

Bayesian Meta-Analysis to Validate Correlate of Protection for High Vaccine Efficacy Clinical Trials

Igwebuike Enweonye and Edith Uzoma Umeh

Abstract—In clinical trials, a correlate (surrogate) of protection (CoP) endpoint must be properly validated through rigorous sound methods before it may be approved for use. The validation of surrogate in the context of high vaccine efficacy trials, however, poses great challenge due to sparse data; and conventional methods for statistical validation of surrogate are no longer adequate. Although idea of surrogacy was developed in the context of a single trial, the meta-analytic approach, which allows both individual and trial level surrogacy, has become well accepted. However, the meta-analytic joint bivariate full models suffer computational issues. To ease the challenge, aggregate data may be used but it leads to loss of information. In this manuscript the direct application of individual level (instead of aggregate) data in a Bayesian Hierarchical Modelling framework was proposed. The proposed method uses reduced bivariate models with trial specific random effects of treatment on the endpoints and no correlated residuals. Simulated data consist several scenarios, each of which has 5000 participants data, 50 subgroups (used as trials) characterised by size of 100 participants per trial randomised in the ratio 1:1 to vaccinated and unvaccinated treatment groups. The meta-analysis showed improved quality of the CoP compared to literature based on aggregate data. There were no computational issues with the proposed hierarchical model.

Index Terms—Validation, Surrogate, clinical endpoint, Bayesian, Hierarchical Modelling.

I. INTRODUCTION

To evaluate a vaccine's efficacy, it is generally useful to identify the level of an immune marker above which vaccinees have a defined probability of being protected. It is called the *protective threshold*, and is used to calculate the *protective response rate* [1]. During clinical development, if such a protective threshold (otherwise known as correlate of protection) is known, one can then define a level (a titer, a concentration or a fold change) above which the vaccinated subject has responded to the vaccine, that is, the *vaccine response threshold*, and it's used to calculate the *response rate* [1]. However, during clinical development, vaccine correlate of protection is generally unknown [2]. A number of disease areas suffer unmet medical needs; warranting that treatments are approved quickly for the patients and health care providers. Vaccines are mostly given as prophylactics - of which the true clinical endpoint is difficult to measure and clinical development relies largely on immunogenicity endpoints.

When clinical endpoints of primary interest are hard to measure, or unethical, surrogate endpoints may be used in lieu [3]. Surrogate endpoints are useful when they can be measured earlier, more conveniently, or more frequently than the true endpoints [4]. The use of surrogate endpoints in clinical trials is increasing, necessitating the development of sound statistical methods in the validation process [5]. Before a surrogate endpoint can be accepted in place of a true clinical outcome, it must demonstrate sufficient evidence, including evidence from epidemiological studies and clinical trials. Between 2010 and 2012, the United States Food and Drug Administration (US FDA) approved 45 percent of new drugs applications based on various surrogate endpoints. If a surrogate endpoint clearly predicts a beneficial effect through appropriate studies, its use generally allows for more efficient drug development programs [6].

[7] formalized a definition of surrogate endpoints, and outlined how they could be validated, and discussed intrinsic limitations in the surrogate marker validation quest, in the case of a single trial and single surrogate endpoint. His landmark paper became the beginning of the statistical validation of surrogate endpoints. Prentice suggests that surrogate endpoint S should capture any relationship between the treatment Z and the true endpoint T . That is, a test of H_0 of no effect of treatment on surrogate is equivalent to a test of H_0 of no effect of treatment on true endpoint [7]. The approach was criticized as too stringent and not straightforward to verify, leading to other proposals [8] [9] and [10]. But now the meta-analysis which allows both individual and trial level surrogacy has become a well accepted method of validation.

