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## A Hierarchical Bayesian Model to Predict the Duration of Immunity to *Haemophilus influenzae* Type b

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**SUMMARY.** A hierarchical Bayesian regression model is fitted to longitudinal data on *Haemophilus influenzae* type b (Hib) serum antibodies. To estimate the decline rate of the antibody concentration, the model accommodates the possibility of unobserved subclinical infections with Hib bacteria that cause increasing concentrations during the study period. The computations rely on Markov chain Monte Carlo simulation of the joint posterior distribution of the model parameters. The model is used to predict the duration of immunity to subclinical Hib infection and to a serious invasive Hib disease.

**KEY WORDS:** Bayesian estimation; Hierarchical growth curve models; Latent data; Markov chain Monte Carlo simulation; Subclinical infection with *Haemophilus influenzae* type b.

### 1. Introduction

The important role of serum antibodies in the protection against many diseases is a cornerstone for the use of vaccines to control diseases and their transmission. Before the introduction of a large-scale vaccination program, a new vaccine is routinely tested for its immunogenicity, safety, and efficacy. Studies addressing these issues involve collecting data on vaccine-induced antibody responses in individuals and on long-term protection against the disease. The statistical analyses relating to protection usually rely on the nondynamic description of such data as measured, for example, by the relative risk of contracting the disease in the vaccinated and the nonvaccinated groups. However, the dynamics related to the rate of decline of the antibody concentration has important implications in predicting the consequences of different vaccination programs. These considerations emphasize the importance of statistical methods to analyze the decline of antibodies from longitudinal data.

In the present study, we consider the decline of the concentration of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b (Hib) bacteria. Such antibodies arise naturally as a response to a mucosal encounter with the bacteria and can be induced by vaccination with the capsular polysaccharide vaccine (Mäkelä et al., 1995). This vaccine has been shown to prevent the emergence of clinical disease, but it is not sufficient to hinder the actual transmission of the bacteria (Mäkelä et al., 1995). Therefore, longitudinal data are influenced by antibody responses to subclinical infections (asymptomatic nasopharyngeal carriage). The purpose of the present modeling approach is to account for the possibility of such infections in the data analysis.

The data used in this study were gathered in Finland in 1974 when investigating the age-dependent antibody response and the vaccine-induced clinical protection against serious invasive Hib disease (Käyhty et al., 1984). Here, we analyze some of these data to estimate the rate of decline of the antibody concentration and the duration of immunity to subclinical Hib infection or invasive Hib disease. The results are presented in terms of Bayesian posterior predictive distributions. The force of infection relating to natural exposure to Hib bacteria acts as a nuisance parameter. The results, however, give a useful indication of the magnitude of this hazard and enable us to calculate the predictive distribution of the future cross-sectional antibody concentration in a population under the natural force of infection. The model is applicable to other bacterial infections in which anticapsular polysaccharide antibodies play a significant role, e.g., pneumococcal and meningococcal infections. However, the model needs to be modified for protein-polysaccharide vaccines (e.g., Hib conjugate vaccines) to include the development of immunological memory (Mäkelä et al., 1995).

The statistical and computational means applied in this study rely on some recent developments in the treatment of Bayesian hierarchical models. Markov chain Monte Carlo (MCMC) methods make use of Markov chains to draw samples from a multivariate probability distribution and have proved flexible and efficient in dealing with complex models (Besag et al., 1995). To set up the model, quantities considered relevant for the study are identified, and a joint probability distribution of all parameters and of the observed data is constructed through the specification of their conditional independence structure. Although analytical solutions are often

intractable, the simple local dependencies in the model allow one to construct an MCMC algorithm to draw approximate samples from the joint posterior distribution of all unobserved model parameters. The posterior inferences can then be based on this sample.

The present work is related to a recent study on the rate of decline of serum antibodies to hepatitis B virus in Gambian infants (Spiegelhalter et al., 1996). In that study, the idea of hierarchical modeling coupled with Gibbs sampling was applied to draw inferences from sequential antibody data. The novelty of the present study is that it considers the role of intervening infections in interpreting the data. The approach is made possible by techniques within the MCMC framework that allow the use of models of unknown dimensions (Green, 1995). In our study, the dimension of the model is not prescribed *a priori* because the number of infections during the observation period is unknown and varies from one individual to another.

The article is organized as follows: Section 2 describes the data and introduces the hierarchical model for the dynamics of the antibody concentration. The main inferential results are presented in Section 3, in which we also discuss the fit of the model and the model choice. Section 4 provides a brief discussion of the results obtained. The Appendix includes details of the sampling algorithm and its performance.

