

The types of model for data analysis highly depend on the nature and measurement scale of the outcome variable. In this study, the level of measurement of the variable of interest is ordinal (Table 1). Ordinal data are a specific form of categorical data, where the order of the categories is of importance. Models for binary data have been extended to ordinal categorical outcomes (Aitchison and Silvey, 1957; Genter and Farewell, 1985; Agresti, 2002).

Due to repeated measurements taken from the same subject over time, observations can not be considered as independent. Thus, in such cases, the use of binary (or multinomial) logistic regression model assuming independence of observations taken from the same subject may not be appropriate. In the subsequent Sections, appropriate marginal and random effect models that account for the correlated nature of the data will be presented. Specifically, generalized estimating equations from the marginal model family and mixed effect logistic regression models, partial proportional odds random effects model, generalized ordered logit random effects model and joint generalized linear mixed models from random effects model families will be discussed.

2.1 Marginal Models

In the marginal models settings, the responses are modelled marginalized over all other responses (Molenberghs and Verbeke, 2005). Generalized estimating equations (GEE) introduced by Liang and Zeger (1986) is an intuitively appealing way to model longitudinal data in marginal models framework. The interest in standard GEE focuses on the relationship between the covariates and the probability of response while response correlation is treated as a nuisance parameter. Since the time dependence between the responses within subject is not the focus of the research question, it is regarded as a nuisance characteristic of the data. Thus, second-order GEEs (Zhao and Prentice, 1990) and GEE with odds ratio (Liang *et al*, 1992) will not be discussed further in this report. All the considered marginal models are based on the standard GEE (GEE1) methods.

2.1.1 Marginal Models for Binary Outcomes

To illustrate the model mathematically in the context of the data set, consider the binary response W_{ij} for the i^{th} subject at the j^{th} assessment day. In the model formulation, time-varying covariate day (represented as Day_{ij}) as well as the fixed covariate treatment group (Trt_i) will be considered as predictor variables. The distribution of the binary outcome W_{ij} is assumed Bernoulli (the same for X_{ij}, Z_{ij}) with probability of success at j^{th} occasion for the i^{th} subject, μ_{ij} = E(W_{ij})=$P(W_{ij} = 1|Day_{ij}, Trt_i)$. This distribution of each W_{ij} determines how Var(W_{ij}) depends on μ_{ij}. The mean response for child i at follow-up day j is related to the covariates via the logistic model as follow;

$$logit(\mu_{ij}) = \beta_0 + \beta_{1j} Day_{ij} + \beta_2 Trt_i \tag{1}$$

where, Trt_i takes the value 1 when the subject is assigned to the candidate vaccine and zero otherwise. Day_{ij} has four levels and equal to 1 when W_{ij} observed at day j for subject i, zero otherwise (the first day (day 1) taken as a reference day). The parameter $\boldsymbol{\beta}$'s here have population averaged interpretations, specifically β_{1j} is the log odds of observing the outcome W_{ij}=1 instead of W_{ij}=0 at visiting day j under the control group. The parameter β_0 is the intercept of the model, β_2 is the log odds ratio of the response between the two treatment group at a given day.

Once we have specified the marginal model (1) for each outcome W_{ij}, we need to choose the correlation structure among W_{ij}. For the assumed working correlation structure, the GEE method uses the data to estimate the correlations. Even if the guess about the correlation structure is poor, valid standard errors are obtained which result from an adjustment of GEE method using the empirical dependence of the actual data exhibit (Liang and Zeger, 1986; Agresti, 2002).

In addition to model (1), to see the effect of the treatment at each visiting day and to test the homogeneity of this effect at each follow up day, the following model will be fitted.

$$logit(\mu_{ij}) = \beta_0 + \beta_{1j} Day_{ij} + \beta_2 Trt_i + \beta_{3j} Trt_i * Day_{ij} \tag{2}$$

In GEE, estimates of the parameter $\boldsymbol{\beta}$ are obtained by solving the generalized estimating equations

$$S(\boldsymbol{\beta}) = \sum_{i=1}^{N} \frac{\partial \mu_{\mathbf{i}}}{\partial \boldsymbol{\beta}'} (A_i^{1/2} R_i(\boldsymbol{\alpha}) A_i^{1/2})^{-1} (\mathbf{w}_i - \mu_i) = 0 \tag{3}$$

where A_i is a diagonal matrix with the marginal variance $\nu(\mu_i)$=$Var(\mathbf{w}_i)$ on the main diagonal and $R_i(\boldsymbol{\alpha})$ is the working a correlation matrix that depend on the unknown parameter vector $\boldsymbol{\alpha}$.

Liang and Zeger(1986) showed that using the method of moments concept, when the marginal mean has been correctly specified and when the mild regularity condition hold, the estimator $\hat{\beta}$ obtained by solving the score equation (3) is consistent and asymptotically normally distributed with mean β and asymptotic variance covariance matrix.

2.1.2 Marginal Models for Ordered Categorical Data

Lipsitz, Kim, and Zhao (1994) described how to extend GEEs to multinomial data. When the response categories are ordered, the use of this ordering yield more parsimoniously parameterized models. Further, the resulting odds ratios based on the dichotomized outcome (Section 1.3) may depend on the cut point chosen to dichotomize the outcome (McCullagh, 1980; Hosmer and Lemeshow, 2000). Models that use cumulative probabilities like proportional odds models, adjacent categories logits and Continuation ratio logits (McCullagh, 1980; Ananth and Kleinbaum, 1997; Agresti, 2002) are possible choices for modelling ordinal data. Continuation-ratio model is suited when the underlying outcome is irreversible [1] and adjacent-category model designed for situations in which the subject must 'pass through' one category to reach the next category (Liu and Agresti, 2005) are not used in this analysis.

Proportional Odds Model (POM)

The unique feature of proportional odds model (POM) is that the odds ratio for each predictor is taken to be constant across all possible collapsing of the response variable. When the assumption is met, odds ratios in a POM are interpreted as the odds of being lower or higher on the outcome variable across the entire range of the outcome (Scott *et al*, 1997). In POM, reversing the direction of the response levels will change the direction of the effects but not their magnitude or significance (McCullagh, 1980; Hosmer and Lemeshow, 2000).

Let μ_{ijk} be the probability of the i^{th} subject at the j^{th} visiting day being in the response category k, μ_{ijk} =P($y_{ij} = k$). Further, let the cumulative probability of the response in category k or above represented

[1] Irreversible in the sense that upon attaining a certain level of one outcome, subject's response cannot revert to a lower level.

by $\Pi_{ijk} = P(Y_{ij} \geq k)$. The lowest outcome which corresponds to a baseline level, $\Pi_{ij0} = \mu_{ij0} + \mu_{ij1} + ..+\mu_{ijk} = 1$; $\Pi_{ij1} = \mu_{ij1} + ..+\mu_{ijk}$; $\Pi_{ij2} = \mu_{ij2} + ..+\mu_{ijk}$; $\Pi_{ijk} = \mu_{ijk}$. The POM is represented as follows;

$$logit(\Pi_{ijk}) = \beta_{0k} + \beta_{1j} Day_{ij} + \beta_2 Trt_i \tag{4}$$

where, k is the level of the ordered category. The parameter β_{0k} is the intercept for category k, usually considered as nuisance parameters of little interest (Agresti, 2002). Model (4) assumes an identical effect of the predictors for each cumulative probability. Specifically, the model implies that odds ratios for describing effects of explanatory variables on the response variable are the same for each of the possible ways of collapsing the response to a binary variable. Violation of this assumption leads to an incorrect model. In the considered case study, this assumption does not hold (see Section 3.1.2 and 3.2.2).

In summary, marginal models for longitudinal data separately model the mean response and within child association among the repeated responses. The aim is to make inference about the mean response, whereas the association is regarded as a nuisance characteristics of the data that must be accounted for to make valid inferences about changes in the population mean response. This separate specification of the mean and within child association has an important implication on parameter interpretation. Since the GEE approach does not specify completely the joint distribution, likelihood-based methods to compare models and to conduct inferences about the parameter are not available. To draw inference in a quasi-likelihood approach, Boos (1992), Rotnitzky and Jewel (1990) illustrates a generalization of score tests for different models including models based on GEE.

2.2 Generalized Linear Mixed Models

In many clinical/biomedical researches the longitudinal responses are not necessarily continuous. As a result, the general linear models and general linear mixed models might not apply. Thus, when the longitudinal responses are discrete, Generalized Linear Models (McCullagh and Nelder, 1989) are required to relate changes in the mean responses to covariates. Generalized linear Mixed Models (Berslow and Clayton, 1993) are obtained from GLMs by incorporating random effects in to the linear predictors. Such random effect models can account for a variety of situations, including subject heterogeneity, unobserved covariates and have conditional interpretation with subject-specific effects (Liu and Agresti, 2005). The

assumptions made in GLMMs are (i) conditional on the subject-specific random effect (b_i) and covariates (Day_{ij}, Trt_i) the distribution of Y_{ij} belongs to exponential family (ii) the random effect b_i follows a normal distribution with a mean 0 and variance $\sigma^2_{b_i}$ and (iii) conditional on b_i the repeated measures y_{ij} are independent. In the context of the case-study, the generalized linear mixed model formulations for the binary and ordinal outcomes are presented in the following Subsections.

2.2.1 Random Effect Models for Binary Outcomes

For the considered dichotomized version of the outcome (Section 1.3), μ_{ij} the conditional mean of W_{ij}, given the random effect and known covariates ($\mu_{ij} = E(W_{ij}|Day_{ij}, Trt_i, b_i)$) is linked to the linear predictor through a logit link function as follows:

$$logit(\mu_{ij}) = \beta_0 + \beta_{1j} Day_{ij} + \beta_2 Trt_i + b_i \tag{5}$$

where b_i is subject specific parameter for the i^{th} child, β_{1j} and β_2 are used to measure similar effect as mentioned in model (1) but now conditional upon the given child. The parameter β_2 interpreted as the log odds ratio comparing a child injected with the candidate vaccine with another child injected by the licensed vaccine, both having identical covariate and random-intercept values to observe all intensity levels of pain. Unlike the linear mixed model (Laird and Ware, 1982), under non-linear mixed models, fixed effects only reflect the conditional effects of the covariates. The conditional mean as a function of treatment group and visiting day is given by:

$$E(W_{ij}|b_i) = \frac{exp(\beta_0 + b_i + \beta_{1j} Day_{ij} + \beta_2 Trt_i)}{1 + exp(\beta_0 + b_i + \beta_{1j} Day_{ij} + \beta_2 Trt_i)}$$

Zeger et al (1988) derived an approximative relationship for the population averaged parameters (from GEE) and subject specific parameters with random effect in the linear predictor given by:

$$\frac{\hat{\beta}^{RE}}{\hat{\beta}^{M}} = \sqrt{c^2 \sigma^2_{b_i} + 1}$$

where $\hat{\beta}^{RE}$ and $\hat{\beta}^{M}$ are parameter estimates based on random effect and marginal models respectively, $\sigma^2_{b_i}$ is the variance of the random intercepts and $c^2 = 16\sqrt{3}/15\pi$. Hence, from this relationship it is clear that, conditional effects are usually larger than marginal effects, and increase as the variance ($\sigma^2_{b_i}$) increase. The estimated standard deviation ($\hat{\sigma}_{b_i}$) for the random intercept used as a summary of the degree of

heterogeneity of a population. $\hat{\sigma}_{b_i}$ equal to zero implies that the logistic normal model (5) simplifies to a logistic regression model treating all observations as independent. The size of estimated variance ($\hat{\sigma}^2_{b_i}$) used to determine the scale on which the fixed effects should be judged. Moreover, the random part can be interpreted using measures of dependence. This is due to the fact that, unobserved heterogeneity between subject induces within subject dependence. Thus, in logit random intercept model, correlation(ρ) of the latent responses at any two occasion j and j' given by $\rho = \sigma^2_{b_i}/(\sigma^2_{b_i} + \pi^2/3)$ (Fitzmaurice *et al*, 2009).