A. Meta-analytic Approach

Meta-analysis provides an elegant solution for combining information across related studies to evaluate treatment efficacy. The evaluation of a surrogate endpoint within the meta-analytic setting has been discussed, among others, by [2] [8] [11] [12] and [13]. A first formal Bayesian approach was given by [11] for a case where individual data are not available. [8] extended these ideas using the theory of linear mixed-effects models. In the first stage of their model, they introduced full-fixed effects, and random effects in the second stage. [12] extended it further using generalized estimating equations (GEE) methodology. The authors applied meta-analysis with normally distributed endpoints and proposed a two-stage model for the evaluation of the potential surrogate [13].

A hierarchical framework for assessing immunological correlates of protection in vaccine trials was proposed by

DOI: <http://dx.doi.org/10.24018/ejcompute.2022.2.1.34>

Published on February 26, 2021.

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[14], while [15] provided the relationship between the causal-inference and meta-analytic approach. [13] investigated Bayesian evaluation of surrogate endpoints using individual level data with normally distributed true and surrogate endpoints. [16] discussed meta-analytic validation with binary outcomes. They adopted a latent variable approach, with the assumption that the observed binary variables result from dichotomizing an unobserved continuous variable based on certain threshold.

Among the authors, only [2] offered a statistical solution for assessing correlates of protection in vaccine trials. They investigated a true Bernoulli distributed endpoint and a normally distributed surrogate endpoint with aggregated data. Also, they performed separate linear regression of regression of surrogate on treatment and then true endpoint on treatment for each of the subgroups (trials) and then did a weighted linear regression of the slope of the true endpoint on the slope of the surrogate.

II. MATERIALS AND METHODS

Data sets which include both true clinical and surrogate outcomes were simulated. Each scenario has a size of 5000 participants consisting 50 subgroups (used as trials) characterised by a size of 100 participants per trial randomised in the ratio 1:1 to vaccinated and unvaccinated treatment groups. Bayesian hierarchical model using Markov Chain Monte Carlo (MCMC) method was applied to each simulated scenario. The model combined non-informative prior (NIP) distributions with simulated data as likelihood to obtain the posterior information for inference. Each MCMC simulation has 3 parallel chains, adapting every 1000 steps, 1000 draws were discarded as burn-in samples, and another 10000 draws were used for inference. Standard inference calls R to run the model through JAGS and extract predicted values for the monitored parameters, covariance matrix between random treatment effects of the endpoints, D , and coefficient of determination, R^2 .

Let S_{ij} and T_{ij} represent the continuous and binary underlying values of the surrogate and the true endpoints, respectively, for subject j in trial i and Z_{ij} an indicator for treatment effect. The meta-analytic framework in the single trial setting is considered, in which the units are randomized subgroups of centers. At the first level of the hierarchical bayesian meta-analytic approach we specify a bivariate model as follows:

$$S_{ij} = \mu_S + m_{Si} + (\alpha + a_i)Z_{ij} + \varepsilon_{Sij} \quad (1)$$

$$\text{logit}(T_{ij} = 1) = \mu_T + m_{Ti} + (\beta + b_i)Z_{ij} \quad (2)$$

where μ_S and μ_T are fixed intercepts, m_{Si} and m_{Ti} are trial specific random intercepts, α and β are fixed effects of treatment Z on the endpoints in trial i , a_i and b_i are the trial specific random effects of treatment on the endpoints. That a subject j in trial i has the disease is depicted with $T_{ij} = 1$. The error structure ε_{Sij} are surrogate associated normally distributed random error terms with mean zero and variance

$\sigma_{\mu_S}^2$. The random effects (m_{Si} , m_{Ti} , a_i , b_i) are assumed to be mean-zero normally distributed with covariance matrix

$$\mathbf{D} = \begin{pmatrix} d_{SS} & d_{ST} & d_{Sa} & d_{Sb} \\ & d_{TT} & d_{Ta} & d_{Tb} \\ & & d_{aa} & d_{ab} \\ & & & d_{bb} \end{pmatrix} \quad (3)$$

The surrogate endpoint validation is captured by means of the quantity, the trial-level R^2 . Provided (3) is positive definite, then it follows that,

$$R^2_{trial} = R^2_{b_i|m_{Si},a_i} = \frac{\begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}^T \begin{pmatrix} d_{SS} & d_{Sa} \\ d_{Sa} & d_{aa} \end{pmatrix}^{-1} \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}}{d_{bb}} \quad (4)$$

