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Linking the seroresponse to infection to within-host heterogeneity in antibody production

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ABSTRACT

A recently published model for the serum antibody response to infection appeared well suited for use in statistical analyses of longitudinal serological data. The published model assumed exponential decay with fixed rates for pathogen and serum antibody kinetics, ignoring any within-host heterogeneity in the seroresponse. A bi-exponential model shows that there is rapid initial decay followed by a prolonged period of persistent low serum antibody concentrations. We propose a small modification of the decay model that greatly increases its flexibility by allowing for non-exponential antibody decay.

The modified model produces power functions that may be interpreted as a mixture of exponential decay curves, with a mixing distribution representing the relative contribution of many centres of antibody production to the serum antibody concentration.

Fitting the power function decay model to observed longitudinal data for pertussis shows improved goodness of fit compared to the exponential decay model, with estimates for the shape parameter ($r = 2.2$; 95% CI (1.7–2.8)) that differ from exponential shape ($r = 1$).

The power function decay model predicts more persistent antibody concentrations in the long term (symptomatic threshold reached >30 years after infection) which, when used in biomarker studies, will lead to lower estimates of seroconversion rates compared to exponential antibody decay.

1. Introduction

The kinetics of serum antibodies as observed in longitudinal studies of (symptomatically) infected subjects (Teunis et al., 2002; Versteegh et al., 2005; Strid et al., 2001, 2007) have been described by dynamic mathematical models that assume some form of interaction between pathogens and antibodies (Simonsen et al., 2009; Berbers et al., 2013): antigens from colonizing pathogens activate antibody production, and the circulating antibodies (directly or indirectly) inactivate pathogens and inhibit their growth.

For successful application of such models of the serum antibody response to infection, simplicity not only is enforced by the complex dynamics, but also can be an advantage: ideally, a within-host model provides an explicit mathematical expression for the time course of serum antibody concentrations, while preserving a biological meaning (Casadevall and Pirofski, 2001).

In a previous paper a within-host model was formulated (de Graaf et al., 2014), assuming that the serum antibody response to infection consists of two episodes: first a period of colonization where antibodies interact and inactivate pathogens, followed by a second period of serum antibody decay, where antibodies are slowly removed and their concentration in serum returns to zero.

Upon infection, a number of pathogens enters the host (and their antigens are detected by the host immune system). These pathogens start growing and an immune response is activated, resulting in growth of antibody producing cells, and activation of antibody production in these cells. This may result in antibody production that increases as a double exponential function with time (Asachenkov et al., 1994). Such explosive increase in antibody concentrations can only last for a brief period and for simplicity we remain with the assumption of exponential production of

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antibodies, that inactivate the newly grown pathogens, during the infection episode.

In acute (not chronic) infection in an immunocompetent host the immune response clears infection, and the result is removal of all pathogens. As soon as the pathogen concentration reaches zero, antigen associated stimulation of antibody production stops and decay becomes dominant. As a consequence the net concentration of serum antibodies decreases with time.

This simplified model of the serum antibody response appears flexible and can be easily implemented into multilevel frameworks using Markov chain Monte Carlo methods (de Graaf et al., 2014). Here we will show that a minor change in this model allows for quantitative assessment of within-host heterogeneity in antibody production rates. By assuming a continuous function for describing the variation in antibody kinetics among a great number of production sites, the model can be made even more flexible.

2. Multisite model for antibody production

Suppose there are multiple (K) compartments (hereafter called 'production sites') where antibodies are produced, each with their own kinetics, after which these antibodies are transferred into a single, shared compartment, where the antibodies may interact with antigens (pathogens) and from where antibodies are removed (turnover). For simplicity, we assume that the blood stream represents the shared compartment, where the antibody concentration is measured. The model formulated earlier (de Graaf et al., 2014) is then modified to

Infection/colonization episode	Waning immunity episode
$b'(t) = \mu_0 b(t) - \sum_{k=1}^{K} c_k y_k(t)$	$b(t) = 0$
$y_k'(t) = \mu_k^* y_k(t) - \gamma_0 y_k(t)$	$y_k'(t) = w_k^* y_k(t) - \gamma_0 y_k(t)$