2.2.2 Random Effect Models for Ordinal Outcomes

When proportional odds assumption is met and child specific parameter estimates are of interest, POM discussed in Section 2.1.2 can be easily fitted in random effects modeling framework by introducing random effects specific to child in model (4). In this model, the ordinal nature of the response is taken into account by considering the cumulative probabilities, 1= Π_{ij0}(=P(y_{ij}) $\geq$ 0) $\geq$ Π_{ij1}(=P(y_{ij}) $\geq$ 1) ... $\geq$ Π_{ijk}(=P(y_{ij}) $\geq k$). The model can be written as follows:

$$logit(\Pi_{ijk}) = \beta_{0k} + \beta_{1j} Day_{ij} + \beta_2 Trt_i + b_i \tag{6}$$

where b_i is the random effect specific to child i and β_{0k} is the intercept for category k. The parameters β_{1j} and β_2 represents conditional log-odds ratios of the grouped categories superior to the cutoff (k) compared to the categories inferior to k. To relax the strong assumption of identical log-odds ratio for the outcome by the covariate association in POM, partial proportional odds model (PPOM) and generalized ordered logit model (GOLM) have been developed and can be easily fitted using NLMIXED procedure (SAS code given in Appendix).

Partial Proportional Odds Model (PPOM)

When the proportional odds assumption applies to some but not all of the covariates, the partial proportional odds model (7) can be used. In this model only the effect of treatment allowed to vary across the category levels, while the effects of day fixed at each category as done in POM.

$$logit(\Pi_{ijk}) = \beta_{0k} + \beta_{1j} Day_{ij} + \beta_{2k} Trt_i + b_i \tag{7}$$

where, Π_{ijk} is the cumulative probability of the outcome ($Y_{ij} \geq k$) conditional upon other covariates, k

is the level of the ordered category, β_{1j} is the effect of the Day_{ij} at the k^{th} category level of the outcome and β_{2k} measure the log odds effect of the treatment at k^{th} category level of the outcome given children in both treatment groups having identical covariate and random-intercept, b_i is child specific parameter to the i^{th} child and β_{0k} is the intercept for category k. The covariates and random effects determine conditional mean Π_{ijk} and the regression coefficients $\boldsymbol{\beta}$ can be therefore interpreted as conditional effects of covariates (child-specific), given the random effects b_i. For instance, the parameter β_{2k} interpreted as the log odds ratio comparing a child injected with the candidate vaccine with another child injected by the licensed vaccine, both having identical covariate and random-intercept values on the k^{th} category of the outcome.

Generalized Ordered Logit Model (GOLM)

This general model permits to each covariate to have different effect at each category of the outcome. For the ordinal outcome variable Y_{ij} with predictors treatment group (Trt_i) and the measurement day (Day_{ij}), the cumulative log odds are modeled as

$$logit(\Pi_{ijk}) = \beta_{0k} + \beta_{1jk}Day_{ij} + \beta_{2k}Trt_i + b_i \tag{8}$$

where, Π_{ijk}, β_{2k}, β_{0k} and b_i have the same meaning as mentioned under model (7), now β_{1jk} has also category specific estimate like β_{2k}. Model (7) is special cases of model (8) when the effect of day is similar at each category. The disadvantage of model (8) is the larger number of parameters to be estimated as compared with previous one. But, this higher in number of parameter can not be considered as a disadvantage in a situation when model (8) better fits the data.

We can extend model (7) and (8) which assume identical baseline variability within the child being in either of the categories, by allowing to have different random effects b_{ik} at each category.

$$logit(\Pi_{ijk}) = \beta_{0k} + \beta_{1jk}Day_j + \beta_{2k}Trt_i + b_{ik} \tag{9}$$

Where b_{ik} is the random intercepts for each category of the model and the vector of these random effects assumed to follow a multivariate normal distribution with mean vector zero and (co)variance matrix $\mathbf{D}$

(i.e. $b_{ik} \sim N(\mathbf{0}, \mathbf{D})$). where $\mathbf{D}$ is k x k general covariance matrix with elements d_{rs}.

$$\mathbf{D} = \begin{pmatrix} d_{11} & \cdots & d_{1k} \\ \vdots & \ddots & \vdots \\ d_{k1} & \cdots & d_{kk} \end{pmatrix} \tag{10}$$

The elements of the matrix, d_{rs} represents the (co)variance between b_{ir} and b_{is} (r=1,2,3; s=1,2,3). The advantage of the extended model over model (7) and (8) is that, it enables us to study the association between different category level using b_{ik} covariance matrix. All the considered random-effects models are fitted by maximization of the marginal likelihood, obtained by integrating out the random effects. Since the likelihood function does not have a closed form in this case, model fitting is not an easy task. Numerical approximations will be used (Molenberghs and Verbeke, 2005) to maximize the marginal likelihood. The adaptive Gaussian quadrature which estimates the likelihood by approximating the integral with Newton-Raphson optimization technique will be applied to fit the model using the NLMIXED procedure in SAS.

In GLMMs, although in practice one is usually primarily interested in estimating the parameters in the marginal distribution for Y_{ij}, it is often useful to calculate estimates for the random effects b_i as well. They reflect between-subject variability, which makes them helpful for detecting special profiles (i.e. outlying individuals). Moreover, estimates for the random effects are needed whenever interest is in prediction of subject-specific evolutions.

2.2.3 Joint Generalized Linear Mixed Models

Consider the situation where the adverse events such as pain, redness and irritability after injecting a vaccine are measured simultaneously. Most statistical models for repeated data are restricted to the analysis of one single outcome variable. Those approaches are not flexible when the research question focuses on: (i) association structure of different outcomes (ii) to test homogenous effect of a covariate across different outcomes, (iii) to draw joint inferences about the different outcomes. In order to answer such type of research question, Fieuws and Verbeke (2004, 2005, and 2006) provided detailed explanation on joint modeling. Their approach emphasizes to model the different outcomes jointly using random-effects models, random effects are assumed for each outcome process, and by imposing a joint multivariate distribution on the random effects, the different processes are associated. In Section 2.2, a generalized

linear mixed model (5) was used to analyze binary and repeatedly measured outcomes. Joint models considered here assume GLMMs for each outcome and these models are combined through specification of a joint multivariate distribution for all random effects. Let W_{1ij}, W_{2ij} and W_{3ij} denote the three binary outcomes (Pain, Redness, Irritability) for subject i at visiting day j. Each of the three outcomes can be described by using GLMMs as mentioned before, and the joint model can be written as:

$$\begin{cases} logit[P(W_{1ij}=1|Day_{ij},Trt_i,b_{1i})] = \beta_0+\beta_{1j}Day_{ij}+\beta_2 Trt_i+b_{1i} & Pain \\ logit[P(W_{2ij}=1|Day_{ij},Trt_i,b_{2i})] = \alpha_0+\alpha_{1j}Day_{ij}+\alpha_2 Trt_i+b_{2i} & Redness \\ logit[P(W_{3ij}=1|Day_{ij},Trt_i,b_{3i})] = \gamma_0+\gamma_{1j}Day_{ij}+\gamma_2 Trt_i+b_{3i} & Irritability \end{cases} \quad (11)$$

where $\beta_0 + b_{1i}$, $\alpha_0 + b_{2i}$ and $\gamma_0 + b_{3i}$ are outcome specific intercepts for each subject; β_{1j}, α_{1j}, γ_{1j}, β_2, α_2 and γ_2 have similar interpretation as mentioned for model (5); b_{1i} , b_{2i} and b_{3i} represent the random effects related to each outcome that used to accommodate the repeated nature in the data, and to associate the three outcomes by imposing the vector of these random effects assumed to follow a multivariate normal with mean zero and (co)variance $\mathbf{D}$ as given in (10). When the interest is inference for the association between the three outcomes, the variance-covariance matrix of the modeled outcomes needs to be calculated (Faes *et al*, 2008). The approximate variance-covariance matrix of the three binary outcomes for child i at visiting day j can be given by:

$$\mathbf{V_{ij}} = \begin{pmatrix} \nu_{1ij}^2\sigma_{b_{1i}}^2+\nu_{1ij} & \rho_{12}\nu_{1ij}\nu_{2ij}\sigma_{b_{1i}}\sigma_{b_{2i}} & \rho_{13}\nu_{1ij}\nu_{3ij}\sigma_{b_{1i}}\sigma_{b_{3i}} \\ \rho_{21}\nu_{2ij}\nu_{1ij}\sigma_{b_{2i}}\sigma_{b_{1i}} & \nu_{2ij}^2\sigma_{b_{2i}}^2+\nu_{2ij} & \rho_{23}\nu_{2ij}\nu_{3ij}\sigma_{b_{2i}}\sigma_{b_{3i}} \\ \rho_{31}\nu_{3ij}\nu_{1ij}\sigma_{b_{3i}}\sigma_{b_{1i}} & \rho_{32}\nu_{2ij}\nu_{3ij}\sigma_{b_{3i}}\sigma_{b_{2i}} & \nu_{3ij}^2\sigma_{b_{3i}}^2+\nu_{3ij} \end{pmatrix}$$

and the correlation between the two outcomes induced by the correlation between two random effects, ρ_{mn} (m= 1,2,3; n=1,2,3) approximately equal to:

$$corr(W_{mij},W_{nij}) = \frac{\rho_{mn}\nu_{mij}\nu_{nij}\sigma_{b_{mi}}\sigma_{b_{ni}}}{\sqrt{\nu_{mij}^2\sigma_{b_{mi}}^2+\nu_{mij}}\sqrt{\nu_{nij}^2\sigma_{b_{ni}}^2+\nu_{nij}}} \quad (12)$$

Where, ν_{1ij}=$\mu_{1ij}(b_{1i}=0)[1-\mu_{1ij}(b_{1i}=0)]$, ν_{2ij}=$\mu_{2ij}(b_{2i}=0)[1-\mu_{2ij}(b_{2i}=0)]$, ν_{3ij}=$\mu_{3ij}(b_{3i}=0)[1-\mu_{3ij}(b_{3i}=0)]$, with μ_{pij}= $\exp(\beta_0+\beta_{1j}Day_{ij}+\beta_2 Trt_i)/[1+\exp(\beta_0+\beta_{1j}Day_{ij}+\beta_2 Trt_i)]$, with p=1, 2 , 3 (1=pain, 2=redness, 3=irritability). Note that, the computed correlation based on this approximation is always smaller or equal to the correlation ρ_{mn} among the two random effects (Faes *et al*, 2008) and incase of conditional independence (ρ_{mn}=0), the approximate correlation $corr(W_{mij},W_{nij})$ also equals zero.