The above generalised model is reduced by kicking out the trial-specific intercept and the error term in (1) and the trial-specific intercept in (2), assuming full mediation, leading to,

$$S_{ij} = \mu_S + (\alpha + a_i)Z_{ij} + \varepsilon_{Sij} \quad (5)$$

$$\text{logit}(T_{ij} = 1) = \mu_T + (\beta + b_i)Z_{ij} \quad (6)$$

where,

$$\begin{pmatrix} \mu_S \\ \mu_{TL} \end{pmatrix} \sim N \left[\begin{pmatrix} \alpha_0 + \alpha_1 \cdot Z_{ij} \\ \beta_0 + \beta_1 \cdot Z_{ij} \end{pmatrix}, \Sigma \right] \quad (7)$$

μ_S is mean surrogate, μ_{TL} is mean logit T and Σ is the variance-covariance matrix between the quantities μ_S and μ_{TL} .

And,

$$\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N \left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathbf{D} \right], \mathbf{D} = \begin{pmatrix} d_{aa} & d_{ab} \\ d_{ab} & d_{bb} \end{pmatrix} \quad (8)$$

The R^2 for the reduced models becomes,

$$R^2_{trial(r)} = R^2_{b_i|a_i} = \frac{d_{ab}^2}{d_{aa}d_{bb}} \quad (9)$$

The true clinical endpoint is assumed to follow Bernoulli distribution with parameters n_T being the number of subjects and p_T the probability of being protected by vaccination. The fixed treatment effects α_0 , α_1 , β_0 and β_1 , corresponding to the CoP and the vaccination status are normally distributed with mean 0 and variances $\tau_{\alpha_0}^2$, $\tau_{\alpha_1}^2$, $\tau_{\beta_0}^2$ and $\tau_{\beta_1}^2$ respectively.

At the second level of the hierarchical model, the priors for the fixed effects are specified. For NIP models the following hyper-priors are specified:

$$\begin{aligned}
\theta_T &\sim \text{Bern}[p_T], \\
\alpha_0 &\sim N(0, \tau_{\alpha 0}^2), \\
\alpha_1 &\sim N(0, \tau_{\alpha 1}^2), \\
\beta_0 &\sim N(0, \tau_{\beta 0}^2), \\
\beta_1 &\sim N(0, \tau_{\beta 1}^2), \\
\theta_{\mu_s}^{-2} &\sim U(0, 100), \\
\tau_{\alpha 0}^{-2} &\sim \text{Gamma}(10^{-4}, 10^{-4}), \\
\tau_{\alpha 1}^{-2} &\sim \text{Gamma}(10^{-4}, 10^{-4}), \\
\tau_{\beta 0}^{-2} &\sim \text{Gamma}(10^{-4}, 10^{-4}), \\
\tau_{\beta 1}^{-2} &\sim \text{Gamma}(10^{-4}, 10^{-4}),
\end{aligned} \tag{10}$$

Next, a prior distribution for the association between the treatment effects of the two endpoints and the random effects are specified. As the hyper-prior distribution for the variance-covariance matrices Eqn. 7 and 8, a Wishart distribution is assumed:

$$\begin{aligned}
D^{-1} &\sim \text{Whishart}(R_D) \\
\Sigma^{-1} &\sim \text{Whishart}(R_\Sigma)
\end{aligned} \tag{11}$$

The trial-level surrogacy is assessed using the posterior means for the coefficients of determination. A good surrogate can be adopted when R^2 is sufficiently large. However, statistics is just one aspect of the many judgments that are considered before a final adoption of a surrogate. Other considerations may include, but not limited to clinical and epidemiological judgments as deemed fit by the experts.

