Vaccine 31 (2013) 2756–2761

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Evaluation of vaccine-induced antibody responses: Impact of new technologies

Daniel J. Zaccaro[a], Diane K. Wagener[b,*], Carol C. Whisnant[c], Herman F. Staats[c]

[a] Health Sciences Division, RTI International, 3040 East Cornwallis Road, Research Triangle Park, NC 27709, USA
[b] Health Sciences Division, RTI International, 500 W Harbor Dr. #1114, San Diego, CA 92101, USA
[c] Department of Pathology, Duke University Medical Center, Box 3712, Durham, NC 27710, USA

ARTICLE INFO

Article history:
Received 20 December 2012
Received in revised form 4 March 2013
Accepted 28 March 2013
Available online 11 April 2013

Keywords:
Seroconversion
Change score
Typhoid
Vaccine
Statistics

ABSTRACT

Host response to vaccination has historically been evaluated based on a change in antibody titer that compares the post-vaccination titer to the pre-vaccination titer. A four-fold or greater increase in antigen-specific antibody has been interpreted to indicate an increase in antibody production in response to vaccination. New technologies, such as the bead-based assays, provide investigators and clinicians with precise antibody levels (reported as concentration per mL) in ranges below and above those previously available through standard assays such as ELISA. Evaluations of bead assay data to determine host response to vaccination using fold change and absolute change, with a general linear model used to calculate adjusted statistics, present very different pictures of the antibody response when pre-vaccination antibody levels are low. Absolute changes in bead assay values, although not a standard computation, appears to more accurately reflect the host response to vaccination for those individuals with extremely low pre-vaccination antibody levels. Conversely, for these same individuals, fold change may be very high while post-vaccination antibodies do not achieve seroprotective levels. Absolute change provides an alternate method to characterize host response to vaccination, especially when pre-vaccination levels are very low, and may be useful in studies designed to determine associations between host genotypes and response to vaccination.

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1. Introduction

Analyses of immunologic responses to vaccines are complicated by previous exposure to relevant antigens and pre-existing antibody levels. Measures such as fold change (FC; the ratio of the final to the pre-vaccination value) or percentage change in antibody levels have traditionally been used to quantify response to vaccines, but each has drawbacks that make interpretation of results difficult, both immunologically and mathematically [1,2]. Several authors have discussed methodologies to address problems in the assessment of vaccine immunogenicity in populations with seropositive individuals prior to vaccination [1,3,4]. Some have noted that pre-existing antibody titers significantly affect response to vaccines [3,5–11]. Numerous measures of pre-post change have been considered [2,3,12,13], especially when seropositive individuals comprise a substantial portion of the pre-vaccination sample [1].

The Population Genetics Analysis Program (PopGen) investigated genetic determinants of vaccine immunogenicity in an Indian population using a vaccine to *Salmonella typhi* [14]. Because 45% of participants demonstrated pre-vaccination typhoid antibody levels that were considered seroprotective as revealed by the bead assay [15], we examine different methods of computing immunogenicity to quantify antibody production while also accounting for pre-vaccination immunity. We demonstrate that data analyses using different methods to calculate the response to vaccination may dramatically affect the outcome measure and that when researchers select a method to calculate response to vaccination, they must carefully consider the question(s) being asked.

2. Methods

2.1. PopGen population

In a stratified random sampling design, 997 participants receiving vaccine to *S. typhi* were recruited from eight strata (two age groups: 6-to-25 years and >25 years; both genders; and two ethnic groups: Hindu and Muslim) [14,15]. The research design entailed a longitudinal assessment of vaccination response in a large ethnic population recruited from several wards in Kolkata, India. Typhoid infections are endemic in this population, comprising primarily

* Corresponding author at: 500 W Harbor Dr., #1114, San Diego, CA 92101, USA. Tel.: +1 619 485 5628; fax: +1 919 541 5966 (c/o D. Zaccaro).
E-mail addresses: dzaccaro@rti.org (D.J. Zaccaro), dwagener@rti.org (D.K. Wagener), carolwhiswhip@gmail.com (C.C. Whisnant), herman.staats@duke.edu (H.F. Staats).

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http://dx.doi.org/10.1016/j.vaccine.2013.03.065

Hindu lower caste groups and their Muslim counterparts. Persons with typhoid infections in the previous 12 months were excluded. Blood was collected from all participants at baseline (just before vaccination) and 3 days and 28 days post-vaccination. This report focuses on the baseline and Day 28 results. Data from this study are included in the National Institute of Allergy and Infectious Diseases ImmPort repository (immport.niaid.nih.gov).

2.2. Bead assay to assess antibody levels

A new laboratory assay—a bead-based immunoassay of anti-Vi IgG—was developed for this project [15]. Assays were performed for 997 study participants, but two sera did not yield Day 28 bead assay values and four yielded Day 28 values that were below Day 0 values, so 991 are included in the present analyses. Approximately 45% of the pre-vaccination population was seropositive. Assay data used in the current study was obtained from IMMPORT (immport.niaid.nih.gov).

2.3. Statistical methods

We provide the change statistics (both fold (FC) and absolute (AC)) as unadjusted statistics and as adjusted statistics per Beyer et al. [1]. We do not discuss another commonly used statistic, the relative percent increase, because it completely correlates with FC as it is FC minus 1, expressed as a percentage.

