Regression models for censored serological data

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The impact was assessed of censored serological measurements on regression equations fitted to data from panels of sera tested by different laboratories, for the purpose of standardizing serosurvey results to common units. Several methods that adjust for censoring were compared, such as deletion, simple substitution, multiple imputation and censored regression. Simulations were generated from different scenarios for varying proportions of data censored. The scenarios were based on serological panel comparisons tested by different national laboratories and assays as part of the European Sero-Epidemiology Network 2 project. The results showed that the simple substitution and deletion methods worked reasonably well for low proportions of data censored (<20%). However, in general, the censored regression method gave estimates closer to the truth than the other methods examined under different scenarios, such as types of equations used and violation of regression assumptions. Interval-censored regression produced the least biased estimates for assay data resulting from dilution series. Censored regression produced the least biased estimates in comparison with the other methods examined. Moreover, the results suggest using interval-censored regression methods for assay data resulting from dilution series.

INTRODUCTION

Serological surveys can provide valuable information on the performance and future requirements of a vaccination programme by identifying population groups with low seroprevalence that are at risk of infection. Moreover, international comparisons of seroprevalence estimates allow overall assessments towards global and regional targets, as well as comparisons of different vaccination programmes, in order to optimize them. This information forms part of the strategy for the containment or elimination of vaccine-preventable diseases as established by the World Health Organization (WHO) goals (WHO, 2005, 2006).

The European Sero-Epidemiology Network 2 (ESEN2) project was a study funded by the European Commission aiming to estimate seroprevalence in Europe. It was initiated in 2001 as a continuation of the ESEN project (Osborne et al., 1997). As part of the ESEN2 project, serosurveys of 1000–3000 samples were collected from 22 countries and tested for up to eight viral antigens [measles, mumps, rubella, pertussis, diphtheria, varicella-zoster virus, hepatitis A virus (HAV), hepatitis B virus] in each country’s national laboratory (Nardone et al., 2004).

To enable valid comparisons of seroprevalence among countries, a method of standardizing assay results was used to adjust for a variety of assays and laboratory methods between the national laboratories. The standardization method was introduced for the ESEN project and was later developed further for ESEN2 (Andrews et al., 2000; Kafatos et al., 2005).

In brief, for each antigen, one of the national laboratories was chosen as the reference centre. This reference laboratory prepared a panel of ~150 samples covering the full assay range of quantitative results that was sent and tested by each national laboratory. Each testing laboratory’s results (on the y axis) were regressed against those of the reference centre (on the x axis), thus obtaining standardization equations. Note that the reference centre tested the panel samples multiple times and that the mean was taken in an attempt to minimize the measurement error. These equations were used to convert the quantitative serosurvey measurements into common units, which were subsequently classified into negative (susceptible) or positive (protected) according to the reference assay cut-off (Andrews et al., 2000; Kafatos et al., 2005). The choice of standardization equation was crucial, as it had a direct impact on the seroprevalence estimates. Therefore, it was important to select an equation that fitted the panel data well, particularly around the positive/negative cut-off point, where misclassification is more likely to occur (Andrews et al., 2000; Kafatos et al., 2005).
Following the assay testing, a number of serological results were reported as censored due to assays being constrained by detection limits (DLs). One reason for setting a detection range could be the failure of instruments to detect levels below or above certain values (say, \( D_L \) and \( D_U \), respectively). Any results below or above the assay DLs were reported as \(<D_L\) or \(>D_U\), respectively. Laboratories were asked to produce uncensored results, even outside the assay range, despite the fact that these were expected to have higher measurement error due to background noise (for measurements below \( D_U \)) (Lim, 2006; Whitcomb & Schisterman, 2008). Whilst most reference centres provided such results, often the other laboratories did not.

A number of methods exist for fitting a regression model in the presence of censored data (Helsel, 2012; Lubin et al., 2004; Thompson & Nelson, 2003). For the ESEN2 project, the methods of deletion and simple substitution were used. For the deletion method, the censored observations were simply omitted prior to the analysis, whereas for the simple substitution method, they were substituted by a constant. Various strategies have been suggested for the value of this constant such as DL, DL/2, \(D_L/\sqrt{2}\) or 2DL/3 (Helsel, 2012; Krishnamoorthy et al., 2009; Lubin et al., 2004; Thompson & Nelson, 2003). However, deletion and substitution methods have generally been shown to give more biased regression estimates compared with other methods such as censored regression and multiple imputation (MI) (Lubin et al., 2004; Thompson & Nelson, 2003).

