STATISTICS IN MEDICINE, VOL. 16, 2103–2115 (1997)

FIRST YEAR SEROLOGIC RESPONSE TO TREATMENT FOR SYPHILIS: A MODEL FOR PREDICTION OF SEROREVERSION

M. SARAH ROSE[1]*, GORDON H. FICK[1], BARBARA ROMANOWSKI[2] AND EDGAR J. LOVE[1]

[1] *Department of Community Health Sciences, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada*
[2] *STD Services, Alberta Health, Calgary, Alberta, Canada*

SUMMARY

There is no straightforward test available, within weeks of treatment for syphilis, to assess adequacy of serologic response. We propose a method to predict non-treponemal seroreversion based on short term response. To develop and illustrate this method, we used data from 370 individuals with infectious syphilis. Individual serologic response appears to be a linear function of (log) time, suggesting the possibility of using rapid plasma reagin titres recorded in the first few months after treatment to determine the slope of the linear treatment response line. The slope of the response line, during the first year after treatment, is an important predictor of seroreversion but must be considered in conjunction with pre-treatment titre. We recommend development of an action line be developed based on these variables. Such a line would indicate the necessity for retreatment if the line plotted from the patient's first year response failed to fall below the action line.

Statist. Med., **16**, 2103–2115 (1997)
No. of Figures: 4 No. of Tables: 2 No. of References: 19

1. INTRODUCTION

From a public health perspective, it is important to institute prompt cure for patients with syphilis. However, there is no straightforward test available within weeks of treatment to determine adequacy of serologic response to treatment. Therefore, the objective of this paper is to propose a method of predicting eventual non-treponemal seroreversion (that is, cure) based on the short term response to treatment. That is, we wish to provide a means for deciding in a relatively short time (that is, within months after treatment) whether a treated patient requires additional treatment or will be cured without further intervention.

Non-treponemal tests provide a quantitative measure of antibody response to a substance called reagin which is formed in the sera of patients with syphilis. The non-treponemal test is reported as non-reactive, reactive or weakly reactive. If the result is reactive, serial dilutions are carried out to quantitate the result. The result of the test, the titre, is reported as $1 : n$ where n is the highest dilution at which the test remains reactive. Patients treated for syphilis are followed over

* Correspondence to: Dr. M. S. Rose, Department of Community Health Sciences, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada

CCC 0277–6715/97/182103–13$17.50

Received September 1995
Revised November 1996

time to assess response to treatment by means of non-treponemal tests. A return to the non-reactive state is called seroreversion. Romanowski *et al.* point out that when the serologic test becomes non-reactive, the patient is considered cured but when it remains positive a clinical dilemma arises.[1]

It has been suggested that it takes one or two years for non-treponemal serology to serorevert after treatment for primary and secondary syphilis.[2–5] Other studies have indicated that the serology in a large percentage of patients with primary and secondary syphilis remains reactive even after two years.[1,6,7] Brown *et al.* suggested that the physician needs to determine whether the patient is responding adequately to treatment or whether he/she needs retreatment long before the one or two year mark.[8] This seems essential for an infectious disease in which patients are frequently lost to follow-up.

In a recent review of the literature on sexually transmitted disease treatment, Levine *et al.*[9] suggested that due to the numerous case reports of treatment failures and their severity, standard therapy for syphilis is not always sufficient, particularly among patients with human immunodeficiency virus (HIV). Clearly, if we must retreat treatment failures, we must detect them promptly, rather than wait the recommended 12 to 24 months to see whether there has been an adequate drop in rapid plasma reagin (RPR) titre.

To provide improved guidelines for response to treatment, Brown *et al.* constructed exponential curves that describe serologic response for patients classified by their physician as cured on the basis of clinical evaluations and serologic tests.[8] This analysis led the authors to suggest that a fourfold decline in titre by three months post-treatment and an eightfold decline by six months indicated that the patient's serologic response was equivalent to that of patients eventually clinically cured. The time element was crucial for the prediction of clinical cure.

Romanowski *et al.* reported a descriptive analysis of the cumulative proportion of seroreversion of all patients treated for infectious syphilis in Alberta during the years 1981–1987.[1] In Alberta during this time there was a sudden sustained epidemic of infectious syphilis. Data were collected on all cases of syphilis, and their traced contacts, who were treated in Alberta during the years 1981–1987. Treated patients were requested to attend for follow-up at regular intervals. Follow-up serology used the RPR non-treponemal test. This previous analysis used life table methods to provide the cumulative seroreversion rates and decreases in titre by stage of disease, initial RPR titre and disease episode.

