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Use of generalized ordered logistic regression for the analysis of multidrug resistance data

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ABSTRACT

Statistical analysis of antimicrobial resistance data largely focuses on individual antimicrobial's binary outcome (susceptible or resistant). However, bacteria are becoming increasingly multidrug resistant (MDR). Statistical analysis of MDR data is mostly descriptive often with tabular or graphical presentations. Here we report the applicability of generalized ordinal logistic regression model for the analysis of MDR data. A total of 1,152 *Escherichia coli*, isolated from the feces of weaned pigs experimentally supplemented with chlortetracycline (CTC) and copper, were tested for susceptibilities against 15 antimicrobials and were binary classified into resistant or susceptible. The 15 antimicrobial agents tested were grouped into eight different antimicrobial classes. We defined MDR as the number of antimicrobial classes to which *E. coli* isolates were resistant ranging from 0 to 8. Proportionality of the odds assumption of the ordinal logistic regression model was violated only for the effect of treatment period (pre-treatment, during-treatment and post-treatment); but not for the effect of CTC or copper supplementation. Subsequently, a partially constrained generalized ordinal logistic model was built that allows for the effect of treatment period to vary while constraining the effects of treatment (CTC and copper supplementation) to be constant across the levels of MDR classes. Copper (Proportional Odds Ratio [Prop OR] = 1.03; 95% CI = 0.73–1.47) and CTC (Prop OR = 1.1; 95% CI = 0.78–1.56) supplementation were not significantly associated with the level of MDR adjusted for the effect of treatment period. MDR generally declined over the trial period. In conclusion, generalized ordered logistic regression can be used for the analysis of ordinal data such as MDR data when the proportionality assumptions for ordered logistic regression are violated.
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1. Introduction

Epidemiological studies of antimicrobial resistance (AMR) typically involve testing of isolated bacterial strains against a panel of various antimicrobial agents which results in a multivariate outcome (Agga, 2013). However, statistical analysis of phenotypic AMR data are largely univariate focusing on individual outcomes of the antimicrobials tested (Scott et al., 2005; Alali et al., 2008). Such univariate analysis however, fails to account for the pharmacological, biological (i.e. the outcomes were derived from same isolate) or genetic dependences of the outcomes. Multivariate analysis on the other hand accounts for such co-dependences among multiple AMR outcomes. Bivariate and multivariate probit models (Agga et al., 2014, 2015) for multivariate analysis of multiple binary outcomes, and multivariate linear regression model for multiple quantitative outcomes (Agga et al., 2015) were previously applied for the analysis of AMR data. Other multivariate approaches (Agga, 2013) that were used for the analysis of AMR data include cluster analysis (Berge et al., 2003; Alali et al., 2010), factor analysis (Wagner et al., 2003) and more recently Bayesian networks (Ludwig et al., 2013; Ward and Lewis, 2013).

Bacterial multidrug resistance (MDR), due to cross resistance between pharmacologically similar antimicrobial agents or through co-resistance of genetically linked resistance determinants, is an increasing problem. Considering MDR as an outcome can detect emerging resistance profiles, that may not be easily detected by univariate analysis of individual AMR results (Wagner et al., 2003). For example, *Salmonella* isolates exhibiting a penta-resistance profile (ACSSuT) against five different antimicrobial classes (ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline) has significant epidemiological relevance. MDR can be defined in three ways: (1) as the number of antimicrobial agents to which bacterial strain is resistant to, (2) as the number of antimicrobial classes to which each bacterial strain is resistant and (3) as resistance to ≥3 antimicrobial classes commonly used

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by National Antimicrobial Resistance Monitoring System (NARMS) (FDA, 2013). Defining MDR based on the number of antimicrobial classes overcomes the problem of pharmacological dependence between related antimicrobial agents that arises as a result of testing multiple antimicrobial agents in each class. However this does not solve the problem of biological dependence between multiple classes since such data arise from testing a single bacterial isolate.