A. Software

Markov chain simulation is based on drawing values of θ from approximate distributions and then correcting those draws to better approximate the target posterior distribution, $p(\theta|y)$ [17], [18]. The sampling is sequential, with the distribution of sampled draws depending on the last value drawn; hence, the draws for a Markov chain. In the context of probability theory, a Markov chain is an integer-time process, $\{X_n \geq 0\}$, for which the sample values for each random variable X_n , $n \geq 1$, lie in a countable set S and depends on the past only through the most recent random variable X_{n-1} , [19]. For all positive integers n , and for all choices of i, j, k, \dots, l in S ,

$$\begin{aligned}
Pr\{X_n = j | X_{n-1} = i, X_{n-2} = k, \dots, X_0 = l\} = \\
Pr\{X_n = j | X_{n-1} = i\}
\end{aligned} \tag{12}$$

for all conditioning events $X_{n-1} = i, X_{n-2} = k, \dots, X_0 = l$ of positive probability [19].

Gibbs Sampling is MCMC methods which involves successive sampling from the complete conditional densities. Samples may be drawn from standard densities or non-standard densities [20]. If the full conditionals are non-standard but of a certain mathematical form, then adaptive rejection sampling [21] may be used within the Gibbs sampling for those parameters. In other cases, alternative schemes based on the Metropolis-Hastings algorithm, may be used to sample from non-standard densities [22]. [20] [17] and [18] discussed the

working of MCMC algorithms. Modeling was performed using Just Another Gibbs Sampler in R (RJAGS) as an interface to JAGS (JAGS 4.3.0 release July 18 2017). In JAGS there is no flexibility of specifying any one sampling method rather it runs as a black box and chooses the most efficient sampling method among those available.

III. DATA SIMULATION, MODELLING AND RESULTS

A. Simulation of Data

Data was simulated with a true binary outcome and a continuous surrogate, using the reduced models in Eq.(5) and (6) without random intercepts. Each scenario has sample size $N=5000$ and consists of 50 trials and 100 subjects per trial with a 1:1 randomisation to either vaccinated and unvaccinated groups. Our Simulation recreated the same data used in Callegaro & Tibaldi (2019) with these parameters: $\mu_S = 4.609$; $\mu_T = (-2.0, -3.5, -4.0, 4.5, -5.0, -5.6, -7)$; $\alpha = 5.458$; $\beta = (-1.43, -1.45, -1.7591, -3)$; $Var(a_i) = 10$; $Var(b_i) = 4$. The correlation between the treatment random effects is $\rho = Cor(a_i, b_i) = \sqrt{0.9}$, with $R^2 = 0.9$.

A total of 70 scenarios in R with a range of vaccine efficacy (VE = 0.75, 0.82, 0.95, 0.96, 0.97, 0.98 and 1) were simulated. Vaccine efficacy is expressed as:

$$VE = \left(1 - \frac{P(T=1|Z=1)}{P(T=1|Z=0)}\right) 100\% \tag{13}$$

where $P(T=1|Z=1)$ and $P(T=1|Z=0)$ are the the probabilities of disease among vaccinated and unvaccinated individuals, respectively.

The small subgroups were used as units for the meta-analysis. For VE=95% the simple statistics of the simulated data are shown in Table I and Table II. Table I presents the distribution of participants by trial and treatment group. The summary statistics of the simulated continuous surrogate endpoint is displayed in Table II. And the distribution of diseased participants by trial and treatment group is presented in Table III.

Table I shows the size of all the 50 trials used as subunits in the meta-analysis (VE=95%). A total of 5,000 individual data were generated. Each of the 50 different trials has a size of $n=100$ with 50 subjects on either vaccinated or unvaccinated groups.

Table II shows the summary statistics of the simulated continuous surrogate endpoint for the 50 trials used as subunits in the meta-analysis (VE=95%). The mean for each trial surrogate, standard deviation as well as minimum and maximum surrogate values are displayed.

From Tables III and IV, $n_1 = 73$ and $n_2 = 1540$ vaccinated and unvaccinated subjects who also got the disease. It gives a total of 1613 diseased subjects in both treatment groups. Using Eq. (13), it can be shown that VE=95% for these data.