Moreover, the binary outcome joint model (11) extend to the more general ordinal outcome model (8)

and the joint generalized ordered logit model (13) is fitted using SAS NLMIXED procedure.

$$logit\left(P(Y_{mij} \geq k|Day_{mij}, Trt_{mi}, b_{mi})\right) = \beta_{0mk} + \beta_{mkj}Day_{mij} + \beta_{mk}Trt_i + b_{mi} \tag{13}$$

where Y_{mij} is the observation for child i at visiting day j for the m^{th} outcome with m=1, 2, 3 (1= pain, 2=redness, 3= irritability). Trt_i is an indicator variable equal to 1 for children treated by the candidate vaccine, and 0 otherwise. Hence $\exp(\beta_{mk})$ represents the multiplicative effect of the candidate vaccine on the odds of observing symptoms with level of intensity $\geq$ k for the m^{th} adverse event, for children in both treatment group have identical covariate and random-intercept values at k^{th} category of the m^{th} outcome. The model intercept β_{0mk} and the effect of measurement day (β_{mkj}) allows adverse event specific intercept as well as visiting day.

2.3 Model Selection and Diagnosis

Model selection and the assessment of goodness of fit are important issues for inference in both quasi-likelihood and likelihood modelling approaches. Even though, GEE is an increasingly important method for correlated data, likelihood based model selection and goodness fit test are not available. To assess the overall goodness-of-fit of the regression model for correlated data using GEEs, different extension to Hosmer and Lemeshow (1980) methods are proposed (Barnhart and Williamson, 1998; Horton *et al*, 1999; Pan, 2002; Lee and Qaqish, 2004; Lin, 2010).

Likewise, diagnostics methods to identify observations or clusters which have a disproportionately large influence on the estimated regression parameters are not well established. Preisser and Qaqish (1996), introduce deletion diagnostics which account for the leverage and residuals in a set of observations to determine their influence on regression parameter estimates and fitted values. The effect of deleting an entire cluster(child) information on parameter estimates will be assessed for model (1). The studentized Cook distance statistic also computed to measure the influence of deleting an entire cluster on the overall model fit using PROC GENMOD SAS procedure.

For the random effect models, since they are likelihood based; Aikakes Information Criterion(AIC), likelihood ratio tests and max-scaled R^2 are used to compare different models. The max-scaled R^2

(Frees, 2004), defined as $R^2_{ms} = R^2/R^2_{max}$, where

$$R^2 = 1 - \left(\frac{\exp(L_0/N)}{\exp(L_\beta/N)}\right)^2$$

and R^2_{max} =$1 - [\exp(L_0/N)]^2$. Here, L_0 and L_β are the log likelihood of the model with only model intercept and all covariates in the model including the intercept respectively. N represents the number of observations.

In order to test the proportional odds assumption and to compare other nested models, a likelihood ratio test is calculated by subtracting the value of -2loglikelihood associated with full model from that of the reduced (nested to the full) model. Further, since the null hypothesis value of the variance of the random intercepts is at the boundary of the parameter space ($H_0 : \sigma^2_{b_i} = 0$), the null distribution of the test statistics is a mixture of $\chi^2_{(0)}$ and $\chi^2_{(1)}$ distributions, each with equal weight 0.5 (Verbeke and Molenberghs, 2000). All models were fitted using SAS version 9.2.1 and hypothesis tests were done at 5% significance level.

3 Analysis of the Case Study

In this section, the data introduced in Section 1.3 are analyzed and results of the analysis based on the two model family will be discussed. Recall that the aim of the study is to test whether there is a difference between the candidate and licensed vaccine in terms of percentage of subjects who showed any level of solicited symptom (Pain, Redness, Irritability) taking in to account the repeated nature of the data, and if there is a difference, to describe how does this difference between treatment groups develops over time. Section 3.1 focuses on results based on GEEs and Section 3.2 presents results from random effect models.

3.1 Marginal Models

3.1.1 Marginal Models for Binary Outcomes

For the dichotomized version of the adverse events (according to Section 1.3), standard GEE models was fitted to assess difference between the candidate and licensed vaccine. Since the number of measurements taken from each subject is not large (4 measurements per subject), unstructured working correlation which is more realistic and flexible is considered. Due to few number of counts to observe at least moderate and severe redness (Table 10), when we fitted model (2) using this working correlation, GEEs

score statistic algorithm failed to converge for day covariate. Autoregressive working correlation was then chosen based on the quasi-likelihood information criterion(QIC) value of the model and the difference between model based and empirical based standard errors.

In order to test whether there is a difference between the two treatment groups over the visiting day, the saturated model (2) was fitted and the interaction effect was found to be non significant (Table2; Table 12) for any intensity levels of pain, redness, or irritability, except for severe redness for which results could not be obtained. This non-significant result for the interaction effect implies that, the effect of the treatment does not depend on the visiting day.

Model (1) was then fitted to assess the overall effect of treatment group and follow-up day on the outcome variable by testing the hypothesis $H_0 : \beta_2$=0 and $H_0 : \beta_{12} = \beta_{13} = \beta_{14}$=0, respectively. Among all the fitted models for all intensity levels of solicited symptom versus no solicited symptom (W_{ij}), a significant difference between the treatment groups were observed only for redness (Table 2). There is no statistically significant difference between the two treatment groups to observe all intensity levels of pain or irritability at 5% level of significance (Table 2). Note that, observing any solicited symptom highly depend on the visiting day. Summary of Parameter estimates for the fitted model (1) on the log scale, with their

Table 2: *Summary of score test results for models observing any solicited symptom*

Fitted	Tested	All pain			All Redness			All Irritability		
Model	Effect	χ^2	df	P-value	χ^2	df	P-value	χ^2	df	P-value
Model(1)	day	1097.00	3	0.0001	792.12	3	0.0001	449.15	3	0.0001
	Trt	2.53	1	0.112	9.50	1	0.002	2.39	1	0.122
	day	606.60	3	0.0001	494.69	3	0.0001	103.86	3	0.0001
Model(2)	Trt	4.02	1	0.084	10.45	1	0.001	1.35	1	0.245
	Trt *day	5.75	3	0.124	2.00	3	0.572	6.50	3	0.089

d.f.= Degrees of freedom

respective 95% CI provided in Table 11, Table 13 and Table 14 (Appendix A) for all, at least moderate and severe intensity levels, respectively. At a given visiting day, on average, the odds of observing all intensity levels of redness for children injected with the candidate vaccine is exp(−0.259)=0.77 times those children injected by the licensed vaccine (Table 3). Thus, children assigned to the licensed vaccine are 1.30 (1/0.77) times more likely to show any level of redness than children injected with the candidate

vaccine controlling for the follow up day. There is no significance difference between children injected by the two treatment groups to observe severe intensity level of redness (Table 14). Results for estimated odds ratio along with their 95% CI based on model (1) and for which β_2 was statistically significant are summarized in Table 3. The odds ratio for all and at least moderate intensity levels of redness reduced by 23% and 30% for children injected with the candidate vaccine as compared with those injected by the licensed vaccine, respectively. Since the interaction effect based on model (2) is not significant for at

Table 3: *Estimated odds ratios(OR) with their respective 95% confidence intervals based on model (1)*

	All redness		Moderate redness		Moderate pain		Severe pain	
Parm	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
β_0	1.73	(1.49, 2.01)	0.09	(0.07, 0.11)	0.42	(0.35, 0.51)	0.07	(0.05, 0.10)
β_{12}	0.16	(0.14, 0.18)	2.60	(2.16, 3.12)	0.49	(0.43, 0.55)	0.43	(0.30, 0.60)
β_{13}	0.43	(0.39, 0.48)	1.34	(1.08, 1.66)	0.12	(0.09, 0.15)	0.14	(0.07, 0.26)
β_{14}	0.95	(0.86, 1.04)	0.44	(0.33, 0.59)	0.04	(0.03, 0.06)	0.09	(0.04, 0.20)
β_2	0.77	(0.66, 0.91)	0.70	(0.54, 0.91)	0.64	(0.52, 0.80)	0.33	(0.21, 0.54)

least moderate intensity levels of pain (X_{ij}) and redness (Table 12), to see the overall difference between the two treatment group to observe at least moderate level of adverse event, model (1) was fitted. Significant differences between the two treatment groups were found only for pain and redness adverse events to observe at least moderate levels of intensity (Table 13). On average, the odds of observing at least moderate intensity levels of pain and redness for children enrolled under the candidate vaccine are $\exp(-0.445) = 0.64$ and $\exp(-0.374) = 0.70$ times those children who were injected with the licensed vaccine respectively (Table 3). Thus, the odds ratio for at least moderate and severe intensity levels of pain reduced by 36% (1-0.64) and 67% for children injected with the candidate vaccine as compared with those injected by the licensed vaccine, respectively. To identify observations which have large influence on the estimated regression parameters, different diagnostic statistics were explored based on model (1) for at least moderate intensity levels of pain. The effect of deleting i^{th} child information (cluster i) on the estimated treatment effect parameter is very small (Table 15). The global influence of the cluster on all the predicted values and influence of the cluster on its own predicted value assessed by computing the cluster cook distance and Cluster difference on fitted value respectively, influential clusters were not observed (Figure 2). Furthermore, from Figure 2, we can see that, computed Pearson residual values for observations taken from children who received the licensed vaccine are smaller (in absolute value) while

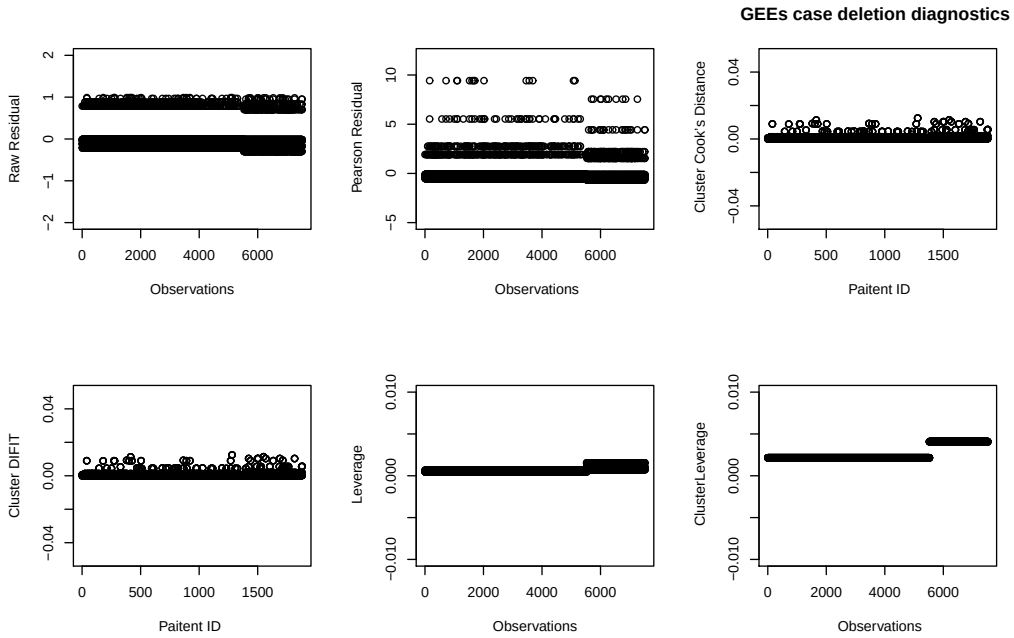

Figure 2: *Different model diagnostics plot for generalised estimating equations*

the cluster leverage and leverage values (bottom right panel of Figure 2) of those observation higher as compared with observations from the candidate vaccine. In addition to assessing influential observations, Figure 2 is presented here, in order to provide insight for the readers that GEEs model diagnostics techniques are available as mentioned in Section 2.4.