In this report, we use this slope summary statistic in a proportional hazards regression model analysis of time to seroreversion. The aim is to provide a prototype of a model to describe the first year response to treatment for patients treated for syphilis and to assess the importance of the first year response as a predictor of eventual seroreversion in conjunction with other prognostic variables. Specifically, we demonstrate that the slope of the first year response is one of the most important predictors of seroreversion, and, therefore, is of potential utility in the development of an 'action' line for the clinical management of syphilis. In an earlier report, we demonstrated that the profile of RPR titre over time is appropriately modelled using a simple linear regression slope statistics when analysed on a logarithmic scale.[10]

We note that in this analysis we used the patient's serologic response in the first year after treatment to predict eventual seroreversion, whereas our objective concerns a method to assess response adequacy within a few months of treatment. The data for this study, were collected retrospectively with common clinical practice requesting most patients to return for follow-up serology usually at 3, 6, 12 months. Therefore, in most cases there were insufficient data points in the first few months after treatment for this analysis; hence, we used data from the first year. The

advantage of the linear response, however, is that the slope of the line remains the same whether we assess the three-month post-treatment response or the first year post-treatment response. If we find this method an acceptable means to assess serologic response to treatment, the treating physician can request that the patient return for follow-up 3–4 times within the first 3–4 months.

2. METHODS

2.1. Subjects

We used data from a larger data set described by Romanowski *et al.*[1] to develop and illustrate our proposed method. All patients were diagnosed with a first episode or repeat episode of primary, secondary or early latent syphilis. RPR titres at treatment ranged from 1:1 to 1:2048.

To have sufficient information on each patient to fit a regression line to the first year serologic response of each patient, we included only the data from those patients who had four or more serological tests recorded. Out of a total of 882 patients there were 376 individuals who met this requirement; of these, 370 had complete data and comprise the analysis sample. Since we used these data to develop and describe this new method of assessing adequate response, rather than to draw conclusions about the population of interest, we did not feel that this was a limitation of our analysis.

2.2. The Proportional Hazards Model

To determine whether this first year response to treatment predicted the time to seroreversion, we used proportional hazards regression modelling with the time to seroreversion as the dependent variable.[11] In general terms, the hazard function, $\lambda(t)$, is a convenient specification of the distribution of survival time, T, and is

$$\lambda(t) \approx P(T < t + \Delta t \mid T \geqslant t)/\Delta t$$

where $\Delta t > 0$ is 'small'. The Cox proportional hazard model states that $\lambda(t) = \lambda(t; \mathbf{z})$ for an individual with covariates $\mathbf{z} = (z_1, \ldots, z_p)^{\mathrm{T}}$, is the product:

$$\lambda(t) = \lambda_0(t)\exp(\beta^{\mathrm{T}}\mathbf{z})$$

where $\lambda_0(t)$ is an unknown and unspecified baseline hazard function for individuals with covariate values all equal to zero and $\beta = (\beta_1, \ldots, \beta_p)^{\mathrm{T}}$ is a vector of regression coefficients.

The exact time of seroreversion is not known, but it is known to lie in the interval between the last positive test and the first non-reactive test. We used the midpoint of this interval to approximate the time to seroreversion. The hazard function specifies the instantaneous rate of seroreversion at any time, given that the individual has not seroreverted prior to that time. For brevity, we refer to this as the 'seroreversion rate'. We can think of the ratio of seroreversion rates for two different sets of values of the prognostic variables as an instantaneous relative rate. We censored cases if they were lost to follow-up, or experienced clinical relapse with or without re-exposure, defined as a fourfold rise in the RPR titre after therapy.

We developed two multivariable proportional hazards models to investigate the prognostic significance of the first year slope. The first included the RPR titre at treatment and the first year slope only. We then extended this model to include other significant explanatory variables. We used the extended model to determine if short term response affects the seroreversion rate in the

presence of other prognostic factors and after adjusting for the effects of confounding variables. In particular, we wished to investigate whether there was an interactive effect between the first year slope and the other potential explanatory variables. We assessed the proportional hazards assumption using a plot of rescaled Schoenfeld residuals against time[12] and tested it using time-dependent covariates.[11] The Schoenfeld residuals[12] are defined as a matrix of residuals, where there is one row for each death time and one column for each covariate. Let $Z_{ij}(t)$ represent the matrix of j covariates of the ith individual at time t. Then the Schoenfeld residual s_{ij} is defined by $s_{ij}(\beta) = Z_{ij}(t_i) - \dot{Z}_j(\beta, t_i)$ where $\dot{Z}_j(\beta, t_i)$ is a weighted covariate mean for those still at risk at time t_i. Thus the Schoenfeld residuals are increments in time of the total score process and if the proportional hazards assumption holds should be a random walk. We used the rescaled Schoenfeld residual which corrects for correlation among covariates. A smooth plot of these residuals against time will be horizontal if the proportional hazards assumption holds.