TABLE I
DISTRIBUTION OF PARTICIPANTS BY TRIAL AND TREATMENT GROUP

Trial	Treatment Unvaccinated	Vaccinated	Total
1	50	50	100
2	50	50	100
3	50	50	100
4	50	50	100
5	50	50	100
6	50	50	100
7	50	50	100
8	50	50	100
9	50	50	100
10	50	50	100
11	50	50	100
12	50	50	100
13	50	50	100
14	50	50	100
15	50	50	100
16	50	50	100
17	50	50	100
18	50	50	100
19	50	50	100
20	50	50	100
21	50	50	100
22	50	50	100
23	50	50	100
24	50	50	100
25	50	50	100
26	50	50	100
27	50	50	100
28	50	50	100
29	50	50	100
30	50	50	100
31	50	50	100
32	50	50	100
33	50	50	100
34	50	50	100
35	50	50	100
36	50	50	100
37	50	50	100
38	50	50	100
39	50	50	100
40	50	50	100
41	50	50	100
42	50	50	100
43	50	50	100
44	50	50	100
45	50	50	100
46	50	50	100
47	50	50	100
48	50	50	100
49	50	50	100
50	50	50	100
Total	2500	2500	5000

TABLE II
SUMMARY STATISTICS OF THE SIMULATED CONTINUOUS
SURROGATE ENDPOINT

Trial	N	Mean	Std Dev	Minimum	Maximum
1	100	5.581438	6.1651858	-8.777572	22.885934
2	100	4.837318	7.8500809	-15.144460	24.032939
3	100	4.267704	6.9706549	-10.524979	17.334508
4	100	4.904133	10.616876	-16.456664	24.207671
5	100	5.277160	13.702893	-21.938412	30.055330
6	100	5.035137	5.7989486	-9.398212	17.210702
7	100	4.050326	5.6114143	-10.972088	15.879384
8	100	4.858999	8.1021170	-11.305976	22.873098
9	100	4.466606	8.9696209	-12.676011	22.772712
10	100	4.182363	7.1674432	-18.756919	19.798907
11	100	3.501445	9.1579968	-16.062646	21.133237
12	100	4.164714	7.6470250	-13.184587	20.527125
13	100	4.609674	7.5609869	-9.475160	22.699017
14	100	4.745974	9.9425728	-18.114636	27.753646
15	100	4.880797	6.1425425	-12.334095	14.804802
16	100	4.384276	7.1194461	-11.213029	19.169553
17	100	5.180079	6.1556448	-8.981596	20.045202
18	100	4.904610	11.046530	-17.752468	30.708110
19	100	5.553957	8.6872886	-13.770109	32.432280
20	100	4.190875	5.2559122	-8.506581	13.363654
21	100	4.771295	7.7088417	-16.978198	22.759771
22	100	4.070592	5.8188742	-13.195764	17.282023
23	100	5.095078	6.9626785	-18.721462	23.932188
24	100	3.765213	5.5350100	-9.847606	18.733710
25	100	4.964316	6.7875249	-13.862187	25.635083
26	100	4.913065	5.9643540	-14.698751	21.459851
27	100	4.619510	5.6488913	-8.483222	15.407704
28	100	3.734606	7.8461926	-15.301765	20.093127
29	100	4.436181	6.2002855	-10.716768	24.624555
30	100	4.053188	12.493655	-23.087152	28.316030
31	100	4.395517	5.6881188	-8.688193	20.487168
32	100	4.119432	6.2146165	-13.838350	18.221781
33	100	4.701447	8.7476955	-14.662209	22.561478
34	100	4.683116	6.5561742	-9.382967	25.893110
35	100	4.527117	7.4434411	-12.651727	20.697940
36	100	4.069786	5.7621704	-8.866993	15.964277
37	100	3.734505	9.2712482	-17.766321	27.337677
38	100	5.027859	5.2845974	-7.032070	16.449617
39	100	4.876242	8.9533238	-12.741366	22.629380
40	100	4.367727	5.7649069	-9.865854	17.288580
41	100	3.950626	8.3180258	-13.645328	19.983897
42	100	4.827151	12.277922	-18.825413	26.358662
43	100	4.315786	8.5729784	-15.243096	20.136459
44	100	4.790851	7.0193751	-13.537639	20.207349
45	100	4.543627	8.5230425	-14.644288	20.885733
46	100	4.870899	8.5394262	-14.255570	20.150958
47	100	4.749415	7.1898926	-14.807515	23.182370
48	100	5.121407	8.3375612	-11.139927	20.640268
49	100	4.533490	6.0677157	-18.546704	24.117296
50	100	5.409503	8.9605473	-19.800214	24.616188