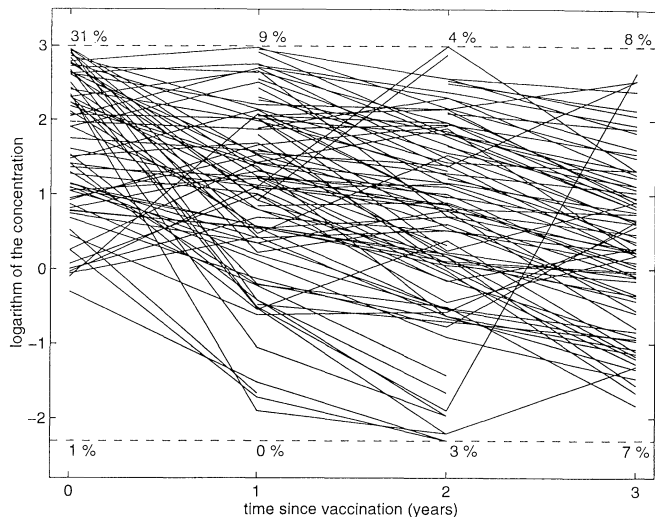
## 2. The Data and the Model

### 2.1 The Data

The data comprise sequential antibody measurements in a cohort of 110 children who participated in a vaccine efficacy trial in Finland in 1974 (Käyhty et al., 1984). These 110 children received the Hib polysaccharide vaccine between the ages of 4 and 7 years. Up to four postvaccination measurements of the level (i.e., concentration) of serum antibodies to Hib were performed at 1-year intervals. There were 4 children with two, 14 with three, and 92 with four follow-up measurements. Apart from dropouts, missing values also occurred intermittently. Because of the antibody detection method, the data were censored at 20  $\mu\text{g}/\text{ml}$  (upper level) and 0.1  $\mu\text{g}/\text{ml}$  (lower level). There were 6, 17, 35, and 51 individuals with one, two, three, and four uncensored measurements, respectively. Thus, approximately 17% (69/418) of the observations were censored. Right censoring (at the upper level) occurred in 14% (57/418) of the observations, whereas left censoring (at the lower level) occurred in only 3% (12/418) of the observations. The uncensored fraction of the data is presented in Figure 1. The time of the first measurement, 1 month after the actual vaccination, when antibody response was considered to be at its maximum, was considered as the time of vaccination. At this time, 31% (34/110) of the observations were right censored, and one observation was left censored. Because all children were over 3 years of age, it was not important to consider an age dependency of the response in the models (Käyhty et al., 1984).

### 2.2 The Dynamic Regression Model

The model is specified as a joint probability distribution of the data  $y$  and parameters  $\theta$ . Figure 2 presents the hierarchical model as a directed acyclic graph in which the data items and the parameters are represented by nodes. Based on the conditional independence structure depicted by the graph, the



**Figure 1.** The uncensored fraction of the data. The logarithmic values of the observed antibody concentrations that lie between the detection levels  $\log(0.1) = -2.3$  and  $\log(20) = 3.0$  (horizontal dashed lines) are presented for consecutive observations. The horizontal axis shows follow-up time since vaccination; the zero point is 1 month after the actual vaccination. The lines join each individual's observations. The percentage of right and left censoring at each measurement point is indicated in the figure.

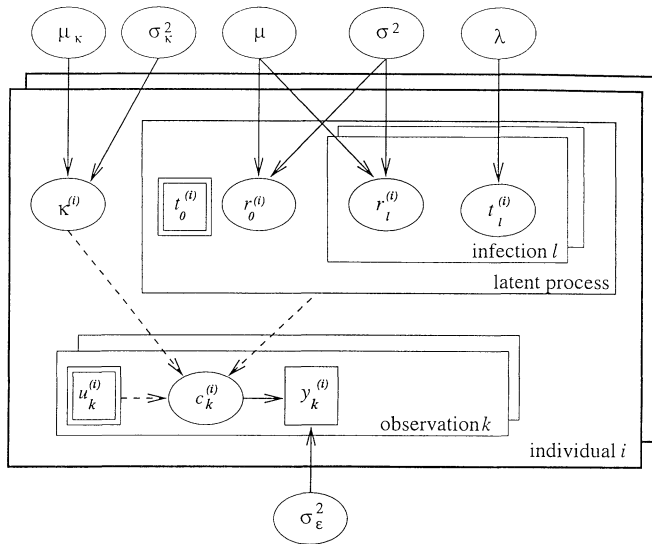
joint distribution of  $(y, \theta)$  can be factorized in terms of simple conditional densities (Lauritzen and Spiegelhalter, 1988) as

$$p(y, \theta) = \prod_{\text{node}} p(\text{node} \mid \text{parents of node}). \quad (1)$$

The nodes without parents are population parameters common to all individuals and require (marginal) prior distributions to be specified. In this section, starting from the observed data level, we define the model working through the graph toward levels with unobserved variables, indicating at each stage the form of the conditional densities. Given the population parameters, we assume independence across individuals so that expression (1) factorizes further into a product over individual contributions. In the following, it is thus sufficient to consider a single individual.