The following variables were available for the assessment of confounding or interaction with our main effect of interest (first year slope). The clinical variables used were: pre-treatment RPR; type of case (index or traced contact); sexual preference; treatment; stage of disease, and illness episode. We used the logarithm to base two of pre-treatment RPR titre. Occasionally the RPR titre was not recorded at treatment. In these cases, we used an earlier RPR titre as the pre-treatment titre, provided that it was recorded during the 21 days prior to treatment. Since sexual preference was assessed for male patients only, for modelling purposes we created a three category nominal variable labelled sex/preference. The three categories were 'females', 'heterosexual male' and 'homosexual or bisexual male'. Although there were several different treatments used, for modelling purposes we dichotomized treatment into either penicillin or tetracycline. We considered the three stages of infectious syphilis; primary; secondary, and early latent, coded as indicator variables. Patients were classified according to whether they received treatment for their first episode, or a repeat episode, of syphilis. The demographic variables we considered were age (years), sex and race (white or non-white). We included a variable in the final model if it was a significant predictor of seroreversion or if there was a significant interaction between that variable and first year slope.

2.3. Comparison of the Proposed Method with Current Standards

To compare our method to Brown's (the current standard) we developed three additional proportional hazards models in which we replaced the first year slope variable with two indicator variables; one that indicated whether the patient experienced a fourfold drop in titre within three months of treatment and the other that indicated whether the patient had experienced an eightfold drop within six months. In the first model we included these two indicator variables only, since this mirrors the current standards proposed by Brown *et al.* We then extended this model to include pre-treatment titre and the third model also included other significant explanatory variables.

2.4. Evaluation of the Proposed Predictive Models

We first evaluated and compared the resulting models by examining the R^2 measure suggested by Nagelkirke.[13] This R^2 can be interpreted as the proportion of variance explained by the proportional hazards model. An alternative way of evaluating a predictive model is to examine the percentage of subjects correctly classified by the model according to a gold standard. One

cross-tabulates the model (predicted) classification against the gold standard classification to create a two by two table of true positive, false positive, true negative and false negative predictions. One then reports the percentage of correct classifications as the true positive rate (TPR or sensitivity) and false positive rate (FPR or 1-specificity). Clearly, we strive for a model that has a high TPR and a low FPR.

We evaluated each model at two time points: two years and three years post-treatment. We determined the gold standard as follows: at each time t (either two or three years), we classified a patient as 'cured' if he/she had seroreverted before time t or 'not yet cured' if he/she was still under observation at this point. Necessarily, we excluded patients censored before time t from this classification.

For each subject using the estimated baseline hazard function and the estimated regression coefficients from the proportional hazards regression model, we estimated the probability of remaining seropositive as a function of time since treatment for his/her values of the explanatory variables.[14] The result was an estimate of that person's probability of seroreverting by time t. We then classified each patient according to whether he/she was probably cured by time t (that is, the estimated value of the survivor function equal or 'close' to zero) or probably not cured by time t (that is, a non-zero value of the survivor function). To form the prediction classification, we need to declare a cutpoint p_c so that we classify a patient with a risk estimate greater than p_c as probably not cured and a patient with a risk estimate less than p_c as probably cured. The sensitivity and specificity of the prediction, which are necessarily inversely related, depend upon the value of p_c that we choose. Therefore, we estimated a receiver operating characteristic (ROC) curve for each model, where we plotted the sensitivity (TPR) of the prediction against 1-specificity (FPR) for various values of p_c. A model with good predictive ability will have an ROC curve in the upper left-hand corner of the unit square (that is with both high specificity and sensitivity).

3. RESULTS

Complete data were obtained on 370 patients (257 female and 113 male) with a mean age of 33·6 (SD = 12·8). The majority (69·5 per cent) had primary syphilis, 25·0 per cent had secondary syphilis and 5·5 per cent had early latent syphilis. Most (85·9 per cent) were experiencing a first illness episode, 79·5 per cent were index cases, 20·5 per cent were traced contacts and 59·2 per cent of the sample were Caucasian. The median pre-treatment titre was 1 : 64, with interquartile range from 1 : 16 to 1 : 64 and minimum (1 : 1) and maximum (1 : 2048).

3.1. First Year Slope

Figure 1 presents an illustration of the serologic response to treatment, using logarithmic transformations. The maximum number of data points for any one individual was 13. We chose the four cases that had 13 points for this illustration. As indicated earlier, statistical analysis confirmed that, using these logarithmic scales, a linear function of time well describes serological response to treatment.[10] The first year slope was approximately normally distributed with mean $-4{\cdot}02$ and standard deviation 2·15.

