Methods and Applications

A Novel Adaptive Design Approach for Early-Phase Clinical Trials to Optimize Vaccine Dosage

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ABSTRACT

Introduction: Vaccines are a cornerstone of global health, with their efficacy and safety dependent on appropriate dosage determination. Early-phase vaccination trials face significant challenges due to minimal toxicity and nonmonotonic dose response curves, creating a major obstacle in vaccine development. To address this gap, we propose a novel Bayesian phase I/II trial design for dose response curves exhibiting plateau or unimodal patterns to identify the optimal biological dose (OBD), effectively balancing efficacy and toxicity.

Methods: We employ a logistic dose-efficacy design that makes dose-escalation and de-escalation decisions while simultaneously considering both efficacy and safety parameters. Extensive simulation studies evaluate the performance of this design.

Results: Comparative analyses with commonly used vaccine dose-finding designs demonstrate that our method excels in identifying the optimal toxicity-efficacy trade-off, offering both simplicity and accuracy. Sensitivity analyses across various prior settings confirm the robustness and efficiency of our approach. Additionally, our design provides a user-friendly framework for clinicians, with superior operating performance compared to existing designs, particularly in terms of accuracy and robustness.

Discussion: Our innovative Bayesian design represents a significant advancement in addressing the inherent challenges of early-phase vaccination clinical trials, offering improved accuracy and efficacy in vaccine dosage determination.

Vaccines are a cornerstone of global health, offering immense potential for significant clinical benefits. Recent global infectious disease outbreaks have underscored the urgent need for novel and innovative clinical trial designs. The current use of outdated methods, such as directly adopting dose-finding trials from oncology treatments, may result in suboptimal dosing decisions for vaccines. For example, early-phase oncology clinical trials have focused primarily on assessing toxicity, while most vaccines have minimal toxicity but uncertain efficacy. Therefore, the primary objective of early-phase vaccine clinical trials is to determine efficacy before toxicity. Continuing to use traditional dose-finding methods will likely lead to suboptimal dosing.

Vaccine clinical trials are inherently more unpredictable than most first-in-human trials because of the complex and variable nature of immune system responses, which cannot be easily extrapolated from animal studies (*1*). Another reason for selecting suboptimal vaccine doses is the variability in dose response curves among different vaccines. For example, vaccines for HIV, malaria, adenovirus (Ad35), and influenza exhibit peaked dose response curves, indicating that there is a minimum dose that elicits no response, followed by rapid escalation and a plateau above a certain dose threshold (*2*).

Current methods to optimize vaccine doses are predominantly empirical (*3*), whereas the drug development field employs advanced quantitative methodologies for dosing determination (*4*–*7*), accelerating decision-making. Numerous studies have outlined phase I clinical trial designs aimed at determining the maximum tolerable dosage (MTD) of cytotoxic anticancer drugs, based on the incidence of dose-limiting toxicity (DLT) (*8*). These designs assume that the toxicity and efficacy curves of cytotoxic drugs exhibit monotonicity (*9*), meaning that as the dose increases, both toxicity and efficacy increase predictably (*10*). However, most existing dose-finding designs are unsuitable for vaccine studies without modifications because of the unique properties of vaccines and various other factors (*11*).

Vaccines investigated in early-phase clinical trials aim to determine doses that are safe and immunogenic for subsequent efficacy studies. Ensuring both efficacy and safety is contingent upon appropriate dosage

determination (*12*). To overcome the challenges mentioned above, we propose a novel Bayesian phase I/II trial design for dose-finding, specifically addressing the issues of minimal toxicity and nonmonotonic dose response curves. Our method separately models efficacy and toxicity and is tailored for dose response curves exhibiting plateaued or unimodal patterns. The participants are adaptively assigned to the dose that optimizes both the efficacy and safety profiles. Our design is computationally easy to implement and facilitates clear and straightforward decision-making for dose escalation and de-escalation.

The remainder of the article is organized as follows. In Section 2, we introduce the novel Bayesian phase I/II trial design. Section 3 details a simulation study that investigates the operating characteristics of our proposed design and compares it with existing designs. The interpretation of the simulation results is provided in Section 4. Section 5 conducts a sensitivity analysis to evaluate the robustness of our proposed design. Finally, we conclude with a discussion in Section 6.

METHODS

Toxicity Monitoring

We assume that the number of individuals experiencing DLT events at dose level i, denoted by x_i, follows a binomial distribution $binom(n_i, \rho)$, where n_i is the sample size at dose level i and ρ is the true, but unknown, toxicity probability. To incorporate prior knowledge, we specify a beta(α, β) prior distribution for ρ (detailed rationale is provided at Supplementary Material, available at https://weekly.chinacdc.cn/).