The observations on individual  $i$  comprise measurements  $y_k^{(i)}$  of the logarithmic antibody level at the times  $u_k^{(i)}$ ,  $k = 1, \dots, n^{(i)}$ . Given the “true” underlying log levels  $c_k^{(i)}$ , variables  $y_k^{(i)}$  are assumed to be independent draws from a logistic distribution with mean  $c_k^{(i)}$  and residual error variance  $\sigma_\epsilon^2$ :  $y_k^{(i)} \mid c_k^{(i)}, \sigma_\epsilon^2 \sim \text{Logistic}(c_k^{(i)}, \sigma_\epsilon^2)$ . This yields the joint conditional density of the observations as a product of  $n^{(i)}$  logistic density terms. For censored observations, we use the tail probabilities, which is particularly convenient in the case of the logistic distribution (Kalbfleisch and Prentice, 1980).

Next, we define the model for the underlying antibody dynamics. The log-level  $c_k^{(i)}$  at the  $k$ th observation depends



**Figure 2.** The structure of the model. Ellipses and squares denote unknown and fixed (observed) model quantities, respectively, and the double squares denote fixed covariate information. The solid and dashed arrows indicate direct probabilistic and deterministic dependencies between the nodes, respectively. This graph corresponds to the model without temporary immunity to infection. The symbols are  $u_k^{(i)}$ , the time of the  $k$ th observation;  $c_k^{(i)}$ , the underlying antibody level at the  $k$ th observation depending on the latent process in the way specified in Section 2.2;  $y_k^{(i)}$ , the observed log level of antibodies at the  $k$ th observation;  $\sigma_\epsilon^2$ , the variance of the residual error;  $\mu_\kappa$  and  $\sigma_\kappa^2$ , the population mean and variance of the individual rates of decline  $\kappa^{(i)}$ ;  $t_0^{(i)} = u_1^{(i)}$ , the time at vaccination;  $\mu$  and  $\sigma^2$ , the population mean and variance of the logarithm of individual responses  $r_0^{(i)}$  (to vaccination) and  $r_l^{(i)}$  (to the  $l$ th infection);  $\lambda$ , rate of (subclinical) Hib infection; and  $t_l^{(i)}$ , the  $l$ th time of infection. Repeated structures are indicated by overlapping sheets.

on the time  $u_k^{(i)} - t_{l_k}^{(i)}$  elapsed since the most recent infection or vaccination preceding the observation, the logarithmic magnitude  $r_{l_k}^{(i)}$  of the response, and the rate  $\kappa^{(i)}$  of decline, according to the following deterministic model:

$$c_k^{(i)} = r_{l_k}^{(i)} - \kappa^{(i)} (u_k^{(i)} - t_{l_k}^{(i)})^\alpha \tag{2}$$

The rate of decline  $\kappa^{(i)}$  is modeled as an individual-dependent, normally distributed parameter with mean  $\mu_\kappa$  and variance  $\sigma_\kappa^2$ :  $\kappa^{(i)} \mid \mu_\kappa, \sigma_\kappa^2 \sim \text{Normal}(\mu_\kappa, \sigma_\kappa^2)$ . For biological reasons, the distribution will be truncated to positive values. A positive parameter  $\alpha$  ( $\leq 1$ ) controls the rate of decline by reducing it over time: for  $\alpha = 1$ , model (2) has an exponential decline of the absolute antibody level, whereas for  $\alpha < 1$  the rate of decline is attenuated in comparison with the exponential model. Parameter  $\alpha$  will not be a target for the formal estimation, but its value is chosen as described in later sections.

Each individual is vaccinated at a known time  $t_0^{(i)} = u_1^{(i)}$ .

Subsequent subclinical infections are assumed to arise according to a Poisson process with constant intensity (force of infection)  $\lambda$ ; the sequence of infection times of individual  $i$  is denoted by  $(t_1^{(i)}, \dots, t_{L^{(i)}}^{(i)})$  if a total of  $L^{(i)}$  (unobserved) infections occur during the observation period  $\Delta^{(i)}$ . At vaccination and at each infection there is an associated antibody response. Based on the identical structure of the Hib polysaccharide vaccine and the polysaccharide capsule of the Hib bacteria (Mäkelä et al., 1995), the logarithmic responses  $r_l^{(i)}$ ,  $l = 0, \dots, L^{(i)}$ , are assumed to obey the same normal sampling distribution with mean  $\mu$  and variance  $\sigma^2$ . A simplifying assumption of independence is suggested by the lack of an immunological memory (Käyhty et al., 1984) that would clearly imply dependent responses. Considering the responses as real-valued marks on the infection times, the joint conditional density of the times  $t_1^{(i)} < \dots < t_{L^{(i)}}^{(i)}$  and the log responses of individual  $i$  are given by (e.g., Arjas, 1989)

$$p(t_1^{(i)}, \dots, t_{L^{(i)}}^{(i)}, r_0^{(i)}, \dots, r_{L^{(i)}}^{(i)} \mid \lambda, \mu, \sigma^2) \propto \lambda^{L^{(i)}} \exp(-\lambda |\Delta^{(i)}|) p(r_0^{(i)}, \dots, r_{L^{(i)}}^{(i)} \mid \mu, \sigma^2). \tag{3}$$

Here  $|\Delta^{(i)}|$  is the total length of the observation period. The last term yields a product of  $L^{(i)}$  normal density terms for log responses:  $r_l^{(i)} \mid \mu, \sigma^2 \sim \text{Normal}(\mu, \sigma^2)$ ,  $l = 0, \dots, L^{(i)}$ .