(1)

In the above model, $b(t)$ is a measure for the antigen (pathogen) concentration and $y_k(t)$ is a measure for the serum antibody concentration at production site k ($k = 1, 2, \ldots, K$). Upon infection at time zero, $b(0)$ is set to some positive value b_0, the (effective) inoculated dose. At that time, the antibody concentration in the shared compartment $y(0)$ is at some positive baseline value y_0 resulting from a previous infection. Numbers of pathogens grow with an intrinsic rate μ_0, the inactivation of pathogens effected by antibodies from these multiple sources is represented by the weighted sum $\sum_k c_k y_k(t)$, c_k being a measure of the strength of the contribution from production site k ($c_k \geq 0, \forall_k$). During infection, the antibodies produced from any site k increase with rate μ_k^*. At any time antibodies are removed from the shared (blood) compartment. This turnover of antibodies is assumed to occur with a fixed rate γ_0, so that for site k the net rate of exponential increase is $\mu_k = \mu_k^* - \gamma_0$. During the infection episode with stimulated antibody production it is assumed that $\mu_k > 0$ for all production sites ($k = 1, b, \ldots, K$). Post infection, during the waning immunity episode (when $b(t) = 0$) antibodies are produced with rate w_k^*, and it is assumed that the net rate $-w_k = w_k^* - \gamma_0 < 0$ for all k compartments (any compartment with net rate >0 would result in long term increase in antibody concentrations). We can therefore write

Infection/colonization episode	Waning immunity episode
$b'(t) = \mu_0 b(t) - \sum_{k=1}^{K} c_k y_k(t)$	$b(t) = 0$
$y_k'(t) = \mu_k y_k(t)$	$y_k'(t) = -w_k y_k(t)$

(2)

Pathogen concentrations change as

$$b(t) = \begin{cases} b_0 e^{\mu_0 t} - \sum_{k=1}^{K} \frac{c_k y_{0,k} \left(e^{\mu_0 t} - e^{\mu_k t}\right)}{\mu_0 - \mu_k} & (t < t_1) \\ 0 & (t \geq t_1) \end{cases} \quad (3)$$

and the serum antibody concentration is the sum of contributions from all production sites.

Although an explicit expression cannot be obtained for the point in time t_1 when the pathogen concentration reaches zero, the antibody concentration peaks at that same time t_1, because at all production sites antibody concentrations increase monotonically prior to t_1 and decrease monotonically after t_1. If the peak antibody concentration for site k is $y_{1,k}$ then

$$y(t) = \sum_{k=1}^{K} y_k(t) = \begin{cases} \sum_{k=1}^{K} y_{0,k} e^{\mu_k t} & (t < t_1) \\ \sum_{k=1}^{K} y_{1,k} e^{-w_k (t - t_1)} & (t \geq t_1) \end{cases} \quad (4)$$

Before time t_1 antibodies are produced as a set of K exponentially increasing contributions to the concentration in serum. At t_1 the observable peak serum antibody concentration from Eq. (4) is

$$y(t_1) = \sum_{k=1}^{K} y_{1,k} = y_1 \quad (5)$$

After t_1 antibodies decay only, with different net decay rates w_k at each site. Contributions from different antibody production sites may vary during infection ($t < t_1$) and during the waning immunity episode ($t \geq t_1$) as the population of antibody producing (B) cells is not stationary (Amanna and Slifka, 2010).

2.1. Two sites

In the above model, heterogeneity in serum antibody production was represented by the set of K antibody production sites, each with their own contribution to the antibody concentration in serum, during infection and waning immunity. Although perhaps more realistic than the simple model in de Graaf et al. (2014), practical application in models for estimating seroconversion rates requires a simpler model with fewer parameters, so that there are no problems with parameter identification and estimation is possible.