3.2. Results of the Proportional Hazards Modelling

Model 1 in Table I presents regression coefficients for proportional hazards models that include first year slope and pre-treatment titre only.

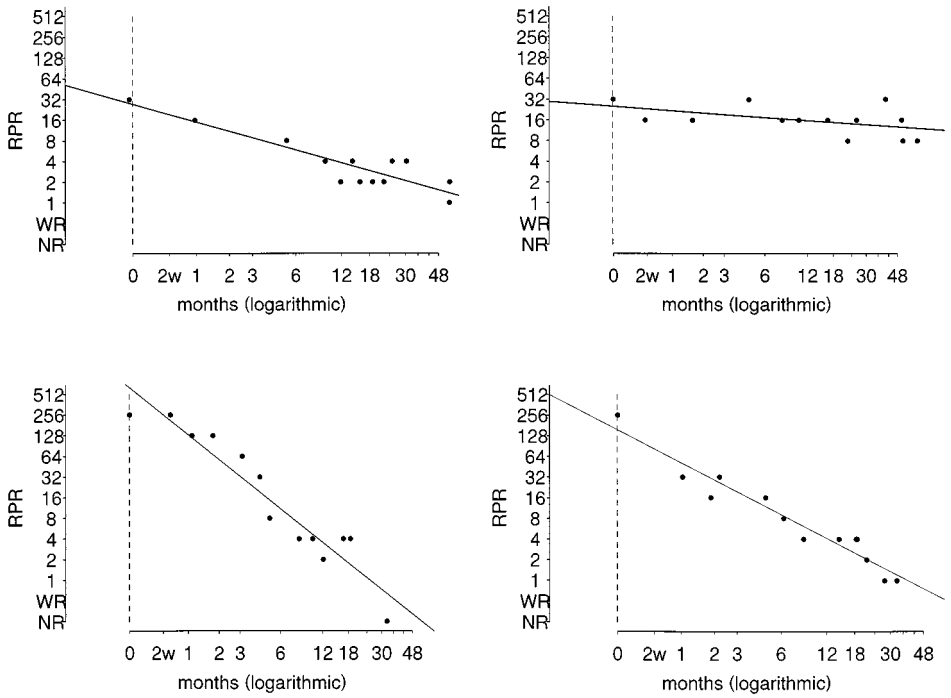

Figure 1. An illustration of the serologic response to treatment, using logarithmic transformations for the four cases in our sample which had the maximum number of 13 observations

Table I. Regression coefficients for the proportional hazards regression models, using first year slope to predict the seroreversion rate

Variable	Model 1			Model 2		
	Estimated regression coefficient	Standard error	*p*	Estimated regression coefficient	Standard error	*p*
First year slope	− 0·500	0·606	< 0·001	− 0·528	0·590	< 0·001
Pre-treatment titre	− 0·565	0·0568	< 0·001	− 0·575	0·562	< 0·001
Race (baseline = Caucasian)				− 0·615	0·541	< 0·001
Illness episode (baseline = first)				− 0·718	0·488	0·031
R^2		0·394			0·420	

Careful inspection of these regression coefficients indicates that both these variables are important predictors of seroreversion individually and also that we must take into account pre-treatment titre when we use first year slope to predict seroreversion. There was a confounding effect of the variable pre-treatment titre on the estimation of the effect of first year slope. The

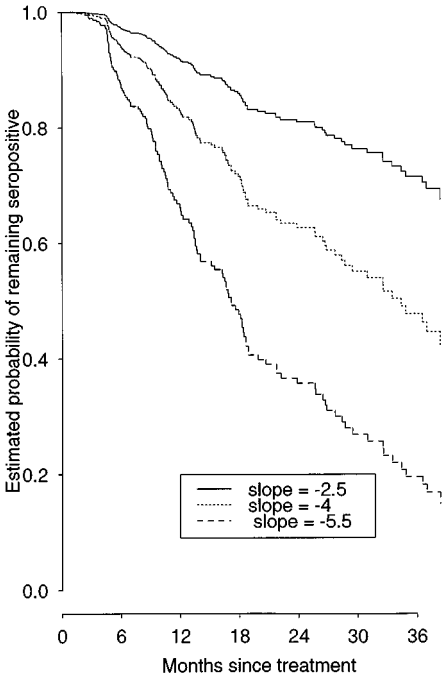

Figure 2. The estimated survivor functions for cases who are Caucasian with a first episode of syphilis and pre-treatment titre of 1 : 64 with relatively flat slope (−2·5), average slope (−4) and steep slope (−5·5) in the first year after treatment