Analysis of MDR data is mostly descriptive and is presented as frequency distribution in bar graphs or tables (Scott et al., 2005; Lowrance et al., 2007; Alali et al., 2008; Platt et al., 2008; Tadesse et al., 2012; FDA, 2013) sometimes combined with univariate analysis using a χ^2 test on binary classified MDR data. Such univariate analysis does not allow for simultaneous evaluation of more than one risk factor on the occurrence of MDR. Furthermore it suffers from a problem of multiple comparisons and such binary categorization can result in loss of information. Poisson regression defining MDR as the number of antimicrobial agents to which an individual isolate was resistant potentially ranging from zero to the maximum number of antimicrobial agents tested was used (Varga et al., 2009). Multinomial logistic regression also can be used to analyze the different established dichotomies comparing each of the MDR categories to a selected baseline category (Ananth and Kleinbaum, 1997; Hosmer and Lemeshow, 2000; Varga et al., 2009). However, all of the methods described above do not consider the generally ordinal nature of the MDR counts.

Ordered logistic regression takes the natural ordering of MDR data into account to examine the effect of different risk factors on MDR count (Hosmer and Lemeshow, 2000). When the proportional odds assumptions (i.e., the equality of the log-odds across the different cut points (categories) of the outcome variable) are met, a cumulative logit model (proportional odds model) can be used for the analysis of such ordered data (McCullagh, 1980; Hosmer and Lemeshow, 2000). However, it is exceedingly rare that these parallel line assumptions are met. Unconstrained ordinal logistic regression model, a form of generalized ordered logistic regression (gologit) model, can be used to relax the proportionality assumptions (Williams, 2006). Partial proportional odds model, is another form of gologit model in which coefficients of variables for which the proportionality assumptions are met are constrained while allowing the coefficients of the variables for which proportionality assumptions are not met to vary without any constraint.

We have previously used ordinal logistic regression model to evaluate the effect of treatment on the number of tetracycline resistance gene determinants detected from swine fecal metagenome (Agga et al., 2015). However, to the best of our knowledge, there are no published papers that used generalized ordinal logistic regression model for the analysis of MDR data. Therefore the objective of this paper was to show the applicability of generalized ordinal logistic regression model for the analysis of MDR data. The MDR data used for the present analysis is based on susceptibility results of *Escherichia coli* isolates from a previously reported trial conducted to investigate the impact of copper and CTC supplementation of weaned pigs on antimicrobial resistance of fecal bacteria (Agga et al., 2014).

2. Materials and methods

2.1. Phenotypic antimicrobial resistance data

Phenotypic AMR data used in this paper was originated from *E. coli* isolates obtained from experimental study conducted to investigate the impact of CTC and copper supplementation on the gut bacterial flora of weaned pigs. A full description of the study design, study population, sampling scheme, and determination of phenotypic antimicrobial resistance of the *E. coli* isolates is available elsewhere (Agga et al., 2014). Briefly, the study design was a full factorial cluster randomized trial in which 32 pens (each with five pigs) were randomly allocated to control, CTC, copper or copper plus CTC groups. Pens were supplemented with experimental doses of copper, CTC or their combination continuously for 21 days. This was followed by post-treatment period of 14 days. A total of 576 fecal samples were collected weekly from three pigs per pen for six weeks. Two non-type specific *E. coli* isolates were isolated per fecal sample giving rise to 1,152 isolates. Each isolate was then characterized for phenotypic and genotypic antimicrobial resistance.

Antimicrobial susceptibility testing was done using broth microdilution following Clinical Laboratory Standards Institute (CLSI) Veterinary Antimicrobial Susceptibility Testing standards (CLSI, 2008). Minimum inhibitory concentration (MIC) was determined for 15 antimicrobial agents for each isolate by using Sensititre™ semi-automated system (Trek Diagnostic Systems, Cleveland, OH) using NARMS custom panels (CMV1AGNF and CMV2AGNF). The MIC values of each *E. coli* isolate were categorized as resistant or susceptible (including intermediate MIC results) based on CLSI breakpoints for all but streptomycin for which NARMS consensus breakpoint was used. The 15 antimicrobial agents were categorized into eight classes according to CLSI definition (CLSI, 2008). The antimicrobial classes were: aminoglycosides, β-lactam/β-lactamase inhibitor combinations, cephems, folate pathway inhibitors, penicillins, phenicols, quinolones and tetracyclines. The macrolides class, represented by azithromycin, was excluded since all the isolates were not tested for azithromycin resistance (Agga et al., 2014).