Based on the observed data x_i and n_i from the trial, we construct the likelihood function. Using Bayesian updating, we derive the posterior distribution of ρ as beta$(\alpha + x_i, \beta + n_i - x_i)$, from which the posterior probability $P(\rho > \pi|H)$ is calculated, where π represents the target toxicity rate and H denotes the accumulated trial data. To ensure monotonicity in toxicity, isotonic transformation is applied to the probability. If $P(\rho > \pi|H)$ exceeds the prespecified toxicity threshold T, the current dose level i is deemed excessively toxic. Consequently, this dose level is excluded from further consideration for subsequent participant cohorts, ensuring participant safety and optimizing dose selection.

Efficacy Endpoint

We assume that y_i out of n_i individuals experience efficacy at dose level i, where τ_i is the efficacy probability and d_i denotes the dosage at dose level i. Additionally, we specify a lower boundary of the efficacy rate ϕ for futility monitoring. For the efficacy endpoint, we employ a logistic regression model specified as follows:

$$\log\left(\frac{\tau_i}{(1-\tau_i)}\right) = a + b \times d_i + c \times d_i^2, i = 1, \ldots, I \quad (1)$$

The detailed mathematical derivation and explanation for efficacy monitoring are provided at Supplementary Material.

In the Bayesian framework, we specify the Cauchy distribution for the unknown parameters following Gelman's recommendation (*13*):

$$a \sim Cauchy(0, 10)$$

$$b \sim Cauchy(0, 2.5)$$

$$c \sim Cauchy(0, 2.5)$$

The likelihood function $L(H|a, b, c)$ is proportional to:

$$\prod_{i=1}^{I}\left(\frac{e^{a+b\times d_i+c\times d_i^2}}{1+e^{a+b\times d_i+c\times d_i^2}}\right)^{y_i}\left(\frac{1}{1+e^{a+b\times d_i+c\times d_i^2}}\right)^{n_i-y_i} \quad (2)$$

By integrating the prior distribution with the likelihood function and employing Markov Chain Monte Carlo (MCMC) sampling, we derive posterior distributions for the parameters: a, b, and c, where convergence diagnostics are conducted using trace plots. Leveraging this model, we predict the dose associated with peak efficacy given the current dataset, thus providing guidance for dose decision-making.

Dose Escalation Rules

The proposed Bayesian logistic dose-finding method follows a systematic approach:

Initial cohort treatment: Administer the first cohort of participants at the lowest dose or a prespecified dose level i.

Interim data collection: At dose level i, collect interim data where n_i patients have been treated (calculated as the cohort size multiplied by the number of recruited cohorts), with x_i experiencing toxicity and y_i showing an immune response.

Toxicity monitoring: Based on the interim data, identify doses where $P(\rho > \pi|H) < T$ and consider them as safe doses. If no safe dose is identified, the trial should be terminated, and no optimal biological dose (OBD) should be declared.

Efficacy monitoring: Determine the dose level i^* with the highest posterior estimate of efficacy

probability τ to treat the next cohort.

Iteration: Steps 2 and 3 are repeated until the maximum sample size is reached. At the end of the trial, the posterior estimate of the efficacy probability τ of all doses is calculated based on the final dataset.

OBD selection: Select the final OBD using the following criteria:

a. If $\tau > \phi$, declare the dose with an efficacy probability of τ as the OBD.

b. If $\tau < \phi$, declare no OBD due to ineffectiveness.

The dose escalation process is illustrated in a flow chart (Figure 1).

Simulation

To evaluate the performance of our proposed design, we conducted extensive simulation studies across six distinct scenarios (Figure 2). These scenarios were carefully selected to comprehensively assess the proposed method under typical conditions encountered in phase I/II clinical trials. We based our scenario settings on a vaccine trial example (*14*) (Supplementary Materials). Across all scenarios, dose-toxicity curves were assumed to increase monotonically, while we considered various dose-response relationships that might occur in vaccine clinical trials. For all scenarios, we specified a target toxicity rate of $\pi = 0.2$, a prespecified toxicity threshold of $T = 0.8$, and a lower boundary of the efficacy rate $\phi = 0.2$. The simulations employed a cohort size of 3 participants with a maximum of 30 participants for the entire trial.

