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Early Waning of Maternal Measles Antibodies in the Era of Measles Elimination: a longitudinal study

Running title: Maternal Measles Antibodies

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What this paper adds box

- Infants of women vaccinated against measles receive less maternal antibodies and are therefore shorter protected compared to infants of women with naturally acquired immunity, according to previous studies. Is the amount of maternal antibodies still sufficient to protect infants until the first vaccination dose is administered, in the era of changing measles epidemiology with increasing vaccination coverages and low endemicity of measles?
- The results of the present longitudinal study with 7 different time-points of antibody measurement in infants until the age of 1 year, show an increasing gap of susceptibility between the loss of maternal antibodies and the administration of a first vaccine dose, not only in infants of vaccinated women but also in infants of women with naturally acquired immunity. Lowering the age of first vaccination, however, could jeopardize the immune response to the currently available vaccine. This study certainly underlines the importance of timeliness of administration of a first measles containing vaccine at 12 months of age and supports the vaccination of infants under the age of 1 year in case of measles outbreaks or travelling or migrating infants to endemic areas.

Word count: 3100 words for the manuscript, 300 words for the abstract.

Abstract

Objective

To investigate the duration of the presence of maternal antibodies to measles in infants. The amount and kinetics of maternal antibodies in infants of vaccinated women are compared to infants of naturally immune women.

Design

Prospective study conducted between May 2006 and November 2008.

Setting

Recruitment among pregnant women attending 5 hospitals in the Province of Antwerp, Belgium.

Participants

Of 221 women recruited, 207 healthy woman–infant pairs were included. Women were allocated in a vaccinated group (N=87) and a naturally immune group (N=120) according to vaccination documents and anamnesis.

Main outcome measure

Measles IgG antibodies measured by ELISA (Enzygnost® Dade Behring). Blood samples were taken at 7 time points (cord-month1-month3-month6-month9-month12). Linear mixed models were used to model maternal antibody decay in infants over time.

Results

Vaccinated women had significantly less IgG antibodies (GMT 779 mIU/mL(95%CI 581-1045) compared to naturally immune women (GMT 2687 mIU/mL(95%CI 2126-3373) ($p<0.0001$). Maternal values were highly correlated with neonatal values (rho=0.93 at birth). Infants of vaccinated women had significantly lower antibody levels compared to infants of naturally immune women ($p<0.0001$ at all ages over the follow up period). Presence of maternal antibodies endured 2.61 months on average; 3.78 months for infants of naturally infected women and 0.97 months for infants of vaccinated women. At 6 months of age, over 99% of infants of vaccinated women and 95% of infants of naturally immune women had lost maternal antibodies according to the model.

Conclusions

The present study describes a very early susceptibility to measles in both infants of vaccinated women and women with naturally acquired immunity. This finding is of importance in view of recent outbreaks. Moreover, it is an argument for timeliness of the first dose of a measles vaccine and vaccination of travelling or migrating children under the age of 1 year.

Key words: measles, vaccination, maternal antibodies

Footnote page

1/ Contributors: EL and PVD were responsible for the conception and design of the study. VH, EL and MI performed the laboratory tests. EL, NH and MA undertook the analysis and interpretation of the data. EL, NH and PVD drafted the manuscript and completed critical revisions. Final approval of manuscript lay with all authors. EL acts as guarantor.

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3/ Ethical approval: Study protocol and documents were reviewed and approved by the ethics committee at each participating institution, the leading ethics committee is based at the University Hospital in Antwerp (22/02/2006).

4/ Data sharing: No additional data available.

5/ Competing interests: all authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that none of the authors have financial interests that may be relevant to the submitted work. The corresponding author certifies that all authors have agreed to all the content in the manuscript, including the data as presented.

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Introduction

Reduction of measles related mortality is one of the World Health Organization goals. Measles vaccination is administered globally with good results: between 2000 and 2007, measles deaths fell by 74% worldwide [1]. However, measles is re-emerging in low incidence countries with 2 dose vaccination programmes in place, as demonstrated by recent outbreaks [2].