2.2. Statistical approaches

Sampling days (d0–d35) were categorized into treatment periods as pre-treatment, during treatment and post-treatment. A full factorial model approach was used in the analysis to examine the effects of copper and CTC supplementations. In this approach, the copper plus CTC group was categorized as treatment group when evaluating copper and CTC effects independently. Moreover, the copper group was used as a control when evaluating the CTC effect; and the CTC group was used as a control when evaluating copper effect. Full factorial approach increases power by doubling the sample size both in the treatment and control groups. Control group (in which CTC or copper was not given) and the pre-treatment period were considered as referent groups; and $P < 0.05$ was considered significant. Data analysis was carried out in STATA 12 (STATA Corp LP, College Station, TX). For this paper we defined MDR as the number of antimicrobial classes to which each isolate was resistant.

2.3. Proportional ordered logistic regression model: assessing assumptions and model selection

In a proportional ordered logistic regression, the log-odds, and thus the odds ratios, are assumed to be constant across the ordered categories of the outcome and assumed only to differ by the levels of explanatory variable. However, the intercepts are allowed to vary across the categories of the outcome variable thus giving a series of parallel lines with constant slope but with different intercepts (Hosmer and Lemeshow, 2000; Dohoo et al., 2009). First proportional ordinal logistic regression model was fitted to assess the significance of each term (treatment, treatment period and all 2- and 3-way interactions) and to assess the proportionality assumption. This model accounts for the ordinal nature of the MDR outcome ranging potentially from 0 to 8 antimicrobial classes. Three isolates in the pan-susceptible category (resistant to 0 antimicrobial classes) were re-categorized to a category with resistance to one antimicrobial class. Moreover, all isolates were

susceptible to the antibiotics of the quinolone class (ciprofloxacin and nalidixic acid). Accordingly, only seven classes were modeled. Proportional odds model produces one beta coefficient (β) for each variable in the model.

For model selection we used Akaike information criterion (AIC). First a full model including all the main effects of treatment group and period, 3- and 2-way interactions was built. Then each term was removed starting with the 3-way interaction and the significance of each removed term was manually assessed by comparing the AIC values of the models. Since proportional ordered logit model estimates one equation over all levels of our dependent variable MDR, there is a concern whether this one-equation model is valid or a more flexible model is required. The proportionality assumption of the proportional odds model was assessed by Brant test for the parallel regression assumption (Long and Freese, 2006). A Brant test (Long and Freese, 2006) provides both global test of whether any variable is significant in the model, as well as specific significance test for each explanatory variable separately (Williams, 2006).

2.4. Generalized ordered logit model

Generalized linear model with a logistic cumulative distribution function for ordinal logit model and multinomial distribution was used to examine the effect of treatment and treatment period on the number of antimicrobial classes to which a single isolate was resistant. In the unconstrained form of the gologit model, both the intercepts and the slope (β's) are allowed to vary across the categories of the outcome variable. When the ordinal dependent outcome variable has more than two categories, the gologit model is equivalent to a series of binary logistic regressions where the categories of the dependent variable are dichotomized at each cut off. Generalized ordered logit model with *gologit2* command written for STATA (Williams, 2006) was used. In this model, only the main effects of treatment group and period were fitted. Generalized ordinal logistic regression relaxes the proportionality assumptions; but it is less parsimonious than the proportional odds model. It fits *J*-1 binary logistic regression models where *J* is the number of the categories of the outcome variable. Accordingly, six binary equations were fitted corresponding to the seven classes to which resistances were observed. The number of antimicrobial classes (1–7) to which a single isolate was resistant to was first modeled with fully unconstrained ordinal logistic model.

The *autofit* command option also was used to test for the proportionality assumptions. Similar to the Brant test, the *autofit* option also indicated that parallel lines assumption was not significantly violated for copper ($P = 0.7129$) and CTC ($P = 0.6155$) but it was significantly violated for the effect of during-($P < 0.00001$) and post-treatment periods ($P = 0.00338$). Subsequently, partially constrained generalized ordinal logistic regression was fitted. In this partially constrained generalized ordinal logistic regression model, constraints for parallel lines were imposed on treatment (copper and CTC). However, constraints were not imposed for during-treatment and post- treatment period and were allowed to vary by the outcome categories.

Generalized ordered logistic regression model compares all the categories greater than the current category to those less than or equal to the current category (i.e. > vs. ≤ categories comparison). Hence, positive coefficients indicate that higher values of the explanatory variable are associated with higher category levels of the outcome variable (in this case MDR count) than the level of category under consideration. On the other hand, negative coefficients indicate that higher values of the explanatory variable increase the likelihood of being in the current or a lower category (Williams, 2006). When interpreting results for each panel, an expressed category of the outcome variable and all the lower coded categories serve as a reference group.

