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# Modeling Pneumococcal Resistance to Penicillin in Southern Sweden Using Artificial Neural Networks

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## ABSTRACT

**In recent decades, penicillin-resistant pneumococci (PRP) have emerged and spread rapidly between and within countries over the world. In this study we developed an iterative artificial neural network (ANN) model to describe and predict the spread of PRP in space and time as a function of antibiotic consumption and a number of different confounders. Retrospective data from 1997 to 2000 on an international epidemic PRP clone (serotype 9V) and antibiotic consumption data from Southern Sweden were used to train the ANN models and data from 2001 to 2003 for evaluation of the model predictions. Five different ANN models were trained, each with independent topology optimization for alternative sets of input variables to find the most descriptive model. The model containing all variables was the only one performing better than the reference linear models, as assessed by the correlation between predictions and observations. The inability to identify a smaller subset of most predictive parameters may reflect either diffuse causal mechanisms or just the absence of critical experimental indicators from the dataset. The iterative ANN model identified is useful to predict future data. The sensitivity analysis of the model suggests that past incidence has a small effect on the number of PRP cases.**

## INTRODUCTION

*STREPTOCOCCUS PNEUMONIAE* (the pneumococcus) is the main bacterial cause of respiratory tract infections associated with morbidity and mortality. It is estimated that pneumococcal infections every year cause the death of 1–2 million children. In recent decades, penicillin- and multiresistant strains have emerged and spread rapidly between and within countries in Europe and the world.[5] Some countries have experienced a situation with 60–70% resistance rates to penicillin, resulting in fewer treatment options and greatly increased costs for caring for patients with pneumococcal infections.[18]

To understand the effect of preventive measures against pneumococcal infections, efficient surveillance is of paramount importance. In Sweden, infections with and carriage of penicillin-resistant pneumococci (PRP) with penicillin G (PcG) MIC $\geq$ 0.5 mg/L have been notifiable since 1996 according to the Communicable Disease Act.

Sweden is still a country with a comparatively low rate of infection of *S. pneumoniae* with reduced susceptibility to penicillin (MIC $\geq$ 0.12 mg/L). For many years, the percentage of such isolates was well below 5%, with the exception of parts of the Skåne Region in southern Sweden, where the rate increased in the early 1990s to about 8–15%.[9,10,16,23]

A large proportion of penicillin- and multiresistant pneumococci strains belong to a limited number of international epidemic clones. A previous study has described the introduction and spread of an international type 9V PRP clone (resistant to PcG and trimethoprim-sulfamethoxazole; TMP/SMX) in southern Sweden.[19] This clone has since spread to large parts of Sweden.[13] In the Skåne Region of southern Sweden, the spread of this clone has tended to persist in communities with a high-level consumption of antibiotics by preschool children and to abate in communities with a low consumption. A cross-sectional study in the same county has shown that the frequency of penicillin-resistant pneumococci in children is correlated to community utilization of antibiotics.[20]

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Although, the evidence of the importance of antibiotic consumption for the spread of PRP is overwhelming,[2,7,8,12,20] the conditions that favor the spread of resistant clones are only partially understood. Mathematical models provide a convenient framework for improving our understanding of the patterns of infection and the effect of preventive measures. For surveillance data on infectious diseases that typically comprise a number of time series of disease counts, each representing a specific geographical area, models that incorporate both the spatial and temporal effect tend to be cumbersome to formulate. In this paper, an artificial neural network (ANN)-based approach is applied to analyze a data set of monthly counts of the incidence of an international epidemic PRP clone in the 32 municipalities of the Skåne Region in the southern part of Sweden from 1997 to 2003.

ANNs are a wide class of computational techniques for flexible nonlinear regression and discriminate models, data reduction models, and nonlinear dynamical systems.[3] During the last decade, this class of techniques has gained increased popularity and has been proposed as a supplement or alternative to standard mathematical and statistical tools. These techniques are widely used in other medicine disciplines,[17] and have been shown to be ideally suited to the analysis of complex data sets when the underlying mechanisms are unknown or too complex for explicit formulation. However, knowledge of the performance of ANN for describing and predicting infectious diseases is insufficient.[1] Using the search terms 'infections AND neural networks' yields 80 hits searching PubMed (December, 2005), which promotes further research in the field.