RESULTS

We conducted simulation studies across six

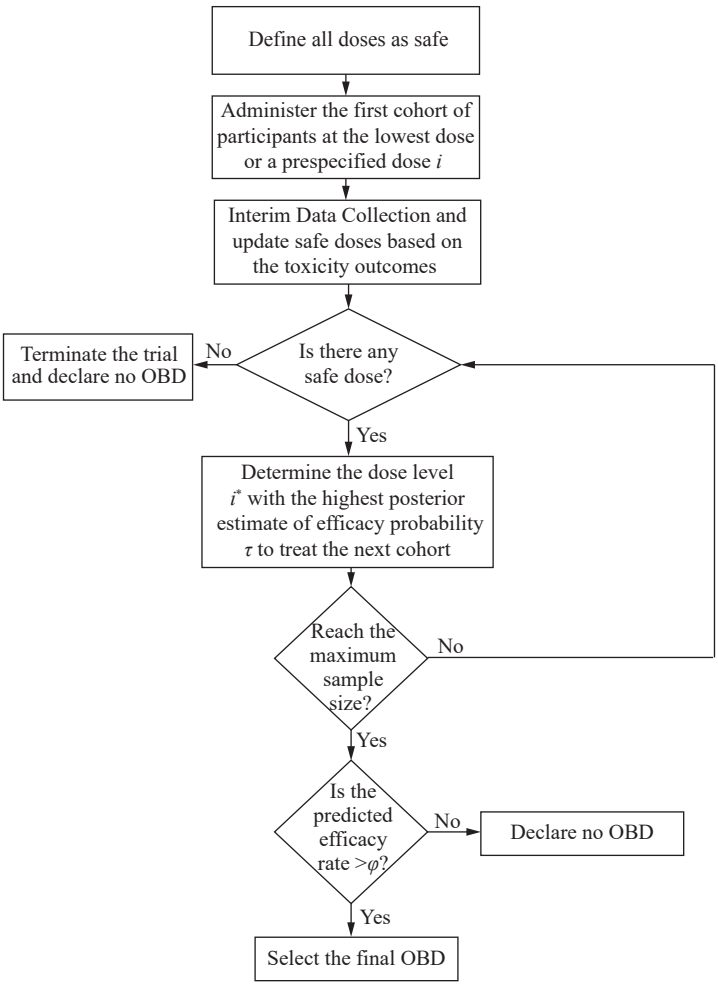

FIGURE 1. Dose escalation decision flow chart.
Note: φ means the lower boundary of efficacy rate.
Abbreviation: OBD=optimal biological dose.

