

Chapter 358

Non-Inferiority Tests for Vaccine Efficacy using the Ratio of Two Negative Binomial Rates

Introduction

This module provides power analysis and sample size calculation for non-inferiority tests for vaccine efficacy (VE) using the ratio of two negative binomial incidence rates.

VE is a traditional index of the protective efficacy of a vaccine. It is calculated as

$$VE = \frac{\lambda_1 - \lambda_2}{\lambda_1} = 1 - \frac{\lambda_2}{\lambda_1}$$

where λ_2 and λ_1 are *incidence rates* of the disease being studied among those vaccinated with a new vaccine and those not vaccinated with the new vaccine. An incidence rate is the average number of events per subject per unit of time. An analysis of vaccine effectiveness reduces to an analysis of the ratio of two incidence rates.

Note that because $\lambda_2 < \lambda_1$ (because lower rates are better), the value of $VE < 1$.

The calculation details are found in Zhu (2017). Some of the details are summarized below.

Technical Details

Definition of Terms

The following table presents the various terms that are used.

Group	1 (Control)	2 (Treatment)
Sample size	N_1	N_2
Individual event rates	λ_1	λ_2
Dispersion parameter:	φ (Negative binomial dispersion)	
Average exposure time:	μ_t	
Non-inferiority margin ratio:	R_0 ($R_0 < 1$)	
Non-inferiority VE boundary:	VE_0 ($VE_0 < 1$)	
Sample size ratio:	$\theta = N_2/N_1$	

Hypotheses

When higher rates are worse, the non-inferiority test hypotheses are

$$H_0: \frac{\lambda_2}{\lambda_1} \geq R_0 \quad \text{vs.} \quad H_1: \frac{\lambda_2}{\lambda_1} < R_0$$

where $R_0 < 1$.

In terms of VE , the statistical hypothesis tested by the non-inferiority test can be written as

$$H_0: VE \leq VE_0 \quad \text{vs} \quad H_1: VE > VE_0.$$

Note that $VE_0 = 1 - R_0$.

Sample Size and Power Calculations

Sample Size Calculation

Zhu (2017) bases the sample size calculations on a non-inferiority test derived from a *negative binomial regression* model. The sample size calculation is

$$N_1 \geq \frac{(z_\alpha \sqrt{V_0} + z_\beta \sqrt{V_1})^2}{(\log R_0 - \log(\lambda_2/\lambda_1))^2}$$

$$N_2 = \theta N_1$$

where

$$V_1 = \frac{1}{\mu_t} \left(\frac{1}{\lambda_1} + \frac{1}{\theta \lambda_2} \right) + \frac{(1 + \theta)\varphi}{\theta}$$

$$R_0 = 1 - VE_0$$

and V_0 may be calculated in any of 3 ways.

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V_0 Calculation Method 1 (using assumed true rates)

$$V_{01} = \frac{1}{\mu_t} \left(\frac{1}{\lambda_1} + \frac{1}{\theta \lambda_2} \right) + \frac{(1 + \theta)\varphi}{\theta}$$

Using Method 1, V_0 and V_1 are equal.

V_0 Calculation Method 2 (fixed marginal total)

$$V_{02} = \frac{(1 + R_0\theta)^2}{\mu_t R_0 \theta (\lambda_1 + \theta \lambda_2)} + \frac{(1 + \theta)\varphi}{\theta}$$

V_0 Calculation Method 3 (restricted maximum likelihood estimation)

$$V_{03} = \frac{2a}{\mu_t (-b - \sqrt{b^2 - 4ac})} \left(1 + \frac{1}{\theta R_0} \right) + \frac{(1 + \theta)\varphi}{\theta}$$

where

$$a = -\varphi \mu_t R_0 (1 + \theta),$$

$$b = \varphi \mu_t (\lambda_1 R_0 + \theta \lambda_2) - (1 + \theta R_0),$$

$$c = \lambda_1 + \theta \lambda_2$$

Zhu (2017) did not give a recommendation regarding whether Method 1, 2, or 3 should be used, except to say that “for many scenarios, Methods 1 and 2 gave the smallest and largest sample sizes, respectively, while the sample sizes given by Method 3 were between the other two methods and had the closest simulated power values to the targeted power.”