In this study we developed an ANN to describe and predict the spread of PRP in space and time as a function of antibiotic consumption and a number of different confounders.

## MATERIALS AND METHODS

### *PRP cases*

Notification of PRP (PcG MIC $\geq$ 0.5 mg/L) is done in parallel to the Swedish Institute for Infectious Disease Control (SMI) and to the County Medical Officers of Communicable Disease Control. This timely notification includes both laboratory notification of all isolates (one from each patient) and clinical notification of carriage and/or infection from the clinicians. All reports are made with full person identity, and the various notifications on the same patient are merged into case records, using a unique personal identification number issued to all Swedish residents.[15] The isolated PRP strains are routinely sent to the SMI for further typing; all isolates are serotyped and selected isolates are further genetically typed, using pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST). All persons identified through the notification system since 1996 carrying or infected with the epidemic 9V clone were considered for inclusion in the study, but due to the limited number of cases in parts of the country, the initial retrospective study was based on data from the Skåne Region alone.

### *Antibiotic consumption*

In Sweden, antibiotic products can only be obtained by physician prescriptions from pharmacies owned by Apoteket AB (the National Corporation of Swedish Pharmacies). This corporation regularly collects and processes detailed and extensive information on drug utilization in a national database. From this database, we obtained data on the weekly number of dispensed oral outpatient antibiotic prescriptions for systemic use (the whole J01 group of the Anatomical Therapeutic Chemical [ATC] Classification System) to children aged 0–6 years in each municipality in the Skåne Region.[14] Data expressed as number of prescriptions was chosen in favor of defined daily dose to better reflect prescribing activity to children, and make data less sensitive to changes in dosage and length of treatment courses. Data on antibiotic consumption show a strong seasonal effect.[14] Therefore, to separate the effect of consumption in the analysis from that of season, data on antibiotic consumption was deseasonalized.[6]

### *Travel intensity*

To capture the spatial interactions between different municipalities, we obtained data from the National Travel Survey on the number of travels between different municipalities as-

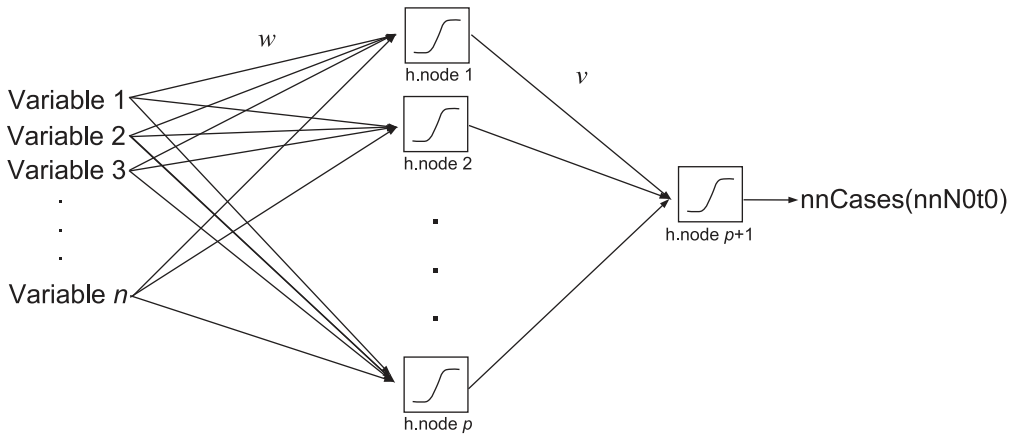


**FIG. 1.** Topology of the ANN model. All input variables contribute to the sum in the $p$ hidden nodes. The contribution is multiplied with a weight listed in the $w$ matrix. The output from the hidden nodes in the hidden layer to the single hidden node in second layer is multiplied with a weight listed in the $v$ vector. The outcome of the second layer is the predicted number of PRP cases.

sembled by Statistics Sweden. These data are based on a monthly random sample of phone interviews to 1,000 households. The interviewees were asked about the dates and destinations of short and long (>100 km) travels during the last 30 days.[24] The total number of travels (long and short) into a municipality during the whole study period was used as an explanatory variable.

