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Methods for Evaluating Waning Efficacy of Rotavirus Vaccines

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An abstract of
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Abstract

Methods for Evaluating Waning Efficacy of Rotavirus Vaccines

By Wenrui Qi

The purpose of this study is to compare four different methods (descriptive method, Durham's method, Tian's method and time-dependent covariate method) to detect true waning of rotavirus vaccines efficacy (VE) and to estimate the magnitude of temporal changes in VE. The methods used in this study can be divided into two groups: a descriptive method and methods based on Cox proportional hazard model (Durham's method, Tian's method and time-dependent covariate method). We used stochastic agent-based simulation software that generates data from rotavirus VE studies under different scenarios of true VE waning. From the results of these comparisons we conclude that Durham's method is more powerful in terms of detecting VE waning and providing more information about the temporal behavior of VE. More research is needed to derive better estimates of VE waning.

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1. Introduction

Rotavirus is a double-stranded RNA virus belonging to the Reoviridae family. It is one of the main pathogens that cause diarrhea in infants and children. It is estimated that rotavirus causes 150,000 deaths annually all over the world.[1, 2] Most rotavirus-related deaths occur in developing countries. It is estimated that 85% of rotavirus-related deaths occur in Asia and Africa.[3]

The rotavirus vaccine is one of the most important vaccines all over the world. Ninety-six countries have included rotavirus vaccination in their national immunization programs by 2019.[4] There are only two kinds of vaccines that are available worldwide: GlaxoSmithKline's (GSK's) monovalent vaccine and Merck's pentavalent vaccine.[5] However, there are two serious challenges regarding rotavirus vaccines in low-income settings. First, rotavirus vaccines are less effective in low-income settings than in high-income settings because of differences in immunological phenomena.[2] The response to vaccines is better in children who live in high-income settings. Second, the vaccines are not accessible to many children in low-income settings.[6] Another problem related to rotavirus vaccines all over the world is that the vaccine effectiveness may wane over time.

Many articles have studied the difference in effectiveness of rotavirus vaccines in different settings and the waning effectiveness of rotavirus vaccines. These studies found that the

effectiveness of rotavirus vaccines decreases over time mainly in poor environment settings. A study by Mohan et al. found that protection by vaccination may wane over a long period (two years) in low-income countries.[2, 7] Child mortality rates are associated with the effectiveness of rotavirus vaccines. Baker found that rotavirus vaccines are less effective in high child mortality settings because these areas have worse immunological phenomena.[4] Meanwhile, Clark et al. used a Bayesian hierarchical Poisson meta-regression model to estimate the pooled cumulative vaccine efficacy (VE) and its waning for three mortality strata.[1] The study found that rotavirus vaccine immunogenicity is lower in high-mortality settings. In addition, vaccine efficacy wanes more rapidly in these settings. Rogawski et al. reached similar conclusions; they explain that waning of VE over time may be due to the fact that unvaccinated children are more likely than vaccinated children to get infected and acquire partial immunity to subsequent infection (after the first infection). Therefore, the difference in protection between vaccinated and unvaccinated children seems to decease over time. There are other factors that may affect the estimate of VE over time even if the true VE remains the same.

The main goal of this study is to compare different methods to detect true waning of rotavirus vaccine efficacy and estimate the magnitude of temporal changes in vaccine efficacy. All data used in this thesis is collected from rotavirus studies in developing countries.

2. Materials and Methods

The data for this thesis was obtained from a multi-country birth cohort study, MALED, on

enteric infections and malnutrition in 8 countries from April 2009 to February 2014.[7] Healthy children were enrolled within 17 days of birth and were followed until 24 months of age. We used data from 4 countries where no vaccination was done (Bangladesh, India, Nepal and Pakistan) to estimate the age-specific incidence of the first occurrence of rotavirus diarrhea (RVD) in unvaccinated children during the first year of life.