In this paper, we aimed to assess the validity of the methods used to obtain standardization equations for the ESEN2 project and to compare these with a censored regression method. Simulations, based on regression equations as estimated for the ESEN2 panel comparisons, were used for method validation. The robustness of the methods under different scenarios, such as linear and non-linear curves, violation of regression assumptions and interval censored data, were assessed.

**METHODS**

Regression equation methods in the presence of censored data. In the ESEN2 project, simple substitution was most used often for left- and right-censored data. Data below the assay DL were halved (\(D_L/2\) and those above were doubled (\(2D_U\)) prior to \(\log_{10}\)-transforming the data. A normal error regression equation was subsequently fitted, using the substituted data. A regression equation was also fitted after the measurements outside the assay DL had been removed (method of deletion). The impact of the substituted data was assessed by comparing the regression equation estimates following simple substitution and deletion. Given the importance of the model fitting well around the positive/negative cut-off point, the two models were compared using the cut-off ratio (COR), i.e. the ratio of the difference of the two lines at the reference cut-off point over the range of the y axis data (in order to obtain comparable differences). In those situations where the difference was large (a large difference was arbitrarily defined as COR \(>0.075\) based on empirical evidence), the regression by deletion method was preferred (Kafatos et al., 2005).

Another method that has been proposed in the past for estimating regression equations in the presence of censored data is the censored regression method. Maximum-likelihood estimation was used to estimate censored regression models as follows:

Suppose the observed response variable \(y_i\) consists of \(n\) measurements of which (i) the first \(\ell\) are uncensored, (ii) there are a number of left-censored observations \(y_{c+1} \geq DL\), for \(i = c+1, \ldots, n\), where all that is known is that the true value \(y_i < DL\), and (iii) there are a number of right-censored observations \(y_{c+1} = DU\), for \(i = c+1, \ldots, n\), where all that is known is the true value \(y_i > DU\). Note that the subscript \(i\) is added to the notation \(D_L\) and \(D_U\) to account for potentially different censoring bounds. Let also \(F(.)\) and \(f(.)\) be the normal cumulative distribution function and the normal probability density function, respectively.

Then, for a model \(E(y_i|x_i) = g(x_i) = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \ldots + \beta_k x_i^k\), where \(\beta_0, \beta_1, \ldots, \beta_k\) are \(k+1\) parameters and \(x_i\) is the explanatory variable, the log-likelihood for the censored regression model (Breen, 1996; Iain et al., 2008; Lubin et al., 2004) is:

\[
\ln(L) = \sum_{i=1}^{n} \left[ \sum_{j=1}^{\ell} \ln(f(y_{c+1}|x_i,\sigma)) + \sum_{j=\ell+1}^{c} \ln(F(y_{c+1}|x_i,\sigma)) + \sum_{j=c+1}^{n} \ln(1-F(y_{c+1}|x_i,\sigma)) \right]
\]

The serological results were generally reported as uncensored within the assay DL. However, some of the results were of a ‘semi-censored’ format due to the way sera were diluted. More specifically, each sample was tested by dilution and, if found positive, was further diluted until a negative result was obtained. The final dilution was taken as the serum result. For simplicity, when analysing such data, this special feature is usually ignored and the data are treated as continuous. A method proposed here is to treat these semi-censored measurements as interval-censored data. Interval-censored regression can then be used to eliminate the bias resulting from treating the data as exact values rather than interval censored.