During the infection phase, antibody increase tends to be dominated by the production sites with the highest rate of increase. Shortly after inoculation, antibody increase is expected to increase exponentially, even in the presence of heterogeneity in production. Conversely, after infection has cleared, production sites with relatively rapid decay cease to contribute early during the decay phase of the seroresponse, leaving those sites where decay is relatively slow for sustaining long term antibody presence in circulation. Heterogeneity in antibody production kinetics therefore is expected to cause detectable deviations from simple exponential kinetics only during the decay phase of the seroresponse.

Suppose there are two populations of antibody producing cells (Amanna and Slifka, 2010), each with their own discrete decay rate, α_0 and α_1, so that decay is bi-exponential

$$y(t > t_1) = (1 - \pi) e^{-\alpha_0 (t - t_1)} + \pi e^{-\alpha_1 (t - t_1)} \quad (6)$$

with proportion π indicating the relative contributions of either cell population to the circulating antibodies. If $\alpha_0 \gg \alpha_1$ then there is rapid initial decay with rate (approximately) α_0, followed by a slow decay phase with rate α_1. Existence of two different decay rates

has been attributed to the presence of two different populations of antibody producing cells (Slifka et al., 1995, 1998).

2.2. Many sites

Although there may be two different cell types involved in serum antibody production, this does not imply that their decay rates may be governed by only two fixed rates. We assume that among these two cell populations there is a large number of antibody production sites (Stromberg et al., 2013). Such sites may be regions in the antibody producing tissues, but could also represent individual antibody producing cells, or even intracellular compartments where antibody production takes place.

Eq. (4) describes the serum antibody concentration as a sum of contributions from sites with decay rate w_k and (initial) strength $y_{1,k}$. Without sacrificing generality the pairs $(y_{1,k}, w_k)$ may be arranged, by increasing w_k. The joint serum antibody concentration may then be approximated as

$$y(\tau) = \sum_{k=1}^{K} y_{1,k} e^{-w_k(\tau)} \approx \int_{x=0}^{\infty} y_1(x) e^{-w(x)\tau} dx \tag{7}$$

assuming many production sites ($K \to \infty$). The time from peak level $\tau = t - t_1$ and $y_1(x)$ is the contribution to y_1 dependent on some continuous variable $x \in (0, \infty)$, with $w(x)$ a strictly increasing continuous function describing how the decay rate depends on x. Thus, $w(x)$ is invertible and x can be expressed as a function of w.

With a change of variable

$$y(\tau) = \int_{w(0)}^{w(\infty)} y_1(x(w)) e^{-w\tau} \left(\frac{dw}{dx}\right)^{-1} dw \tag{8}$$

we may write

$$y(\tau) = y_1 \int_{w(0)}^{w(\infty)} \frac{y_1(x(w))}{y_1} \left(\frac{dw}{dx}\right)^{-1} e^{-w\tau} dw = y_1 \int_{w=0}^{\infty} f(w) e^{-w\tau} dw \tag{9}$$

where y_1 is the peak serum antibody concentration as defined in Eq. (5) and

$$f(w) = \frac{y(x(w))}{y_1} \left(\frac{dw}{dx}\right)^{-1} \tag{10}$$

so that $\int_0^\infty f(w) dw = 1$. Thus, $f(w)$ may be interpreted as a probability density, describing the distribution of antibody decay rates among production sites.

It may be noted that for the infection episode, a similar argument for heterogeneous antibody production may be developed. Nevertheless, collection of blood samples very early during infection is rare, so that there usually is little empirical information from serum antibody data for the shape of the antibody increase during infection. Because the production site with fastest exponential increase will rapidly dominate joint antibody production, we persist to assume the simplest possible case of exponential increase.