In summary, from the fitted binary marginal model, we observed that, there is a significance difference between the two treatment groups in terms of percentages of children who experienced all and at least moderate intensity levels of redness, and at least moderate and severe intensity levels of pain. The difference between treatment groups become high for severe intensity level of pain as compared with the other intensity levels of solicited symptoms. The odds ratios for severe intensity levels of pain reduced by 67% (1-0.33) for children injected with the candidate vaccine as compared with those injected by the licensed vaccine. Significant difference between the two treatment groups were not found for all intensity levels of pain symptom and severe intensity level of redness. Concerning irritability adverse event, significant difference was not observed between the two treatment groups for all, at least moderate and severe intensity levels irritability. Moreover, the non-significant interaction effect in all the considered adverse event models implies that, the odds ratio of treatment effect can be considered constant over the follow-up day.

3.1.2 Marginal Models for Ordinal Outcomes

When the responses are ordinal the usual χ^2 test of independence ignores the ordering information to test whether there is association between the response and treatment. To test the general association between the two treatment groups and their response at the end of the study, a general Cochran-Mantel-Haenszel statistics had been performed and significant (p-value=0.001) result was obtained. The assumption of proportional odds (identical log odds ratios across different categories) was tested using score test and significant result was observed ($\chi^2(8)$= 34.07, p-value=0.0001). Furthermore, from a separate analysis, it was found that the effect of the candidate vaccine on the outcome vary across different categories (Table 4: Figure 6) which is an indication for the violation of proportional odds assumption. Therefore,

Table 4: *Estimated odds ratio for the candidate vaccine at different level of intensity*

	Modeled Level of Intensity							
	All		Moderate		Severe		POM	
Adverse Event	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Pain	0.86	(0.72,1.02)	0.64	(0.52,0.80)	0.33	(0.21,0.54)	0.77	(0.65,0.91)
Redness	0.77	(0.66,0.91)	0.70	(0.54,0.91)	0.96	(0.58,1.59)	0.75	(0.64,0.88)
Irritability	0.86	(0.72,1.02)	0.78	(0.58,1.03)	0.79	(0.46,1.36)	0.85	(0.72,1.02)

drawing valid inference based on parameter estimates obtained by fitting model (4) may not be valid. For instance, based on POM, subjects injected with the licensed vaccine are 1.30 (1/0.77) times more likely to show pain adverse event than subjects injected with the candidate vaccine controlling other factors. While, based on a separate analysis, this odds ratio increases to 1.56 (1/0.64) and 3.03 (1/0.33) to observe at least moderate and severe intensity levels of pain, respectively (Table 4). Since the procedure PROC GENMOD in the current version of SAS 9.2.1 does not allow to deal with partial POM and GOLM in the marginal modelling framework, model (7) and model (8) will be fitted using NLMIXED procedure (SAS code given in Appendix). Hence, analysis for a more general ordinal models that allow the effect of the vaccine to vary across different category levels as needed will be done under Section 3.2.2 in the random effects model framework.

3.2 Generalized Linear Mixed Models

Analysis in Section 3.1 focused on modeling the marginal distributions of clustered responses within child, treating the joint dependence structure as a nuisance. In this section results based on an alternative approach using child (cluster) level terms in the model will be discussed. Given the discrete nature of time varying covariate (day) a random intercept model which adjusts only the intercept but does not modify the fixed effects was considered.

3.2.1 Random Effect Models for Binary Outcomes

When the proportion of observing any symptom during the visiting time is less for some subjects and higher for the others, marginalized proportions may poorly estimate the true proportions. In such cases, random effect models that incorporate additional parameters b_i for each child can provide better estimates. To investigate the difference between the treatment groups in terms of percentage of children experiencing solicited symptoms, as a starting point the saturated model with interaction terms, model (14)

$$logit(\mu_{ij}) = \beta_0 + \beta_{1j} Day_{ij} + \beta_2 Trt_i + \beta_{3j} Trt_i * Day_{ij} + b_i \tag{14}$$

was fitted, but we kept main effect model (5), since the estimated interaction effects are non-significant and change in log-likelihood are small. Moreover, the likelihood ratio tests that compare the saturated model (14) with model (5) supports that model (5) better fits the data than model (14) for different intensity levels of solicited symptoms (Table 5). Table 6 summarizes the estimated odds ratio with their 95%CI obtained by fitting model (5) for pain adverse event. The estimated odds ratios of 0.449 and

Table 5: *Summary of likelihood ratio tests that compare model (5) versus model (14)*

Test	Modeled outcome of Pain			Modeled outcome of redness			Modeled outcome of irritability		
Result	All	Moderate	Severe	All	Moderate	Severe	All	Moderate	Severe
LRT	5.6	2.1	5.3	2.2	1.7	7.7	3.2	5.8	6.1
d.f	3	3	3	3	3	3	3	3	3
p-value	0.133	0.552	0.151	0.532	0.637	0.053	0.362	0.122	0.107

LRT=likelihood ratio tests, d.f =degrees of freedom

0.162 for treatment (Table 6) can be interpreted as the odds ratio comparing a child injected with the candidate vaccine with another child injected by the licensed vaccine, both having identical covariate

and random-intercept values to observe at least moderate and severe intensity levels of pain, respectively. Significant treatment difference is not observed in observing all intensity levels of pain for a given child, similar conclusion was drawn in the marginal model discussed earlier.

Table 6: *Summary of ML odds ratios estimate for the random effects model (5) for Pain adverse event*

	All		Moderate		Severe	
Parameter	OR	95%CI	OR	95%CI	OR	95%CI
β_0	4.807	(3.561, 6.488)	0.167	(0.113, 0.244)	0.002	(0.001, 0.008)
β_{12}	0.196	(0.160, 0.237)	0.262	(0.204, 0.340)	0.230	(0.121, 0.432)
β_{13}	0.020	(0.016, 0.027)	0.027	(0.018, 0.040)	0.038	(0.014, 0.105)
β_{14}	0.003	(0.002, 0.005)	0.006	(0.003, 0.011)	0.021	(0.006, 0.069)
β_2	0.748	(0.549, 1.020)	0.449	(0.301, 0.677)	0.162	(0.069, 0.407)
$\sigma^2_{b_i}$		6.25		7.73		13.42

The variance of the random intercept ($\sigma^2_{b_i}$) reflects the heterogeneity between subjects in observing a certain level of symptom. For instance, $\sigma^2_{b_i} = 7.73$ represents the baseline variability of observing at least moderate intensity levels of pain between children and this variability become higher for severe intensity level of pain ($\sigma^2_{b_i} = 13.42$). Thus, based on the estimated variance of the random intercept, the residual intraclass correlation of the latent responses is estimated as 0.701 ($7.73/(\pi^2/3 + 7.73)$) for at least moderate intensity levels of pain and 0.803 for severe intensity level of pain.

Similar analyses were done for redness and irritability adverse events. Summary results in terms of odds ratio are presented in Table 7 for redness adverse event. A significant treatment difference for a given

Table 7: *Maximum likelihood odds ratios estimate for redness adverse event*

	All		Moderate		Severe	
Parameter	OR	95%CI	OR	95%CI	OR	95%CI
β_0	3.078	(2.268, 4.178)	0.004	(0.002, 0.008)	0.0004	(0.0001, 0.002)
β_{12}	0.892	(0.742, 1.072)	6.756	(4.781, 9.545)	4.496	(2.416, 8.365)
β_{13}	0.183	(0.150, 0.223)	1.740	(1.234, 2.452)	1.731	(0.894, 3.351)
β_{14}	0.027	(0.021, 0.035)	0.241	(0.155, 0.374)	0.061	(0.012, 0.305)
β_2	0.585	(0.422, 0.811)	0.482	(0.282, 0.825)	1.074	(0.515, 2.23)
$\sigma^2_{b_i}$		7.40		12.50		8.01

child was found for all intensity levels of redness and for observing at least moderate intensity level of

redness, but not for severe intensity level of redness (Table 7). For irritability adverse event, there is no significant difference between the candidate and licensed vaccine at all, in agreement with the marginal model (1) results.

The distribution of subject specific parameter estimates are presented in Figure 5 (Appendix B). The figure shows that, child specific parameter estimates to observe all intensity levels of redness are fairly distributed from -2.71 to 3.56 with mean 0.08. While, for moderate and severe intensity levels, more than 75% of the parameter estimates fall between -0.33 to -0.188 and -0.024 to -0.025, respectively. Thus, the estimated child specific parameters are near to zero of at least moderate and severe intensity levels of redness as compared with subject specific parameters for all intensity levels of redness.

The estimated variance of the random intercept is relatively large, $\sigma^2_{b_i}$ =7.4 and $\sigma^2_{b_i}$ =12.5 for all and at least moderate intensity levels of redness, respectively. This implies that there is substantial variability in the propensity to experience a certain levels of adverse event, since approximately 95% of the children have a baseline risk of showing all levels of redness and at least moderate level of redness symptoms that vary from (1.5% to 99.85%) and (0.3% to 99.96%), respectively. One can visualize this baseline variability from Figure 3. Figure 3 displays a plot of E($W_{ij}|Trt_i, b_i$) and E($W_{ij}|Trt_i$)versus the visiting day using

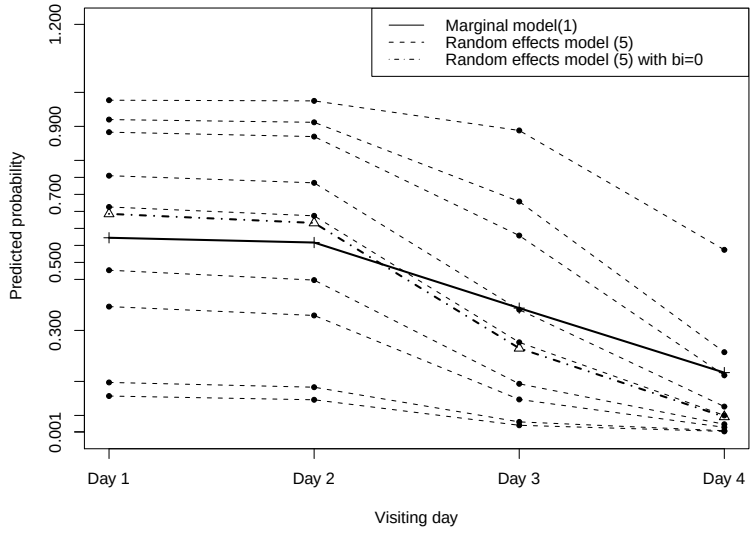

Figure 3: *Conditional (dotted line) and marginal(solid line) probability of observing all redness*

model (5) for randomly selected 16 children using their subject specific estimate (dashed line), a plot of

model (5) with b_i=0 (bold dashed line) and a plot of marginal probability of observing all intensity levels of redness based on model (1) (solid line). The Figure reveals that, there is substantial variability between children at day 1 (day of the vaccination). Furthermore, predicted probability based on model (1) lower at day 1 and day 2 and higher at visiting day 3 and day 4 (solid line) as compared with model (5) by setting the random terms zero (bold dashed line). When subject specific logistic plots are compared to the population average plot it is apparent that, the estimated probability ranges from 0.003 to 0.97 for random effects model and 0.18 to 0.57 for the marginal model (1).