instantaneous relative risk of seroreversion for a one unit increase in first year slope was 1·29 (95 per cent confidence interval 1·19–1·40) when considered alone and 1·65 (95 per cent confidence interval 1·53–1·78) when included in the model with pre-treatment titre. Similarly, the instantaneous relative risk of seroreversion for a one dilution difference in pre-treatment titre was 1·32 (95 per cent confidence interval 1·22–1·42) when considered alone and 1·76 (95 per cent confidence interval 1·70–2·11) when included in the model with first year slope. This indicates the importance for inclusion of both these variables when assessing seroresponse.

The prognostic importance of the first year slope and pre-treatment RPR retained its statistical significance in the extended model which controlled for illness episode and race (Table I, model 2). Individuals with a first illness episode have an instantaneous relative risk of seroreversion twice that of those with a repeat illness episode (95 per cent confidence interval 1·07–3·94), with the same first year slope and pre-treatment titre. Similarly, given a constant first year slope and pre-treatment titre, Caucasian cases have an instantaneous relative risk of 1·85 times that of non-Caucasian cases (95 per cent confidence interval 1·29–2·65).

The median first year slope in the sample was −4·06, with interquartile range −5·69 to −2·53. We can see the clinical importance of the first year slope by examining the difference in time to seroreversion for individuals with different values of the first year slope. Figure 2 shows estimated survival curves for Caucasian cases with a first episode of syphilis and pre-treatment titre of 1 : 64 with relatively flat (slope = −2·5), average (slope = −4·0) and steep (slope = −5·5) first year slopes. We can see that 50 per cent of the individuals with a steep slope (−5·5) have reached

Table II. Regression coefficients for the proportional hazards regression models, using Brown's criteria to predict the seroreversion rate

Variable	Unnumbered model			Model 3			Model 4		
	Estimated regression coefficient	Standard error	*p*	Estimated regression coefficient	Standard error	*p*	Estimated regression coefficient	Standard error	*p*
Fourfold drop in 3 months (1 = yes, 0 = no)	0·356	0·201	0·077	0·438	0·219	0·045	0·448	0·218	0·040
Eightfold drop in 6 months (1 = yes, 0 = no)	0·726	0·220	< 0·001	1·515	0·220	< 0·001	1·467	0·261	< 0·001
Pre-treatment titre				− 0·466	0·048	< 0·001	− 0·449	0·632	< 0·001
Age (in years)							0·0127	0·0065	0·053
Illness episode (baseline = first)							− 0·680	0·507	0·044
R^2		0·070			0·296			0·309	

seroreversion by 18 months after treatment, but it will take almost twice as long for 50 per cent of those with an average slope ($-4{\cdot}0$) to serorevert. By 36 months after treatment, we can expect less than 25 per cent of such individuals with a relatively flat slope ($-2{\cdot}5$) to serorevert.

Table II presents regression coefficients for the proportional hazards models that assess the predictive ability of the recommendations from Brown's method (that is, they include pre-treatment titre and the two variables that indicate whether patients have experienced a twofold drop in titre at three months and a fourfold drop in titre at six months). The first model, which we have left unnumbered, shows the regression coefficients for the indicator variables representing the current standard. This indicates that although the eightfold drop in six months is a significant predictor of seroreversion, the fourfold drop in three months is not when considered alone. If we include only the two indicator variable in the model, we obtain very poor predictive power compared to all the other models.

In model 3 we have included the pre-treatment titre in addition to the indicator variables for Brown's recommendations, to facilitate comparison with model 1 in Table I. Inclusion of the pre-treatment titre, in addition to the two indicator variables, substantially improves the predictive power of this model. Current standards, however, do not specify the role of the pre-treatment titre in the recommendation for adequate response to treatment. In model 4 we included the other significant explanatory variables; age and illness episode. There was no evidence against the assumption of proportional hazards in any of the models.

3.3. Evaluation of the Proposed Predictive Models

Comparison of Nagelkirke's R^2 statistic for model 1 and model 3 shows that when we use this criterion for assessing the model containing adequate treatment (first year slope in model 1 and Brown's criteria in model 3), and pre-treatment titre only, we obtain a much higher value using the first year slope ($0{\cdot}394$ compared with $0{\cdot}296$). Similarly, when we extend these models to include other explanatory variables, we also obtain a higher value of R^2 when we use the first year slope in the model rather than the indicator variables for Brown's criteria ($0{\cdot}402$ compared to $0{\cdot}309$).