2.3. Heterogenous antibody decay

The Gamma distribution is a popular model for describing variation in rates (Thorne and Kishino, 2002; Huelsenbeck et al., 2001; Pyke and Thompson, 1986). If $f(w)$ is a gamma probability density (shape α, scale β) then

$$y(\tau > 0) = y_1 \left(1 + \beta\tau\right)^{-\alpha} \tag{11}$$

using the moment generating function of the gamma distribution. Antibody decay thus can be described as a power function, instead of exponential decay. Taking the derivative in Eq. (11)

$$y'(\tau) = -\alpha\beta y_1^{-1/\alpha} y(\tau)^{1+1/\alpha} \tag{12}$$

This motivates a slightly more general model, derived from de Graaf et al. (2014). Consider the following model:

$$\begin{array}{ll} \text{Infection/colonization episode} & \text{Waning immunity episode} \\ b'(t) = \mu_0 b(t) - c y(t) & b(t) = 0 \\ y'(t) = \mu y(t) & y'(t) = -\nu y(t)^r \end{array} \tag{13}$$

if $f(w)$ would be a gamma distribution, then $r = 1 + 1/\alpha$ and $\nu = \alpha\beta y_1^{-1/\alpha}$.

The left part of the model, describing the dynamics of pathogen concentration $b(t)$ and serum antibody concentration $y(t)$ during the infection episode, remains identical to the published model (de Graaf et al., 2014).

However, addition of only a single parameter to the model for the waning immunity episode profoundly changes antibody decay. From $t = t_1$ antibody decay proceeds as

$$y(t > t_1) = y_1 (1 + (r-1) y_1^{r-1} \nu (t - t_1))^{-1/(r-1)} \tag{14}$$

When the shape parameter $r > 1$, initial decay is more rapid than exponential, followed by a period of slower than exponential decay. Note that for the limit $r \downarrow 1$ (i.e. the limit to exponential decay of the antibody concentration) $\alpha \to \infty$ and the function $f(w) \to \delta(w - \nu)$. Here δ refers to the Dirac delta function. Therefore, when $r \downarrow 1$, $w = \nu$ with probability one. Also note that the peak concentration y_1 depends on the scale parameter β: the function $f(w)$ in Eq. (9) defined the relative contributions of sites to the serum antibody concentration in the shared compartment.

In summary the following response is obtained, for pathogens $b(t)$ and for antibodies $y(t)$

$$b(t) = \begin{cases} t \le t_1: & b_0 e^{\mu_0 t} - \dfrac{c y_0 \left(e^{\mu t} - e^{\mu_0 t}\right)}{\mu - \mu_0} \\ t > t_1: & 0 \end{cases}$$

$$y(t) = \begin{cases} t \le t_1: & y_0 e^{\mu t} \\ t > t_1: & y_1 (1 + (r-1) y_1^{r-1} \nu (t - t_1))^{-\dfrac{1}{r-1}} \end{cases} \tag{15}$$

It follows (de Graaf et al., 2014) that

$$t_1 = \frac{1}{\mu - \mu_0} \log\left(1 + \frac{(\mu - \mu_0) b_0}{c y_0}\right) \tag{16}$$

2.4. Parameter estimation

Although all parameters in the model in Eqs. (15) or (6) may have a biological meaning, they cannot all be estimated when only serum antibody data are available.

The serum antibody response to infection is completely characterized by the baseline level y_0, the peak level y_1, the time to peak t_1, and the decay parameters ν and r. Given the above parameters, the rate of antibody increase during infection may be calculated

$$\mu = \frac{1}{t_1} \log\left(\frac{y_1}{y_0}\right) \tag{17}$$

The reduced parameter $c_0 = c/b_0$ (de Graaf et al., 2014) and the pathogen growth rate μ_0 cannot be estimated, only their relation can be expressed as

$$c_0 = \frac{\mu - \mu_0}{y_0(e^{(\mu-\mu_0)t_1} - 1)} \quad (18)$$

When the data contain little information on the shape of the response during infection, estimating y_1 and t_1 has the advantage that these two parameters may be specified as a plausible range, as prior information in the model fitting procedure. The pertussis data used here and in de Graaf et al. (2014) do not require such informed priors because they include observations during the infection episode. In other studies capturing such early seroresponse data may not be possible (Simonsen et al., 2009; Teunis et al., 2012).