Primary protection at birth against infectious diseases is provided mainly by maternal antibodies [3]. These antibodies could hamper humoral antibody response of the infant to vaccination [4-6]. Therefore, the timing of vaccination should take their presence into consideration. Several factors determine the amount of maternal antibodies in young infants. Gestational age defines placental transfer: preterm neonates receive significantly less antibodies [7]. Additionally the coverage of universal immunization programs influences the amount of maternal antibodies: a higher coverage lowers the probability of natural boosting. Furthermore, the mean age at first pregnancy is increasing and therefore the time since maternal measles vaccination. Finally, the rate of decay of maternal antibodies after birth defines the duration in infants.

International differences in the prevalence of maternal measles antibodies in infants have been described [8 9]. Results of former studies show lower starting levels at birth and faster decay of antibodies in infants of vaccinated women [8]. Since many countries implement universal measles infant immunization at the age of 12 to 15 months, the possibly increasing gap of susceptibility due to the early loss of maternal antibodies is increasingly of concern. In addition, several studies report a considerable delay in administration of a first vaccine dose in infants, which is increasing the gap even more [10 11]. In Flanders, Belgium, measles vaccination is recommended since 1984 within the universal vaccination program at the age of 15 months. Since 2002, this first dose is administered at 12 months [12]. A second dose at the age of 11-12 years is recommended since 1994 [13].

The objective of the present study is to investigate the duration of the presence of maternal antibodies to measles in infants based on 7 different time points, for the first time in a longitudinal study. The amount and kinetics of maternal antibodies in the offspring of

vaccinated women are compared to the offspring of women with naturally acquired immunity. Furthermore the used modelling system can for the first time predict the time to loss of maternal antibodies in infants based on the maternal antibody titer.

Methods

- *Study design*

A prospective study was conducted in accordance with the Helsinki Declaration and procedures established by Belgian law. The study was approved by the ethics committee of the University hospital of Antwerp, Belgium. The main aim of the study was to investigate differences in maternal antibodies in infants from vaccinated women and naturally infected women. According to a sample size calculation, at least 200 participants were needed to detect a 10% difference in GMT between both groups of infants with a probability of 99%.

Healthy pregnant women and their healthy offspring were included, starting April 2006 and follow-up lasted until November 2008. Exclusion criteria were impaired immunology in mother or child, administration of immunoglobulins or blood products during the study period, preterm delivery (<36 weeks) and low birth weight (<2400 g). Inclusion criteria were age 18-40 years and residence in Belgium for the duration of the study. A questionnaire was completed on demographics, validated vaccination history and medical history. Growth parameters, breastfeeding, day-care attendance, immunization data, and medical histories for all household members were registered at each visit.

Women were classified in two groups. One group was vaccinated during infancy (VACC) and for each woman vaccination documents were sought. The other group obtained natural immunity to measles (NAT). Natural infection was presumed through anamnesis, also anamnesis of the woman's parents. Women of foreign origin were only included if they had written proof of vaccination or anamnesis of disease. Informed consent was obtained from all participants and from both parents of the participating children.

Venous whole blood was collected during pregnancy (week 36, 10cc), at birth (10 cc of cord blood), in all infants (2cc) at month 1 (27-34 days), month 3 (84-99 days) and month 12 (358-372 days) and randomly at either month 6 (175-189 days) or month 9 (267-282 days). All samples except for cord blood, were collected during home visits. Samples were centrifuged at 2000 rpm within 8 hours after sampling and stored at -20°C.

- *Determination of antibodies*

Measles quantitative measurement of IgG was analyzed with ELISA Enzygnost® Anti-Measles IgG (Dade Behring, Germany). The analysis was performed at the Division of Virology, Scientific Institute of Public Health and the University Hospital of Antwerp. The assay was calibrated against the international reference preparation of measles antigen, and results are presented in milli-International Units per milliliter. If corrected Optical Density (OD) was >0.2, the sample was considered positive, if corrected OD was <0.1, the sample was negative. Between OD >0.1 and <0.2 the sample was inconclusive. Quantitative results were calculated using kit dependent parameters. If corrected OD<0.1, quantitative results could not be trusted. The estimated 'protective' cut-off value was set on 300mIU/mL based on the optical density measurements. A protective cut-off value for measles is not known using ELISA. The same test is used at the Institute of Public Health in Belgium for surveillance purposes, making comparison with other national data possible.

- *Statistical analyses*

Statistical methodology consisted of two analyses.