3.2.2 Random Effect Models for Ordinal Outcomes

The assumption of proportional odds across different categories were tested using the likelihood ratio test, by comparing model (6) with model (7) and model (8). In line with the marginal model results, the test suggests that, proportional odds assumption was not satisfied (p-value=0.0015). Therefore, partial proportional odds model (7) and generalized ordered logit model (8) were fitted for the ordered outcomes (SAS code given in Appendix). Table 17, provides summary of goodness of fit measures for different random effect models which are valid under different assumptions as described in Section 2.2.2. The AIC, -2ll value and R^2_{ms} suggests that the extended model (9) better fits the data (Table 17). The estimated ORs with their respective 95%CI obtained by fitting model (7), model (8) and model (9) in the case of partial proportional odds model for children with zero random effects term are summarized in Table 8. The results show that, when we fitted the extended model (9) in the case of PPOM using category specific random effect terms, over model (7) which assumes only the same baseline variability at each category, the difference between the two treatment groups increase for high cutoff (Table 8). For instance, based on model (7), the odds ratio comparing a child injected with the candidate vaccine with another child injected by the licensed vaccine, both having identical covariate and random-intercept values at 3^{rd} category of the outcome is 0.326, while based on model (9) it is 0.065.

The results for the fixed effects parameters from the three models generally agree in terms of indicating children injected with candidate vaccine are less likely to show at least moderate and severe intensity levels of pain as indicated by less than one odds ratio (Table 8). Since, the 95%CI confidence does not include 1 for the effect of treatment at category 2 and 3, this differences between the two treatment

Table 8: *Maximum Likelihood Estimates and Approximate 95% Confidence Intervals for PPOM based on model (7) and model (9) and GOLM with random intercept for pain adverse event*

	Model (7)		Model (8)		Model (9) for PPOM	
Parameters	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Fixed part:Odds Ratios						
β_{21} Treatment at category 1	0.750	(0.561, 1.003)	0.751	(0.562, 1.001)	0.765	(0.545,1.073)
β_{22} Treatment at category 2	0.513	(0.367, 0.719)	0.523	(0.371, 0.732)	0.401	(0.239,0.672)
β_{23} Treatment at category 3	0.329	(0.188, 0.576)	0.344	(0.198, 0.593)	0.065	(0.015,0.292)
Random part:Variances						
$\sigma^2_{b_i}$ Var(b_i)		5.46		5.55		
$\sigma^2_{b_{i1}}$ Var(b_{i1})						7.618
$\sigma^2_{b_{i2}}$ Var(b_{i2})						12.710
$\sigma^2_{b_{i3}}$ Var(b_{i3})						40.468

Treatment at category k (k=1,2,3) refers OR of the candidate vaccine on outcome category k

groups are statistically significant at 5% level of significance. Approximately similar residual intra class correlation was obtained for the latent responses and was estimated as 0.63 ($\sigma^2_{b_i}/(\pi^2/3 + \sigma^2_{b_i})$) for both model (7) and model (8).

Extensions for Random Effect Models with Ordinal Outcomes

Even though, it is very computationally intensive due to the increased number of random effects, to allow different category specific random terms and to study the association between category levels, the extended model (9) is fitted for pain adverse event. A significant (p-value=0.001) positive association ($\rho_{12} = 0.33$) between the first and the second category level random effects was observed from the estimated (co)variance matrix. This suggests the correlation between the first category (all intensity levels of pain) and the second category (at least moderate intensity levels of pain) for child i at visiting day j less or equal to the correlation between the two random effects ($\rho_{12} = 0.33$). While, since the third random effect term is independent (with p-value $\geq$0.39) with the first and the second category level random effects term, significant association between severe intensity level with the other category levels were not observed. The estimated random effects (co)variance matrix (* refers significantly different from zero at 5% level of significance) which reflects the baseline heterogeneity between children at each

category of the outcome is

$$\mathbf{D} = \begin{pmatrix} 7.618* & 5.69* & -1.495 \\ & 12.71* & -0.33 \\ & & 40.46* \end{pmatrix}$$

The variability between children at severe intensity level of pain ($\sigma^2_{b_{i3}}$=40.468) is higher as compared with the variability observed in at least moderate ($\sigma^2_{b_{i2}}$=12.71) and all intensity levels of pain ($\sigma^2_{b_{i1}}$=7.618). This relatively large baseline heterogeneity between children implies that, there is substantial category specific variability in the propensity to experience a certain levels of adverse event. For instance, approximately 95% of the children have a baseline risk of showing at least moderate levels and severe level of pain symptoms that vary from (0.007% to 98.83%) and (0% to 99.86%), respectively. Based on the estimated category specific variance of the random intercepts, the estimated intra class correlation for the latent responses becomes 0.70, 0.79 and 0.93 at category 1 (all), category 2 (at least moderate) and category 3 (severe), respectively.

3.2.3 Joint Generalized Linear Mixed Models

In order to examine the effect of the treatment on the joint process of the three solicited symptoms and the association between these outcomes, model (11) is applied to the case study. The joint model was fitted in SAS using NLMIXED procedure with initial values obtained from the univariate analyses. Summary of maximum likelihood estimates based on model (11) for the three solicited symptoms are presented in Table 18. Figure 4 shows the predicted probability of observing all intensity levels of solicited symptoms at each visiting day. Further, in order to compute the correlation between different outcomes for child i at visiting day j based on equation (12), first the random effects co(variance) matrix ($\mathbf{D}$) considered and ρ_{mn} found not significantly different from zero (with p-value$\geq$ 0.76) from the $\mathbf{D}$ matrix. In the $\mathbf{D}$ matrix * refers significantly different from zero.

$$\mathbf{D} = \begin{pmatrix} 6.25* & < -0.0001 & < -0.0001 \\ & 7.395* & < 0.0001 \\ & & 10.306* \end{pmatrix}$$

Since outcome specific random effect terms are independent (ρ_{mn}=0) as shown in the $\mathbf{D}$ matrix, the $corr(W_{mij}, W_{nij})$ in equation (12) becomes zero. Thus, for child i at visiting day j, the three outcomes of interest (Pain, Redness and Irritability) are independent. This independence was also supported by identical parameter estimates obtained by fitting both the univariate model (5) and joint model (11) (See

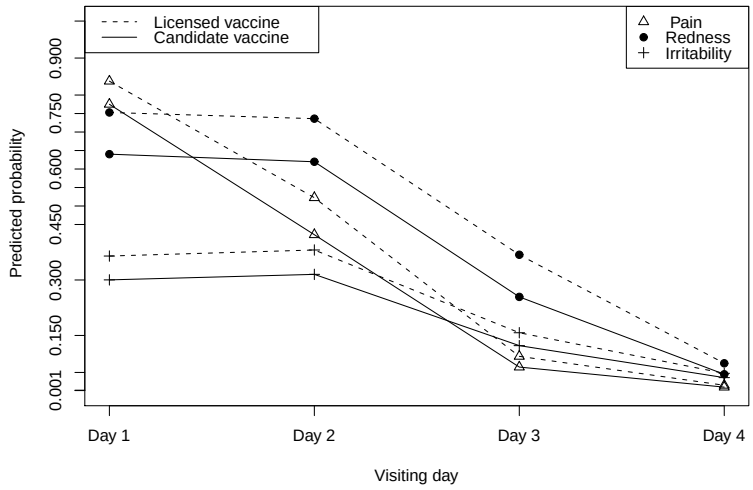

Figure 4: *Predicted probability at each visiting day for the three adverse event*

Table 18, Table 16). Even though, most scholars used joint models to study the association between outcome variables, if each outcome has the same covariate, it is possible to test whether the covariate effect is similar across different outcomes. Thus, in order to do this, the reduced form of model (11) which assumes $\beta_2 = \alpha_2 = \gamma_2$, was fitted. Since the reduced model (15) is nested with model (11), likelihood ratio test (LRT) was used to test the homogenous effect of treatment across different solicited symptoms.

$$\begin{cases} logit[P(W_{1ij}=1|Day_{ij},Trt_i,b_{1i})] = \beta_0 + \beta_{1j}Day_{ij} + \beta_2 Trt_i + b_{1i} & Pain \\ logit[P(W_{2ij}=1|Day_{ij},Trt_i,b_{2i})] = \alpha_0 + \alpha_{1j}Day_{ij} + \beta_2 Trt_i + b_{2i} & Redness \\ logit[P(W_{3ij}=1|Day_{ij},Trt_i,b_{3i})] = \gamma_0 + \gamma_{1j}Day_{ij} + \beta_2 Trt_i + b_{3i} & Irritability \end{cases} \tag{15}$$

Where, β_2 is the common treatment effect for different outcomes.

The value of the computed LRT =-2($ll_{model(15)}$ -$ll_{model(11)}$)=21944 -21942=2, compared with $\chi^2_{(2)} = 5.99$, and this nonsignificant test result (p-value=0.368) indicates that, the effect of the treatment group is similar across the three solicited symptoms. The estimated common treatment effect $\hat{\beta}_2$, is -0.36 with 95%CI (-0.553, -0.169). Thus, the estimated odds ratio $\exp(-0.36) = 0.70$ can be interpreted as the odds ratio comparing a child injected with the candidate vaccine with another child injected by the licensed vaccine, both having identical covariate and random-intercept values to observe all intensity levels of a specific solicited symptom. Hence, children injected with the licensed vaccine are 1.43 time more likely to

show either of the adverse events as compared with children injected by the candidate vaccine. Based on the estimated random effects (co)variance matrix $\mathbf{D}$, the variability between children are approximately similar for pain and redness adverse events, while a bit higher variability observed for irritability adverse event.

Similar analysis for the ordered outcome based on model (13) was also done and due to independence between outcome specific random effects, significant association between the solicited symptoms were not observed. Since, integrating the likelihood for model (13) is computationally intensive, homogeneous effect of the treatment across the solicited symptoms were not tested based on model (13).

4 Discussion and Conclusion

4.1 Discussion

In this report, we have presented marginal and random effect models to analyze repeated categorical measurements concerning solicited symptoms coming from vaccine clinical trials. In case of marginal models the correlated nature of the data is acknowledged inside the estimating equation, while for random effects model it is done through the random effect part. Eventhough, both the considered marginal and random effect models are extensions of generalized linear model (McCullagh and Nelder, 1989), the different way of accounting within child association has a consequence for the interpretation of the regression model parameters. In the random effect approach the goal is to determine child-specific changes in the risk of observing solicited symptoms over the courses of the study, while in the marginal model the emphasis is to determine the overall change.