Power Calculation

The corresponding power calculation to the sample size calculation above is

$$Power \geq 1 - \Phi \left(\frac{\sqrt{N_1} (\log R_0 - \log (\lambda_2 / \lambda_1)) - z_\alpha \sqrt{V_0}}{\sqrt{V_1}} \right)$$

Example 1 – Calculating Sample Size

Researchers wish to determine whether the average negative binomial rate of those receiving a new vaccine is not inferior to the current control. The average exposure time for all subjects is 1 year. The incidence rate of the control group is 0.1 events per year. Overdispersion is not anticipated. The desired power is 0.8 and the significance level will be 0.025. The variance calculation method used will be the restricted MLE.

How large of a sample is needed to detect a change in vaccine efficacy from -0.5 to 0.1, 0.3, 0.5?

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load this procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	Sample Size
Variance Calculation Method.....	Restricted Maximum Likelihood Estimation
Power.....	0.90
Alpha.....	0.025
$\mu(t)$ (Average Exposure Time)	1
Group Allocation	Equal (N1 = N2)
Vaccine Efficacy Input Type	Enter VE0 and VE1
VE0 (Non-Inferiority Vaccine Efficacy) ...	-0.5
VE1 (Actual Vaccine Efficacy)	0.5 0.3 0.1
λ_1 (Control Group Incidence Rate).....	0.1
ϕ (Dispersion).....	1

Annotated Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Numeric Results

Higher Event Rates Are: Worse

Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

Variance Calculation Method: Restricted Maximum Likelihood

	Average Exposure Time			Incidence Rate			Vaccine Efficacy		Dispersion		
	N1	N2	N	Cntl λ_1	N.I. Vax $\lambda_{2.0}$	Act Vax $\lambda_{2.1}$	N.I. VE0	Act VE1	ϕ	Alpha	
Power	949	949	1898	1	0.1	0.15	0.09	-0.5	0.1	1	0.025
0.90038	477	477	954	1	0.1	0.15	0.07	-0.5	0.3	1	0.025
0.90032	266	266	532	1	0.1	0.15	0.05	-0.5	0.5	1	0.025

References

Zhu, H. 2017. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' *Statistics in Biopharmaceutical Research*, 9(1), 107-115, doi:10.1080/19466315.2016.1225594.

Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2009. *Sample Size Tables for Clinical Studies*, 3rd Edition. Wiley-Blackwell. Chichester, UK.

Nauta, Jozef. 2020. *Statistics in Clinical and Observational Vaccine Studies*, 2nd Edition. Springer. Cham, Switzerland.

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Report Definitions

Power is the probability of rejecting the null hypothesis when it is false.

N_1 and N_2 are the number of subjects in groups 1 and 2, respectively.

N is the total sample size. $N = N_1 + N_2$.

$\mu(t)$ is the average exposure (observation) time across subjects in both groups.

λ_1 is the event rate per time unit in Group 1 (control).

$\lambda_{2.0}$ is the incidence rate per unit in vaccine group under the null hypothesis. This may be thought of as a non-inferiority bound for the incidence rate.

$\lambda_{2.1}$ is the incidence rate per unit in vaccine group under the alternative hypothesis.

VE_1 is the vaccine efficacy under the alternative hypothesis. $VE_1 = 1 - \lambda_{2.1} / \lambda_1$.

VE_0 is the vaccine efficacy under the null hypothesis. This may be thought of as the non-inferiority bound for vaccine efficacy.

ϕ is the negative binomial dispersion parameter. Overdispersion is modelled by setting $\phi > 1$.

Alpha is the probability of rejecting the null hypothesis when it is true.