1) The first analysis modelled the maternal antibody decay in infants with time, taking heterogeneity among, and homogeneity within infants into account. A linear mixed model was used to relate the log maternal antibody level of the infant over time and other potentially influential factors. The Akaike information criterion was used to select the appropriate model using a forward selection procedure up to the third order for all factors. This allows for the estimation of individual-specific profiles over time [14]. Missing values are taken into account by assuming they are missing at random ('direct likelihood' approach)[14]. We used a log-transformation of the antibody level: log(AB+1) to symmetrise the response distribution. The validity of the normality assumption was assessed using the Kolmogorov-Smirnov test (p-value 0.14). P values were considered significant if <0.01.

2) Based on the antibody decay model from 1) and assuming immunity was lost whenever the antibody level < 300mIU/mL, we could estimate the individual time to loss of immunity which was related to the log antibody level of the mother using normal regression.

Results

1. Population

221 women and their 226 infants were included. Women who received vaccination and experienced natural infection, as well as women who had neither vaccination nor natural infection, were excluded with their infants from the analysis (N=7). Woman-child pairs of which the infant(s) met exclusion criteria, were also excluded (N=9). In the end, data of 207 women and their 210 infants were analysed. 120 women belonged to the naturally immune group, 87 were vaccinated. All vaccinated women received a single dose of measles vaccine during childhood. Their mean age at immunization was 3.3 years (median 1.6 y). 3 foreign women were included, 2 originated from the Netherlands and 1 from the UK.

13% of the infants' samples were missed at different time points due to difficult bleeding.

Table 1 shows general characteristics of both women and their infants. 76% (158/207) of all participating women was expecting a first child, 16% a second child (33/207) and 5.8% a third child (12/207).

	ALL	Vaccinated women (VACC)	Naturally immune women (NAT)	Difference VACC - NAT p-value
Number of women	207	87	120	
Mean age (years) women (min-max)	30 (23-41)	28 (23-35)	32 (24-41)	0.267*
Primiparous	76%	85%	70%	0.018*
Caesarian section	20%	25%	16%	0.104*
Number of infants	210	87	123	
Girls/Boys	113/97	45/42	68/55	0.79*
Mean gestational age (weeks-days)	39w4d	39w4d	39w4d	0.56**
Mean birth weight (grams)	3365	3407	3335	0.33**
Mean duration breastfeeding (total number of children receiving breastfeeding)	19.5 weeks	20.0 weeks (N=71)	19.1 weeks (N=107)	0.76**
Day-care attendance	76%	80%	73%	0.9*

*Table 1: general characteristics of women and infants with significant differences between vaccinated women and naturally immune women indicated by p value * Chi square (2*2) test, ** student's t-test*

2. Serological results

Overall GMT (Geometric Mean Titer) of IgG at week 36 of pregnancy was 1593 mIU/mL (95%CI 1306-1944); 8% of NAT and 26% of VACC women did not reach the cut-off value with the used ELISA test (IgG≤300mIU/mL). GMT in women differed significantly between vaccinated women (779 mIU/mL(95%CI 581-1045)) and naturally immune women (2687 IU/mL(95% CI 2126-3373)) (p<0.001). Maternal values were highly associated with for neonatal values at birth (correlation=0.93): infants of vaccinated women had significantly less antibodies at birth compared to infants of naturally infected women (p<0.001) (Table 2).

	GMT in mIU/ml (95% CI) (number of positive samples*/ total number of tested samples)			
Time point	ALL	Vaccinated women (VACC)	Naturally immune women (NAT)	Difference VACC-NAT p-value**
women at week 36 of pregnancy	1593 (1306 to 1944) (181/214)	779 (581 to 1045) (67/90)	2687 (2126 to 3373) (114/124)	<0.001***
cord	1369 (1106 to 1695) (152/189)	698 (521 to 935) (55/79)	2221 (1702 to 2899) (97/110)	<0.001***
month 1	928 (735 to 1173) (122/160)	493 (364 to 668) (41/67)	1463 (1076 to 1989) (81/93)	<0.001***
month 3	304 (238 to 387) (72/158)	179 (132 to 243) (21/73)	477 (340 to 670) (51/85)	0.003***
month 6	79 (58 to 108) (11/72)	37 (27 to 50) (1/31)	142 (94 to 215) (10/41)	0.01***
month 9	15 (12 to 18) (0/89)	12 (8 to 16) (0/44)	19 (14 to 24) (0/45)	0.03***
month 12	11 (6 to 9) (0/156)	6 (4 to 8) (0/68)	9 (7 to 11) (0/88)	0.04***