TABLE III
DISTRIBUTION OF DISEASED PARTICIPANTS BY TRIAL AND TREATMENT
GROUP

Trial	Treatment Unvaccinated	Vaccinated	Total
1	36	0	36
2	13	0	13
3	34	0	34
4	8	4	12
5	0	20	20
6	47	0	47
7	49	0	49
8	9	3	12
9	27	2	29
10	31	0	31
11	11	1	12
12	34	1	35
13	33	0	33
14	17	0	17
15	43	0	43
16	42	0	42
17	40	0	40
18	23	0	23
19	12	2	14
20	46	0	46
21	30	1	31
22	48	0	48
23	42	0	42
24	50	0	50
25	46	1	47

TABLE IV

DISTRIBUTION OF DISEASED PARTICIPANTS BY TRIAL AND TREATMENT GROUP

Trial	Treatment Unvaccinated	Vaccinated	Total
26	35	0	35
27	47	0	47
28	24	1	25
29	32	0	32
30	1	21	22
31	42	0	42
32	46	0	46
33	36	1	37
34	34	0	34
35	18	0	18
36	49	0	49
37	7	1	8
38	50	0	50
39	25	2	27
40	47	0	47
41	36	1	37
42	7	5	12
43	31	0	31
44	39	1	40
45	22	0	22
46	31	3	34
47	38	0	38
48	14	1	15
49	48	0	48
50	10	1	11
Total	1540	73	1613

B. Modelling

We specified the reduced models in (5) and (6) without random intercepts as well as the noninformative priors. The simulated data were loaded and prior values specified for MCMC. 1000 samples were used for burn in while 10,000 iterations for inference. The sampler adapts its behaviour to maximize their efficiency after every 1000 iterations. The Trace plots, Figures (1) and (2) reveal the stability and proper mixing of the parameters R^2 and variance-covariance matrix across the 3 parallel chains.

C. Results

The coefficient of determination R^2 estimated by Bayesian model as a function of VE are presented in Table V. For an empirical comparison the data for VE=75%, 82% and 95% are compared with logistic, Firths and WIP models [19]. Those methods were based on two-stage approach. The results show that the Bayesian model outperform R^2 all models with the smallest standard deviations. The comparison shows very strong correlation, R^2 value (0.99), between a_i and b_i , the trial specific random effects of treatment on the surrogate and the true outcome respectively for the Bayesian model. The correlation between treatment effect on the true outcome (β_i) and the treatment effect on the surrogate ($\hat{\alpha}_i$) are observed with an estimated R^2 of (0.24, 0.51 and 0.54) for logistic, Firth and Gelman's WIP models [19], all performing less than

the Bayesian model, value =0.99 for vaccine efficacy of 95%. The trend is similar for all vaccine efficacies and the Bayesian R^2 show near perfect surrogacy and less biased.