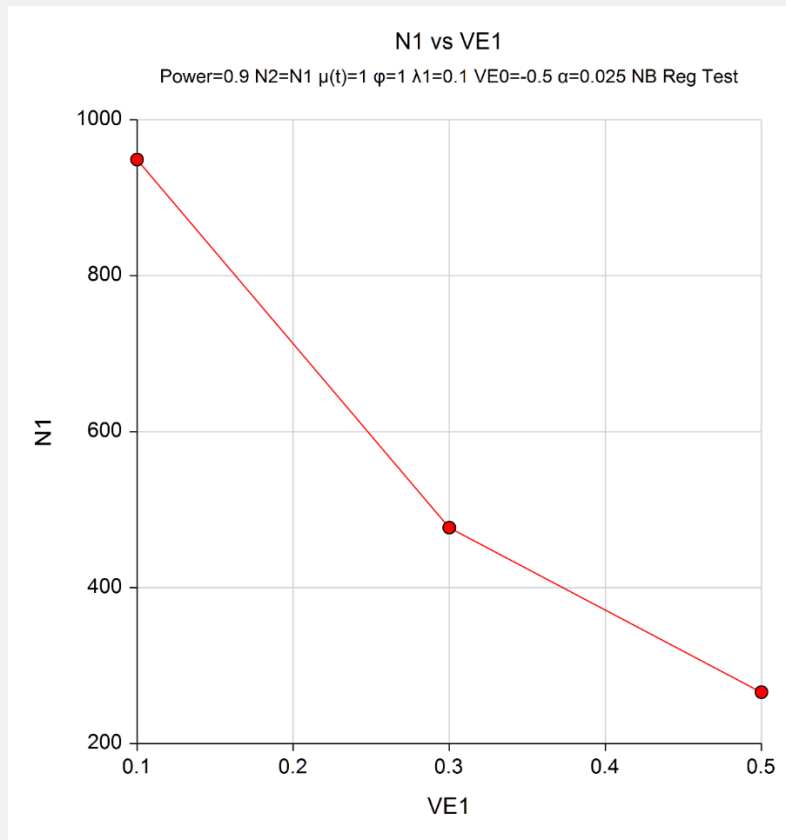
Summary Statements

A non-inferiority test of vaccine efficacy (VE) of $H_0: VE \leq VE_0$ versus $H_1: VE > VE_0$ (assuming that the data follow a negative binomial distribution and that higher event rates are worse) uses the restricted maximum likelihood estimation variance calculation method. Samples of 949 and 949 subjects with average exposure time 1 achieve 90% power to detect a vaccine efficacy of 0.1 above the VE non-inferiority bound of -0.5. The incidence rate of the control group (λ_1) is 0.1, the non-inferiority bound ($\lambda_{2.0}$) is 0.15, and the alternative hypothesis ($\lambda_{2.1}$) is 0.09. The dispersion coefficient is 1 and the significance level (alpha) is 0.025.

This report shows the sample sizes for the indicated scenarios.

Chart Section

Chart Section



This plot presents the required sample sizes for various values of VE1.

Example 2 – Validation using Zhu (2017)

Zhu (2017) presents an example of solving for sample size where lower negative binomial rates are better, the event rates are both 1.5, the dispersion is 0.24, the average duration is 0.85, the non-inferiority ratio is 1.1, the power is 0.9, and the Type I error rate is 0.025. These rates translate to $VE_0 = -0.1$ and $VE_1 = 0$.

Using the restricted MLE variance method, the sample size in each group is found to be 2372.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load this procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Variance Calculation Method.....	Restricted Maximum Likelihood Estimation
Power.....	0.9
Alpha.....	0.025
$\mu(t)$ (Average Exposure Time)	0.85
Group Allocation	Equal (N1 = N2)
Vaccine Efficacy Input Type	Enter VE0 and VE1
VE0 (Non-Inferiority Vaccine Efficacy) ...	-0.1
VE1 (Actual Vaccine Efficacy)	0
λ_1 (Control Group Incidence Rate).....	1.5
ϕ (Dispersion)	0.24

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Numeric Results												
Higher Event Rates Are:		Worse										
Hypotheses:		H0: $VE \leq VE_0$ vs. H1: $VE > VE_0$										
Variance Calculation Method:		Restricted Maximum Likelihood										
Power	N1	N2	N	Average Exposure Time $\mu(t)$	Incidence Rate			Vaccine Efficacy		Dispersion ϕ	Alpha	
					Cntl λ_1	N.I. Vax $\lambda_{2.0}$	Act Vax $\lambda_{2.1}$	N.I. VE0	Act VE1			
0.90006	2372	2372	4744	0.85	1.5	1.65	1.5	-0.1	0	0.24	0.025	

The value of $N_1 = 2372$ matches the previous procedure, so this procedure is validated.