### *Study area*

Skåne is the third largest county of Sweden, with 33 municipalities and approximately 1.15 million inhabitants, including 84,112 children aged 0–6 years (2003). It is located in the very south of Sweden and has sea borders with Denmark, Germany, and Poland. In 2003, a total of 68,072 recipes (the whole ATC group J01) were prescribed to children aged 0–6 years and in the same year 156 cases of PRP were notified to the SMI.

### *Artificial neural networks*

For the development and training of the neural networks, we used a Web-based ANN computing tool (http://bioinformatics.musc.edu/webnn) created and maintained at the Medical University of South Carolina, which follows guidelines suggested in ref. 3. A mirror version is also publicly and freely available by Microcortex Inc. (http://www.microcortex.com). That report is referred to for further information regarding implementation of cross validation and topology design criteria. This software library has been used and validated by several subsequent applications relevant to this study, such as clinical decision making,[21] time-series modeling,[25] implicit modeling,[27] and statistical inference.[4] The topology of the resulting ANNs is illustrated in Fig. 1 as fully connected multilayered perceptrons with one hidden layer and one sigmoid layer output. The perceptron is a nonlinear model for predicting the outcome $y_t$, at time-point $t$, in our case the number of PRP cases, as a function of some independent variables $x_{1,t}, x_{2,t}, \ldots, x_{n,t}$. The ANN model is shown mathematically in Equation 1a:

$$y_t(x_{1,t}, x_{2,t}, \ldots, x_{n,t}, v_1, v_2, \ldots, v_p, w_1, w_2, \ldots, w_{n \cdot p}) = \frac{1}{1 + e^{-\sum_{j=1}^{p} v_j A_{j,t}}} \quad (1a)$$

$$A_{j,t}(x_{1,t}, x_{2,t}, \ldots, x_{n,t}) = \tanh\left(\sum_{i=1}^{n} w_{ij} X_{j,t}\right)$$

where $X$ is a matrix with ones in the first column and the independent variables $x_{1,t}, x_{2,t}, \ldots, x_{n,t}$ column 1 to $n$, $w$ and $v$ represent the set of weights used, and $p$ is the number of neurons in the hidden layer in the model (see Fig. 1). The outcome $y_t$ is a real number between 0 and 1, which is scaled to a number between the minimum and maximum number of cases in the training data set.

Five different models constructed with different sets of explanatory variables were trained and evaluated. In model 1, the simplest case, the incidence of PRP is explained by the sea-

Table 1. Description of Input Variables

| *Variable number* | *Variable name* | *Description* |
|---|---|---|
| 1 | Week | Week number, 1–53 (independent of year) |
| 2 | dsRecipe1 | The number of antibiotic recipes last week (this municipality), deseasonalized. |
| 3 | dsRecipe2 | The number of antibiotic recipes 2 weeks back (this municipality), deseasonalized |
| 4 | dsRecipe3 | The number of antibiotic recipes 3 weeks back (this municipality), deseasonalized |
| 5 | dsRecipe4 | The number of antibiotic recipes 4 weeks back (this municipality), deseaonalized |
| 6 | Children | The population (0–6 years) this year (this municipality) |
| 7 | Population | The total population this year (this municipality) |
| 8 | Not1 | Number of PRP cases last week (this municipality) |
| 9 | Not2 | Number of PRP cases 2 weeks back (this municipality) |
| 10 | Not3 | Number of PRP cases 3 weeks back (this municipality) |
| 11 | N1t1 | Number of PRP cases last week (most common travels municipality) |
| 12 | N1t2 | Number of PRP cases 2 weeks back (most common travels municipality) |
| 13 | N1t3 | Number of PRP cases 3 weeks back (most common travels municipality) |
| 14 | N2t1 | Number of PRP cases last week (second most common travels municipality) |
| 15 | N2t2 | Number of PRP cases 2 weeks back (second most common travels municipality) |
| 16 | N2t3 | Number of PRP cases 3 weeks back (second most common travels municipality) |
| 17 | N3t1 | Number of PRP cases last week (third most common travels municipality) |
| 18 | N3t2 | Number of PRP cases 2 weeks back (third most common travels municipality) |
| 19 | N3t3 | Number of PRP cases 3 weeks back (third most common travels municipality) |
| 20 | TfN1 | Number of travels from most common municipality to this municipality (total for period) |
| 21 | TfN2 | Number of travels from second most common municipality to this municipality (total for period) |
| 22 | TfN3 | Number of travels from third most common municipality to this municipality (total for period) |
| 23 | Last4Weeks | Number of PRP cases the last 4 weeks (this municipality) |
| 24 | Cases (Noto) | (Target variable = outcome) The number of PRP cases (index + contact) this week (this municipality) |