To avoid unwarranted downward jumps in the antibody level, only responses that increase the preexisting level are assumed to affect the future antibody level. A downward response remains “silent” in the sense that it does not affect the future evolution of the process. Although we do not pursue the interpretation further, it is possible to view these silent responses as futile attempts to colonize the host with the bacteria. Technically, in expression (2), we actually employ the most recent infection with the “nonsilent” response before the observation. Because we do not model the decline process before the vaccination, response  $r_0^{(i)}$  is assumed to be nonsilent for convenience. This scheme may lead to concerns about identifiability as the number and the magnitudes of silent responses are not directly related to the process and thus to the observed data. However, in the application, the proportion of silent responses remained as small as 15% of all responses triggered.

Previous studies suggest a temporary immunity to infection if the antibody level is above 10  $\mu\text{g/ml}$  (Kauppi, Eskola, and Käyhty, 1995). Immunity can be incorporated in the model by excluding the possibility of infection while the antibody level is above this protective level. In expression (3), this amounts to requiring that all times  $t_l^{(i)}$  occur during  $\Theta^{(i)}$ , defined as the union of all intervals within  $\Delta^{(i)}$  during which the antibody level is below 10  $\mu\text{g/ml}$ , and to replacing  $\Delta^{(i)}$  by  $\Theta^{(i)}$  in the exponent. The presence of immunity introduces a dependence of the infection intensity on the times and magnitudes of the preceding responses, which breaks up the simple independence structure concerning times  $t_l^{(i)}$ . It does not, however, complicate the expression of the likelihood as a product of conditional densities as specified here.

To complete the specification of the probability model, we define the prior distributions of the population parameters. Independently for each parameter, we adopt the following

priors:  $\mu, \mu_\kappa \sim \text{Normal}(0, 10,000)$ ,  $\sigma^{-2}, \sigma_\kappa^{-2}, \sigma_\epsilon^{-2} \sim \text{Gamma}(0.001, 0.001)$ , and  $\lambda \sim \text{Gamma}(2, 2200)$ . The priors of  $\mu$  and  $\sigma^{-2}$  (the mean and the precision of the log response),  $\kappa$  and  $\sigma_\kappa^{-2}$  (the mean and the precision of the decline rate), and  $\sigma_\epsilon^{-2}$  (the precision of the residual error) reflect diffuse prior knowledge; for the precision parameters, the mean and the variance of the gamma priors are 1 and 1000, respectively. The prior of intensity  $\lambda$  supports a wide range of values while attempting to avoid the use of too diffuse a prior. On average, the prior mean corresponds to one subclinical infection in 3 years per nonimmune child.

In the model there are population parameters, common to all individuals, and parameters specific to each individual in the data: rate of decline and parameters of the latent process, i.e., the number and the times of infections, and the associated responses. The unobserved times and responses can be viewed as missing data, but in the model they are treated as any unknown parameter. Our main interest lies in population-level inferences through the estimation of the distribution of the decline rate and in the prediction of the general behavior of the postvaccination antibody level.

### 3. Application to the Data

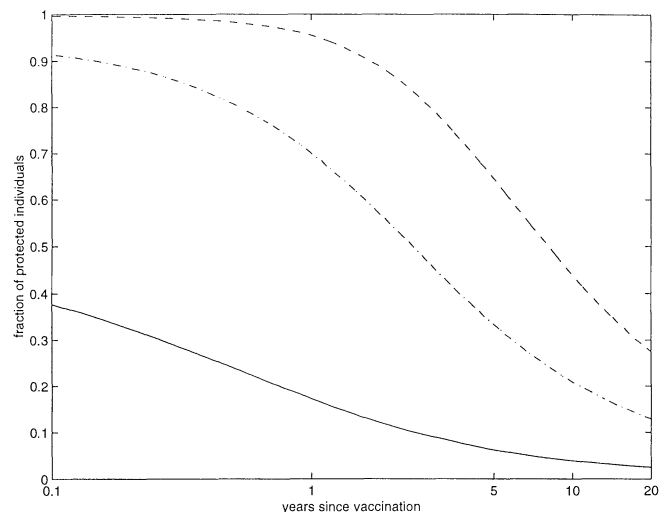
#### 3.1 Posterior Inferences

The statistical inference is based on approximate samples from the posterior distribution of the model parameters, defined as  $p(\theta | y) = p(y, \theta) / p(y) \propto p(y, \theta)$ . The samples were realized by MCMC simulation (see the Appendix for details on the sampling algorithm and its performance). The posterior mean and 90% marginal equal-tail posterior intervals of the population parameters are presented in Table 1. The protective Hib antibody level against infection was set at 10  $\mu\text{g/ml}$  on the absolute scale, and the parameter  $\alpha$  was 0.5. The choice of this particular value is discussed in Section 3.2.