2.1 Simulation model and software

We used a new stochastic agent-based simulation model. The model assumes that a cohort of two thousand 60-day old infants is followed up until they reach the age of 360 days. A pre-set proportion of the children in the simulated cohort study are effectively vaccinated against rotavirus infection just prior to the beginning of the study. Vaccination is done at random. We decided to start the simulated study at the age of 60 days because in real life, children become effectively vaccinated during their first 60 days of life. The study duration (300 days) is divided into 10 periods of 30 days each. The input parameters for each period are as follows: (1) β, which denotes the daily probability of an unvaccinated susceptible child to contract her/his first RVD, and (2) θ, which is defined such that the daily probability of RVD in a vaccinated child is β *θ. Hence, the true vaccine efficacy is:

$$VE = 1 - \theta = 1 - \frac{hazard\ of\ vaccined\ person}{hazard\ of\ unvaccined\ person}$$

The values of these parameters are fixed during each period but may vary from one period to the next. We used the smoothed incidence rates from each of the 4 countries in the MALED

study to estimate the β's for each country and each period. For the θ 's we assumed that at the beginning of the study VE was 0.6, and we considered 3 levels of vaccine efficacy waning: (1) no waning (i.e. θ was fixed over all periods), (2) moderate waning, where we let the absolute VE decrease 0.03 in each 30-day period, and (3) severe waning, where the absolute VE decreased 0.06 per period.

For each combination of country and level of waning we conducted one hundred simulations. The output from each simulation was an 'outcomes file' which included each child's vaccination status and the age (in days) at the first RVD episode (if any). Only the child's first episode was recorded. Three methods (to be described in the next section) were used to test the null hypothesis that the efficacy of the rotavirus vaccine does not change over time and to estimate the rate of waning. These methods were applied to each outcomes file, and the proportion of simulations where the null hypothesis of no waning was not accepted was determined. When there is no waning, this proportion estimates the type I error of the statistical test. When there is waning, this proportion is an estimate of the power of the test. In addition, we used 2 methods to estimate the value of VE in each period and the magnitude of change in VE from one period to the next. The data in this study were analyzed by using SAS version 9.4.

2.2 Descriptive Analysis

In the descriptive analysis, the average (over all simulations) of the vaccine effectiveness

is estimated from the data by country in each period of the study. First, the proportions of infection in vaccinated and unvaccinated participants are calculated. Then, vaccine efficacy is estimated by the formula:

$$VE = 1 - \frac{proportion\ of\ infection\ in\ vaccinated\ persons}{proportion\ of\ infection\ in\ unvaccinated\ persons}$$

VE is equal to 1 minus the relative risk of rotavirus infection in a vaccinated person compared with an unvaccinated person. Note that for the descriptive method VE is estimated using the proportions of infected in each period at a time, and that only participants not infected before the onset of the period are included in the denominators of the proportion. Temporal changes in VE can be detected from the trend of estimated values of the vaccine effectiveness over the ten periods. We built a simple linear regression with period as the explanatory variable (X) and the mean VE for each period as the dependent variable (Y) to estimate the decrease per period in VE. The slope of the regression line is an estimate of average change in VE per period.

2.3 Analytic methods based on the Cox proportional hazard Model

We believe that in order to evaluate temporal changes in vaccine effectiveness, it is best to define the true VE at a given time point t as one minus the ratio of the hazard of infection between vaccinated and unvaccinated persons at this time point. Note that the hazard of infection at time t is based only on those persons who are still at risk (i.e., uninfected) just prior to this time point. The hypothesis that VE does not change over time is equivalent to the hypothesis of a fixed ratio when comparing the hazards of a vaccinated and a vaccinated person.

This is also called the proportional hazard hypothesis. The most common estimate of a fixed hazard ratio is based on Cox's proportional hazard model. Under this model, we can write this hazard function as:

$$\lambda(t|V) = \lambda_0(t) \cdot Exp\{\alpha \cdot V\},$$

where t is the time (in days) from vaccination, V is the binary vaccination status, $\lambda(t|V)$ is the hazard of infection for a person of vaccination status V at time t, and $\lambda_0(t)$ is the hazard of an unvaccinated person at time t, (the baseline hazard). . Then the fixed hazard ratio is $HR = Exp(\alpha)$, and the coefficient α can be estimated from the data. Therefore, the fixed VE is estimated as one minus the estimate of $Exp(\alpha)$.

Under the above model, changes in vaccine VE over time violate the proportional hazard assumption. Therefore, the Cox model presented above has to be replaced by a more general model, such as: $\lambda(t|V) = \lambda_0(t) \cdot Exp\{\alpha(t) \cdot V\}$

Then the vaccine efficacy at time t is $VE(t) = 1 - Exp(\alpha(t))$, and the null hypothesis that there is no waning is equivalent to $\alpha(t) \equiv \alpha$ for all time points t. We will consider three methods for testing this hypothesis.