To fix ideas on the difference between marginal and random effects model, let us reconsider the estimated effect of the candidate vaccine under different model formulation (Table 9). The estimated treatment effect 0.64 and 0.33 (Table 9) from the marginal model (1) describes how the average rates (in terms of odds ratio) of observing at least moderate and severe intensity levels of pain would increase in the study population if children are injected by the candidate vaccine. While, the estimated treatment effect 0.449 and 0.162 from the random effect model (5) describes how the odds of observing at least moderate and severe levels of pain increase for any child treated with the candidate vaccine.

Table 9: *Summary of estimated odds ratios (95%CI) of the candidate vaccine based on marginal and random effects model for the three adverse events*

Fitted	Adverse	Modeled intensity level of adverse event			AIC
Model	Event	All	Moderate	Severe	
Model (1)	Pain	0.86(0.72,1.02)	0.64(0.52, 0.80)	0.33(0.21, 0.54)	
	Redness	0.77(0.66,0.91)	0.70(0.54,0.91)	0.96(0.58,1.59)	
	Irritability	0.86(0.72,1.02)	0.78(0.58,1.03)	0.79(0.46,1.36)	
Model (5)	Pain	0.75(0.55,1.02)	0.45(0.30,0.68)	0.16(0.07,0.41)	
	Redness	0.59(0.42,0.81)	0.48(0.28,0.83)	1.07(0.52,2.23)	
	Irritability	0.74(0.50,1.10)	0.61(0.31,1.18)	0.74(0.30,1.83)	
		For Ordinal Outcomes			
Model (7)	Pain	0.75(0.56,1.00)	0.51(0.37,0.72)	0.33(0.19,0.58)	10266
	Redness	0.61(0.46,0.79)	0.61(0.43,0.85)	1.22(0.68,2.18)	11472
	Irritability	0.76(0.53,1.09)	0.78(0.51,1.22)	0.80(0.41,1.53)	10355
Model (8)	Pain	0.75(0.56,1.00)	0.52(0.37,0.73)	0.34(0.20,0.59)	10261
	Redness	0.60 (0.45,0.79)	0.61(0.43,0.86)	1.21(0.67,2.17)	11334
	Irritability	0.76(0.52,1.09)	0.79(0.51,1.23)	0.80(0.42,1.53)	10270
$Model^a$(9)	Pain	0.77(0.55,1.07)	0.40(0.24,0.67)	0.07(0.02,0.29)	10087
$Model^b$ (9)	pain	0.77(0.56,1.07)	0.38(0.22,0.68)	<0.01(0.00,0.003)	10029

AIC=Aikakes Information Criterion, $Model^a$ (9)=nonproportional odds only for treatment
$Model^b$ (9)=nonproportional odds for both treatment and visiting day

Note that, the same odds ratio are significant across both the random effects model and marginal models, but the magnitude of the effect can differ (Table 9). Therefore, the answer for the question "how the candidate vaccine is beneficial?" will depend on whether the interest is in its impact on the study population or on an individual drawn from that population. The estimated treatment effect difference from the marginal model a somewhat smaller than the estimated treatment effect from random effect model (Table 9), and this discrepancy becomes high when the estimated variance for the random intercept based on the random effect models becomes large. These differences in the estimated coefficients and odds ratios are due to different interpretations of $\boldsymbol{\beta}$ in the two model families, that is these two classes of models estimate parameters that address substantively different questions. More precisely, the estimates of fixed effects of the treatment in model (5) describe the effect of the treatment on a specific child to observe solicited symptom. While, the corresponding effects in the marginal model (1) describe the effects of treatment on the prevalence of observing solicited symptom in the population of children injected by the candidate vaccine. The approximate relationship between the two model parameters mentioned in

Section 2.1.1 highlights how the parameters estimates for marginal model are attenuated relative to the corresponding fixed effects in model (5).

Moreover, since the joint distribution of the responses is not specified in GEEs method, likelihood based inferences are not available. Hence, if the interest is to model the heterogeneity among children and to draw likelihood based inferences, we prefer to fit random effect models over GEE. In random effects model, each child is assumed to have its own level of adverse event. Thus, it is well known that fixed effects parameters do not maintain their interpretation when random effects are introduced in the model. Therefore the fixed effects odds ratio no longer is an odds ratio between any two child as mentioned by Zeger *et al* (1988).

Among the considered models that account the ordinal nature of the data, the extended model (9) with category specific random terms better fits the data (Table 17) for pain adverse event. Further, since the considered random effects model accounts only baseline heterogeneity, it is also possible to extend those models by introducing visiting day specific random effects b_{ij}, where b_{ij} is the random effect for subject i at occasion day j (j=1 to 4) and vector of b_{ij} follows a multivariate normal distribution with mean vector 0 and (co)variance matrix D. But, in practice, when the number of visiting days increase, it is difficult to introduce more than few random effects due to computational intensive integration methods. Even the result presented in Table 9 for $model^a$ (9) and $model^b$ (9) with three random effect terms took approximately 470:18 hour and 774:37 hour on 2.5GHz PC, respectively. Moreover, NLMIXED procedure fail to integrate the likelihood for less than 20 quadrature points. Among the considered optimization techniques (Levenberg-Marquardt Method, Newton-Raphson, Trust-Region Method), Trust-Region Method is very time consuming and fail to integrate the likelihood. Thus, all the presented parameter estimates were obtained using Newton-Raphson optimization techniques.

4.2 Conclusion

Both marginal and random effect modeling approaches provide similar conclusions about the significant difference between the two vaccines. A significance difference between the candidate and licensed vaccine in terms of percentage of children who showed at least moderate and severe intensity levels of pain, all and at least moderate intensity levels of redness were found in both modeling approaches. The difference

between the two treatment groups become high for severe intensity level of pain as compared with the other intensity levels of solicited symptoms. In both marginal and random effect models, significant difference between the two treatment groups were not found for all intensity levels of pain symptom and severe intensity level of redness. Further, in all analyses, significant difference was not observed between the two treatment groups for all, at least moderate and severe intensity levels irritability. Moreover, the non-significant interaction effect in all the considered adverse event models implies that, the difference between the two treatment groups can be considered constant over the follow-up period. The association between the three outcome recorded from the same child over time assessed using the joint generalized mixed model and nonsignificant association between the three outcomes in all visiting days was found. Further, results based on the joint mixed model reveals that the effect of the candidate vaccine is similar across different outcomes (Pain, Redness, Irritability).

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Appendix

Appendix A: Tables

Table 10: Relative frequencies for different solicited symptom by the level of intensity and treatment group at each follow-up day

Percentage of observed solicited symptom								
	Day 1		Day 2		Day 3		Day 4	
	Trt	Control	Trt	Control	Trt	Control	Trt	Control
Pain								
All	67.3	66.7	44.4	50.5	19.1	23.2	7.4	9.8
Moderate	21.7	28.7	11.1	18.6	3.1	5.0	1.0	2.0
Severe	2.2	6.6	1	2.8	0.5	0.4	0.3	0.4
Redness								
All	57.7	62.1	55.7	62.5	36.5	42.9	17.1	23.0
Moderate	5.8	7.8	13.7	18.2	7.4	10.8	2.2	4.6
Severe	1.3	0.4	3	3.2	1.4	2.2	0.1	0.0
Irritability								
Any	41.3	44.3	42.5	43.7	29.9	32.9	17.8	23.0
Moderate	6.4	6.2	10.8	13.4	8.3	10.8	5.0	7.6
Severe	1.4	0.8	2.5	3	1.5	2.8	0.6	0.8

Trt= Candidate vaccine for meningococcal infection, Control= licensed vaccine

Table 11: *Parameter estimates with their respective 95% CI based on model (1) for observing all level of adverse events*

Models for observing presence of any solicited symptom						
	Pain		Redness		Irritability	
Parm	Estimate	95% CI	Estimate	95% CI	Estimate	95% C I
β_0	0.819	(0.655, 0.982)	0.550	(0.399, 0.703)	-0.217	(-0.374, -0.059)
β_{12}	-0.875	(-0.979, -0.770)	-0.057	(-0.154, 0.040)	0.031	(-0.06, 0.122)
β_{13}	-2.089	(-2.224, -1.955)	-0.843	(-0.952, -0.734)	-0.495	(-0.60, -0.387)
β_{14}	-3.155	(-3.339, -2.972)	-1.836	(-1.970, -1.703)	-1.118	(-1.245, -0.99)
β_2	-0.141	(-0.312, 0.031)	-0.259	(-0.422, -0.096)	-0.141	(-0.314, 0.033)

Table 12: *Summary result for the score test based on different model formulation for different adverse events*

Pain adverse event										
Fitted	Tested	All			Moderate			Severe		
Model	Effect	χ^2	d.f	p-value	χ^2	d.f	p-value	χ^2	d.f	p-value
Model (1)	day	1097	3	0.0001	424.10	3	0.0001	53.92	3	0.0001
	Trt	2.84	1	0.092	14.24	1	0.0002	13.31	1	0.0003
	day	593.54	3	0.0001	130.54	3	0.0001	30.37	3	0.0001
Model (2)	Trt	4.02	1	0.045	8.93	1	0.0028	13.46	1	0.0002
	Trt*day	5.75	3	0.124	3.54	3	0.316	3.44	3	0.328
Redness adverse event										
Model (1)	day	792.12	3	0.0001	219.60	3	0.0001	71.80	3	0.0001
	Trt	9.50	1	0.002	6.87	1	0.008	0.02	1	0.876
	day	206.00	3	0.0001	68.55	3	0.0001	✠		
Model (2)	Trt	2.99	1	0.0836	2.22	1	0.136	✠		
	Trt*day	2.00	3	0.572	2.32	3	0.508	✠		
Irritability adverse event										
Model (1)	day	449.15	3	0.0001	96.12	3	0.0001	31.66	3	0.0001
	Trt	2.33	1	0.122	1.77	1	0.183	0.57	1	0.445
	day	299.23	3	0.0001	66.66	3	0.0001	23.31	3	0.001
Model (2)	Trt	2.91	1	0.088	2.41	1	0.121	0.21	1	0.651
	Trt*day	6.50	3	0.089	3.49	3	0.322	4.45	3	0.217

✠ =*Test results not available,since the generalized Hessian matrix is not positive definite*

Table 13: *Parameter estimates with their respective 95% CI based on model (1) for observing at least moderate level of adverse event*

Models for observing at least moderate solicited symptom						
	Pain		Redness		Irritability	
Parm	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
β_0	-0.859	(-1.044, -0.674)	-2.432	(-2.684, -2.180)	-2.555	(-2.813, -2.291)
β_{12}	-0.721	(-0.851, -0.592)	0.954	(0.790, 1.118)	0.653	(0.471, 0.836)
β_{13}	-2.116	(-2.362, -1.870)	0.293	(0.079, 0.507)	0.380	(0.177, 0.584)
β_{14}	-3.183	(-3.589, -2.777)	-0.827	(-1.135, -0.520)	-0.113	(-0.345, 0.120)
β_2	-0.445	(-0.662, -0.229)	-0.374	(-0.628, -0.121)	-0.199	(-0.479, 0.081)