Not surprisingly, the marginal posterior distributions of the mean and of the standard deviation ( $\mu$  and  $\sigma$ ) of the log response are derived from the first measurements taken after vaccination (known exposure). Within the population parameters, the strongest negative posterior correlations were between  $\sigma_\epsilon$  and  $\lambda$  ( $-0.71$ ) and between  $\sigma_\epsilon$  and  $\mu_\kappa$  ( $-0.49$ ). This implies that the model achieves a better fit to the

data (a smaller residual error) by introducing more latent infections with a faster decline of the antibody level. The posterior correlations between  $\lambda$  and  $\mu$  and between  $\lambda$  and  $\mu_\kappa$  were  $-0.29$  and  $0.52$ , respectively. Indeed, to explain the data, the model exploits either frequent infections with small responses (and a fast decline of the antibody level) or less-frequent infections and higher responses. The variability across individuals in the rate of decline is large compared to the mean; for the rate  $\kappa^{(i)}$ , the posterior mean of the coefficient of variation was 0.70. The relative decrease in the absolute antibody level depends only on the rate  $\kappa$ . The predicted mean decrease was 71, 84, and 93% 1, 3, and 10 years after vaccination, respectively.

Levels of antibodies exceeding 0.15  $\mu\text{g/ml}$  are considered to provide immunity to serious clinical forms of Hib disease (Käyhty et al., 1983; Käyhty and Mäkelä, 1984). The model can be used to predict how long after vaccination antibodies are above this threshold without the effect of external boosting (i.e., with  $\lambda = 0$ ). According to model (2), the duration  $s_K$  of immunity with threshold  $K$  (measured in micrograms per milliliter) is given by  $s_K = [(r_0 - \log K) / \kappa]^{1/\alpha}$ . The predictive distribution of duration  $s_K$  is presented in Figure 3 for three tentative thresholds: 0.15, 1.0, and 10.0  $\mu\text{g/ml}$ . The qualitative effect of the “attenuated” timescale is evident from the behavior of the curves for the three thresholds. The model predicts long-term protection against invasive Hib disease while indicating only short-term protection against subclinical infection. In more than 95% of the children, the antibody level exceeds 0.15  $\mu\text{g/ml}$  1 year after vaccination, whereas only in about 15% is it above 10.0  $\mu\text{g/ml}$ .



**Figure 3.** The predictive distribution of the duration of immunity with three different thresholds. The curves show the “survivor function” of the duration with thresholds 10  $\mu\text{g/ml}$  (solid line), 1  $\mu\text{g/ml}$  (dot-dashed line), and 0.15  $\mu\text{g/ml}$  (dashed line). The force of infection is set to zero in these predictions. The scale on the time axis is logarithmic. The distribution for each threshold is based on 1,000,000 samples drawn from the posterior predictive distribution.

**Table 1**

*Summary of the marginal posterior distributions of the population parameters, based on 1,000,000 simulated draws from the joint posterior distribution of the parameters. The credible intervals are 90% equal-tail posterior intervals. The protective level against infection was set at 10  $\mu\text{g/ml}$ , and parameter  $\alpha$  was 0.5.*

Parameter	Mean	Median	Credible interval
$\mu$	2.37	2.37	2.15–2.59
$\sigma$	1.33	1.32	1.14–1.52
$\mu_\kappa$	0.074	0.074	0.059–0.088
$\sigma_\kappa$	0.051	0.050	0.040–0.063
$\lambda$ (1/year)	0.25	0.24	0.12–0.39
$1/\lambda$ (years)	4.7	4.1	2.6–8.6
$\sigma_\epsilon$	0.43	0.42	0.33–0.55

The interpretation of  $\lambda$  is not straightforward because, marginally, it describes “alternative realities” related to latent processes with a different number of unobserved infections even within one individual. According to model averaging, rate  $\lambda$  is a summary measure of all possible explanations of the data through subclinical infections. The posterior magnitude of  $\lambda$  seems to be reasonable, indicating, on average, one infection in less than 5 years for a nonimmune individual. The posterior mean of  $\lambda$  is less than the prior mean, and the posterior distribution has shrunk considerably from the prior.

We used the model to predict future antibody levels in the vaccinated cohort under the estimated force of infection  $\lambda$ . Interestingly, the prediction exhibited an almost linear decline of the (mean) antibody level, which would suggest the use of a logarithmic time transformation in model (2) (as in Coursaget et al., 1991). However, this type of model would omit the possibility of latent infections.