2.3.1 Durham's Method

This method is based on smoothing scaled residuals from the proportional hazard model.[8] It consists of four steps. First, an ordinary proportional hazard model is fitted. Second, Schoenfeld residuals are calculated (this residual is the difference between the

covariate at the failure time and the expected value of the covariate at this time. It is used to test the independence between residual and time). Third, these residuals are scaled and added to the coefficient from the ordinary proportional hazard model. Fourth, after smoothing the estimated proportional hazard coefficient and the scaled Schoenfeld residuals we can get the estimated hazard ratios as function of time. This allows the estimation of vaccine efficacy at each time point. After that, we built a simple linear regression with period as the explanatory variable (X) and the mean VE for each period as the dependent variable (Y) to estimate the decrease per period in VE. The slope of the regression line is an estimate of the decrease.

2.3.2 Tian's Method

In this method, kernel-weighted partial likelihood approach was used to estimate the time-dependent coefficients in the generalized Cox model. Let $Z(t)$ be time-dependent covariate. Define t is a fixed time point, α_0 (t) is a smooth function of t, the partial likelihood function to estimate α_0 (t) is:

$$L(\alpha, t) = (nh_n)^{-1} \sum_{i=1}^{n} \int_0^{\tau} K\left(\frac{s-t}{h_n}\right) * \{ \alpha' Z_i(s) - \log\left(\sum_{j=1}^{n} Y_j(s) e^{\alpha' Z_{j(s)}}\right)\} dN_i(s),$$

where the kernel function $K(x) = \frac{3(1-x^2)}{4}$, $h_0 = O(n^{-v})\ with\ v > 0$; $Y_j(t) = I\left(X_j \geq t\right)$; τ is a prespecified constant which $P(X_i > \tau) > 0$; $N_i(t) = I(X_i \leq t, \Delta_i = 1)$ ($X_i = \min(T_i, C_i)$ where T_i is failure time and C_i is censoring time, $\Delta_i = 1$ if $X_i = T_i$). In conjunction with this approach, an integrated function of the estimate for the regression coefficient was used to

test the adequacy of the hypothesis of proportional hazards assumption for time-dependent covariates.[9]

2.3.3 Time-dependent Covariates Method

In this method, one fits a Cox proportional hazards model with a time-dependent covariate:

$$\lambda(t|V) = \lambda_0(t) \cdot Exp\{\, \alpha \cdot V + \gamma \cdot V \cdot g(t)\} \ ,$$

where $g(t)$ is an arbitrary function of time; usually the function $g(t) = \log(t)$ is used. This is a proportional hazards model with two covariates: the time-fixed covariate V and the time-dependent covariate $V \cdot g(t)$. Under this model, vaccine efficacy at time t is:

$$VE(t) = 1 - \frac{\lambda(t|V=1)}{\lambda(t|V=0)} = 1 - \exp(\alpha + \gamma \cdot g(t))$$

Therefore, the hypothesis of no vaccine efficacy waning is equivalent to H_0: $\gamma = 0$.[10]

3. Results

3.1 Results of MALED

We used data from the 4 MALED countries where no vaccination was done to calculate mean daily probabilities of an unvaccinated child to contract her/his first rotavirus infection in each country for each period. Moving average smoothing was used to smooth these values

of β. The results are shown in Table 1. For Bangladesh, Nepal and Pakistan, the daily probability of an unvaccinated child to contract her/his first rotavirus disease increased first and then decreased. In Bangladesh, β increased from period 1 (0.00026) until period 6 (0.00167) and then decreased. In Nepal, β increased from period 1 (0.00019) until period 6 (0.00101), then decreased from period 6 to period 8 (0.00054) and then increased from period 8 to period 10 (0.00073). In Pakistan, β increased from period 1 (0.00053) until period 4 (0.00097) and then decreased. For India, the probability of an unvaccinated child to contract her/his first rotavirus disease kept increasing throughout the 360 days period. These values of beta were used as input parameters for the simulations.

3.2 Comparison between the Descriptive and Durham's Method for Estimating VE

The means of estimated VEs over 100 simulations for each period for the descriptive method and Durham's method are shown in Table 2 to 5. The estimated VEs for these two methods were compared with true VEs used in simulations. Table 2 showed the mean estimated VEs and the true VE per period for Bangladesh. For both descriptive and Durham's method, there was no obvious trend in the VEs of different periods in no waning scenarios. For the moderate waning scenario, there was a gentle decreasing tendency for both methods of estimation. For the severe waning scenario, there was a sharp decreasing tendency. Similar patterns were observed for the other 3 countries in Tables 3, 4 and 5. Figure 1 to 4 also show these patterns for VEs estimated by using Durham's method.