3. Results: application of the within host model

The code for fitting the two-phase seroresponse model (de Graaf et al., 2014) to serum antibody data has been modified to include alternative decay functions, either bi-exponential or power function decay. Thus modified, the seroresponse model can now be used to analyze serum antibody data for natural infection by *Bordetella pertussis*. The model was implemented in JAGS (Plummer, 2003). Details of parameter estimation and prediction of antibody concentrations as given in de Graaf et al. (2014) remain the same, except for the addition of the parameters describing non-exponential decay (π, α_1 and α_2, or ν and r). See Appendix for more details.

3.1. Changes in predicted antibody responses

Both non-loglinear decay models result in improved fit, as judged by the smaller residuals compared to the simple exponential decay model, Fig. 1. Parameter estimates for the updated seroresponse models are given in Table 1. Predicted responses from the updated model can be compared with previous output (Fig. 2), showing that both models provide a better fit to the early stages of serum antibody decay. Initial rapid decay within the first year post-infection is followed by an extended period of slower decay.

Also, the predicted intervals are narrower for the power function model, more closely following the observed antibody concentrations (Fig. 2c). It is interesting to see that when a third exponential decay function is added, the predicted intervals tend towards those of the power function decay model (Appendix, Fig. A3).

In addition to the four characteristic features of the seroresponse: baseline antibody concentration, time to peak, peak antibody concentration, and rate of antibody decay, the power function model adds a fifth parameter: the shape parameter of antibody decay. As Table 1 shows, the shape parameter differs from exponential ($r = 1$), it is close to 2.

3.2. Heterogeneity in serum antibody decay

From the estimated parameters for the pertussis serum antibody reponse, the distribution of decay rates among antibody production sites may be calculated.

This can be done for the exponential model, simply as a density graph of the posterior sample for the decay rate α. This illustrates (posterior) uncertainty in α (Fig. 3a). Similarly, using the posterior samples of the two decay rates α_0 and α_1 in the bi-exponential model, and weighting these by the proportion ($1 - \pi$ and π, respectively), the uncertainty in the decay rate for the bi-exponential model can be shown (Fig. 3b). For the power function model, the variation in decay rate among antibody producing sites is represented by the gamma distribution defined by (scale) ν and (shape) r (Fig. 3c).

These distributions are highly skewed, indicating strong heterogeneity, so that graphing the $_{10}$log of the decay rates more clearly shows the shape of its distribution (Fig. 3d–f). The decay rate appears to vary over four orders of magnitude, ranging from 0.5 to 0.0005 day^{-1}. Note that in Fig. 3c and f shading density represents

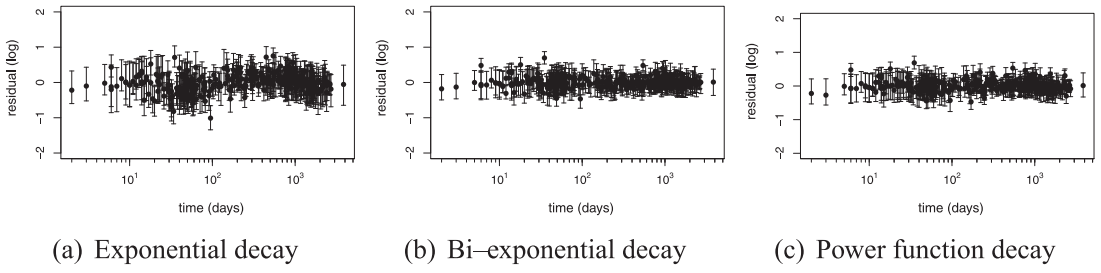


Fig. 1. Residuals for the three models for the serum antibody response.

Table 1
Estimated parameter values for the updated seroresponse model: baseline (pre-infection) antibody concentration y_0; peak antibody concentration y_1; time to peak t_1. For bi-exponential decay: rapid initial decay rate α_0; slow final decay rate α_1; proportion parameter π. For power function decay: decay rate parameter ν; shape parameter r.