The procedure can be described as follows: for a dataset of size \(n\), let a subset of size \(\ell\) consist of interval-censored data, with \(\ell_j\) samples lying within each of \(N\) different ranges \(y_{ij} \in [y_{ij+1}, y_{ij+2})\). Also let \(i = \ell + 1, \ldots, c\) be left-censored data and \(i = c+1, \ldots, n\) be right-censored data. Then, a generalization of the log-likelihood shown above becomes (Breen, 1996; Lyles et al., 2001; Zhang & Sun, 2010):

\[
\ln(L) = \sum_{j=1}^{N} \sum_{i=1}^{\ell_j} \ln(F(y_{ij}|x_i,\sigma)) - F(y_{ij}|x_i,\sigma)]
+ \sum_{j=\ell_j+1}^{c} \ln(f(y_{ij}|x_i,\sigma)) + \sum_{j=c+1}^{n} \ln(1-F(y_{ij}|x_i,\sigma))
\]

MI is an alternative method for fitting regression equations when censoring occurs. A simple version of the MI method was used that consisted of two steps: (i) estimation of the model parameters using the censored regression method, and (ii) using these estimated parameters to draw random samples (from a normal distribution) to replace the censored observations. Once the censored observations have been imputed, a regression equation can provide the imputation estimates.

The process was repeated multiple times (10 times in the examples shown here) and the mean of the imputation estimates gave the MI estimate (Lynn, 2001). By combining the two variance components, the within- and between-imputation variance, it was possible to obtain a pooled variance and hence 95% confidence intervals (CIs) around the MI estimates. Assuming that \(K\) denotes the number of parameters and \(m\) the number of imputations, then the pooled variance can be defined as:

\[
T_K = WI^2 + (1 + \frac{1}{m})B\]

where \(WI\) is the within-imputation variance and \(B\) the between-imputation variance (Carpenter & Goldstein, 2004; Krishnamoorthy et al., 2009; Schafer, 2010).
Comparison of regression equation methods for censored data using simulations. The simple substitution and deletion methods were compared with censored regression and MI methods using simulations. Observations were randomly generated to represent the testing laboratory results (y axis) from a regression model based on standardization equations as estimated from the ESEN2 project using the reference centre’s data. For validating equations of quadratic form, observations were simulated from $y = -0.4 + 1.1x + 0.12x^2$ with random error $\varepsilon \sim N(0, \sigma^2)$ and $\sigma = 0.26$, the regression equation obtained by regressing the Israel laboratory’s HAV panel results against the Greek reference centre’s results. This panel was chosen as an example, as it was considered to be a typical panel comparison, with uncensored results for the reference laboratory and approximately one-fifth of the $y$ axis data censored. For validating linear equations, the same example was used excluding the quadratic term. For this example, any data below 0.005 IU ml$^{-1}$ ($-2.3$ on the log$_{10}$ scale) were treated as censored, whereas the reference cut-off was 0.01 (Anastassopoulou et al., 2009).

Following the results of each simulation, depending on the method to be used, any measurements outside the assay DL were either omitted (deletion and MI method) or substituted by a constant (simple substitution and censored regression method) prior to fitting any regression equation. The assay DL was varied to obtain different proportions of data censored, although never to the extent that the DL was above the assay cut-off. Given that the main interest was the region around the assay cut-off, the predicted value at the cut-off point (standardized cut-off) was estimated. The process was repeated 1000 times and the mean of the estimates was determined. The coverage probability was used to describe the uncertainty around the regression parameters, whereas the 95% percentile interval (PCI) was used for the standardized cut-off estimate (the PCI is the interval ranging from the 2.5th to the 97.5th of the ranked estimated cut-offs).

A further issue was performance within non-linear regression models. The simulations were based on the German reference panel for rubella that was sent to and tested by Cyprus, resulting in a regression equation of the sigmoid type:

$$y = -0.3 + \frac{2.5}{1 + e^{4.3x}}$$

(Equation 1)

with $\sigma = 0.16$. The reference assay cut-off was 4 IU ml$^{-1}$ (0.6 on the log$_{10}$ scale) and the assay detection range for Cyprus was (1, 200) (in

![Fig. 1. Method comparison using simulated data between simple substitution and deletion methods. (a) Model $y = -0.4 + 1.1x + 0.12x^2$ with $\sigma = 0.26$. (b) Model $y = -0.4 + 1.1x$ with $\sigma = 0.26$. Note that for graphical purposes one set of simulations was plotted in each of (a) and (b).](http://jmm.sgmjournals.org)
IU ml⁻¹). Note that, in practice, the Cypriot serosurvey results were standardized using a different equation that was based on a second panel testing (Tischer et al., 2007).