Therefore, the larger the daily multiplier for daily probability of infection with vaccines (θ) was, the more severe the waning was. The estimated values of VEs for both descriptive method and Durham's method were usually close to the true VEs we used in simulations. Generally, VEs estimated using Durham's method were closer to the true VEs than the estimates obtained from the descriptive method. The largest absolute difference between Durham's estimated VE and the true VE was 0.094. On the other hand, the largest absolute difference between VE estimated by the descriptive method and the true VE was 0.191. The negative bias in no waning scenario in simulation process caused such a large difference between VE estimated by the descriptive method and the true VE.

3.3 Comparison of Estimated Drop in VE per Period between the Descriptive and Durham's Method

We compared the average drop in VE per period using Durham's method and the descriptive method to the true drop per period used in the input to the simulation software. The results are shown in Table 7. For both descriptive and Durham's method, the average change in VEs per period was close to 0 in the no waning scenarios. For the moderate waning scenarios, for both methods, estimated changes in VE per period were close to the true value of -0.03. For the severe waning scenario, the estimated change in VE per period were close to the true value of -0.06.

In general, the absolute difference between estimated and true changes in VE per period were similar in both methods.

3.4 Comparison of Proportion Rejections of the Null Hypothesis of no VE waning between Durham's Method, Tian's Method and Time-dependent Covariates Method

For each of the methods based on the Cox proportional hazard model (Durham's method, Tian's method and time-dependent covariates method) we determined the proportion of simulations where the null hypothesis of no VE waning was rejected (Table 6). In the no waning scenario, this proportion should be around or below the significance level of 0.05. This was satisfied with all three methods in the simulations that used the incidence rates from Bangladesh, India and Nepal. In the simulations that used the incidence rates from Pakistan, the proportions of rejections in the no waning scenario were > 0.05 with all 3 methods (0.08, 0.07, 0.08).

Under the moderate and severe waning scenarios, where the proportion of rejections estimates the power of the test of no waning, the proportion of rejections with Durham's method was higher than with the other two methods in all four countries. For example, for the simulations based on Bangladesh's incidence rates, under the severe waning scenario the proportions of rejections with Durham's Tian's and the TDC methods were 0.63, 0.55 and 0.55, respectively.

4. Discussion

We used four different methods to evaluate waning of rotavirus vaccines. All these four methods can detect drops in VEs over time when we use simulated data with true decreasing VE.

We used three criteria to compare the methods. We found that (1) Durham's method is more likely to reject the null hypothesis of no VE waning, i.e., it has the highest power of detecting true VE waning. (2) This method also provides more accurate estimates of VE in each period, relative to the descriptive method. The reason is that Durham's method does estimation daily and descriptive method does estimation monthly. Besides, the estimation of Durham's method is based on hazard ratio and the estimation of descriptive method is based on cumulative incidence. The difference of theory may cause the difference in accuracy. (3) In terms of estimating the rate of decline in VE (i.e. change in VE per period), estimates from Durham's method and from the descriptive method have about the same accuracy. Tian's method and the TDC method do not provide estimates of VE in each period and cannot be used to estimate the rate of VE waning. Output from Durham's method can also be used to plot the estimated VEs as a function of time since vaccination. These plots provide the user with important information about the temporal behavior of VE.

In summary, we conclude that Durham's method is more powerful than the other two Cox

proportional hazards regression-based methods in terms of detecting VE waning and provides more information about the temporal behavior of VE. Estimates based on this method are also more accurate, compared to the descriptive method. This method has a few limitations. First, though Durham's method has the highest power for rejecting the hypothesis of no waning, the power is still a bit low. Even in the severe waning scenario, when VE declines by 0.06 in each 30-day period, the power we observed in this simulation study ranged between 0.25 and 0.63. Under moderate waning, where the true decline in VE was 0.03 per period, the power ranged between 0.17 and 0.23. Hence, future research will be needed to develop more powerful methods for detecting VE waning. Second, this method is based on the assumption that the hazard of infection follows the (generalized) Cox regression model, i.e., the hazard can be written as $\lambda(t|V) = \lambda_0(t) \cdot Exp\{\alpha(t) \cdot V\}$, where t is the time since vaccination and V is the binary vaccination status. Third, this method assumes that vaccination status does not depend on time. In contrast, Tian's method allows persons to receive the vaccine at different times or ages.