3.2 *Fit of the Model and the Model Choice*

We checked the fit of the model by examining how plausible some characteristics of the observed data were under the predictive distribution of replicated data. To realize the distribution in a sample-based calculation, population parameters  $\theta_1$  were first drawn from their posterior distribution  $p(\theta_1|\mathbf{y})$ , where the complete set of observed data is denoted by  $\mathbf{y} = (y_k^{(i)})$ ,  $i = 1, \dots, 110$ ,  $k = 1, \dots, n^{(i)}$ . Individual parameters  $\theta_2$  were then drawn from their posterior predictive distribution  $p(\theta_2 | \theta_1)$ . Finally, simulated data  $\mathbf{y}^*$  were drawn from their predictive distribution  $p(\mathbf{y}^*|\theta_2)$ . One set of replicated data thus consisted of 110 sequences of simulated observations, based on parameters  $\kappa^{(i)}$  and  $r_0^{(i)}$  drawn from their predictive distribution and, for each of the 110 individuals, a subsequent realization of the antibody process. We note that conditioning on the population, rather than on the individual parameters, should provide a fairly strict test on the fit of the model.

The main inferences depend on the combined estimation of the rate of decline and the force of infection. We defined a test statistic as

$$T_1(\mathbf{y}) = \sum_{i=1}^{110} \sum_{k=2}^{n^{(i)}} |y_k^{(i)} - y_{k-1}^{(i)}|$$

to detect inadequacy of the model to describe the population pattern of the changes in antibody level over the observation intervals. In the case of equidistant observations,  $T_1$  is proportional to the sum of absolute values of observed gradients. A Bayesian p value can be computed as the fraction of the  $M$  Monte Carlo samples  $\mathbf{y}_h^{\text{rep}}$  of replicated data that yield a more extreme test value than the observed one (Gelman et al., 1995):

$$P(T_1(\mathbf{y}^{\text{rep}}) \geq T_1(\mathbf{y}) | \mathbf{y}) \simeq \frac{1}{M} \sum_{h=1}^M \mathbf{I}\{T_1(\mathbf{y}_h^{\text{rep}}) \geq T_1(\mathbf{y})\}. \tag{4}$$

Here the probability is determined under the posterior predictive distribution of the replicated data. For the test statistic  $T_1$ , the p value was 0.77, indicating a satisfactory fit.

When sampling responses  $r_l^{(i)}$ , the model was aimed at

“borrowing strength” from the actually observed response at known exposure (vaccination). Therefore, it is important to check the stability of the fit with respect to these observations. Two additional statistics,  $T_2$  and  $T_3$ , were determined as the 10 and 69% quantiles of the predicted observation  $y_1^{\text{rep}}$  (the upper one corresponds to the level at which observations were censored). The p values for test statistics  $T_2$  and  $T_3$  were 0.55 and 0.58, respectively, also indicating a good fit to the data. Test statistic  $T_3$  also implied that a logistic model of the residual error rather than a Gaussian one was more appropriate.

Models with different values of parameter  $\alpha$  were fitted to the data ( $\alpha = 0.15, 0.3, 0.5, 0.7, 0.85, 1.0$ ). We also fitted a model with a linear relationship between the logarithmic antibody level and logarithmic time; this type of model was found appropriate to describe the decline of the concentration of antibodies to hepatitis B (Coursaget et al., 1991; Spiegelhalter et al., 1996). The performance of each model was evaluated in terms of the test statistics as defined above and the posterior predictions on the antibody level. The estimation of the distribution of the log response was stable for most of the models (in terms of test statistics  $T_2$  and  $T_3$ ). On the contrary, test statistic  $T_1$  was quite sensitive to the model choice. In general, the posterior predictive distributions of  $T_1$  suggested “too large” values, and the lack of fit can thus be explained by an excessive number of infections and the consequent overestimation of rate  $\lambda$ .

Models with large values of parameter  $\alpha$  (0.85, 1.0) resulted in too fast a decline of the long-term predictions of the antibody level as compared to the data and to overall cross-sectional observations on Hib antibody levels in the population. Models with small values of  $\alpha$  (0.3, 0.15, and the “log-log” model) resulted initially in too fast a decline during the first year after vaccination, and subsequently in overly smoothed stationary behavior. The estimated magnitude of the residual error was relatively large in all models, being largest in models with small  $\alpha$  values. Based on the overall performance of estimation and prediction, we consider the model with  $\alpha = 0.5$  as the most appropriate of the models discussed in the present study.