3. Results

Frequency distribution of the number of antimicrobial classes to which isolates were resistant is given by CTC and copper supplementation (Table 1) and by treatment periods (Table 2). As can be seen from the tables, the number of *E. coli* isolates increases as the number of MDR resistance class category increases.

3.1. Proportional ordered logistic regression model

Results of the final model from proportional ordinal logit regression model are shown in Table 3. In this model, MDR was significantly lowered during treatment period (Proportional odds ratio [Prop OR] = 0.50, 95% CI = 0.33–0.75) and post-treatment period (Prop OR = 0.42; 95% CI = 0.25–0.72). However, both copper and CTC supplementation were not significantly associated with MDR ($P > 0.05$). Brant test showed that the assumption of proportionality of the log odds (β's) across the different categories of MDR (cut offs) was significantly violated for treatment periods ($P < 0.05$) but not for copper ($P = 0.502$) and CTC ($P = 0.261$) supplementations (Table 4).

3.2. Generalized ordinal logistic regression

Results of partially constrained generalized ordinal logistic regression model assessing the effects of copper, CTC and treatment periods on the level of MDR are shown in Table 5. For the seven categories of the outcome variable (MDR class), six regression equations were fitted. Copper and CTC have a single constant Beta coefficient across all the six regression equations while treatment period and post-treatment period have different coefficients for each of the MDR categories. Copper (Prop OR = 1.03; 95% CI = 0.73–1.47) and CTC (Prop OR = 1.1; 95% CI = 0.78–1.56) supplementation were not significantly associated with the level of MDR. Treatment period was significantly and negatively associated with MDR. This started to become evident when comparing resistance to greater than three classes to three or lower classes. For example at cut off value of three different classes, *E. coli* isolates obtained in the post-treatment period were less likely (OR = 0.43; 95% CI = 0.25–0.74) to be resistant to more than three different classes when compared with isolates obtained before treatment.

4. Discussion

In this paper we have shown the applicability of generalized ordered logistic regression model for the analysis of MDR data. We have applied generalized ordered logistic regression to MDR data from a previously published study (Agga et al., 2014). Using the generalized ordinal logistic regression, we did not observe a significant effect of CTC and copper supplementations on the occurrence of MDR among fecal *E. coli* isolates obtained from weaned pigs. Based on the binary definition of MDR as resistance to ≥3 antimicrobial classes (Agga et al., 2014) only CTC supplementation was found to be significantly associated with higher proportion of MDR *E. coli* isolates. However, this result was based on univariate analysis only for the treatment group, without accounting for the treatment period effect. The present analysis, on the other hand, was a multivariate analysis with ordered logistic regression model that utilized all available information from the entire MDR categories. The current analysis also included both the effects of treatment group and treatment period; thus the effect of treatment group was adjusted for the effect of treatment period. Similar to the previous analy-

Table 1
Frequency distribution of the multidrug resistance (MDR) by copper and chlortetracycline (CTC) supplementation, expressed in terms of the number of antimicrobial classes, of *E. coli* isolates (n = 1,152) obtained from fecal samples of weaned pigs supplemented with copper, CTC, both or neither.

MDR class category	Copper supplementation		CTC supplementation		Total
	Yes	No	Yes	No	
0	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	3 (0.3)
1	38 (6.6)	32 (5.6)	28 (4.9)	42 (7.3)	70 (6.1)
2	18 (3.1)	18 (3.1)	17 (3.0)	19 (3.3)	36 (3.1)
3	94 (16.3)	96 (16.7)	95 (16.5)	95 (16.5)	190 (16.5)
4	46 (8.0)	58 (10.1)	51 (8.9)	53 (9.2)	104 (9.0)
5	63 (10.9)	57 (9.9)	56 (9.7)	64 (11.1)	120 (10.4)
6	108 (18.8)	125 (21.7)	132 (22.9)	101 (17.5)	233 (20.2)
7	207 (35.4)	189 (32.8)	195 (33.9)	201 (34.9)	396 (34.4)
8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	576 (100)	576 (100)	576 (100)	576 (100)	1,152 (100)

Table 2
Frequency distribution of the multidrug resistance (MDR) by treatment period, expressed in terms of the number of antimicrobial classes, of *E. coli* isolates (n = 1,152) obtained from fecal samples of weaned pigs supplemented with copper, chlortetracycline (CTC), both or neither.