In summary, we found that Durham's method performs better than the other three methods (descriptive, Tian and TDC) in terms of detecting and estimating of waning efficacy of rotavirus vaccines. More research is needed to allow this method to be applied to situations where persons are vaccinated at different times. In addition, it is possible to develop methods that allow researchers to use information on temporal changes in the prevalence of infection in the population by modeling the hazard of infection as a function of the prevalence.

5. References

1 Andrew Clark, Kevin van Zandvoort, Stefan Flasche, Colin Sanderson, Julie Bines, Jacqueline Tate, Umesh Parashar, and Mark Jit, 'Efficacy of Live Oral Rotavirus Vaccines by Duration of Follow-Up: A Meta-Regression of Randomised Controlled Trials', *The Lancet Infectious Diseases,* 19 (2019), 717-27.

2 B. A. Lopman, and V. E. Pitzer, 'Waxing Understanding of Waning Immunity', *J Infect Dis,* 217 (2018), 851-53.

3 J. E. Tate, A. H. Burton, C. Boschi-Pinto, U. D. Parashar, and Network World Health Organization-Coordinated Global Rotavirus Surveillance, 'Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013', *Clin Infect Dis,* 62 Suppl 2 (2016), S96-S105.

4 Julia Marie Baker, " Multi-scale assessment of rotavirus vaccination: determinants of immunological, clinical and population-level effects ", 2019

5 Global Immunization News November to December 2019

6 U. Desselberger, and H. I. Huppertz, 'Immune Responses to Rotavirus Infection and Vaccination and Associated Correlates of Protection', *J Infect Dis,* 203 (2011), 188-95.

7 V. R. Mohan, R. Karthikeyan, S. Babji, M. McGrath, S. Shrestha, J. Shrestha, E. Mdumah, C. Amour, A. Samie, E. Nyathi, R. Haque, S. Qureshi, P. P. Yori, A. A. M. Lima, L. Bodhidatta, E. Svensen, P. Bessong, T. Ahmed, J. C. Seidman, A. K. M. Zaidi, M. N. Kosek, R. L. Guerrant, J. Gratz, J. A. Platts-Mills, D. R. Lang, M. Gottlieb, E. R. Houpt, G. Kang, Risk Factors Etiology, Infections Interactions of Enteric, Malnutrition, Health the Consequences for Child, and Investigators Development Network, 'Rotavirus Infection and Disease in a Multisite Birth Cohort: Results from the Mal-Ed Study', *J Infect Dis,* 216 (2017), 305-16.

8 L Kathryn Durham, Ira M. Longini, Jr., M. Elizabeth Halloran, John D. Clemens, Azhar. Nizam, and Malla Rao, ' Estimation of Vaccine Efficacy in the Presence of Waning: Application to Cholera Vaccine, Am J Epidemiol, 1998 May 15;147(10):948-59

9 Lu Tian, David Zucker, and L. J. Wei, 'On the Cox Model with Time-Varying Regression Coefficients', *Journal of the American Statistical Association,* 100 (2005), 172-83.

10 Z. Zhang, J. Reinikainen, K. A. Adeleke, M. E. Pieterse, and C. G. M. Groothuis-Oudshoorn, 'Time-Varying Covariates and Coefficients in Cox Regression Models', *Ann Transl Med,* 6 (2018), 121.

6. Figures and Tables

6.1 Tables

Table 1. Smoothed daily probabilities of an unvaccinated child to contract her/his first rotavirus infection in four countries in each 30-day period

Period	Bangladesh	India	Nepal	Pakistan
Period 1	0.00026	0.00010	0.00019	0.00053
Period 2	0.00047	0.00015	0.00039	0.00044
Period 3	0.00104	0.00024	0.00049	0.00093
Period 4	0.00151	0.00029	0.00078	0.00097
Period 5	0.00151	0.00039	0.00097	0.00088
Period 6	0.00167	0.00044	0.00107	0.00066
Period 7	0.00141	0.00044	0.00078	0.00066
Period 8	0.00151	0.00059	0.00054	0.00062
Period 9	0.00099	0.00059	0.00063	0.00057
Period 10	0.00102	0.00066	0.00073	0.00053

Table 2. Comparison between true* vaccine efficacy and estimated vaccine efficacies using descriptive method and Durham's method in Bangladesh**