4. **Discussion**

In this study, the longitudinal data on Hib antibodies were influenced by intervening exposures to the bacteria. Without this contamination, a standard “random effects” growth curve model (Spiegelhalter et al., 1996) might be sufficient to describe the decline of the antibody concentration. In our case, the estimation of the rate of decline would be biased toward smaller values. The posterior probability  $P(\tilde{\mu}_\kappa > 0.074)$  was 0.003, where  $\tilde{\mu}_\kappa$  is the population mean rate under a standard model, and 0.074 is the posterior mean of the rate under the model including the latent infections (cf. Table 1). Because of individual variation, for the individual rates,  $P(\tilde{\kappa} > 0.074)$  was 0.34.

Without the latent infections in the model, the estimated standard deviation of the residual error almost doubled. A standard model may thus prove problematic for the purpose of prediction of the latent “true” antibody level. Introducing unobserved infections at random time points during the observation period can be interpreted as a semifunctional description of the biological process in the individual. A model

accommodating external boosting thus enhances a natural interpretation of predictive antibody levels.

The model combines probability modeling, in a fully Bayesian sense, with rather strong assumptions, e.g., the choice of the protective level against infection and the choice of the value of parameter  $\alpha$ . Although possible in principle, it does not seem reasonable to treat all these characteristics as random because there is a practical drawback in dealing with large models with a considerable support for alternative explanations of the data. Averaging out the wide posterior uncertainty for a weakly identifiable parameter may in fact lead to less useful inferences about other model parameters. More frequent observations and less censoring of the data might have improved the efficiency of the estimation. With a Bayesian hierarchical model, the most coherent way to view the results of the model is in terms of its full posterior distribution. In our case, we have used this distribution to make predictions on the effects of vaccination on the immunity.

Our model implies a qualitatively different behavior of the antibody concentration as compared to the model of the decline of antibodies to hepatitis B (Spiegelhalter et al., 1996). In that model, the logarithmic time transformation effectively decelerates the decline according to the absolute timescale. This may be because of the different nature of polysaccharide (in the case of Hib) and protein (in the case of hepatitis B) antibodies. In a previous study on Hib carriage in families (Auranen et al., 1996), the force of infection was estimated to be smaller than in the present work. The major reason for this is probably related to the different nature of the data. In that article, the analysis of the data on antibodies was not included. With only two points at which Hib infection (asymptomatic nasopharyngeal carriage) was recorded, the analysis may have ignored unobserved infections. Another possible explanation is that Hib carriage is not the only cause for increasing antibody levels; infections with other cross-reacting bacteria could also increase the concentration of antibodies to Hib. This would have important consequences on the epidemiology of Hib and on the understanding of carriage and antibody data.

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#### RÉSUMÉ

Un modèle de régression bayésien hiérarchique est ajusté à des données longitudinales d'anticorps sériques anti *Haemophilus influenzae* type b (Hib). Afin d'estimer le taux de décroissance de concentration d'anticorps, le modèle considère des infections subcliniques non observées dues à la bactérie Hib, qui provoquent de fortes hausses de concentration durant la période de l'étude. Les calculs reposent sur une simulation de Monte Carlo par chaîne de Markov de la distribution jointe *a posteriori* des paramètres du modèle. Le modèle est utilisé pour prédire la durée de l'immunité d'une infection subclinique et d'une infection patente à Hib.

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## APPENDIX

To draw samples from the posterior distribution, we constructed a random-scan, single-site updating Metropolis–Hastings algorithm (Besag et al., 1995). At each iteration of the algorithm, a random choice was made among the following 10 categories of moves: update one of the population parameters (six move types), update the infection times or responses in the individual latent processes (two move types), update the individual rates  $\kappa^{(i)}$ , and add/remove infections in the individual latent processes. To obtain a reversible chain, individual parameters were updated using a forward–backward visiting schedule (Besag et al., 1995). For each model, we realized 2,000,000 iterations (on average 200,000 updates per population parameter). For posterior inferences, we discarded the first 1,000,000 of these as a burn-in phase. On an unloaded Pentium II 400 MHz computer, a run of 2,000,000 iterations took approximately 3 hours.

When the number of infections in the latent processes is fixed, the standard Metropolis–Hastings method works. A proposal  $\nu^*$  for parameter  $\nu$  is first drawn from a density  $q(\nu^* | \theta)$  that may depend on the current values of the parameters. Parameter vector  $\theta^*$ , in which  $\nu$  is replaced by  $\nu^*$ , is then accepted as a new sample value with probability  $\min\{1, A\}$ , where the acceptance ratio is  $A = \{p(\theta^* | y)q(\nu | \theta^*)\} / \{p(\theta | y)q(\nu^* | \theta)\}$ . If the proposal is rejected, the current parameter vector  $\theta$  is taken into the sample. The method exploits the hierarchical model structure and the local dependencies between the various nodes. Indeed, by factorization (1) the acceptance ratio can be reduced to an expression that includes only terms concerning the parents, coparents, and children of parameter  $\nu$  (Lauritzen and Spiegelhalter, 1988; Besag et al., 1995).