	Mean	Median	95% predictive interval	Units
Bi-exponential decay				
y_0	2.03	1.99	$1.28–3.02 \times 10^{-1}$	IU/ml
y_1	1.65	0.86	$0.09–8.12 \times 10^{3}$	IU/ml
t_1	3.89	3.07	$0.82–12.33 \times 10^{1}$	days
α_0	2.42	1.65	$0.35–9.34 \times 10^{-2}$	1/days
α_1	4.93	3.73	$0.67–16.12 \times 10^{-4}$	1/days
π	7.50	7.15	$3.75–12.84 \times 10^{-2}$	
Power function decay				
y_0	1.87	1.83	$1.08–2.94 \times 10^{-1}$	IU/ml
y_1	7.76	1.23	$0.03–50.92 \times 10^{3}$	IU/ml
t_1	3.69	3.14	$0.96–9.49 \times 10^{1}$	days
ν	1.49	0.92	$0.12–6.18 \times 10^{-5}$	1/days
r	2.19	2.16	$1.74–2.82 \times 10^{0}$	

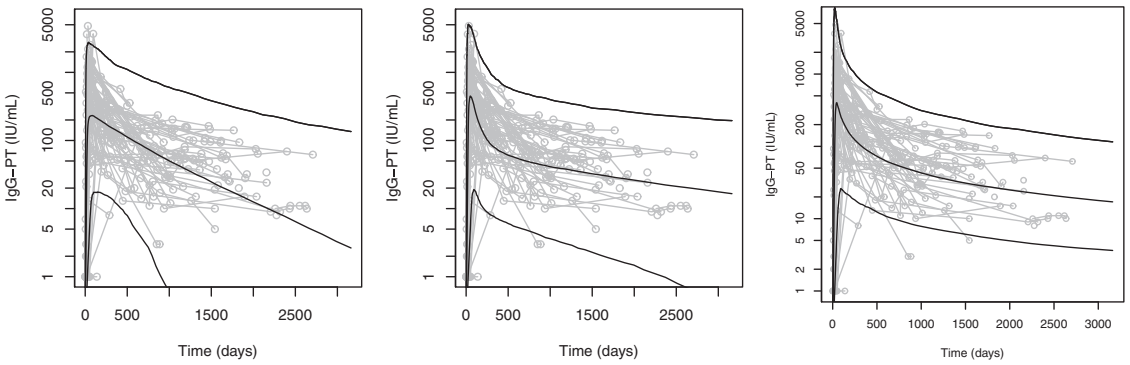


Fig. 2. Nonlinear decay of IgG-PT antibody concentrations in serum of symptomatic patients (Versteegh et al., 2005). (a) Exponential antibody decay (de Graaf et al., 2014); (b) bi-exponential decay; (c) power function decay. All graphs show contours of predicted IgG-PT concentrations ($_{10}$log-scale), median and 95% predictive interval. Also shown are observed data: repeated observations of subjects are connected.

quantiles, with median in black and lighter shades indicating lower and higher percentiles of the posterior density.

3.3. *Antibody persistence*

Having identified a persistent fraction of antibody production sites, it is also of interest to look at persistence of antibodies in serum (Fig. 4). When using the power function decay model, 20% of infected cases have antibody concentrations below 100 IU/ml immediately following infection, 80% of subjects still have concentrations above 10 IU/ml 10 years later, and 30 years post-infection 80% would still be above 5 IU/ml, close to the symptomatic threshold estimated in de Graaf et al. (2014). Assuming, of course, that there are no re-infections during that period.