	No Waning			Moderate Waning			Severe Waning		
	True	Descriptive	Durham	True	Descriptive	Durham	True	Descriptive	Durham
Period 1	0.600	0.500	0.604	0.600	0.521	0.579	0.600	0.486	0.535
Period 2	0.600	0.562	0.603	0.570	0.531	0.561	0.540	0.467	0.507
Period 3	0.600	0.562	0.604	0.540	0.519	0.535	0.480	0.455	0.467
Period 4	0.600	0.589	0.601	0.510	0.508	0.513	0.420	0.424	0.419
Period 5	0.600	0.589	0.600	0.480	0.456	0.489	0.360	0.352	0.363
Period 6	0.600	0.587	0.599	0.450	0.450	0.458	0.300	0.283	0.318
Period 7	0.600	0.583	0.601	0.420	0.387	0.417	0.240	0.191	0.254
Period 8	0.600	0.566	0.599	0.390	0.364	0.362	0.180	0.134	0.181
Period 9	0.600	0.596	0.600	0.360	0.327	0.310	0.120	0.090	0.097
Period 10	0.600	0.554	0.609	0.330	0.229	0.268	0.060	0.043	0.017

*True vaccine efficacy used in the simulations

** Means over 100 simulations

Table 3. Comparison between true* vaccine efficacy and estimated vaccine efficacies using descriptive method and Durham's method in India**

	No Waning VE			Moderate Waning VE			Severe Waning VE		
	True	Descriptive	Durham	True	Descriptive	Durham	True	Descriptive	Durham
Period 1	0.600	0.419	0.591	0.600	0.522	0.545	0.600	0.485	0.528
Period 2	0.600	0.574	0.596	0.570	0.439	0.539	0.540	0.297	0.479
Period 3	0.600	0.546	0.598	0.540	0.487	0.522	0.480	0.365	0.444
Period 4	0.600	0.477	0.594	0.510	0.439	0.512	0.420	0.305	0.392
Period 5	0.600	0.551	0.598	0.480	0.420	0.486	0.360	0.321	0.341
Period 6	0.600	0.577	0.601	0.450	0.398	0.462	0.300	0.173	0.285
Period 7	0.600	0.576	0.601	0.420	0.303	0.421	0.240	0.176	0.233
Period 8	0.600	0.577	0.596	0.390	0.291	0.391	0.180	0.076	0.172
Period 9	0.600	0.521	0.601	0.360	0.287	0.342	0.120	0.038	0.109
Period 10	0.600	0.567	0.604	0.330	0.277	0.311	0.060	-0.026	0.043

*True vaccine efficacy used in the simulations

** Means over 100 simulations

Table 4. Comparison between true* vaccine efficacy and estimated vaccine efficacies using descriptive method and Durham's method in Nepal**

	No Waning VE			Moderate Waning VE			Severe Waning VE		
	True	Descriptive	Durham	True	Descriptive	Durham	True	Descriptive	Durham
Period 1	0.600	0.409	0.580	0.600	0.493	0.576	0.600	0.482	0.506
Period 2	0.600	0.635	0.587	0.570	0.518	0.555	0.540	0.479	0.477
Period 3	0.600	0.541	0.597	0.540	0.498	0.528	0.480	0.393	0.437
Period 4	0.600	0.569	0.597	0.510	0.446	0.505	0.420	0.386	0.401
Period 5	0.600	0.561	0.600	0.480	0.466	0.484	0.360	0.292	0.357
Period 6	0.600	0.567	0.600	0.450	0.435	0.467	0.300	0.271	0.310
Period 7	0.600	0.576	0.597	0.420	0.331	0.445	0.240	0.201	0.256
Period 8	0.600	0.575	0.601	0.390	0.311	0.409	0.180	0.082	0.199
Period 9	0.600	0.562	0.605	0.360	0.364	0.354	0.120	0.119	0.147
Period 10	0.600	0.582	0.605	0.330	0.311	0.310	0.060	0.016	0.042

*True vaccine efficacy used in the simulations

** Means over 100 simulations

Table 5. Comparison between true* vaccine efficacy and estimated vaccine efficacies using descriptive method and Durham's method in Pakistan**