Table 14: *Parameter estimates with their respective 95% CI based on model (1) for severe level of adverse event*

	Modeling Severe solicited symptom					
	Pain		Redness		Irritability	
Parm	Estimate	95% C.Limits	Estimate	95% C.Limits	Estimate	95% C.Limits
β_0	-2.666	(-3.011, -2.311)	-4.502	(-5.077, -3.927)	-4.231	(-4.743, -3.72)
β_{12}	-0.853	(-1.202, -0.505)	1.085	(0.638, 1.532)	0.771	(0.368, 1.173)
β_{13}	-2.002	(-2.658, -1.345)	0.411	(-0.138, 0.959)	0.426	(-0.039, 0.892)
β_{14}	-2.408	(-3.215, -1.602)	-2.312	(-3.759, -0.866)	-0.657	(-1.251, -0.062)
β_2	-1.101	(-1.585, -0.618)	-0.042	(-0.550, 0.466)	-0.225	(-0.77, 0.320)

Table 15: *Summary for the effect of deleting i^{th} subject information on the model parameter estimates*

	Difference in Parameter estimates				
	β_0	β_{12}	β_{13}	β_{14}	β_2
Minimum	-0.0027	-0.002978	-0.0032	-0.0034	-0.0108
First quartile	-0.0037	$7x10^{-5}$	0.0001	0.0001	-0.0008
Mean	$-3x10^{-7}$	10^{-8}	$5x10^{-8}$	$4x10^{-9}$	$3x10^{-7}$
Third Quartile	-0.00003	0.00014	0.000114	0.0001	0.002
Maximum	0.0096	0.0048	0.01558	0.043	0.0057
	Measure of over all influence				
Measure	minimum	First quartile	Mean	Third Quartile	Maximum
Leverage	0.0005	0.0005	0.0006	0.0007	0.0015
Cluster Levearage	0.0021	0.0021	0.0026	0.0040	0.0040
Cook Distance	$7x10^{-9}$	$6x10^{-8}$	$2x10^{-6}$	$2x10^{-5}$	0.0113
ClustercookD	0.00004	0.00004	0.0005	0.0006	0.0125
ClusterDfit	0.00004	0.00004	0.0005	0.0006	0.0126

Table 16: *Summary of ML estimates for the random effect model (5) for Pain adverse event*

	All		Moderate		Severe	
Parm	LogOR	95%CI	logOR	95%CI	logOR	95%CI
β_0	1.569	(1.273, 1.865)	-1.793	(-2.177, -1.408)	-6.266	(-7.703, -4.829)
β_{12}	-1.634	(-1.832, -1.436)	-1.336	(-1.588, -1.084)	-1.471	(-2.106, -0.836)
β_{13}	-3.888	(-4.164, -3.613)	-3.622	(-4.037, -3.206)	-3.258	(-4.264, -2.251)
β_{14}	-5.701	(-6.077, -5.328	-5.155	(-5.764, -4.546)	-3.857	(-5.048, -2.665)
β_2	-0.287	(-0.595, 0.022)	-0.797	(-1.199, -0.395)	-1.816	(-2.733, -0.899)
$\sigma^2_{b_i}$	6.250		7.727		13.422	
AIC	6902.5		3798.3		875.8	

logOR=Estimated log odds ratio , ML= maximum likelihood

Table 17: *Summary of goodness of fit measures for the fitted ordinal random effect models for pain adverse event*

Measure	One random effect			Three random effect		
	POM	PPOM	GOLM	POM	PPOM	GOLM
-2*ll*	10259	10246	10229	10069	10057	10029
No. Parameters	8	10	16	13	15	21
AIC	10275	10266	10261	10095	10087	10071
R^2_{ms}	0.430	0.431	0.433	0.450	0.450	0.453
Model	Likelihood ratio test					
Comparison	LRT	df	p-value			
One Random effect						
POM versus PPOM	13	2	0.0015			
POM versus GOLM	30	8	0.0002			
PPOM versus GOLM	17	6	0.0093			
Three Random effect						
POM versus PPOM	12	2	0.0025			
POM versus GOLM	40	8	<0.001			
PPOM versus GOLM	28	6	<0.001			

LRT= Value of computed likelihood ratio test, df=degrees of freedom

Table 18: *Summary of ML estimates for the joint model (11) for all intensity levels of the three solicited symptoms*

	Pain		Redness		Irritability	
Parm	Estimate	95%CI	Estimate	95%CI	Estimate	95%CI
β_0	1.569	(1.273, 1.865)	1.124	(0.819, 1.430)	-0.538	(-0.894, -0.181)
β_{12}	-1.634	(-1.832, -1.436)	-0.115	(-0.298, 0.070)	0.070	(-0.126, 0.266)
β_{13}	-3.888	(-4.164, -3.612)	-1.700	(-1.899, -1.498)	-1.117	(-1.325, -0.909)
β_{14}	-5.701	(-6.077, -5.326)	-3.620	(-3.882, -3.358)	-2.447	(-2.691, -2.203)
β_2	-0.287	(-0.595, 0.022)	-0.537	(-0.863, -0.210)	-0.295	(-0.685, 0.095)
$\sigma^2_{b_i}$	6.250		7.39		10.31	

Appendix B: Figures

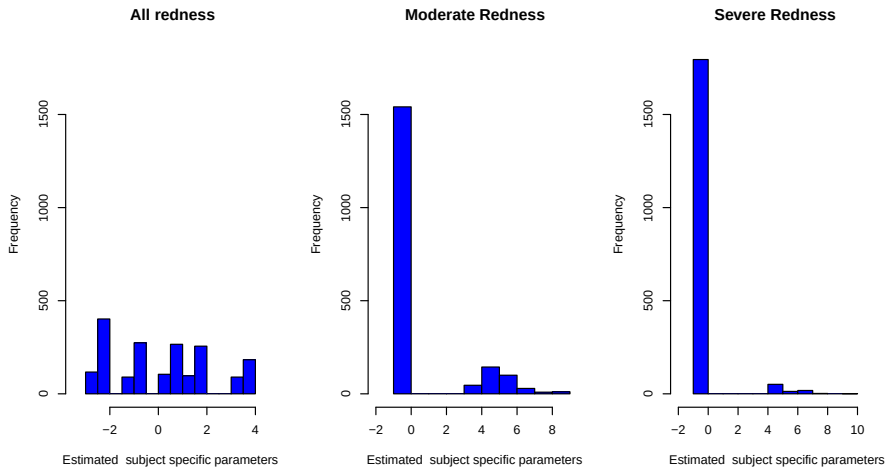

Figure 5: *Distribution of estimated subject specific parameters using model (5)for redness*

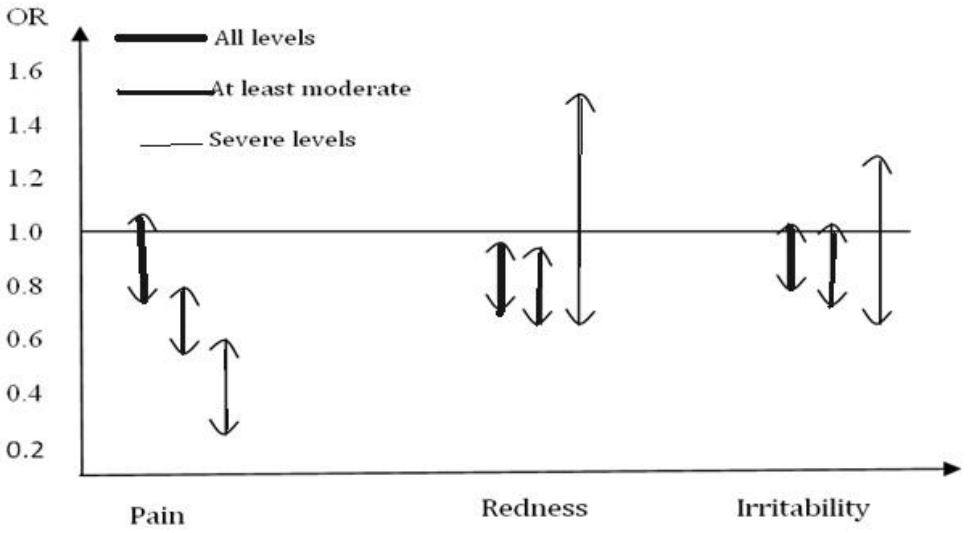

Figure 6: *Estimated odds ratios with their 95%CI for different levels of intensity for different solicited symptoms*

Appendix C: SAS Codes

1. Marginal Models (GEE)

```
 proc genmod data=binary descending; title 'GEE for any Pain';
class PID timecls  day  Trt /descending;
model resp1= day Trt/dist=bin link=logit type3 aggregate INFLUENCE  OBSTATS;
repeated subject=PID/ type= un corrw within=timecls modelse;
output out=pred p=phat DFBETAC=_all_; run;
```

2. Binary outcome Random effects Model

```
proc glimmix data=random3 method=RSPL; /*To get intial values for NLMIXED Procedure*/
class PID;nloptions maxiter=50; model all = d2 d3 d4 Trt / dist=bin solution;
random intercept / subject=pid; run;
proc nlmixed data=random3 qpoints=20; /* Main effect model*/
parms beta0 -0.2469 beta1 0.04549 beta2 -0.7387
beta3 -1.6253  beta4  -0.1792  d11 3.4969;
eta = beta0 + beta1*d2 + beta2*d3 + beta3*d4  + beta4*trt + b1;
expeta=exp(eta);p=expeta/(1+expeta);  model all ~ binary(p);
random b1 ~ normal([0], [d11]) subject=pid; run;


proc nlmixed data=random3 qpoints=20; /* Model With interaction effect*/
parms beta0 -0.2537 beta1 -0.03732 beta2 -0.743 beta3 -1.4678  beta4 -0.1703
beta5 0.1121 beta6 0.005896 beta7 -0.2199 d11 3.4969;
eta = beta0 + beta1*d2 + beta2*d3 + beta3*d4  + beta4*trt +  beta5*(d2*trt)+
beta6*(d3*trt)+beta7*(d4*trt)+ b1;   expeta=exp(eta); p=expeta/(1+expeta);
model severe ~ binary(p); random b1 ~ normal([0], [d11]) subject=pid; run;
```

3. Proportional Odds model with random intercept

```
proc nlmixed data=random1 qmax=5000 qpoints=20 tech=newrap  maxiter=1000;
```

```
   Title 'POM for Pain: one random effect';
parms beta01 -4.9008 beta02 -1.6228 beta03 1.506 beta1 -1.4268 beta2 -3.5633
 beta3 -5.2607  beta4 -0.4168 d11 5.4812;
eta3 = beta01  + beta1*(day=2) + beta2*(day=3) + beta3*(day=4) + beta4*Trt + b1;
eta2 = beta02  + beta1*(day=2) + beta2*(day=3) + beta3*(day=4) + beta4*Trt + b1;
eta1 = beta03  + beta1*(day=2) + beta2*(day=3) + beta3*(day=4)+ beta4*Trt + b1;
if (pain=3) then model=1/(1+exp(-eta3));
else if (pain=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (pain=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (pain=0) then model= 1 - 1/(1+exp(-eta1));
ll=log(model); model pain ~ general(ll);
random b1 ~ normal(0,d11) subject=Pid out= EB;run;
```