Table 2. List of Variables Used in the Models

| *Variable number* | *Variable name* | *Model 1* | *Model 2* | *Model 3* | *Model 4* | *Model 5* |
|---|---|---|---|---|---|---|
| 1 | Week | X | X | X | X | X |
| 2 | dsRecipe1 | | X | X | X | X |
| 3 | dsRecipe2 | | | | X | X |
| 4 | dsRecipe3 | | | | X | X |
| 5 | dsRecipe4 | | | | X | X |
| 6 | Children | | | X | X | X |
| 7 | Population | | | | | X |
| 8 | Not1 | | | | | X |
| 9 | Not2 | | | | | X |
| 10 | Not3 | | | | | X |
| 11 | N1t1 | | | | | X |
| 12 | N1t2 | | | | | X |
| 13 | N1t3 | | | | | X |
| 14 | N2t1 | | | | | X |
| 15 | N2t2 | | | | | X |
| 16 | N2t3 | | | | | X |
| 17 | N3t1 | | | | | X |
| 18 | N3t2 | | | | | X |
| 19 | N3t3 | | | | | X |
| 20 | TfN1 | | | | X | X |
| 21 | TfN2 | | | | X | X |
| 22 | TfN3 | | | | X | X |
| 23 | Last 4 Weeks | | | | | X |
| **Number of variables** | | **1** | **2** | **3** | **9** | **23** |

sonality. Cross validation yields an optimal network with three hidden nodes, which turns Equation 1a into the following:

$$y_t(x_t,v_1,v_2,v_3,w_1,w_2,w_3) = \frac{1}{1 + e^{-\sum_{j=1}^{3} v_j A_{j,t} + \varepsilon}} \quad (1b)$$

$$A_{j,t}(x_t) = \tanh\,(w_j x_t)$$

where $x_t = \{\{1, \ldots, 53\}, \ldots, (1, \ldots, 53\}\}$ and $v_i$ and $w_i$ are real number weights (parameters). The recursiveness in the model implementation was achieved by embedding the time series.[11]

### *Sensitivity analysis*

To investigate the effect on the outcome of each parameter in the ANN model, sensitivity analysis was used.[26] Each variable in the input was varied whereas the rest of the inputs were held constant. The change in the output compared to the variation in the input yielded the sensitivity, which showed the relative importance among the input variables. A high sensitivity means that a small variation in the input results in a high variation in the output. Equation 2 describes how the sensitivity of variable $x_j$ on the outcome $y$, $S_{y \leftarrow x_i}$, was calculated,

$$S_{y \leftarrow x_i} = \frac{dy}{dx_j} \cdot \frac{x_j}{y} \quad (2)$$

### *Predictability*

As a measure of the performance of a model, the mean square prediction error (MSPE)

$$mspe = \frac{\sum_{i=1}^{n} (\sqrt{y_i} - \sqrt{\hat{y}_i})^2}{n - p} \quad (3)$$

and the correlation coefficient between observed and predicted data was calculated and used to compare the different models.