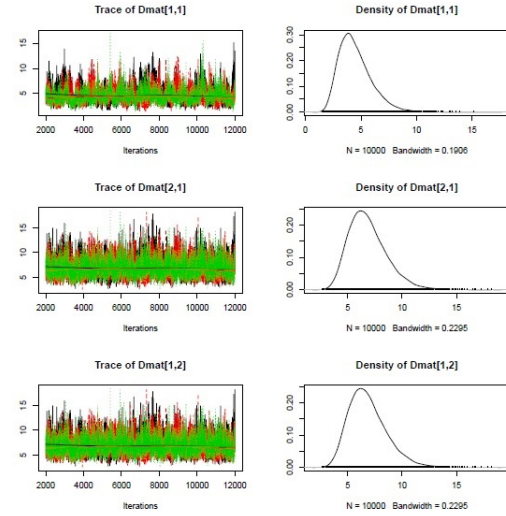


Fig. 1. Trace plots (NIP) model: Dmat[1,1], Dmat[2,1], Dmat[1,2]

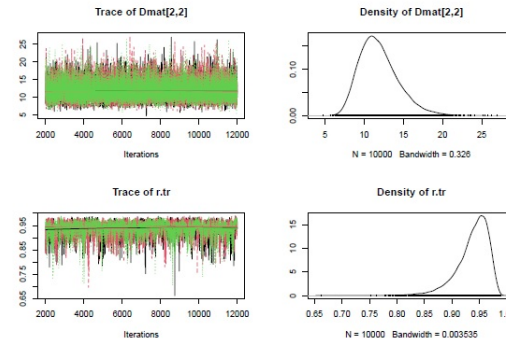
Fig. 2. Trace plots (NIP) model: Dmat[2,2], r.tr (R^2)

TABLE V

ESTIMATED R^2 (MEAN, MEDIAN, STANDARD ERROR, 95% CONFIDENCE INTERVALS AND MSE) FOR DIFFERENT MODELS AND VALUES OF VES

Model	VE	Mean (R^2)	Median (R^2)	Std (R^2)	95% LL	95% UL	MSE (R^2)
WIP	0.75	0.71	0.72	0.09	0.51	0.85	0.05
Firth	0.75	0.72	0.73	0.09	0.54	0.86	0.04
Logistic	0.75	0.59	0.61	0.16	0.24	0.84	0.12
Bayesian	0.75	0.90	0.90	0.04	0.90	0.90	0.00
WIP	0.82	0.71	0.72	0.10	0.48	0.87	0.05
Firth	0.82	0.73	0.75	0.09	0.52	0.87	0.04
Logistic	0.82	0.52	0.54	0.22	0.03	0.85	0.19
Bayesian	0.82	0.89	0.89	0.04	0.89	0.89	0.00
WIP	0.95	0.70	0.71	0.11	0.45	0.87	0.05
Firth	0.95	0.72	0.74	0.10	0.48	0.88	0.04
Logistic	0.95	0.46	0.49	0.26	0.01	0.86	0.26
Bayesian	0.95	0.81	0.85	0.14	0.81	0.81	0.00

Table V and Figure (3) show an empirical comparison of the hierarchical bayesian approach for VE= 95% with previous

models [2] whose methods were based on two-stage approach. The results show that the Bayesian model outperforms all other models with the least mean square error (MSE) < 0.0001 . The comparison shows very strong correlation, R^2 value (0.99), between a_i and b_i , the trial specific random effects of treatment on the surrogate and the true outcome respectively for the Bayesian model. The correlation between treatment effect on the true outcome ($\hat{\beta}_i$) and the treatment effect on the surrogate ($\hat{\alpha}_i$) are observed with an estimated $R^2 = 0.24, 0.51$ and 0.54 for logistic, Firth and Gelman's WIP models respectively [2]. For the Bayesian model $R^2 = 0.99$. The trend is similar for all other vaccine efficacy results showing the Bayesian model performing better and with least MSE.