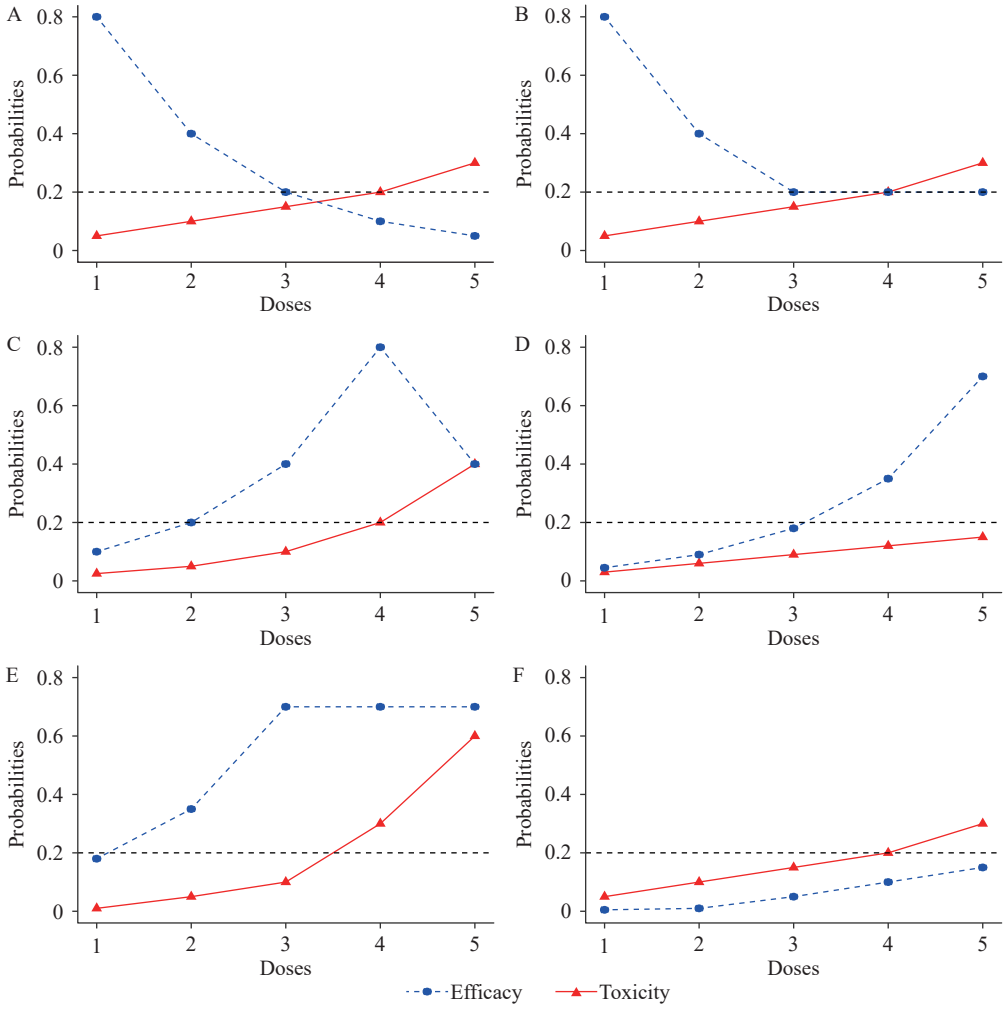

FIGURE 2. Six dose-toxicity and dose-efficacy scenarios considered in the simulation study. A–F represent scenarios 1–6, respectively.
Note: The red solid line represents DLT rate ρ; the blue dashed line represents the immune response probability τ; the horizontal dashed line represents at π= 0.2.

scenarios, each with 5,000 replications, to evaluate the performance of our proposed Bayesian logistic dose-finding method compared with the traditional 3+3 design (*15*) and the EffTox design (*5*). For each simulation, we report the percentages of different doses selected, the average percentages of participants treated at each dose, and the average percentages of DLTs and immune responses (Supplementary Materials). Overall, while the EffTox design achieved near-perfect metrics in certain scenarios, it demonstrated significant instability and variability across different scenarios. Similarly, the 3+3 design showed inadequate performance in both OBD identification and participant allocation. In contrast, our proposed Bayesian logistic dose-finding method demonstrated superior performance across all scenarios, accurately identifying the OBD, optimizing participant allocation, and maintaining robustness across diverse clinical situations.

Sensitivity Analysis

To assess the robustness of our proposed design under different conditions, we conducted a sensitivity analysis by varying prior distributions and sample sizes. The consistency of the OBD selection results highlighted the model's flexibility and reliability in guiding dose-finding decisions.

Varying Prior Distributions

We tested the impact of different prior distributions by modifying the scale parameters of a, b to values of (1,2,3,4,5) according to Andrew Gelman (*13*). As shown in Figure 3, regardless of variations in the prior parameters, the final results remained largely consistent

TABLE 1. Percentages of the different doses selected, the average percentages of participants treated at each dose level, and the average percentages of DLTs and immune responses.