4. Discussion

The addition of only a single parameter changes the seroresponse model of de Graaf et al. (2014) so that an initial period of rapid decay may be followed by a prolonged period with slow decay, possibly representing immunological memory. The method used here therefore achieves responses similar (but not identical) to bi-exponential models, that assume two discrete exponential decay phases, with one additional parameter instead of two (that is, a second decay rate and a mixing parameter). Arguably, a distribution of (many different) decay rates is a more realistic description of the heterogeneity resulting from within-host variation in antibody production than occurrence of exactly two discrete decay rates. Such a discrete class decay model may not be robust. When fitted to serum antibody data that would imply simple exponential decay,

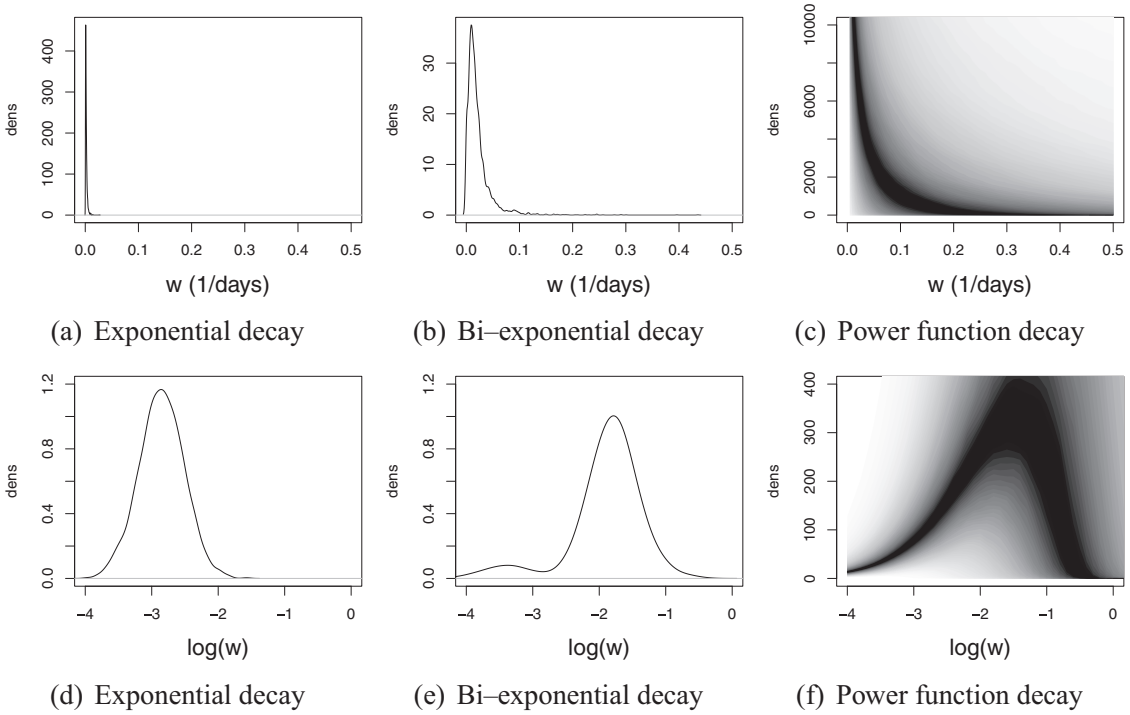
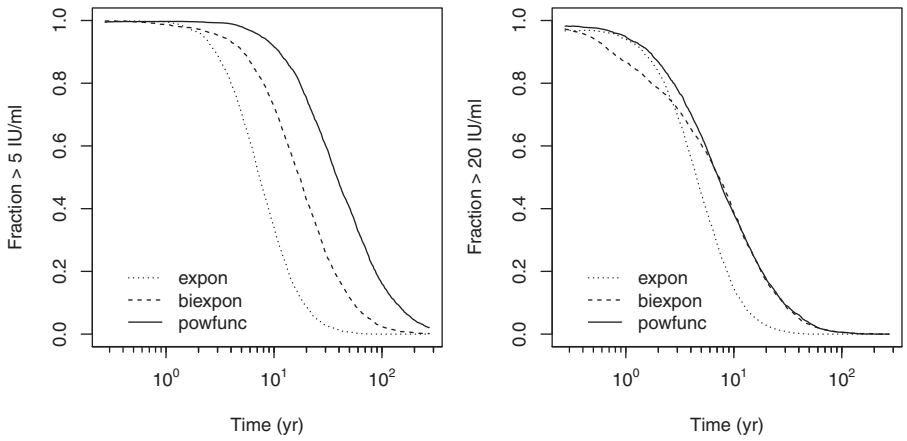