4. Partial Proportional odds Random effects Model

```
proc nlmixed data=random1 qmax=5000 qpoints=20 tech=newrap  maxiter=1000;
Title 'Partial POM for Pain with one random effect'; bounds i1>0, i2>0;
parms beta0 -4.6339  beta1  -3.59  beta2 -2.077  beta3 -0.86  beta41 -0.2911
beta42 -0.6564 beta43 -1.0812 i1 3.0869 i2 3.0416  d11 5.5510;
eta3 = beta0  + beta1*d2 + beta2*d3 + beta3*d4 + beta43*Trt + b1;
eta2 = beta0 + i1 +  beta1*d2 + beta2*d3 + beta3*d4  + beta42*Trt + b1 ;
eta1 = beta0 + i1 + i2 + beta1*d2 + beta2*d3 + beta3*d4  + beta41*Trt + b1;
if (pain=3) then model=1/(1+exp(-eta3));
else if (pain=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3)) ;
else if (pain=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2)) ;
else if (pain=0) then model= 1 - 1/(1+exp(-eta1)); ll=log(model);
model pain ~ general(ll);random b1 ~ normal(0, d11) subject=Pid;
estimate 'int3' beta0 ; estimate 'int2' beta0+i1;
estimate 'int1' beta0+i1+i2; run;
```

```
proc nlmixed data=random1 qmax=5000 qpoints=20 tech=newrap maxiter=1000;
Title 'Partial POM for Pain with three random effect'; bounds i1>0, i2>0;
parms beta0 -4.6339  beta1  -3.59  beta2 -2.077  beta3 -0.86
 beta41 -0.2911 beta42 -0.6564 beta43 -1.0812 i1 3.0869
i2 3.0416 d11 5.5510 d12=0  d22=4.32  d13=0 d23=0  d33=7.62;
eta3 = beta0  + beta1*d2 + beta2*d3 + beta3*d4 + beta43*Trt + b1;
eta2 = beta0 + i1 +  beta1*d2 + beta2*d3 + beta3*d4  + beta42*Trt + b2 ;
eta1 = beta0 + i1 + i2 + beta1*d2 + beta2*d3 + beta3*d4  + beta41*Trt + b3;
if (pain=3) then model=1/(1+exp(-eta3));
else if (pain=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (pain=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (pain=0) then model= 1 - 1/(1+exp(-eta1));
ll=log(model);  model pain ~ general(ll);
random b1 b2 b3 ~ normal([0,0,0],[d11,d12,d22,d13,d23,d33]) subject=Pid out= EB1;
estimate 'int3' beta0; estimate 'int2' beta0+i1; estimate 'int1' beta0+i1+i2;run;
```

5. Generalized Ordered logit Random effects Model

```
proc nlmixed data=random1 qmax=5000 qpoints=20 tech=newrap  maxiter=1000;
Title 'Pain:Generalized ordered logit model with one random effect';
bounds i1>0, i2>0;
parms beta0 -4.6339 beta11 -1.5425 beta12 -1.2968 beta13 -1.3681
beta21 -3.6884 beta22 -3.4010 beta23 -2.8930 beta31 -5.4058
beta32 -4.8126 beta33 -3.3761 beta41 -0.2911 beta42 -0.6564
beta43 -1.0812 i1 3.0869 i2 3.0416 d11 5.5510;
eta3 = beta0  + beta13*d2 + beta23*d3 + beta33*d4 + beta43*Trt + b1;
eta2 = beta0 + i1  + beta12*d2 + beta22*d3 + beta32*d4 + beta42*Trt + b1 ;
eta1 = beta0 + i1 + i2 + beta11*d2 + beta21*d3 + beta31*d4 + beta41*Trt + b1;
if (pain=3) then model=1/(1+exp(-eta3));
```

```
else if (pain=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (pain=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (pain=0) then model= 1 - 1/(1+exp(-eta1));
ll=log(model);  model pain ~ general(ll);
random b1 ~ normal(0,d11) subject=Pid;estimate 'int3' beta0;
estimate 'int2' beta0+i1; estimate 'int1' beta0+i1+i2;run;

proc nlmixed data=random1 qmax=5000 qpoints=20 tech=newrap maxiter=1000;
Title 'Pain:Generalized ordered logit model with three random effect';
bounds i1>0, i2>0;
parms beta0 -4.6339 beta11 -1.5425 beta12 -1.2968 beta13 -1.3681
beta21 -3.6884  beta22 -3.4010 beta23 -2.8930 beta31 -5.4058
beta32 -4.8126 beta33 -3.3761 beta41 -0.2911 beta42 -0.6564
 beta43 -1.0812 i1 3.0869 i2 3.0416 d11 5.5510 d12=0   d22=4.32
d13=0  d23=0  d33=7.62;
eta3 = beta0  + beta13*d2 + beta23*d3 + beta33*d4 + beta43*Trt + b1;
eta2 = beta0 + i1  + beta12*d2 + beta22*d3 + beta32*d4 + beta42*Trt + b2 ;
eta1 = beta0 + i1 + i2 + beta11*d2 + beta21*d3 + beta31*d4 + beta41*Trt + b3;
if (pain=3) then model=1/(1+exp(-eta3));
else if (pain=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (pain=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (pain=0) then model= 1 - 1/(1+exp(-eta1));
ll=log(model); model pain ~ general(ll);
random b1 b2 b3 ~ normal([0,0,0], [d11,d12,d22,d13, d23,d33]) subject=Pid out= EB1;
estimate 'int3' beta0; estimate 'int2' beta0+i1;estimate 'int1' beta0+i1+i2; run;
```

6. Binary outcome Joint mixed models

```
/*Care full data  arrangement for joint modelling  was done*/
proc nlmixed data=jointbinary qmax=5000 qpoints=20 tech=newrap  maxiter=1000;
```

```
Title ' Joint Models for the three  binary outcomes';
parms a0=1.5691  a1=-1.6336 a2=-3.8881 a3=-5.7013 a4=-0.2866
      b0=1.1244 b1=-0.1145 b2=-1.6988 b3=-3.6201 b4=-0.536
     c0=-0.5377 c1=0.07003 c2=-1.1172 c3=-2.4471 c4=-0.2948
     d11=6.2502 d12=0  d22=7.3947 d13=0  d23=0 d33=10.366;
if adversevent=1 then do; /* Pain  modelled here*/
eta = a0 + a1*d2 + a2*d3 + a3*d4 + a4*trt + b1i;
expeta=exp(eta); p=expeta/(1+expeta); end;
else if adversevent=2 then do; /* Redness modelled here*/
eta = b0 + b1*d2 + b2*d3 + b3*d4 + b4*trt + b2i;
expeta=exp(eta); p=expeta/(1+expeta); end;
else if adversevent=3 then do;/* irritability  modelled here*/
eta = c0 + c1*d2 + c2*d3 + c3*d4 + c4*trt + b3i;
expeta=exp(eta); p=expeta/(1+expeta);end; model resp ~ binary(p);
random b1i b2i b3i ~ normal([0,0,0],[d11,d12,d22,d13,d23,d33]) subject=Pid;run;
```

7. Joint Generalized linear Mixed models for Ordinal Outcome

```
proc nlmixed data=joint qmax=5000 qpoints=20 tech=newrap  maxiter=1000;
Title ' Joint Models for the three outcomes';
bounds a1>0, a2>0, b1>0, b2>0, c1>0, c2>0;
parms a0= -4.6339 a11=-1.5425 a12=-1.2968 a13=-1.3681 a21=-3.6884 a22=-3.4010
 a23=-2.8930 a31=-5.4058 a32=-4.8126 a33=-3.3761 a41=-0.2911 a42=-0.6564 a43=-1.0812
 a1=3.0869 a2=3.0416 b0=-2.7067 b11=-0.8754 b12=-0.7306 b13=-0.8868 b21=-2.0903
 b22=-2.1296 b23=-2.0456b31=-3.1558 b32=-3.1991 b33=-2.4907 b41 =-0.1716 b42=-0.5014
 b43=-0.9685 b1=1.8914 b2=1.6566 c0 =-7.3573 c11 =0.09844 c12=0.7254  c13=0.6361
 c21=-1.0083 c22=0.2402 c23=0.1057 c31=-2.2598 c32=-0.5116 c33=-1.3278 c41=-0.2752
  c42=-0.2248 c43 =-0.2221 c1 =2.5312 c2=4.2562
d11=5.5510 d12=0 d22=5.5431 d13=0  d23=0 d33=9.2099;
if adversevent=1 then do; /* Pain  modelled here*/
```

```
eta3 = a0  + a13*d2 + a23*d3 + a33*d4 + a43*Trt + bi1;
eta2 = a0 + a1  + a12*d2 + a22*d3 + a32*d4 + a42*Trt + bi1;
eta1 = a0 + a1 + a2 + a11*d2 + a21*d3 + a31*d4 + a41*Trt + bi1;
if (response=3) then model=1/(1+exp(-eta3)) ;
else if (response=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (response=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (response=0) then model= 1 - 1/(1+exp(-eta1)); ll=log(model); end;
else if adversevent=2 then do; /* Redness modeled here*/
eta3 = b0  + b13*d2 + b23*d3 + b33*d4 + b43*Trt + bi2;
eta2 = b0 + b1  + b12*d2 + b22*d3 + b32*d4 + b42*Trt + bi2;
eta1 = b0 + b1 + b2 + b11*d2 + b21*d3 + b31*d4 + b41*Trt + bi2;
if (response=3) then model=1/(1+exp(-eta3));
else if (response=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (response=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (response=0) then model= 1 - 1/(1+exp(-eta1)); ll=log(model);end;
else if adversevent=3 then do;/* irritability  modeled here*/
eta3 = c0  + c13*d2 + c23*d3 + c33*d4 + c43*Trt + bi3;
eta2 = c0 + c1  + c12*d2 + c22*d3 + c32*d4 + c42*Trt + bi3;
eta1 = c0 + c1 + c2 + c11*d2 + c21*d3 + c31*d4 + c41*Trt + bi3;
if (response=3) then model=1/(1+exp(-eta3));
else if (response=2) then model= 1/(1+exp(-eta2)) - 1/(1+exp(-eta3));
else if (response=1) then model= 1/(1+exp(-eta1)) - 1/(1+exp(-eta2));
else if (response=0) then model= 1 - 1/(1+exp(-eta1));
ll=log(model); end; model response ~ general(ll);
random bi1 bi2 bi3 ~ normal([0,0,0], [d11,d12,d22,d13,d23,d33]) subject=Pid;
estimate'intp3'a0; estimate'inp12'a0+a1; estimate'intp1'a0+a1+a2;estimate'intR3'b0;
estimate 'inpR2' b0+b1; estimate 'intR1' b0+b1+b2;
estimate 'intI3' c0; estimate'inpI2'c0+c1; estimate 'intI1' c0+c1+c2; run;
```

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Statistical modelling of solicited symptoms in vaccine clinical trials

Richting: **Master of Statistics-Biostatistics**
Jaar: **2011**

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Voor akkoord,

Ejigu, Bedilu Alamirie

Datum: **19/09/2011**