Design		Dose level						Efficacy (%)	Toxicity (%)
		1	2	3	4	5	No*		
					Scenario 1				
	True efficacy	**0.800**	0.400	0.200	0.100	0.050			
	True toxicity	**0.050**	0.100	0.150	0.200	0.300			
Logistic	Selection (%)	**79.2**	11.8	3.6	2.4	2.8	0.2	61.9	9.7
	Patients(%)	**71.3**	7.9	3.7	3.4	13.7			
3+3	Selection (%)	**9.0**	17.3	20.4	25.5	25.5	2.4	–	14.7
	Patients(%)	**21.7**	23.0	22.4	18.8	14.1			
EffTox	Selection (%)	**99.0**	0	0	0	0	1.0	–	–
	Patients(%)	**99.0**	0	0	0	0			
					Scenario 2				
	True efficacy	**0.800**	0.400	0.200	0.200	0.200			
	True toxicity	**0.050**	0.100	0.150	0.200	0.300			
Logistic	Selection (%)	**74.7**	9.5	5.3	5.7	4.6	0.2	61.5	10.8
	Patients(%)	**67.2**	5.9	4.3	6.2	16.5			
3+3	Selection (%)	**9.1**	16.9	20.6	25.2	25.6	2.7	–	14.7
	Patients(%)	**21.7**	23.0	22.3	19.0	14.0			
EffTox	Selection (%)	**99.0**	0	0	0	0	1.0	–	–
	Patients(%)	**98.7**	0.3	0	0	0			
					Scenario 3				
	True efficacy	0.100	0.200	0.400	**0.800**	0.400			
	True toxicity	0.025	0.050	0.100	**0.200**	0.400			
Logistic	Selection (%)	10.7	2.8	21.1	**51.6**	8.9	5.0	46.0	19.4
	Patients(%)	24.2	2.5	11.4	**34.7**	27.2			
3+3	Selection (%)	2.4	9.1	25.9	**42.8**	19.0	0.7	–	15.2
	Patients(%)	19.5	20.4	22.1	**22.0**	16.1			
EffTox	Selection (%)	11.0	25.0	32.0	**20.0**	5.0	7.0	–	–
	Patients(%)	28.7	26.3	21.7	**12.7**	6.0			
					Scenario 4				
	True efficacy	0.045	0.090	0.180	0.350	**0.700**			
	True toxicity	0.030	0.060	0.090	0.120	**0.150**			
Logistic	Selection (%)	3.5	1.3	3.9	19.4	**63.6**	8.3	51.4	12.3
	Patients(%)	15.5	1.5	3.8	15.1	**64.1**			
3+3	Selection (%)	3.8	7.3	11.2	14.6	**62.1**	1.0	–	9.3
	Patients(%)	19.6	20.8	21.0	20.2	**18.4**			
EffTox	Selection (%)	1.0	4.0	20.0	13.0	**41.0**	21.0	–	–
	Patients(%)	16.0	15.0	21.7	13.3	**20.0**			
					Scenario 5				
	True efficacy	0.180	0.350	**0.700**	0.700	0.700			
	True toxicity	0.010	0.050	**0.100**	0.300	0.600			
Logistic	Selection (%)	12.8	10.7	**53.1**	22.0	0.1	1.3	55.6	19.6
	Patients(%)	23.4	6.4	**29.3**	27.9	13.0			

Continued

Design		Dose level						Efficacy (%)	Toxicity (%)
		1	2	3	4	5	No*		
3+3	Selection (%)	2.5	9.5	**43.3**	41.1	3.4	0.1	–	17.4
	Patients(%)	19.8	21.7	**23.1**	24.3	11.1			
EffTox	Selection (%)	38.0	28.0	**26.0**	6.0	1.0	2.0	–	–
	Patients(%)	49.0	27.3	**14.7**	6.3	1.0			
				Scenario 6					
	True efficacy	0.005	0.010	0.050	0.100	0.150			
	True toxicity	0.050	0.100	0.150	0.200	0.300			
Logistic	Selection (%)	0.4	0.1	0.9	8.5	7.2	82.9	7.4	17.0
	Patients(%)	35.6	2.0	8.6	24.2	29.5			
3+3	Selection (%)	9.8	16.7	21.2	24.5	24.8	2.9	–	14.7
	Patients(%)	21.9	23.4	22.3	18.7	13.7			
EffTox	Selection (%)	0	0	1.0	5.0	9.0	85.0	–	–
	Patients(%)	10.3	10.3	10.7	10.0	7.7			

Note: No*, the probability for declaring no OBD due to ineffectiveness; The bold values are the results of the true optimal biological dose. "–" means the method does not involve this result.
Abbreviation: Logistic=our proposed design; 3+3=3+3 design; EffTox=EffTox design; Selection (%)=the percentage of correct OBD selection; Patients (%)=the average percentage of patient allocation at the correct OBD; Efficacy (%)=the average percentages of immune responses; Toxicity (%): the average percentages of DLTs; OBD=optimal biological dose; DLT=dose-limiting toxicity.

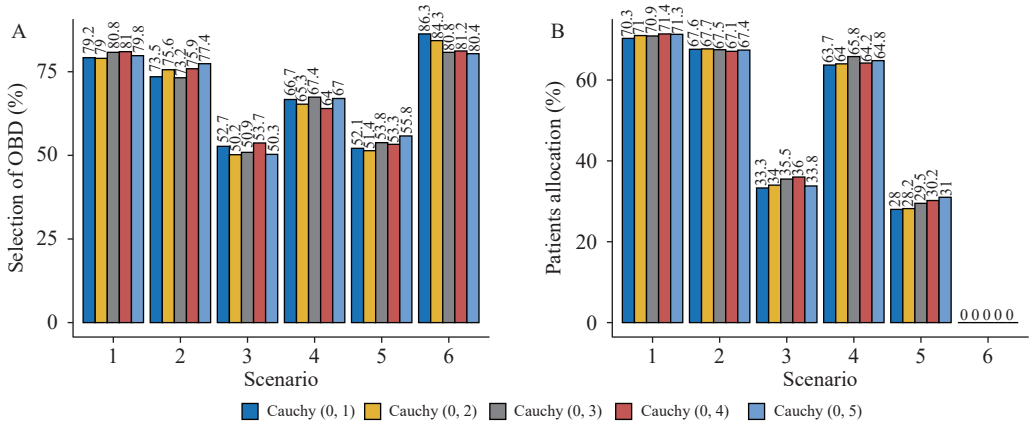

FIGURE 3. Results of sensitivity analysis for different prior settings. A shows the percentage of correct dose selection, B shows the average percentage of participants treated at each dose level under different prior settings.
Note: Different colors represent different prior distributions.
Abbreviation: OBD=optimal biological dose.