	No Waning VE			Moderate Waning VE			Severe Waning VE		
	True	Descriptive	Durham	True	Descriptive	Durham	True	Descriptive	Durham
Period 1	0.600	0.535	0.560	0.600	0.555	0.571	0.600	0.585	0.562
Period 2	0.600	0.545	0.568	0.570	0.521	0.555	0.540	0.460	0.532
Period 3	0.600	0.568	0.543	0.540	0.513	0.532	0.480	0.454	0.492
Period 4	0.600	0.578	0.582	0.510	0.526	0.513	0.420	0.386	0.462
Period 5	0.600	0.572	0.602	0.480	0.432	0.489	0.360	0.347	0.398
Period 6	0.600	0.603	0.611	0.450	0.367	0.463	0.300	0.171	0.344
Period 7	0.600	0.590	0.617	0.420	0.382	0.425	0.240	0.168	0.268
Period 8	0.600	0.569	0.618	0.390	0.364	0.387	0.180	0.118	0.185
Period 9	0.600	0.595	0.620	0.360	0.280	0.346	0.120	0.084	0.104
Period 10	0.600	0.577	0.615	0.330	0.317	0.312	0.060	-0.079	0.011

*True vaccine efficacy used in the simulations

** Means over 100 simulations

Table 6. Proportion of simulations where the hypothesis of no VE waning was rejected

	NO Waning			Moderate Waning			Severe Waning		
	Durham	Tian	TDC	Durham	Tian	TDC	Durham	Tian	TDC
Bangladesh	0.01	0.03	0.02	0.23	0.20	0.18	0.63	0.55	0.55
India	0.04	0.02	0.03	0.18	0.14	0.013	0.25	0.21	0.22
Nepal	0.04	0.06	0.04	0.17	0.15	0.08	0.36	0.31	0.34
Pakistan	0.08	0.07	0.08	0.23	0.21	0.19	0.54	0.48	0.48

Table 7. Estimated change in VE per period (Δ) using descriptive method and Durham's method

	No waning True $\Delta = 0$		Moderate waning True $\Delta = -0.03$		Severe waning True $\Delta = -0.06$	
Country	Descriptive	Durham	Descriptive	Durham	Descriptive	Durham
Bangladesh	0.004	<0.001	-0.032	-0.035	-0.054	-0.058
India	0.008	<0.001	-0.028	-0.027	-0.051	-0.054
Nepal	0.001	0.002	-0.024	-0.028	-0.054	-0.049
Pakistan	0.005	0.008	-0.031	-0.029	-0.067	-0.061