*Table 2: GMT (95%CI)of IgG against measles and proportion of positive samples at each time-point for ALL, naturally infected and vaccinated women and infants; difference between both populations expressed with p value * positive sample ≥300 mIU/mL ,** difference in GMT, *** student's t-test*

At the age of 3 months, 21/73 available samples (30%) of infants of vaccinated women were still considered positive compared to 51/85 samples (58%) of infants of naturally immune women. At the age of 6 months, 11/72 (15%) samples were positive, all but one child from naturally immune mothers. At month 9 and at month 12, no positive samples were left in either group. GMT still differed significantly with increasing age between both groups of infants. However, interpretation should be cautious since the later GMT are <300 mIU/mL for both groups and not reproducible with the ELISA test.

3. Model based analysis

The final linear mixed model included all interactions of time and log-antibody level of the mother. Breastfeeding, parity, gestational age, birth weight, educational level, day-care attendance and Caesarean section did not have a significant impact. Although mothers were clustered within hospitals, no significant cluster effect was found (Testing for a hospital-specific random effect was done using a likelihood ratio test and resulted in p-value 0.0845). The resulting profiles are depicted in Figure 1.

Figure 1: Fitted individual profiles for the log-antibody level "log(AL+1)" decay based on the linear mixed model (gray lines): all data (left panel), infants from naturally immune women(middle panel) and infants from vaccinated women(right panel). The blue line indicates the cut-off at 300 mIU/mL. The black curve is the predicted mean curve in each of the groups with observed means at birth, 1, 3, 6, 9 and 12 months in blue dots.

The rate of decay of maternal antibodies can be calculated from the fitted model and was on average steeper in infants of naturally immune women as compared to in infants of vaccinated women (derivations not shown). This is implicitly reflected in Figure 2 where the proportion immune for the infants of naturally immune women starts of higher and finally reaches the proportion immune for the infants of vaccinated women after 7 months. According to the model, the overall median time to immunity loss is 2.61 months. Based on these predicted profiles, the time to decrease below the cut-off value of the protective amount of antibodies, can be estimated. Figure 2 shows the proportion of infants immune to measles against the time to passive acquired immunity loss. Median time to immunity loss equals 3.78 months for infants of naturally immune women and 0.97months for infants of vaccinated women. At 6 months of age, more than 99% and 95% have lost immunity in the vaccinated and naturally immune group, respectively. Note that negative time to immunity loss corresponds to infants susceptible at birth.

Figure 2: the proportion immune (y axis) of infants of vaccinated women (dashed line)) and infants of naturally immune women (solid line) as a function of the time to immunity loss in months (x axis). The blue line is 5% of the population still immune.

When regressing the estimated time to immunity-loss to the log-antibody level of the mother, R^2 equals 0.97 indicating a very good predictive value. Figure 3 shows a regression plot with 95% prediction intervals (PI) for the time to loss of immunity for a child, given a certain antibody level in the mother. The lower part is the log-antibody level density for naturally immune and vaccinated women. For example: the modus of the log(IgG)of a VACC woman = 6.2. Looking at the regression plot, her child will lose maternal antibodies between 0 (lower line 95%PI) and 2 months of age (upper line 95%PI). For a NAT woman with modus log(IgG)= 8, her child will lose maternal antibodies between 3 and 5 months of age.

Figure 3: Regression fit to predicted time to immunity loss (upper part) with 95% prediction intervals. Density plots (lower part) of the log antibody level at week 36 of pregnancy for

vaccinated (blue) and naturally immune women (black). Note that the x-axis holds for both upper and lower panel and represents the log-transformation of the mother's antibody level at week 36.

Discussion

Principal findings of the study

Starting levels of maternal antibodies in infants depend highly on the level of antibodies in the mother and on her vaccination status. Infants of vaccinated women start with significantly less antibodies compared to infants of naturally immune women. The rate of decay of maternal antibodies in infants of naturally immune women is slightly steeper (fig 2). Median time to loss of immunity is 2.61 months: 0.97 months for infants of vaccinated women and 3.78 months for infants of naturally immune women. We prefer to use the median time to immunity loss instead of the mean time to immunity loss, since ¼ of the infants of vaccinated women started with antibody titres under the used cut-off value at birth, which influences the mean. There is no significant impact from breastfeeding, parity, birth weight, educational level, Caesarean section or day care attendance on the duration of maternal antibodies.