across all simulation scenarios. Changes in scale parameter did not significantly affect either the selection of the OBD or the average percentage of participants treated at the OBD. These results indicate that our design is relatively insensitive to variations in the prior distribution within the tested range. The underlying data tables are shown in Supplementary Table S1 (available at https://weekly.chinacdc.cn/).

Varying Sample Sizes

We also evaluated the impact of different sample sizes by increasing the sample sizes to ranges of 30 and 120 participants in four representative simulation settings, corresponding to scenarios presented in Figure 2. Supplementary Figure S1 (available at https://weekly.chinacdc.cn/) shows that larger sample sizes resulted in a stable or higher average percentage of OBD selections, suggesting that more extensive data collection improves both the precision and stability of dosage decision-making. The underlying data tables are shown in Supplementary Table S2 (available athttps://weekly.chinacdc.cn/).

The sensitivity analysis demonstrates that our proposed design maintains consistent performance despite variations in prior distributions and sample sizes, highlighting its reliability and stability under different conditions.

DISCUSSION

Vaccines are fundamental to global health efforts and offer significant clinical benefits. Early-phase clinical trials are crucial for identifying doses that are both safe and immunogenic, establishing the foundation for subsequent efficacy studies. However, these trials face significant challenges, including minimal toxicity within dose ranges and nonmonotonic dose response curves. Existing dose-finding designs often prove inadequate or require substantial modifications to address the unique properties of vaccines. In this study, we proposed a novel Bayesian phase I/II trial design specifically tailored for vaccine dose-finding. Given that current methods for optimizing vaccine doses are predominantly empirical, we compared our approach with the traditional 3+3 design and the EffTox design. Our results demonstrated that our method excels in balancing the toxicity–efficacy trade-off and optimally allocating participants. The proposed design offers simplicity and accuracy, providing a more effective alternative to traditional methods. Additionally, extensive sensitivity analyses across various prior settings confirmed the robustness and efficiency of our approach, underscoring its reliability in different scenarios. By offering a more precise and reliable framework for dose determination, our Bayesian design addresses the inherent challenges of early-phase vaccination trials, promising enhanced efficacy and safety in vaccine dosage determination.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the National Natural Science Foundation of China (Project Nos. 82404383 to Mengyi Lu, 82173620 and 82373690 to Yang Zhao, 82204156 to Dongfang You, and 82473732 to Fang Shao).

doi: 10.46234/ccdcw2025.097

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Submitted: August 15, 2024
Accepted: April 09, 2025
Issued: April 25, 2025

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SUPPLEMENTARY MATERIAL

Rationale for Beta Distribution as Prior for Toxicity Monitoring

The Beta distribution with hyperparameters α, β is selected as the prior distribution for toxicity rate for two primary reasons. First, the toxicity rate is a probability value ranging between 0 and 1, and the Beta distribution is naturally defined over this interval, making it inherently suitable for modeling probabilities or proportions. Second, in Bayesian analysis, the Beta distribution serves as the conjugate prior for the binomial distribution: when toxic events follow a binomial distribution, combining prior information with observed data yields a posterior distribution that remains a Beta distribution due to conjugacy. This property significantly simplifies the toxicity monitoring process.

The selection of hyperparameters α and β can incorporate prior knowledge from historical data from similar vaccine trials. In this paper, we assume that all investigational doses are safe and eligible for testing during toxicity monitoring before any patients are treated in the trial, meaning $P(\rho > \pi|H) < T$ for all untreated doses. To achieve this goal, we optimize the hyperparameters to satisfy Beta(π, α, β)>1−T, ensuring that all doses meet the initial safety criteria.