## RESULTS

Retrospective data from 1997 to 2000 were used to train the ANN models, and data from 2001 to 2003 were used for evaluation of the model predictions. Five different ANN models were trained, all with different sets of input variables in order to find the most descriptive model. Table 1 contains a description of all variables and Table 2 summarizes the input variables used in each model. Each model was trained five times to control how stable the model was regarding the random weights. As a first selection criterion, we choose the network within a model with the best correlation between observation and predictions as the optimal network, which was then used further in the work. The five models differed in topology (Fig. 1) and the number of hidden nodes and the number of unknown parameters is presented in Table 3.

Table 3. Number of Hidden Nodes and Number of Unknown Model Parameters

| *Class* | *Number of hidden nodes in the first layer* (hn) | *Number of parameters* (p) |
|---|---|---|
| Model 1 | 3 | 6 |
| Model 2 | 3 | 9 |
| Model 3 | 5 | 20 |
| Model 4 | 9 | 90 |
| Model 5 | 9 | 216 |

TABLE 4. THE CORRELATION COEFFICIENT BETWEEN PREDICTIONS AND OBSERVATIONS AS WELL AS THE MEAN SQUARE PREDICTION ERROR (MSPE) FOR EACH MODEL

| *Class* | *Correlation coefficient 1997–2000* | *MSPE 2001–2003* |
|---|---|---|
| Model 1 | 0.007 | 0.227 |
| Model 2 | 0.312 | 0.148 |
| Model 3 | 0.358 | 0.154 |
| Model 4 | 0.396 (3) | 0.158 |
| Model 5 | 0.514 (5) | 0.124 |
| Reference model: "Median per time per county" | 0.413 | 0.126 |
| Reference model: "Median per county" | 0.298 | 0.136 |

Two reference models are included in the table for comparison, namely: The median per time per county and the median per county.

The second selection was made by choosing the model with the highest correlation among the five different models and was considered to perform the best fit and prediction of data. Correlation coefficients for two reference models were: (1) the median number of cases per week and per county and (2) the median number of cases per county are presented for comparison. A model performing worse than the reference models was not considered as useful. The resulting correlation coefficients are presented in Table 4.

Model 5, containing all the explanatory variables, was the only model performing better than the reference models according to the correlation coefficient. However, the differences between different models were relatively small and the additional improvement of the larger model should be compared to the additional complexity of the model. Figure 2 shows a plot using Model 5 containing both training and evaluation data.

### *Sensitivity analysis*

Sensitivity analysis was performed on all trained ANNs (presented in Table 5 and Figure 3). The seasonality had a high impact (sensitivity) at the outcome for all the models. This was not unexpected, because PRP like all respiratory tract infections is known to have a strong seasonal trend. Furthermore, the antibiotic sales (recipes), the child population (children), and the transportation intensity between municipalities (TfN1–TfN3) had some effect on the outcome. In contrast to the autocorrelation function,[6] showing that PRP data were autocorrelated up to 1 year back (Fig. 4), the variables representing the past number of cases all had low sensitivities ($<1\%$) indicating a low or no dependency on the past.

## DISCUSSION

In this paper, we have described a new methodology to describe the space-time pattern of the number of infections with penicillin-resistant pneumococci in the Skåne Region of southern Sweden. Five different ANN models were developed and reviewed, all with similar topology differentiated by the number of input variables. Considering the evaluation data, correlation between predictions and observations as well as the mean square prediction error, yields Model 5 to be the better predictor. Model 5 is the most extensive model with 23 different in-