Strengths and weaknesses of the study

The combination of a comprehensive prospective study and up-to-date statistical methodology is innovative. The used linear mixed model offers the possibility to predict the time to passive immunity loss in a child starting from the maternal anti-measles antibody titer. Taking into account the confidence intervals on the model's prediction, 5-15% will be the remaining protected portion at 6 months of age, which correlates with the serological findings. Based on this study we cannot make a general statement about the prediction of the time to immunity loss using the maternal level at 36 weeks for any population. However, we do believe that this study could play a pivotal role to consider individual-based vaccination programs.

A few shortcomings can be recognised. The cut-off value of the used ELISA test, chosen according to the optical density value, is questionable. However, even if this cut-off value is overestimated and values below are still in the protective range, by the age of 6 months all

antibodies have disappeared. Furthermore the used ELISA is commonly used in practice and referred to in literature [12 15-17].

We can question the representative nature of the study population. However, compared to sero-prevalence data from 2006 in Flanders [18], no significant difference was found in GMT against measles between the female population at childbearing age in the Province of Antwerp (1782mIU/mL) and our study population (p=0.1).

Comparison with other studies

The results of the present study confirm data from literature but report a shortening presence of maternal antibodies. We discussed the relevant publications in a previous review article [8]. Comparison between publications is difficult due to different laboratory tests and different age categories used. In literature the mother's year of birth is mostly used as a proxy for her vaccination status. In the present study the chance for misclassification is reduced to a minimum. Publications from the 1980s showed that women vaccinated with a live attenuated measles vaccine had lower amounts of antibodies and passed on shorter term protection against measles compared to naturally infected women [19 20]. Pabst [21] conducted a longitudinal study in the USA (1992) and found that >90% of infants of VACC women were susceptible to measles by the age of 7 months versus 65% of infants of NAT women. He found a steeper slope of antibodies in infants of naturally infected women. Brugha et al (UK, 1996) [22] found significantly more infants of VACC women between 5-7 months of age with low maternal antibody levels. In a study of De Serres et al (Canada, 1997), ½ of infants of NAT women were still protected at 8 months compared to 15% of infants of VACC women [23]. Klinge et al reported in 2000 that protection in Germany was shortening over time, leaving almost no infants protected at the age of 9 months [24]. In Switzerland in 2004, 19% of infants still had positive titers after 6-9 months [25]. In a recent French study [26], however, only 10% of each group was still protected at month 6. More importantly, no significant difference was found according to the mother's year of birth, nor according to the mother's reported history of measles.

Conclusions and policy implications

The early loss of maternal antibodies in infants has several implications. Recommendations have been made for vaccination at the age of 9 months in epidemic situations, with a second dose at 15-24 months [26 27]. Early vaccination of infants in case of an outbreak can be defended based on the present study although humoral immune response to measles vaccination has been shown to be less efficient due to immunological immaturity [24]. However, T-cell responses are sufficiently elicited to prime humoral response to a second dose [28-30]. If future studies could further demonstrate that measles vaccines can be offered at an earlier age (e.g. at 9 months or even earlier), policy makers could consider, given the present data, to move up the routine measles vaccination programme. For the moment, vaccination at a young age should be considered in case of a situation of early exposure (outbreak situation, contact with siblings with measles etc…). Moreover, the present results can help decision making on individual travelling or migrating infants to endemic areas and support ongoing research for early vaccination. In the personal contact with measles cases, avoiding contact between the case and unvaccinated infants is preferable but yet not feasible.

The use of newly developed vaccines, e.g. a DNA vaccine that induce immune responses at a very young age, could offer the opportunity of vaccinating very young infants more efficiently [8]. Additionally these vaccines would have a beneficial effect on immunologic memory [3]. The present data underline the need for further research on early vaccine administration.