For the construction of the ROC curves, we had a sample size of 232 for the two year evaluation (122 had seroreverted prior to the two year point and 110 were still under observation at two years) and 183 for the three year evaluation (137 had seroreverted prior to the three year point and 46 were still under observation at three years). In Figure 3 we present the ROC curves that compare the predictive accuracy of model 1 (first year slope) and model 3 (Brown's criteria). We fit the curves using a smoothing spline.[15]

At all times, the ROC curve for model 1 is higher than that for model 3. The diagonal line indicates the point at which the sensitivity equals the specificity. This line intercepts the ROC curve for model 1 at $0{\cdot}77$ and the ROC curve for model 3, at $0{\cdot}71$ for $t = 2$ years. For $t = 3$ years, the line intercepts the ROC curve for model 1 at approximately $0{\cdot}80$, and the ROC curve for model 3, at approximately $0{\cdot}73$.

In Figure 4, we present the ROC curves for the regression models that we have extended to include other explanatory variables. The difference between the ROC curves for these models is smaller. In addition, if we obtain the points on the curves at which the sensitivity is equal to the specificity, we note that we apparently have not gained accuracy by including these other

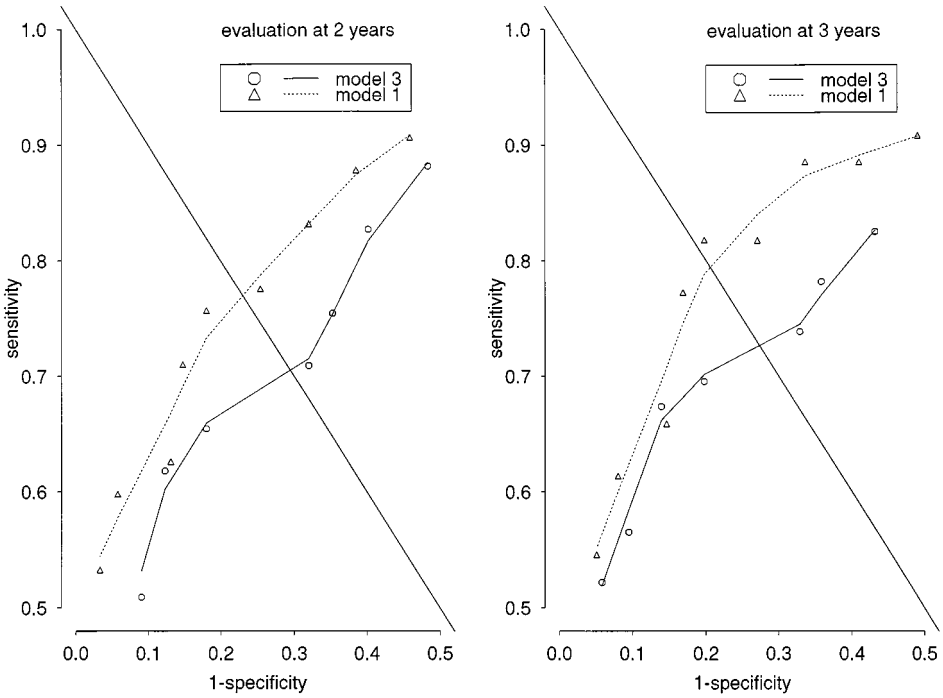

Figure 3. Receiver operating characteristic curves comparing the predictive accuracy of model 1 (using first year slope and pre-treatment titre to predict seroreversion) and model 3 (using indicator variables for Brown's criteria and pre-treatment titre to predict seroreversion)

explanatory variables, since we do not improve the values obtained in the simpler models. Thus, in summary, it appears that the model that includes first year slope and pre-treatment titre is a more appropriate model on which to base the criteria for adequate response to treatment.

4. DISCUSSION

Individual serologic response to treatment appears to be a linear function of time when both axes are logarithmic. Due to this apparent straight line response, RPR titres recorded in the first few months after treatment will determine the slope of the first year response line. With use of the slope of the line determined in the first few months after treatment, the physician can determine whether or not the patient is on the path to the desired measure of adequate response to treatment for syphilis. This suggests the development of an action line similar to that used by physicians who follow cervical dilatation during labour. A cervicograph is a plot of cervical dilatation against time. Studd[16] describes the use of this tool: 'On admission in labour the cervical dilatation is assessed and the stencil used to draw the relevant pencil line of expected progress on the patient's cervicograph, which is then completed in the usual way. This pencil line serves as a nomogram of cervical dilatation. If the patient's cervimetric progress strays two hours to the right of the nomogram, labour is adjudged at that stage to be prolonged, requiring acceleration.' Although the nomograms described above by Studd are curves, we note that starting at 3 cm,