Detailed Mathematical Derivation and Explanation for Efficacy Monitor

The efficacy endpoint τ_i, which ranges between 0 and 1, is transformed using a logit transformation before establishing a regression relationship with dose. To account for the potential non-monotonic relationship between vaccine efficacy and dose, the model incorporates both linear (d_i) and quadratic (d_i^2) terms to accommodate this characteristic.

$$\log\left(\frac{\tau_i}{(1-\tau_i)}\right) = a + b \times d_i + c \times d_i^2, i = 1, \ldots, I$$

In this formula, a represents the intercept, indicating the baseline efficacy when the dose is zero. The coefficients b and c correspond to the linear and quadratic terms, respectively, enabling the model to capture the fundamental trend of efficacy with respect to dose.

Basis for Simulation Scenario Configuration

The simulation settings were primarily based on existing vaccine dosage research from multiple clinical trials and

SUPPLEMENTARY TABLE S1. The percentage of correct OBD selection, the average percentage of patient allocation at the correct OBD with varying prior parameter settings. (Underlying data tables for Figure 3).

Scenario		Cauchy (0, 1)	Cauchy (0, 2)	Cauchy (0, 3)	Cauchy (0, 4)	Cauchy (0, 5)
1	Selection (%)	79.2	79.0	80.8	81.0	79.8
	Patients (%)	70.3	71.0	70.9	71.4	71.3
2	Selection (%)	73.5	75.6	73.2	75.9	77.4
	Patients (%)	67.6	67.7	67.5	67.1	67.4
3	Selection (%)	52.7	50.2	50.9	53.7	50.3
	Patients (%)	33.3	34.0	35.5	36.0	33.8
4	Selection (%)	66.7	65.3	67.4	64.0	67.0
	Patients (%)	63.7	64.0	65.8	64.2	64.8
5	Selection (%)	52.1	51.4	53.8	53.3	55.8
	Patients (%)	28.0	28.2	29.5	30.2	31.0
6	Selection (%)	86.3	84.3	80.8	81.2	80.4
	Patients (%)	–	–	–	–	–

Note: "–" means no patient allocation due to no OBD declared.
Abbreviation: OBD=optimal biological dose; Selection (%)=the percentage of correct OBD selection; Patients (%)=the average percentage of patient allocation at the correct OBD.

SUPPLEMENTARY TABLE S2. The percentage of correct OBD selection, the average percentage of patient allocation at the correct OBD with varying sample size. (Underlying data tables for Supplementary Figure S1)

Sample size	Scenario 1		Scenario 2		Scenario 5		Scenario 6	
	Selection (%)	Patients (%)	Selection (%)	Patients (%)	Selection (%)	Patients (%)	Selection (%)	Patients (%)
30	79.2	71.3	74.7	67.2	53.1	29.3	82.9	–
39	81.3	73.6	77.7	68.7	59.8	36.0	85.6	–
48	84.8	74.9	78.6	70.8	65.3	40.3	88.2	–
57	85.9	76.8	81.8	72.4	67.0	43.5	88.6	–
66	86.8	77.8	85.3	73.2	69.6	48.1	90.3	–
75	86.0	79.0	85.1	74.6	68.2	49.7	92.1	–
84	89.3	79.7	84.8	76.2	73.9	52.8	93.8	–
93	89.3	80.7	86.5	76.5	74.5	55.0	92.9	–
102	88.4	81.4	85.9	77.2	74.9	55.7	92.3	–
111	89.3	81.8	87.6	78.6	74.4	57.5	93.4	–
120	89.2	83.0	88.1	79.1	75.4	58.8	92.8	–

Note: "–" means no patient allocation due to no OBD declared; Selection (%)=the percentage of correct OBD selection; Patients (%)=the average percentage of patient allocation at the correct OBD.
Abbreviation: OBD=optimal biological dose.

clinician recommendations, with particular inspiration from a clinical trial of the 24-valent pneumococcal conjugate vaccine (VAX-24). This trial assessed safety, tolerability, and immunogenicity across three dose levels: Low (1.1 mcg), Mid (2.2 mcg), and Mixed (2.2/4.4 mcg). Since vaccine doses increased in multiples, vaccine efficacy in our simulation settings was defined to vary proportionally. All treatment groups exhibited robust opsonophagocytic activity (OPA) geometric mean titers (GMTs) against the serotypes included in the vaccine, serving as a key efficacy indicator. For example, with serotype 1, the trial results showed efficacy (measured by OPA GMTs) of 190.08, 317.62, and 228.09 for the three respective dose levels. These findings suggest that vaccine efficacy may increase with higher doses (e.g., scenarios Sce3 and Sce4), decrease with higher doses (e.g., scenarios Sce1 and Sce3), or plateau (e.g., scenarios Sce2 and Sce5). Beyond these foundational scenarios, we also considered a case where vaccine efficacy remains uniformly low across all doses to evaluate the method's ability to exclude ineffective doses.