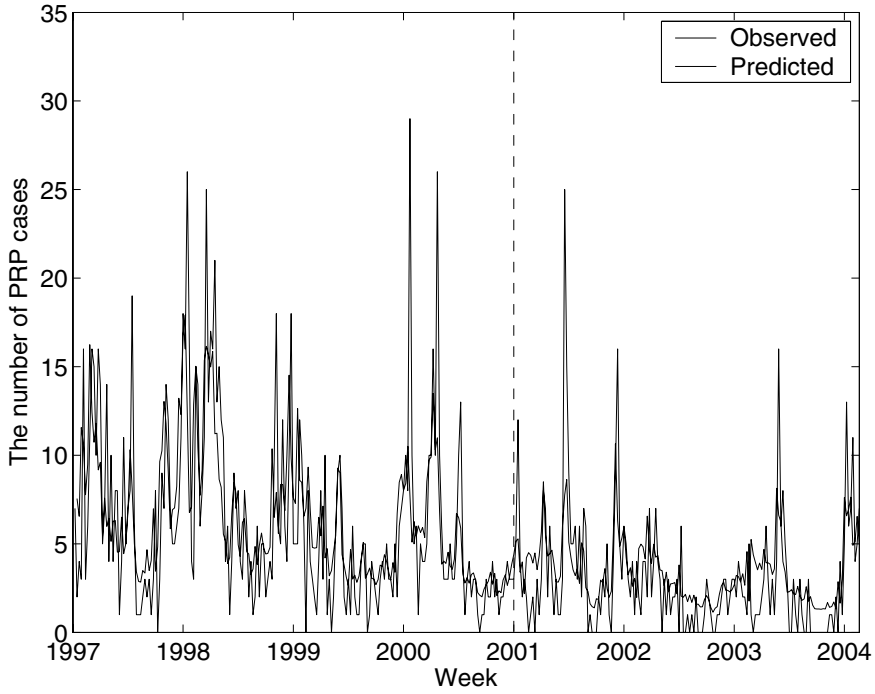


**FIG. 2.** Plot of the predicted number of cases per week in the Skåne Region using Model 5. The model was trained using data from 1997 to 2001 and validated using data from 2001 to 2004.

Table 5. Sensitivities for All Input Variables of Each Model

| *Variable number* | *Variable name* | *Model 1 (%)* | *Model 2 (%)* | *Model 3 (%)* | *Model 4 (%)* | *Model 5 (%)* |
|---|---|---|---|---|---|---|
| 1 | Week | 100 | 52.5 | 40.6 | 12.3 | 1.9 |
| 2 | dsRecipe1 | — | 47.5 | 15.9 | 1.9 | 1.0 |
| 3 | dsRecipe2 | — | — | — | 1.6 | 3.0 |
| 4 | dsRecipe3 | — | — | — | 1.4 | 0.9 |
| 5 | dsRecipe4 | — | — | — | 2.9 | 1.9 |
| 6 | Children | — | — | 43.5 | 4.6 | 7.2 |
| 7 | Population | — | — | — | — | 4.9 |
| 8 | Not1 | — | — | — | — | 0.5 |
| 9 | Not2 | — | — | — | — | 0.2 |
| 10 | Not3 | — | — | — | — | 0.1 |
| 11 | N1t1 | — | — | — | — | 0.5 |
| 12 | N1t2 | — | — | — | — | 0.3 |
| 13 | N1t3 | — | — | — | — | 0.3 |
| 14 | N2t1 | — | — | — | — | 0.5 |
| 15 | N2t2 | — | — | — | — | 0.2 |
| 16 | N2t3 | — | — | — | — | 0.2 |
| 17 | N3t1 | — | — | — | — | 0.1 |
| 18 | N3t2 | — | — | — | — | 0.4 |
| 19 | N3t3 | — | — | — | — | 0.1 |
| 20 | TfN1 | — | — | — | 42.1 | 12.7 |
| 21 | TfN2 | — | — | — | 11.5 | 33.1 |
| 22 | TfN3 | — | — | — | 21.7 | 30.0 |
| 23 | Last 4 Weeks | — | — | — | — | 0.3 |