For interval-censored data, simulations were generated from the equation $y = -0.2 + 1.5x + 0.15x^2$ with $\sigma = 0.26$, the regression equation obtained by regressing the Finnish panel results for diphtheria against the Italian reference centre's results. The reference assay cut-off was 0.01 IU ml⁻¹ and any measurements below 0.004 IU ml⁻¹ or above 1.024 IU ml⁻¹ were treated as censored (data not published). After each simulation, the generated data for the Finnish laboratory were grouped into dilutions as follows: any data within the interval (0, 0.004) were substituted by 0.008 and within (0.008, 0.016) by 0.016. The same pattern continued up to the interval (0.512, 1.024), which was substituted by 1.024.

### Assessing robustness to linear regression assumptions

The multiple linear regression methods used above have the assumption of normally distributed residuals and constant variance of the error term. The validity of these assumptions was investigated by simulations using the quadratic regression example of the HAV panel shown above. Robustness to failure of the normality assumption was examined using a $\gamma$ distribution $\Gamma/\lambda, \tau$ to generate the residuals, where $\lambda$ was the shape parameter and $\tau$ the scale parameter. The distribution was shifted to centralize it at zero, by subtracting its mean $t$. A standard deviation of $\sigma = 0.26$ was used, whereas $\lambda$ was given different values aiming to examine its impact. Using the same simulation example, the effect of heteroscedasticity on regression was examined after generating residuals from $N(0, \sigma)$ for higher concentrations (above the reference assay cut-off) and $N(0, 2\sigma)$ for lower concentrations.

The main statistical software that was used for the data manipulation and analysis was Stata 11.2 (StataCorp). The censored regression model and the non-linear regression equations were fitted using the maximum-likelihood estimation command ml in Stata that uses the

![Fig. 2. Comparison of cut-off estimates for different proportions of data censored, generated from the model $y = -0.4 + 1.1x + 0.12x^2$ with $\sigma = 0.26$.](image)
Table 2. Parameter estimates and 95% coverage probabilities generated from a model of a sigmoid type \( y = -0.4 + 1.1x + 0.12x^2 \) with \( \sigma = 0.16 \) \((D_L = 0, D_U = 2.3)\) using deletion, simple substitution, censored regression and MI methods (~25% of data censored)

<table>
<thead>
<tr>
<th>Method</th>
<th>( \hat{\alpha} )</th>
<th>( \hat{\beta} )</th>
<th>( \hat{\gamma} )</th>
<th>( \hat{\delta} )</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>True model</td>
<td>-0.30</td>
<td>2.50</td>
<td>-4.00</td>
<td>3.50</td>
<td>0.03</td>
</tr>
<tr>
<td>Deletion</td>
<td>-0.00 (10.1%)</td>
<td>2.13 (7.9%)</td>
<td>-5.07 (42.9%)</td>
<td>4.21 (51.5%)</td>
<td>0.16 (0.06, 0.24)*</td>
</tr>
<tr>
<td>Simple substitution</td>
<td>-0.35 (95.5%)</td>
<td>2.59 (81.2%)</td>
<td>-3.93 (95.5%)</td>
<td>3.42 (94.4%)</td>
<td>0.00 (-0.07, 0.08)*</td>
</tr>
<tr>
<td>Censored regression</td>
<td>-0.33 (96.4%)</td>
<td>2.53 (95.9%)</td>
<td>-3.96 (95.6%)</td>
<td>3.48 (94.9%)</td>
<td>0.02 (-0.08, 0.11)*</td>
</tr>
<tr>
<td>MI</td>
<td>-0.30 (97.7%)</td>
<td>2.47 (98.0%)</td>
<td>-4.03 (67.0%)</td>
<td>3.57 (75.2%)</td>
<td>0.03 (-0.07, 0.12)*</td>
</tr>
</tbody>
</table>

*2.5th and 97.5th percentiles given instead of coverage probabilities.

Newton–Raphson algorithm for optimization (Gould & Sribney, 1999). There were no convergence problems for the models fitted in this paper.