Reduction in measles incidence and epidemics could be achieved with timely vaccination [31, 32]. Several studies have shown recently that important percentages of children are immunized with delay [10 11 33 34]. A US study reported 11% of children to be delayed for measles vaccination for 6-8 months during the first 24 months of life [33]. Risk of disease due to delay depends on several factors: disease circulation, transmissibility, likelihood of importation, severity of outcome [31]. The data of the current study can only strengthen the need for timely administration of a first Measles Containing Vaccine dose.

Boosting women at child-bearing age could be a solution for the low amount of maternal antibodies. However, a second vaccine dose consolidates immunity but does not augment

the titer of antibodies over the long term. As a consequence, the amount of maternal antibodies transferred to infants will not be influenced substantially [35,36] [37].

Vaccination of pregnant women is a last option. This ethically burdened discussion goes beyond the scope of this paper.

To conclude, decision makers and clinicians should be aware of the early loss of maternal protection and each country should monitor its own situation. Clinical recognition of measles cases in young infants is of importance for surveillance of the disease.

The results can help decision making on individual travelling or migrating infants to endemic areas and support ongoing research for early vaccination. Most importantly we confirm the extreme importance of timely administration of the first measles vaccination dose.

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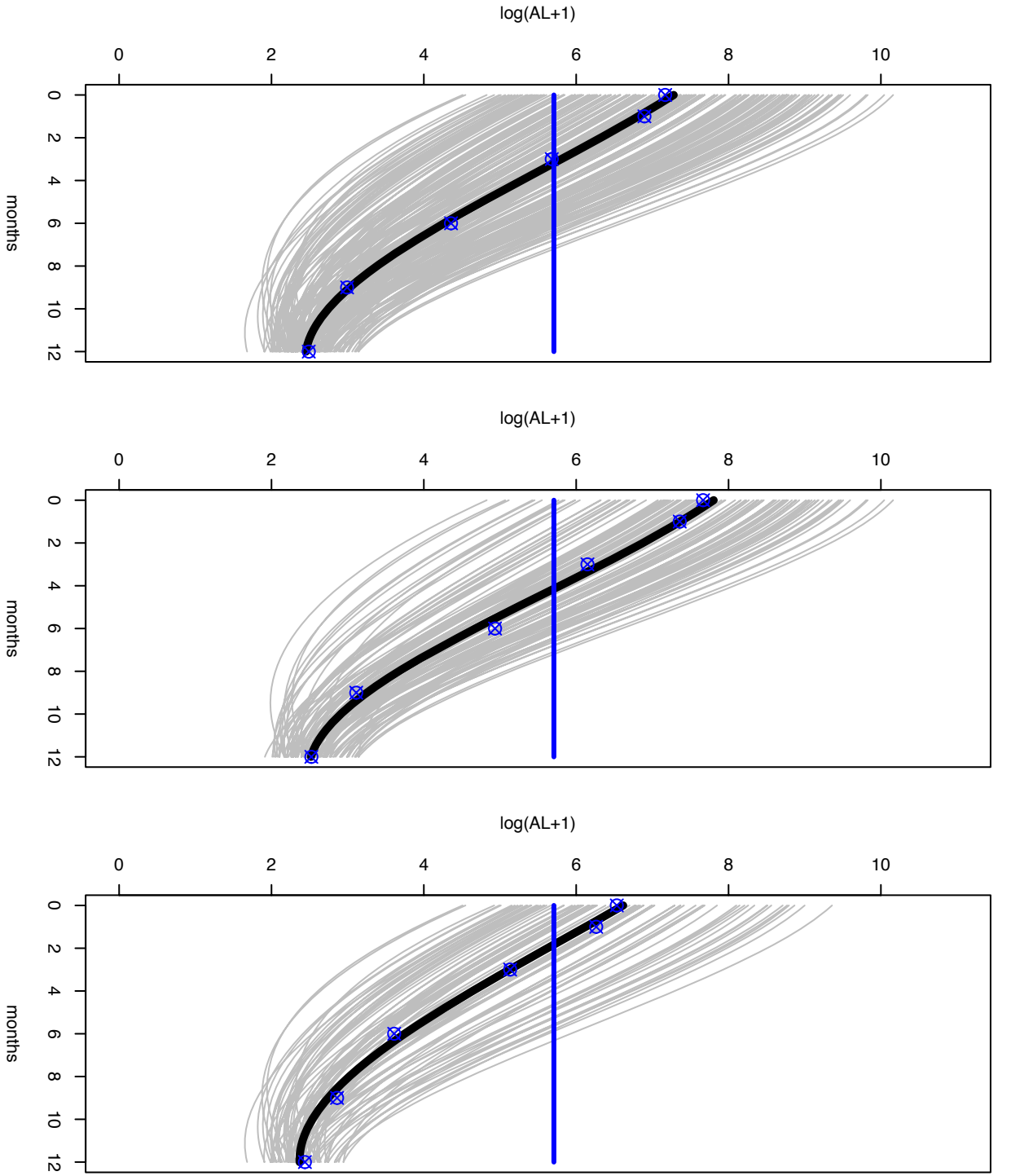
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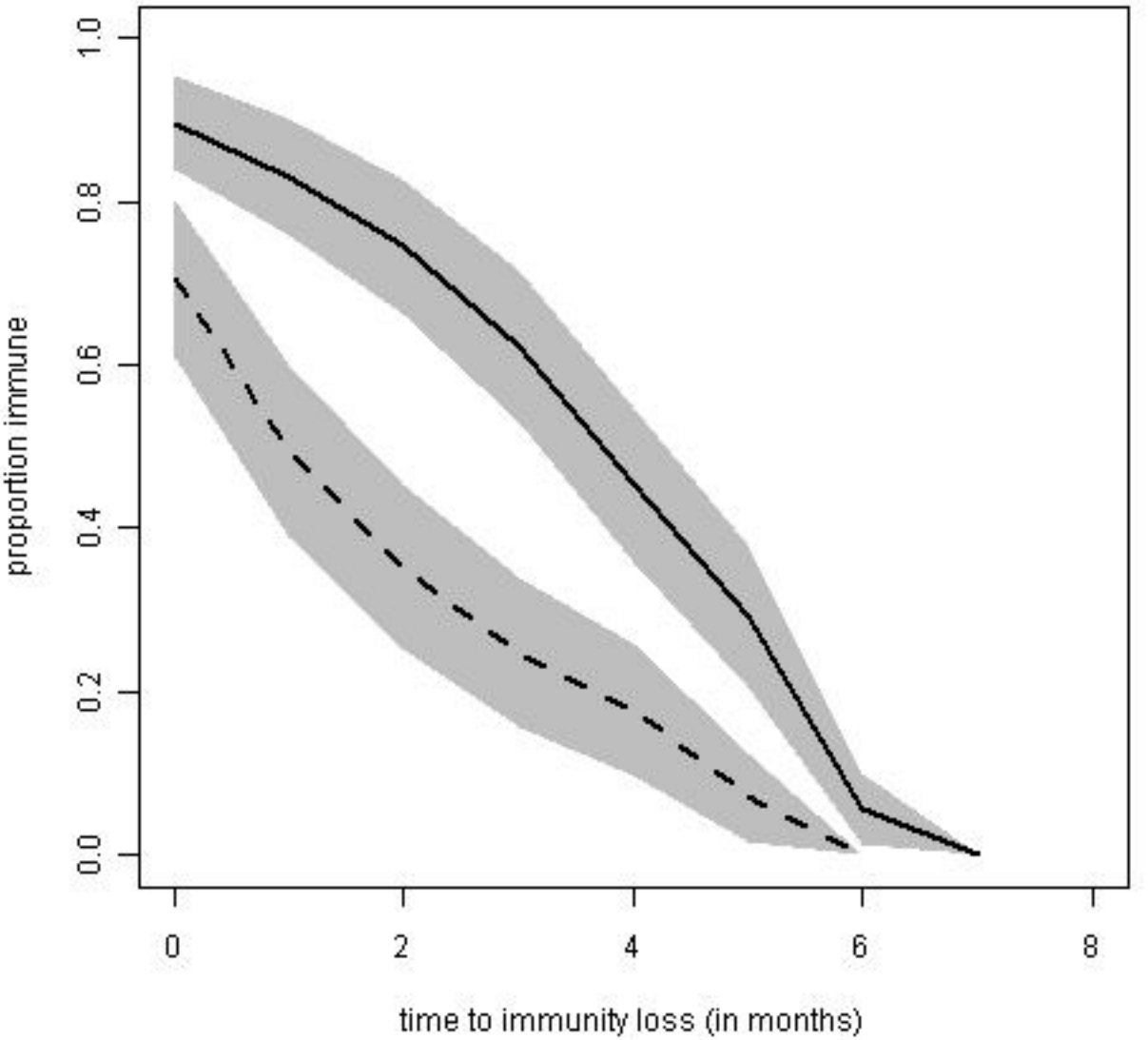
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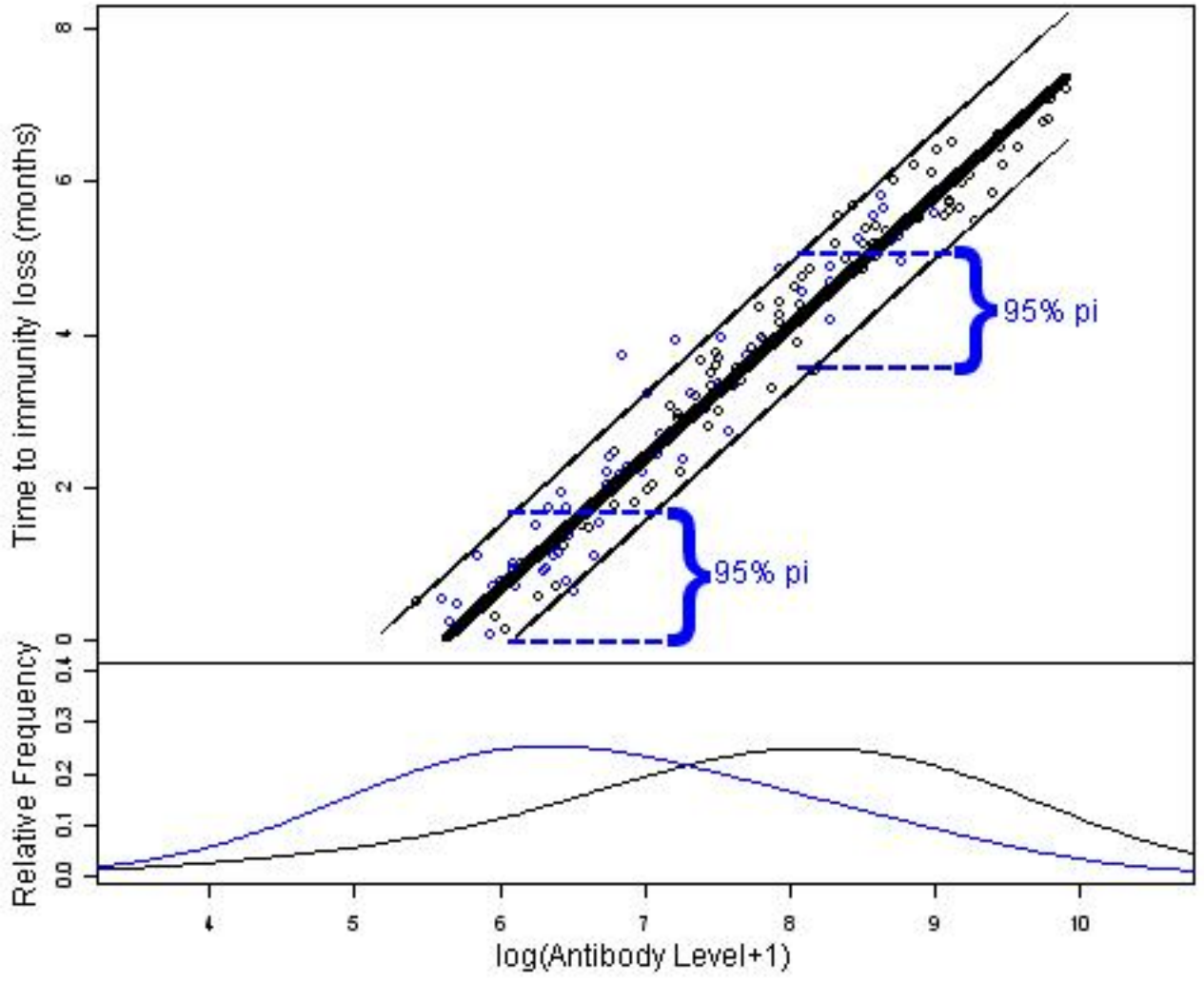
time to immunity loss (in months)


Time to immunity loss (months)
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