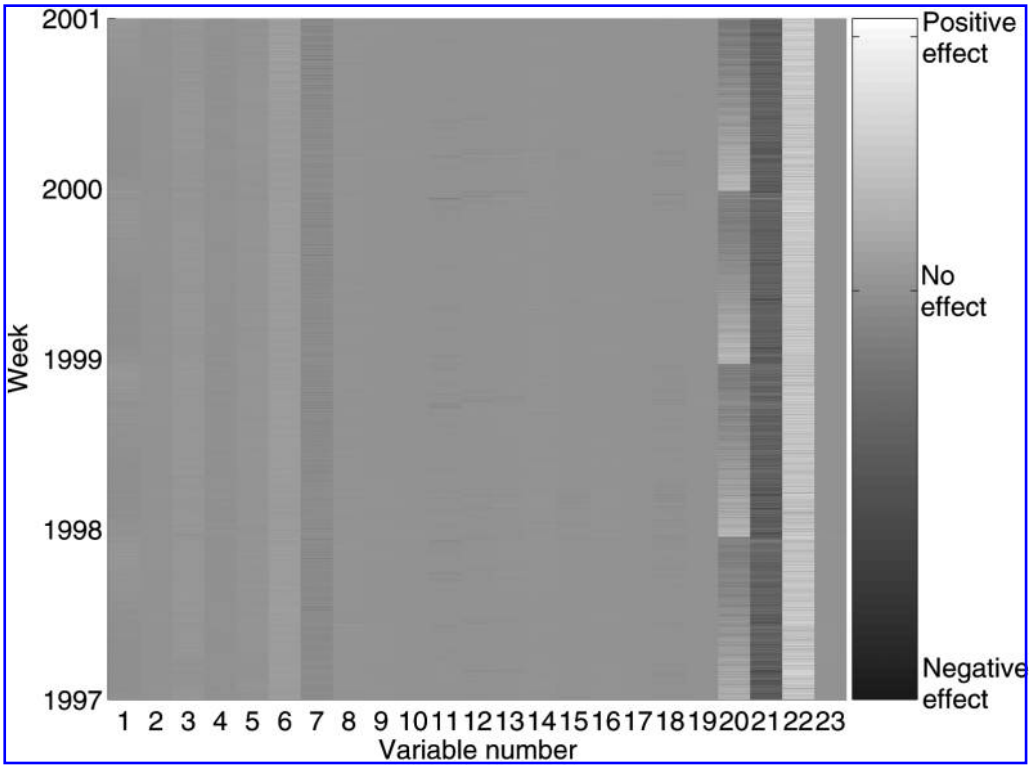


**FIG. 3.** Plot illustrating sensitivity analysis of Model 5, when varying each input at a time with 5%. The graph shows whether or not each variable has a positive or negative effect on the prediction throughout the train data period.

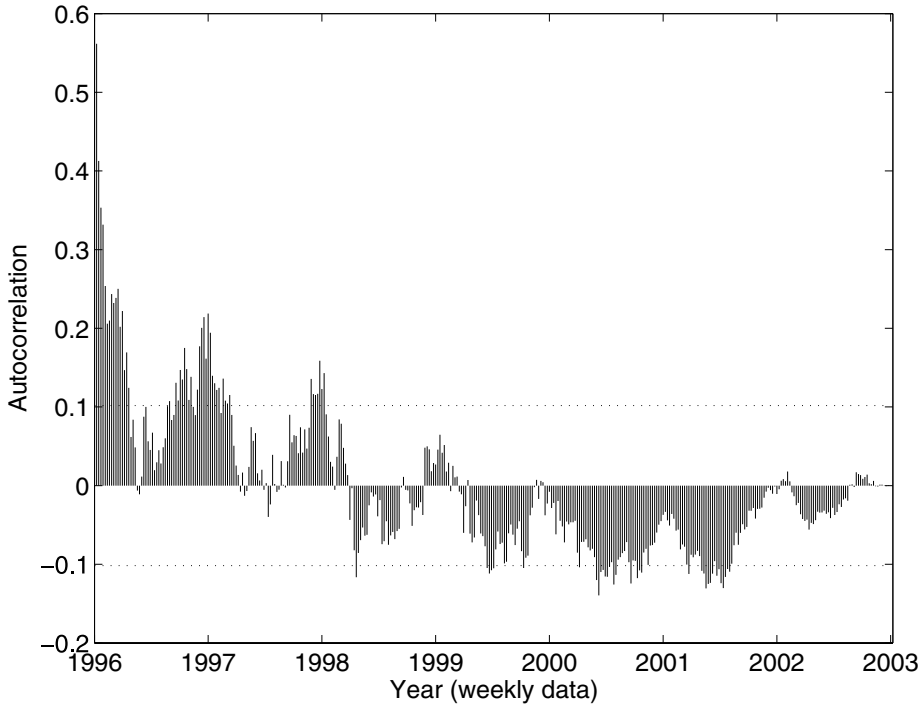


**FIG. 4.** Autocorrelation function for weekly data on the number of PRP cases (all municipalities aggregated). Values above (the upper) or under (the lower) dotted lines represent a 95% significant autocorrelation.

put variables. Figure 2 shows a plot using Model 5 containing both training and evaluation data.