RESULTS

Comparison of regression equation methods for censored data

For the true equation \( y = -0.4 + 1.1x + 0.12x^2 \) with \( \sigma = 0.26 \), using a reference cut-off of \(-2 \) \((0.01\text{ IU ml}^{-1})\), the standardized cut-off was \( E(y|x = -2) = 2.12 \). Following the simulations, the method of deletion gave a cut-off estimate of \( E(y|x = -2) = -1.96 \) \((95\%\text{ PCI: }-2.03, -1.89)\), whereas the method of simple substitution was closer to the true estimate, \( E(y|x = -2) = -2.13 \) \((95\%\text{ PCI: }-2.19, -2.06)\). Using the results of one set of simulations (sim) for illustration, the difference between the estimated cut-off points for these two methods was not very large \((\text{COR} = 0.04)\), which indicated that the regression equation based on simple substitution would have been preferred according to the ESEN2 method (Fig. 1a). Using the same simulation scenario, the censored regression \((E(y|x = -2) = -2.12; 95\%\text{ PCI: }-2.21, -2.05)\) and the MI methods \((E(y|x = -2) = -2.07; 95\%\text{ PCI: }-2.13, -2.02)\) provided cut-off estimates close to the true value (Table 1). The cut-off estimate by each method for different proportions of data censored is given in Fig. 2. Censored regression gave the least biased estimates, followed by simple substitution and MI.

For the true linear equation \( y = -0.4 + 1.1x \) with \( \sigma = 0.26 \), the standardized cut-off was \( E(y|x = -2) = -2.6 \). Using the results of one simulation as an example, there was large difference between the simple substitution and deletion method in the estimated cut-off point \((\text{COR} = 0.09)\), which indicated that the regression equation based on deletion would have been selected (Fig. 1b). The censored regression \((E(y|x = -2) = -2.60; 95\%\text{ PCI: }-2.75, -2.47)\) and MI methods \((E(y|x = -2) = -2.59; 95\%\text{ PCI: }-2.74, -2.45)\) both gave slightly less biased estimates than the deletion method (Table 1b).

For a non-linear regression example, simulated data were generated from the sigmoid model (Equation 1), with \( \sigma = 0.16 \) where the standardized cut-off was \( E(y|x = 0.6) = 0.03 \). The results showed that simple substitution \([E(y|x = 0.6) = 0.00; 95\%\text{ PCI: }-0.07, 0.08]\), MI \([E(y|x = 0.6) = 0.03; 95\%\text{ PCI: }}

![Fig. 3. Method comparison using simulated data generated from the model in Equation 1, with \( \sigma = 0.16 \). Note that for graphical purposes one set of simulated results was plotted.](http://jmm.sgmjournals.org)
and censored regression \[ E(y|x=0.6) = 0.02; 95\% \text{ PCI: } -0.08, 0.11 \] methods all gave cut-off estimates close to the true cut-off given by \( E(y|x=0.6) = 0.03 \) (Table 2, Fig. 3).

The effect of interval-censored data on the regression equations was examined using simulations generated from the model \( y = -0.2 + 1.5x + 0.15x^2 \) with \( \sigma = 0.26 \) and a standardized cut-off of \( E(y|x=-2) = -2.6 \). The interval-censored regression \( [E(y|x=-2) = -2.60; 95\% \text{ PCI: } -2.75, -2.49] \) and the simple substitution \( [E(y|x=-2) = -2.61; 95\% \text{ PCI: } -2.66, -2.56] \) gave cut-off estimates close to the truth \( [E(y|x=-2) = -2.60] \) (Fig. 4). However, the interval-censored regression had the least biased regression estimates with 95\% coverage probabilities of >90\% (Table 3).

**Assessing robustness to linear regression assumptions**

Robustness to failure of the normality assumption for the model \( y = -0.4 + 1.1x + 0.12x^2 \) with \( \sigma = 0.26 \) showed little difference in the cut-off estimates after varying the shape parameter of the \( \gamma \) distribution. The simulation results showed that censored regression, MI and simple substitution methods all produced cut-off estimates close to \( E(y|x=-2) = 2.12 \) for up to 25\% of the data censored (Fig. 5a).

Examining the effect of heteroscedasticity for the model \( y = -0.4 + 1.1x + 0.12x^2 \) with \( \sigma = 0.26 \) for observations higher than the assay cut-off of -2 and \( \sigma = 0.52 \) for smaller concentrations, the censored regression and simple substitution gave cut-off estimates closer to the truth (Fig. 5b).