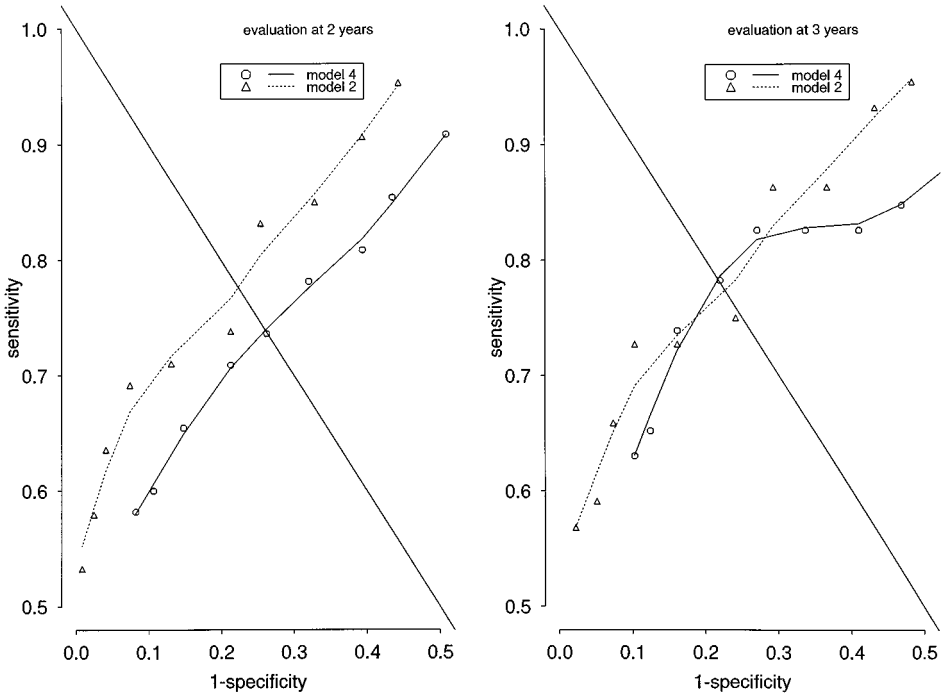

Figure 4. Receiver operating characteristic curves comparing the predictive accuracy of the extended models. Model 2 includes first year slope, pre-treatment titre, race and illness episode to predict seroreversion and model 4 uses the two indicator variables for Brown's criteria, pre-treatment titre age and illness episode to predict seroreversion

a plot of cervical dilatation against time on a semilogarithmic scale results in a straight line.[17] In the case of treatment for syphilis, such a line indicates the necessity for retreatment if the line plotted from the patient's individual first year response failed to fall below the action line. By taking three or four RPR titres in the first three months after treatment and plotting these on this graph the physician can see within the first three months whether the patient has or has not responded adequately to treatment. This precludes the necessity to wait a year after treatment to see whether there has been an adequate reduction in the RPR titre.

This is the first study to consider the serological response to treatment for syphilis both as a straight line and in the presence of other explanatory variables. Response to treatment clearly depends upon certain characteristics of the patient (such as race, age and illness episode) in addition to first year slope and pre-treatment titre. It appears, however, that the action line need not depend on such characteristics.

Levine *et al.*[9] indicated that serologic criteria for assessing treatment for latent syphilis remain unclear due to inconclusive evidence based on a few studies. They indicated that current guidelines for those with an initial titre of 1 : 32 call for further evaluation of patients who do not achieve a fourfold drop in titre at 12 to 24 months. Using our method of evaluating serologic response, the treating physician could determine within 3–6 months whether these patients required retreatment.

Two non-treponemal tests in current use are the VDRL (Venereal Disease Research Laboratory) test and the RPR (rapid plasma reagin) test. The correspondence between these two tests is not exact. The analysis done by Brown *et al.* was limited to patients with a VDRL titre of between 1 : 4 and 1 : 64 inclusive.[8] We illustrated the methods proposed in this paper using the RPR tests and with no restrictions imposed on the pre-treatment RPR titre.

To have sufficient data points to fit straight line, this analysis could only consider individuals who had four or more documented RPR titres. It is possible that the number of laboratory investigations may relate to seroreversion. For example, an individual may have had only three laboratory investigations because he/she had seroreverted quickly. This may occur more often among those with a low titre at treatment. Physicians who treat individuals undergoing seroreversion within a short period of time have no need for such a diagnostic tool.

Due to the fact that we used the midpoint of the interval in the proportional hazards regression, we assumed more precision in the measurements than was warranted. In terms of non-parametric estimation of the survivor function, the midpoint of the interval provides an unbiased estimate of the survivor function but the standard error is underestimated.[18] Therefore, we must issue a caveat regarding the significance of the main effects and the interactions in this model.