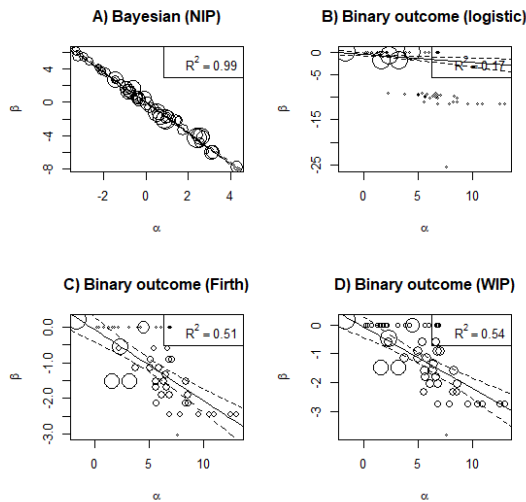


Fig. 3. Bayesian approach compared to Callegaro & Tibaldi (2019). Panels: (a) Bayesian model using Non Informative Prior (NIP); (b) original data results (logistic results on the dichotomised outcome); (c) Firth logistic results on the dichotomised outcome; (d) Weakly Informative Prior (WIP) logistic results on the dichotomised outcome

IV. DISCUSSIONS

Clinical trials are very expensive and can be lengthy yet the problem of getting treatments to the patient population that need them persists. This is putting pressure on the Pharmaceutical companies who are continuously searching for smarter ways of delivering treatments quicker. One way of achieving an accelerated clinical intervention would be through the use a substitute endpoint that is easier, faster and less expensive to measure in lieu of the clinical endpoint. An intermediate clinical endpoint is called surrogate (correlate) of protection (CoP) in the context of vaccine. The current situation with COVID-19 global epidemic and lock-down is a typical scenario where the use surrogate endpoint would be beneficial. And health authorities are becoming more open to possibilities to discuss innovations that can support accelerated approvals of treatments. For example, between 2010 and 2012, the US Food and Drug Administration (FDA) approved 45 percent of new drugs based on a surrogate endpoint [6].

Before a surrogate endpoint can be accepted in place of a clinical outcome, we need sufficient evidence, including evidence from epidemiological studies and clinical trials. Usually

clinical trials are needed to show that the surrogate endpoint can be relied upon to predict, or correlate with, clinical benefit in a context of use [6], [8]. Surrogate endpoints that have undergone extensive testing are called validated surrogate endpoints. Any other short of that will not be accepted by healthy authorities. Validation of surrogate is an exercise with a completed study; and whether the results can be extrapolated to a new study, and to what extent, is always a decision for the clinical team.

A substitute clinical endpoint must be properly validated through rigorous sound methods. The Prentice methods and the meta-analytic are the drivers for statistical validation of surrogate endpoints. High vaccine efficacy trials, however, pose great challenge due to sparse data and conventional methods for statistical validation of surrogate are no longer adequate. Statistical methods tailored towards validating substitute clinical endpoints in high vaccine efficacy trials are not well developed in literature. The Prentice method is suited for validation of single trial and has given way to meta-analysis. And the meta-analytic framework which allows surrogate validation in multiple trials face many computational issues [10]. This report extended the simulation study of [2], through direct application of individual trial data in a meta-analytic framework using Bayesian Hierarchical Modelling paradigm. We applied reduced bivariate model with trial specific random effects of treatment on the endpoints with no correlated residuals.

As clinical data is not readily available, 70 data scenarios with a range of vaccine efficacy (VE = 75% to 100%) were simulated. Each scenario has a size of 5000 participants, randomization in a ratio 1:1 to either vaccinated or unvaccinated groups to 50 trials (n=100), for each trial. It was followed by the application of Bayesian hierarchical models using Markov Chain Monte Carlo (MCMC) simulation with non-informative prior (NIP) distributions. For each MCMC model in RJAGS, 3 parallel chains were requested, and adapting the simulation every 1000 steps, 1000 draws were discarded as burn-in samples, and 10000 draws were used for inference.

V. CONCLUSIONS

A reduced bivariate model with trial specific random effects of treatment on the endpoints with no correlated residuals was applied. The results indicate that the Bayesian model outperforms the other comparators, logistic, Firth and Gelman's WIP models [2] at every vaccine efficacy. The Bayesian model consistently produced near perfect surrogate R^2 with the least mean square error (MSE). And there are no convergence issues if the model is simplified without correlated residuals.

ACKNOWLEDGMENT

The authors would like to thank the Nnamdi Azikiwe University for supporting the work.

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