6.2 Figures

Figure 1. Plot of Estimated VE (Durham's Method) for Bangladesh

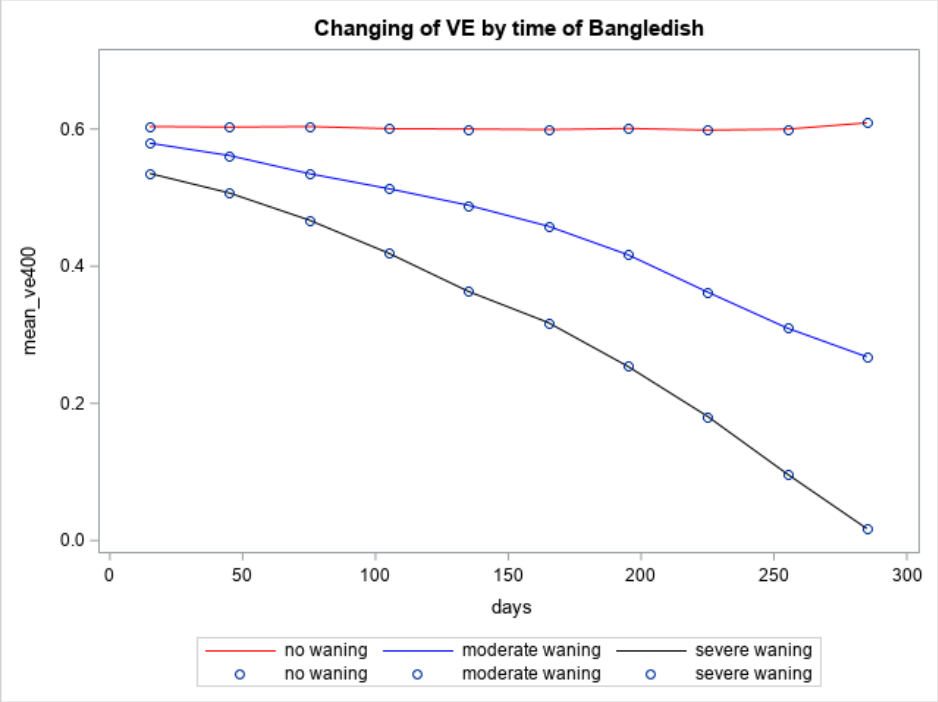

Figure 2. Plot of Estimated VE (Durham's Method) for India

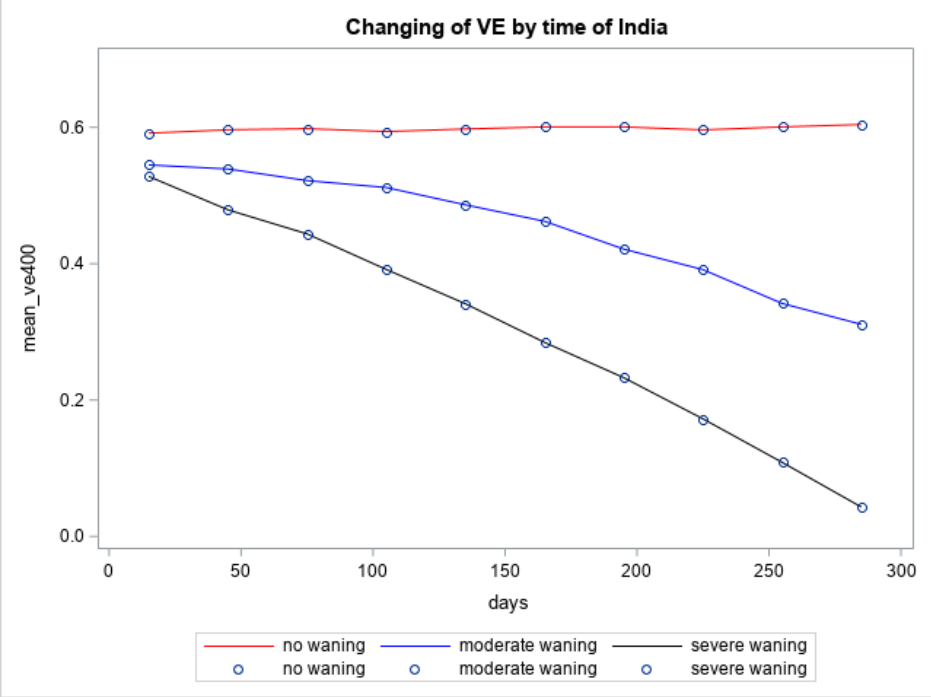

Figure 3. Plot of Estimated VE (Durham's Method) for Nepal

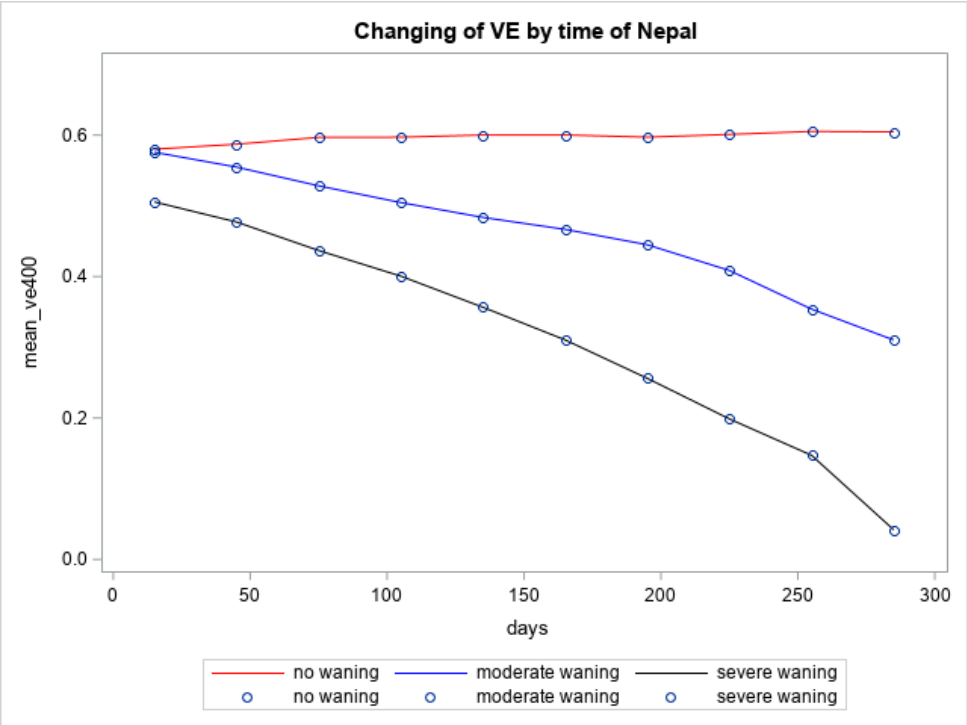

Figure 4. Plot of Estimated VE (Durham's Method) for Pakistan