Although Model 5 gives the better predictions, the difference with Models 2–4 is quite small. It is important to consider the increased model complexity to the difference in prediction quality. Consider also that Models 1–4 make worse predictions than the reference model, i.e., the median number of cases per week and per county. This is a very simple model and Model 5 barely predicts better, which might suggest continuing looking at a model with less complexity.

Even though Model 5 makes good predictions, it is hard to interpret the results. Sensitivity analysis sheds light on what effect the input parameters have on the outcome as well as what type of proportionality that each input parameter has to the outcome. Table 5 and Figure 3 illustrate the sensitivity analysis, which shows that: (1) there is a seasonal trend (variable 1) in the data; (2) the antibiotic sales have a slight positive effect on the outcome; (3) the number of children in a municipality has a positive effect while the total population has a negative effect on the outcome; (4) the number of cases the previous week has a slight positive effect whereas the number of cases weeks before that and in closely related municipalities has no effect on the outcome; and (5) the travel intensity has a high effect on the outcome, although not clearly positive or negative. The lack of an error estimate for the sensitivities makes these results unreliable. One fact does support the result. During the optimization of the ANN, several subsets of input variables were used to train about 25 different ANN models. The sensitivity analysis of these ANN models supports the antibiotic sales, the child population, the total population, and the transportation factor as having a greater effect of the outcome than the other input variables.

One hypothesis that was also demonstrated by the autocorrelation function for the number of PRP cases was that there is a time-dependency between the number of PRP cases. These input variables (variable numbers 8–19) all had a low effect on the outcome according to the sensitivity analysis. All ANN models indicated that the past had less effect on the outcome than the input variables discussed above. The week was important, which is an indicator of the strong seasonality with the highest peak during wintertime in our data. The transportation is thought to be an alias for the population.

Although the more traditional statistical models are relatively intuitive to interpret, ANN models are more complex to interpret and besides that also require more computational time. Rather than testing predefined hypotheses about the dependent and independent variables, the ANNs are treated more like a black box, with the aim toward fast and easy filtering of large data sets for variables that have a greater effect on the outcome than the rest. The resulting ANN model can be used for real-life predictions if it is stable enough, but it is probably better used as an indication on which variables to concentrate on when designing a traditional statistical model. In the project described in this paper, the resulting ANN model makes good predictions when validating them with the data from 2001 to 2003. This indicates that the model will be useful to model future data, but the main result of this study is that antibiotic sales as well as the past have a small effect on the number of PRP cases. Although a general association between antibiotics consumption and resistance *per se* is undisputable, one possible explanation for the small effect on the number of PRP cases in this specific setting is the possibility of a threshold level of antibiotics consumption, below which the selective pressure of antibiotics on

the spread of resistant clones is low compared to other factors. Another possible explanation is a longer lag time between antibiotics consumption and an effect on the transmission rate, as has been suggested in previous studies.[2,22]

One problem with the ANN topology used in this paper is the sigmoid function (definition interval from 0 to 1) in the last layer. This implies that the resulting predictions will vary in the interval from the minimum and maximum number of cases (in the train data set), which is not very realistic. This may be addressed by using an inverse sigmoid or linear function (definition interval $-\infty$ to $\infty$) instead of the sigmoid function. On the other hand, using a bounded output transfer function leads to more conservative predictions. Therefore, the comparative study of transfer function selection for modeling the emergence of antibiotic resistance should be accessed in future studies.

Another concern is the autocorrelation in data. A possible improvement in modeling the PRP spread is the use of a truly recurrent neural network (where the recurrence is topological—an output node is also input node of subsequent iteration—instead as phenomenological recurrence as used here), which implies a similar network topology used in this paper. The main difference is one or more additional "memories," which uses information from previous weeks when making a prediction.

## ACKNOWLEDGMENTS

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