Fig. 3. Distribution of serum antibody decay rates w estimated from observed IgG-PT concentrations in symptomatic patients (Versteegh et al., 2005). (a) Posterior density (uncertainty) of the fixed decay rate ($w = \alpha$) in the exponential decay model; (b) posterior density (uncertainty) of decay rates in the bi-exponential model ($w = (1-\pi)\alpha_0 + \pi\alpha_1$); (c) posterior density of the distribution of w in the power function model (shading illustrates uncertainty). (d), (e) and (f) show the same for $_{10}\log(w)$.



(a) Protection at 5 IU/ml (b) Protection at 20 IU/ml

Fig. 4. Persistence of IgG-PT serum antibodies estimated by the exponential (expon), the bi-exponential (biexpon) and the power function (powfunc) decay models. Fraction IgG-PT concentrations above a protective threshold level of 5 or 20, IU/ml, versus time following (natural) infection.

the parameters defining the additional decay rate cannot be identified. For such data the power function model is well behaved. As the shape parameter r approaches 1 the seroresponse curve approaches exponential decay. The increased flexibility makes this model suitable for fitting to (longitudinal) serum antibody data.

Nevertheless, the power function decay curves produced by the model proposed here can be interpreted as a mixture of exponential decay curves, with a mixing distribution that may be estimated. Applying this model to longitudinal serum antibody data therefore allows estimation of both within-host and between host heterogeneity in seroresponses.

It seems attractive to model non-exponential decay as a mixture of simple exponential decay curves, with different rate constants. Note must be taken however, that the serum antibody response results from the host immune response, as one observable output of a complex regulated signalling network (Thakar et al., 2007).

Production of (serum) antibodies may be driven by several different mechanisms that sequentially activate and deactivate (Traggiai et al., 2003), resulting in complex decay curves that deviate from simple exponential shapes.

It must be noted that during the infection episode, heterogeneity in antibody production must be present as well as during the post-infection episode. Although in all likelihood, deviations from exponential increase in antibody concentrations cannot be detected, the interaction term describing pathogen inactivation $-c_k y_k(t)$ in Eq. (2) may cause pathogen decay different from the simple model in Eq. (15), because of the weighting factors c_k. Since there currently is no means of characterizing such heterogeneity we have chosen to not include it and keep the simple model proposed by de Graaf et al. (2014). At least essential properties of rapid growth followed by rapid die-off of pathogens are thus preserved. A potentially interesting alternative could be to assume that the post-infection distribution of decay rates is also valid for the distribution of variation in antibody production during infection, but with a different scale factor, causing net production instead of decay.

The seroresponse to natural infection with *Bordetella pertussis* decays non-exponentially, with an estimated shape parameter slightly above 2. This implies strong heterogeneity in post-infection antibody production: a small fraction of antibody producing sites (cells) tends to maintain production for decades after a boosting event. Fig. 4 shows that allowing for power function decay leads to much slower decrease in antibody concentrations, than obtained with exponential decay models. This slowdown in antibody decay is quite influential when estimating the duration of protection from serum antibody levels, as illustrated in Fig. 4. The tailing off of the decay curve means that low antibody levels are persistent, for long periods. And, as the present study has argued, these persistent levels may be interpreted as a fraction of involved sites keeping up antibody production for a long period.

The long term presence of low antibody concentrations, long after infection, is also relevant for biomarker applications of serum antibodies (Teunis et al., 2012). Here the antibody concentrations in a cross-sectional population sample are used to estimate the rate with which seroconversions occur: the higher the seroconversion (infection) rate, the more frequent high antibody concentrations are detected. More persistent antibodies lead to lower estimates of the seroconversion rate, as any low concentration in the cross-sectional sample corresponds to a longer time since seroconversion, compared to the estimate from the exponential decay model.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2016.04.001.

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