	Treatment period			
MDR class category	Pre-treatment	During treatment	Post-treatment	Total
0	1 (0.5)	1 (0.2)	1 (0.3)	3 (0.3)
1	6 (3.1)	35 (6.1)	29 (7.6)	70 (6.1)
2	10 (5.2)	13 (2.3)	13 (3.4)	36 (3.1)
3	21 (10.9)	72 (12.5)	97 (25.3)	190 (16.5)
4	13 (6.8)	71 (12.3)	20 (5.2)	104 (9.0)
5	14 (7.3)	78 (13.5)	28 (7.3)	120 (10.4)
6	24 (12.5)	138 (24.0)	71 (18.5)	233 (20.2)
7	103 (53.7)	168 (29.2)	125 (32.6)	396 (34.4)
8	0 (0)	0 (0)	0 (0)	0 (0)
Total	192	576	384	1,152

Table 3
Results of proportional odds regression of the final model for the effect of copper, chlortetracycline (CTC) and treatment period.

					95% Confidence interval	
Variables[a]	Coefficient	Robust Std. Err.	Z-value	$P>Z$	Lower limit	Upper limit
Copper	0.03	0.17790	0.16	0.869	−0.32	0.38
CTC	0.09	0.17580	0.52	0.600	−0.25	0.44
During treatment[b]	−0.69	0.20309	−3.38	0.001	−1.09	−0.29
Post-treatment period	−0.86	0.27353	−3.14	0.002	−1.40	−0.32
/Cut1[c]	−3.30	0.40302			−4.09	−2.51
/Cut2	−2.86	0.36342			−3.57	−2.15
/Cut3	−1.64	0.25981			−2.15	−1.13
/Cut4	−1.21	0.24333			−1.68	−0.73
/Cut5	−0.77	0.22187			−1.20	−0.33
/Cut6	0.08	0.21983			−0.35	0.51

[a] All interaction terms were not significant.
[b] Control and pre-treatment period were considered as reference categories for treatment and treatment period effects respectively.
[c] Cut1–6 = cut points (thresholds) are the intercepts for each of the regression equations estimated on the latent variable used to differentiate the adjacent levels of the multidrug resistance. The coefficients represent the values of the predictors evaluated at zero (for the control and pre-treatment isolates).

Table 4
Estimated coefficients from six binary regressions of the Brant test for parallel regression assumption for the proportional odds model of multidrug resistance of *E. coli* isolates obtained from fecal samples of weaned pigs supplemented with copper, chlortetracycline (CTC), both or neither.

Variables	$y>1$[a]	$y>2$	$y>3$	$y>4$	$y>5$	$y>6$
Copper	−0.21	−0.14	−0.05	0.05	0.01	0.14
CTC	0.39	0.31	0.14	0.13	0.18	−0.05
During treatment[b]	−0.57	0.04	−0.07	−0.32	−0.55	−1.03
Post-treatment period	−0.81	−0.26	−0.84	−0.68	−0.63	−0.88
Constant	3.21	2.26	1.35	0.93	0.58	0.10
Brant test for parallel regression assumption						
Variable	χ^2	$p>\chi^2$	df			
All	76.95	0.000	20			
Copper	4.34	0.502	5			
CTC	6.49	0.261	5			
During treatment period	29.74	0.000	5			
Post-treatment period	13.72	0.017	5			

[a] y represents multidrug resistance class categories.
[b] Pre-treatment period was considered as reference category.

Table 5
Partially constrained generalized logistic regression analysis results for the effects of treatment and treatment period on multidrug resistance (MDR) on the basis of the number of antimicrobial classes, of *E. coli* isolates obtained from fecal samples of weaned pigs supplemented with copper, chlortetracycline (CTC), both or neither.