We give a more detailed account of the nonstandard sampling step that adds and removes infections in reversible pairs of jumps among parameter spaces of different dimensions, each defined on a set of a fixed number of latent infections. As individual processes are conditionally independent, it is sufficient to consider a single such process; for convenience, we omit the superscript  $i$  indicating the individual. We start with a random choice between attempting either of the following moves: “birth”—add a new infection and response to the process, and “death”—remove one of the infections with the associated response from the process. These attempts are chosen with probabilities  $\pi_b$  and  $\pi_d = 1 - \pi_b$ , respectively. If there are no infections in the current process,  $\pi_d$  is the probability of retaining the current state with no action to be taken. If the birth step is chosen, a proposal  $t^*$  for a new infection time (in addition to the  $L$  existing ones) is drawn from a uniform distribution on the observation period  $\Delta$ . Next, an associated log response  $r^*$  is proposed from a normal distribution with mean at the current log level of antibodies  $c$  and variance  $\xi^2$ , where  $\xi$  can be tuned to allow proper mixing of the algorithm. In a corresponding

death step, the time and the response proposed for removal are selected randomly among the  $L + 1$  infections.

Based on the template in Green (1995), the acceptance ratio is now given by

$$A = \{\text{likelihood ratio}\} \times \{\text{prior ratio}\} \\ \times \{\text{proposal ratio}\} \times \{\text{Jacobian}\}. \quad (\text{a})$$

The likelihood ratio is given by  $\Lambda = \Pi_k \{p(y_k | c_k^*, \sigma_c^2) / p(y_k | c_k, \sigma_c^2)\}$ , where  $k$  runs over the observations and  $c_k^*$  is the log level of antibodies at the  $k$ th observation in the proposed process. The prior ratio is determined by the Poisson density of the infection times and by the normal density of the associated log responses. After canceling out terms, this ratio reduces to  $\lambda \exp\{\lambda(|\Theta| - |\Theta^*|)\} p(r^* | \mu, \sigma^2)$ , where  $p(r^* | \mu, \sigma^2)$  is the normal density of the proposed log response. The prior ratio is zero if the proposed process violates the temporary immunity, e.g., if the time  $t^*$  occurs during a period of immunity. The proposal ratio is the ratio between the proposal density from the proposed to the current parameter vector and the proposal density of the reverse move. Taking  $\pi_b = \pi_d = 0.5$ , this ratio reduces to  $\Delta / \{(L + 1)q(r^* | c, \xi^2)\}$ , where  $q(r^* | c, \xi^2)$  is the normal density of the proposal distribution, with mean at the current log level  $c$  of antibodies at time  $t^*$  and with variance  $\xi^2$ . Two additional random variables,  $t^*$  and  $r^*$ , were drawn to propose a move from the current parameter vector  $\theta$  to proposal  $\theta^*$  in a higher-dimensional space. The Jacobian gives the scale of the deterministic transformation between the current and proposed parameter vectors  $\theta$  and  $\theta^*$  (Green, 1995). In our case, the Jacobian is equal to 1. Eventually, multiplying the likelihood ratio with the prior and proposal ratios, ratio (a) is given by

$$A = \Lambda \times \frac{\lambda \Delta}{L + 1} \times \frac{p(r^* | \mu, \sigma^2)}{q(r^* | c, \xi^2)} \times \exp\{\lambda(|\Theta| - |\Theta^*|)\}. \quad (\text{b})$$

The opposite move attempts to remove an existing response from the current process. The acceptance ratio of this move is given by the inverse of (b), with some obvious modifications.

The Markov chain is reversible by construction. It is also irreducible; that is, it can move from any point in the parameter space to any other point in a finite number of steps. On this basis, the chain is ergodic in the sense that expectations with respect to the posterior distribution of functions defined in the parameter space can be approximated by the corresponding Monte Carlo averages over finite sample paths (Tierney, 1994).

In preliminary runs of the algorithm, the ranges of the symmetric uniform proposal densities were adjusted for each parameter so that in the final run, the proportions of accepted proposals were between 0.35 ( $\sigma_c$ ) and 0.53 ( $r_l^{(i)}$ ). Only 18% of the proposed changes in the add/remove step were accepted, which is reasonable, still indicating an efficient mixing between the different parameter spaces. Gelman–Rubin convergence tests (Gelman and Rubin, 1992) were calculated population parameters and for the log value of the posterior density. For a single parameter, the Gelman–Rubin test for all statistic estimates the potential scale reduction in



the estimated variance of the parameter. Running three separate chains of 2,000,000 iterations and starting from overdispersed initial values, the test statistics were less than 1.1 for all population parameters and the posterior log density, which is considered satisfactory in terms of convergence. The Monte

Carlo standard errors for the posterior means of the population parameters were estimated via the monotone initial sequence estimator of Geyer (Geyer, 1992). The errors lie between 2 ( $\mu$ ) and 7% ( $\sigma_\epsilon$ ) of the corresponding posterior standard deviations.