Unfortunately, we concluded our evaluation of the models using the development sample, which may result in an overly positive evaluation. The next stage in the development of this diagnostic tool is to evaluate the models with use of an independent sample.

Hook *et al.* pointed out that evaluation of new antimicrobial agents for treatment of syphilis is difficult because of the inability to culture the organism. They indicated the necessity of serologic evaluation for at least three months after treatment for syphilis to assess therapeutic outcome. Therefore, accurate methods to detect appropriate response to treatment in the early months after treatment are necessary.[19] The assessment of the serologic response by the slope of these straight line plots may prove a useful method to evaluate new drugs.

ACKNOWLEDGEMENTS

This research was supported in part by the National Health and Welfare Research and Development Program through a PhD Fellowship and the University of Calgary through a William Davies Medical Sciences Scholarship. The authors would like to thank the referee for many constructive suggestions.

REFERENCES

1. Romanowski, B., Sutherland, L. R., Fick, G. H., Mooney, D. and Love, E. J. 'Serological response to treatment of infectious syphilis', *Annals of Internal Medicine*, **114**, 1005–1009 (1991).
2. Fiumara, N. J. 'The treatment of seropositive primary syphilis: An evaluation of 196 patients', *Sexually Transmitted Diseases*, **4**, 92–95 (1977).
3. Fiumara, N. J. 'The treatment of secondary syphilis: An evaluation of 204 patients', *Sexually Transmitted Diseases*, **4**, 96–99 (1977).
4. Fiumara, N. J. 'Reinfection primary and secondary syphilis', *Sexually Transmitted Diseases*, **5**, 85–88 (1977).
5. Fiumara, N. J. 'Treatment of primary and secondary syphilis. Serological response', *Journal of the American Medical Association*, **243**, 2500–2502 (1980).
6. Capinski, T. Z., Lebioda, J., Koalasa, B. and Budzanouska, E. 'Antibiotics in the treatment of early syphilis', *in* Luger, A. (ed.), *Current Problems in Dermatology*: *Vol. II. Antibiotic Treatment of Venereal Diseases*, Karger, Basel, 1968.

7. Schroeter, A. L., Lucas, J. B., Price, E. V. and Falcone, V. H. 'Treatment for early syphilis and reactivity of serologic tests', *Journal of the American Medical Association*, **221**, 471–476 (1972).
8. Brown, S. T., Zaidi, A., Larsen, S. A. and Reynolds, G. H. 'Serological response to syphilis treatment: A new analysis of old data', *Journal of the American Medical Association*, **253**, 1296–1299 (1985).
9. Levine, W. C., Berg, A. O., Johnson, R. E., Rolfs, R. T., Stone, K. M., Hook III, E. W., Handsfield, H. H., Holmes, K. K., Islam, M. Q., Piot, P., Brady, W. E. and Schmid, G. P. 'Development of sexually transmitted diseases treatment guidelines 1993', *Sexually Transmitted Diseases*, S96–S101 (1994).
10. Rose, M. S. and Fick, G. H. 'Assessment of lack of fit in simple linear regression: an application to serologic response to treatment for syphilis', *Statistics in Medicine*, **16**, 373–384 (1997)
11. Cox, D. R. 'Regression models and life-tables (with discussion)', *Journal of the Royal Statistical Society*, **21**, 411–421 (1972).
12. Thernau, T. M., Grambsch, P. M. and Fleming, T. R. 'Martingale based residuals for survival models', *Biometrika*, **77**, 147–160 (1991).
13. Nagelkirke, N. 'A note on a general definition of the coefficient of determination', *Biometrika*, **78**, 691–692 (1991).
14. Cox, D. R. and Oakes, D. *Analysis of Survival Data*, Chapman and Hall, London, 1984.
15. Hastie, T. J. and Tibshirani, R. J. *Generalized Additive Models*, Chapman and Hall, London, 1990.
16. Studd, J. 'Partograms and nomograms of cervical dilatation in management of Primigravid Labour', *British Medical Journal*, **4**, 451–484 (1973).
17. Pauerstein, C. J. (ed). *Clinical Obstetrics*, Wiley, New York, 1987.
18. Rose, M. S. 'The analysis of interval censored data and the serological response to treatment for syphilis', PhD thesis 1991, University of Calgary, Canada.
19. Hook, E. W. III, Roddy, R. E. and Handsfield, H. H. 'Ceftriaxone therapy for incubating and early syphilis', *Journal of Infectious Diseases*, **158**, 881–884 (1988).