MDR class	Variable[a]	Coefficient	Robust Std. Err.	*Z*	*P*>*Z*	95% Confidence interval	
						Lowe limit	Upper limit
1	Copper	0.03	0.178978	0.19	0.847	−0.32	0.39
	CTC	0.10	0.177337	0.54	0.591	−0.25	0.44
	During treatment[b]	−0.57	0.419911	−1.35	0.176	−1.39	0.25
	Post-treatment period	−0.81	0.469696	−1.72	0.085	−1.73	0.11
	Constant	3.21	0.442448	7.26	<0.001	2.34	4.08
2	During treatment	0.04	0.368961	0.11	0.910	−0.68	0.76
	Post-treatment period	−0.26	0.390763	−0.67	0.500	−1.03	0.50
	Constant	2.27	0.377557	6.01	<0.001	1.53	3.01
3	During treatment	−0.08	0.225582	−0.34	0.732	−0.52	0.36
	Post-treatment period	−0.84	0.274187	−3.08	0.002	−1.38	−0.31
	Constant	1.34	0.274998	4.86	<0.001	0.80	1.88
4	During treatment	−0.33	0.209276	-1.56	0.120	-0.74	0.08
	Post-treatment period	−0.68	0.290308	−2.34	0.019	−1.25	−0.11
	Constant	0.95	0.229769	4.15	<0.001	0.50	1.40
5	During treatment	−0.55	0.229765	−2.38	0.017	−1.00	−0.10
	Post-treatment period	−0.63	0.259857	−2.41	0.016	−1.14	−0.12
	Constant	0.60	0.215578	2.8	0.005	0.18	1.03
6	During treatment	−1.03	0.223533	−4.63	<0.001	−1.47	−0.60
	Post-treatment period	−0.87	0.262223	−3.33	0.001	−1.39	−0.36
	Constant	0.08	0.207751	0.38	0.701	−0.33	0.49

[a] Since the coefficients for copper and CTC effects were constant they were not repeated at each multidrug resistance class category.
[b] Control and pre-treatment period were considered as reference categories.

sis, copper supplementation was not significantly associated with MDR in *E. coli*. We observed a significant decline in the MDR over the trial period. Even though a similar trend has been reported in calves (Berge et al., 2005), it is difficult to ascribe this effect to the ageing of the pigs given the short study period.

MDR data usually are presented in tabular or graphical formats without any analytical statistics (Scott et al., 2005; Alali et al., 2008) which do not allow for the analysis of risk factors on the occurrence of MDR. Some analytical analysis involving linear regression (Platt et al., 2008) and Poisson regression (Varga et al., 2009) models were applied to MDR data, without considering the natural ordering of the data structure. In a prospective cohort study conducted in calves to investigate risk factors for MDR in fecal *E. coli* (Berge et al., 2005), cumulative multinomial logistic regression was used. In that study, MDR was defined as ordinal dependent variable represented by antibiotic resistance clusters formed by cluster analysis. Although the authors noted that the odds of MDR were not equal across all levels of the cluster hierarchy, they still used proportional odds model for this analysis.

We examined the proportional odds assumptions of the ordinal logistic regression model and the assumptions were not met. Similar to our report here, one study (Sunenshine et al., 2007) attempted to fit linear regression model and ordinal logistic regression model to MDR data but assumptions for both models were not satisfied. We therefore used partially constrained generalized ordinal logistic regression in which the effects of CTC and copper supplementation were modeled as constant while that of treatment period was allowed to vary across the various MDR categories. This model is more parsimonious than the original generalized ordinal logistic regression model (Williams, 2006), however it is less parsimonious compared to the proportional odds model. Proportional odds model does not depend on the level of the outcome giving only a single coefficient for each predictor variable (Dohoo et al., 2009) if the proportionality assumption is met. The constrained variables in the partially constrained ordinal logistic regression model have a single coefficient (Williams, 2006). The original generalized ordered logistic regression model on the other hand produces one coefficient for each predictor variable included in the model (Williams, 2006). However it has to be noted that generalized ordered logistic regression models in general and partially constrained model in particular are more difficult to interpret than the parallel lines ordered logistic regression model (Williams, 2006).

In the present analysis we defined MDR based on the number of antimicrobial classes (ranging from 1 to 7) and modeled it as an ordinal outcome variable. This is contrary to binary analysis of MDR data as resistance to ≥3 antimicrobial classes (Tadesse et al., 2012; FDA, 2013) which results in a substantial loss of information and statistical power (Ananth and Kleinbaum, 1997). Defining MDR on the basis of the number of individual antimicrobial agents and modeling it as ordinal data does not account for pharmacological dependence of antimicrobial agents of the same class. Generalized ordered logistic regression analysis accounts for the ordinal data structure as well as both for the pharmacological and biological dependences while utilizing all available information in the data.

5. Conclusion

In this paper we have evaluated the assumptions of the proportional ordered logistic regression model and showed the applicability of generalized ordered logistic regression model for the analysis of MDR data. In the final model, it was observed that the occurrence of MDR did not depend on copper or CTC supplementation but it was more influenced by treatment period, showing a significant decline over time.

Conflict of interest

The authors declare no conflict of interest.

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