**DISCUSSION**

The results of the simulations showed that, for up to 20\% of censored data, simple substitution and deletion methods generally gave estimates close to the truth at the crucial point of positive/negative cut-off. This is probably sufficient for the panel test comparisons carried out during the ESEN2 project, as small proportions of data were reported as censored in most cases. However, in scenarios with 20–25\% of censored observations, the simple substitution and deletion estimates became biased, whereas censored regression and MI methods continued to give accurate estimates. These findings agree with previous studies that suggest that simple substitution methods produce biased estimates for >25\% of the data censored (Lubin et al., 2004). When

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**Table 3.** Parameter estimates and 95\% coverage probabilities for interval-censored data generated from the model \( y = -0.2 + 1.5x + 0.15x^2 \) with \( \sigma = 0.26 \) (\( D_L = -2.4 \), \( D_U = 0.01 \)) using simple substitution, deletion, interval censored regression and MI methods (20\% of data left- or right-censored)

<table>
<thead>
<tr>
<th>Method</th>
<th>Constant</th>
<th>Linear</th>
<th>Quadratic</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>True model</td>
<td>-0.20</td>
<td>1.50</td>
<td>0.15</td>
<td>-2.60</td>
</tr>
<tr>
<td>Deletion</td>
<td>-0.43 (2.3%)</td>
<td>1.47 (96.3%)</td>
<td>0.22 (88.2%)</td>
<td>-2.51 (-2.66, -2.39)*</td>
</tr>
<tr>
<td>Simple substitution</td>
<td>-0.36 (4.7%)</td>
<td>1.57 (91.9%)</td>
<td>0.22 (53.0%)</td>
<td>-2.61 (-2.66, -2.56)*</td>
</tr>
<tr>
<td>Interval-censored regression</td>
<td>-0.20 (94.7%)</td>
<td>1.50 (94.6%)</td>
<td>0.15 (94.6%)</td>
<td>-2.60 (-2.75, -2.49)*</td>
</tr>
</tbody>
</table>

*2.5th and 97.5th percentiles given instead of coverage probabilities.
regression assumptions were violated, censored regression continued to give acceptable cut-off estimates. Although regression models with normal errors were considered, it is possible to extend these to a very general family of distributions using the generalized additive model for location, scale and shape (GAMLSS; Rigby & Stasinopoulos, 2005).

Although the MI method has the advantage of being a robust method against high proportions of censored data

Fig. 5. Comparison of standardized cut-off estimates for different proportions of data censored generated from the model $y=-0.4+1.1x+0.12x^2$ with $\sigma=0.26$. (a) Robustness to non-normality using $\Gamma(\lambda, \tau)$ (varying $\lambda$). (b) Robustness to heteroscedasticity ($\sigma=0.52$ and $\sigma=0.26$ for measurements below and above $\log_{10} 0.01$, respectively).
(>20%), it is not a straightforward method to implement and some variations can be computer-intensive. The use of censored regression is also advised by Lubin and colleagues (amongst others), who claimed that ‘...multiple imputation is necessary only if explicit values are needed for measurements below DL’ (Lubin et al., 2004).

A new application of the interval-censored method is proposed. Interval-censored regression models have been suggested for assays with dilution series. In the simulation example shown, the interval-censored regression method gave a cut-off estimate closest to the truth.

The simulation examples were carefully selected to reflect scenarios that commonly occur in serological assay comparisons. Such examples are the interval-censored data occurring from dilution series, heteroscedasticity with higher variability occurring in lower measurements and equations of a similar type to the one used here.

In conclusion, the simple substitution and deletion methods used for the ESEN2 project seem to work satisfactorily for the cases found in the project. However, the censored regression method produced more accurate and robust estimates than these methods under all scenarios. Whilst the scenarios found in ESEN2 produced small benefits from using better methods, other scenarios produced much better benefits. The censored regression methods (including an application of interval-censored regression for serological data resulting from dilution series) should be used for future serological standardizations of serological results and assay comparisons, as they are easily implementable.

ACKNOWLEDGEMENTS

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REFERENCES