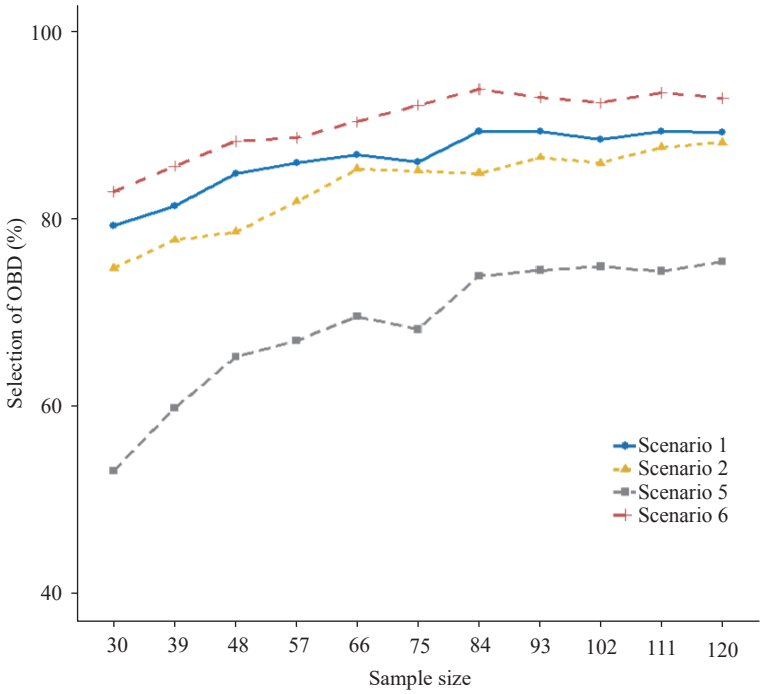
Overview of EffTox and 3+3 Dose-finding Designs

The 3+3 design is a traditional dose-escalation trial method primarily used to identify the MTD based on toxicity. The process begins by enrolling three patients at the starting dose level. If no DLTs occur, the trial progresses to the next higher dose. If one DLT is observed, three additional patients are treated at the same dose. The MTD is defined as the highest dose where no more than one out of six patients experiences a DLT.

EffTox is a Bayesian adaptive dose-finding method that combines efficacy and toxicity outcomes to identify the optimal biological dose (OBD) in clinical trials. The method requires investigators to predefine two thresholds: a fixed upper limit A_T on the probability of toxicity and a fixed lower bound A_E on the probability of efficacy. Another approach uses an efficacy–toxicity trade-off to quantify each dose's desirability and employs an efficacy–toxicity trade-off contour as a criterion to select each cohort's optimal dose.

Interpretation of Operating Characteristics Metrics

For the simulation results, the operating characteristics of the design are evaluated based on the percentage of correctly identifying the true OBD and the average percentage of participants treated at the true OBD. These metrics, with higher values indicating better performance, reflect the probability of accurately determining the true OBD and efficiently allocating participants to it. Additionally, we report the average percentages of DLTs and immune responses, which indicate the toxicity and efficacy of each dose. From a participant safety and benefit perspective, lower DLT percentages are preferable, while higher immune response percentages are more desirable.



SUPPLEMENTARY FIGURE S1. Percentage of the OBD selection, the average percentage of participants treated at OBD with varying sample sizes.
Note: Different colors represent the corresponding scenarios.

Detailed Interpretation of Simulation Results

In Scenario 1, the proposed design recommended dose 1 as the OBD in 79.2% of simulations, with 71.3% of participants allocated to this dose, significantly outperforming the 3+3 design. Scenario 2 demonstrated similar superiority of the proposed design over the 3+3 design, while the EffTox design achieved nearly perfect metrics. In Scenario 3, the proposed design recommended the OBD 51.6% of the time, more than double the rates of the 3+3 (22.0%) and EffTox (20.0%) designs. In Scenario 4, the proposed design recommended the OBD 63.6% of the time and allocated 64.1% of participants to the OBD, compared to 62.1% and 41.0% for the 3+3 and EffTox designs, respectively. In Scenario 5, the proposed design maintained a higher OBD recommendation rate (53.1%) compared to the 3+3 (43.3%) and EffTox (26.0%) designs. The proposed design demonstrated exceptional robustness in Scenario 6, correctly identifying no suitable OBD in 82.9% of simulations, vastly outperforming the 3+3 design (2.9%).