First we define $z_{0,i}$ and $z_{28,i}$ to be the Day 0 (pre-vaccination) and Day 28 (post-vaccination) assay results for the ith participant, respectively. Then, if $x_{0,i} = \log_{10}(z_{0,i})$, the mean $x_{0,i}$ is:

$$\bar{x}_0 = \frac{\sum_{i=1}^{n} x_{0,i}}{n} \tag{1}$$

Finally, we define δ_i to be the log-transformed Day 0 value for the ith participant centered about the mean for all participants as:

$$\delta_i = x_{0,i} - \bar{x}_0 \tag{2}$$

Unadjusted FC. The relative increase, i.e., FC, in antibody levels is given by:

$$\phi_i = \frac{z_{28,i}}{z_{0,i}} \tag{3}$$

FC adjusted for Day 0. For general linear models that adjust for Day 0, we use the log of the FC for the ith participant:

$$\log_{10}(\phi_i) = \log_{10}\left(\frac{z_{28,i}}{z_{0,i}}\right) = \log_{10}(z_{28,i}) - \log_{10}(z_{0,i}) \tag{4}$$

We adjust for Day 0 levels using the following linear model similar to Beyer et al. [1]:

$$\log_{10}(\phi_i) = \beta_0 + \beta_1\delta_i + \varepsilon_i \tag{5}$$

where β_0 and β_1 are parameters estimated from our data and ε_i are the residuals, representing the variation in $\log_{10}$(FC) that is unexplained by $\log_{10}$(Day 0). [In all models we utilize the independent variable δ_i, rather than the $\log_{10}$(Day 0) levels. However, this does not affect the slope of the linear relationship, only the intercept.]

At the value $\delta_i = 0$, the adjusted FC values are equal to:

$$\log_{10}(\phi_i)^A = \hat{\beta}_0 + \varepsilon_i \tag{6}$$

In other words, the residual, ε_i, is directly proportional to the adjusted FC.

Unadjusted AC. An estimate of the quantity of antibody produced in response to vaccination is computed from the AC in the bead assay (untransformed):

$$\Delta_i = z_{28,i} - z_{0,i} \tag{7}$$

AC adjusted for Day 0. For statistical modeling, we compute $\log_{10}(\Delta_i)$, the log of the absolute difference in bead assay. The AC has a meaningful interpretation (estimate of antibody produced), but the distribution of values is not Gaussian. We transform these values for all subsequent analyses. We adjust for Day 0 levels, similar to FC adjustment above:

$$\log_{10}(\Delta_i) = \alpha_0 + \alpha_1\delta_i + \omega_i \tag{8}$$

where α_0 and α_1 are parameters estimated from our data and ω_i are the residuals, representing the variation in $\log_{10}$(AC) that is unexplained by $\log_{10}$(Day 0). Therefore, the adjusted values for AC are computed at $\delta_i = 0$ by:

$$\log_{10}(\Delta_i)^A = \hat{\alpha}_0 + \omega_i \tag{9}$$

Consequently, the residual, ω_i, is directly proportional to the adjusted AC.

Relationship between FC and AC. At any value for Day 0, we may express both FC and AC as linear functions of the mean-centered level δ_i (Eqs. (5) and (8), respectively). By solving Eq. (8) for δ_i and substituting into Eq. (5), we have a linear relationship between $\log_{10}$(FC) and $\log_{10}$(AC):

$$\log_{10}(\phi_i) = \beta_0 - \frac{\beta_1}{\alpha_1}\alpha_0 + \frac{\beta_1}{\alpha_1}\log_{10}(\Delta_i) + \varepsilon_i - \frac{\beta_1}{\alpha_1}\omega_i \tag{10}$$

The rescaled residual term:

$$\varepsilon_i - \frac{\beta_1}{\alpha_1}\omega_i \tag{11}$$

is a weighted (or rescaled) difference between the two residuals. Substituting in from Eqs. (6) and (9), note that this rescaled residual difference is proportional to the difference in the two adjusted statistics:

$$\varepsilon_i - \frac{\beta_1}{\alpha_1}\omega_i = \log_{10}(\phi_i)^A - \frac{\beta_1}{\alpha_1}\log_{10}(\Delta_i)^A - \text{constant} \tag{12}$$

where the constant is a function of the α_0, α_1, β_0, and β_1. We refer to the variable in 11 as the rescaled residual and explore this term in the results below. We used SAS statistical software to conduct all statistical analyses and calculated Pearson's correlation coefficients.

3. Results

Fig. 1A and B illustrate the distributions of Day 0 and Day 28 bead assay results. In the PopGen population, 45% of individuals were seroprotected at Day 0 (Fig. 1A), according to Staats et al. [15] criteria (value ≥0.267 EU/mL). Most individuals (98%) attained a Day 28 level that exceeds the seroprotection cutoff (Fig. 1B). Fig. 1C displays the distribution of FC (unadjusted for Day 0 levels), and Fig. 1D illustrates the distribution of AC (unadjusted for Day 0). Although the AC score, i.e., antibody production (see Fig. 1D), is not a typical computation in vaccine immunogenicity assessment, we include it among possible outcomes to express response to vaccine. (Values for Day 0, Day 28, unadjusted and adjusted FC and AC, and the rescaled residuals for selected participants are given in Appendix I.)

Because a large percentage were seropositive at baseline, the use of unadjusted FC is problematic [1], so we looked at adjusted values. Table 1 shows the measures of antibody levels and response, both unadjusted and adjusted for pre-vaccination levels. It is immediately apparent, as expected, that the adjustment does change the variance, but the means for the entire distribution of FC or AC are not altered. Table 2 provides parameter estimates and statistics related to the adjustment regressions for FC and AC. Although unadjusted FC appears to account for Day 0 (i.e., Day 0 is used in the computation of the ratio), a correlation still exists between $\log_{10}$(FC) and

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