Chapter 359

# Superiority by a Margin Tests for Vaccine Efficacy using the Ratio of Two Negative Binomial Rates

## Introduction

This module provides power analysis and sample size calculation for superiority by a margin 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 $\lambda_2$ and $\lambda_1$ 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 | $\lambda_1$ | $\lambda_2$ |
| Dispersion parameter: | $\varphi$ (Negative binomial dispersion) | |
| Average exposure time: | $\mu_t$ | |
| Superiority margin ratio: | $R_0$ ($R_0 < 1$) | |
| Superiority VE boundary: | $VE_0$ ($VE_0 < 1$) | |
| Sample size ratio: | $\theta = N_2/N_1$ | |

## Hypotheses

When higher rates are worse, the superiority by a margin 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 superiority by a margin test can be written as

$$H_0: VE \leq VE_0 \; vs \; H_1: VE > VE_0.$$

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

$$N_1 \geq \frac{\left(z_\alpha\sqrt{V_0} + z_\beta\sqrt{V_1}\right)^2}{(logR_0 - \log(\lambda_2/\lambda_1))^2}$$

$$N_2 = \theta N_1$$

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.

### $V_0$ 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)

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

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

$$Power \geq 1 - \Phi\left(\frac{\sqrt{N_1}(logR_0 - \log(\lambda_2/\lambda_1)) - z_\alpha\sqrt{V_0}}{\sqrt{V_1}}\right)$$

# Example 1 – Calculating Sample Size

Researchers wish to determine whether the average negative binomial rate of those receiving a new vaccine is superior 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 0.4 to 0.6, 0.7, 0.8?

## 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 | **0.8** |
| Alpha | **0.025** |
| μ(t) (Average Exposure Time) | **1** |
| Group Allocation | **Equal (N1 = N2)** |
| Vaccine Efficacy Input Type | **Enter VE0 and VE1** |
| VE0 (Superiority Vaccine Efficacy) | **0.4** |
| VE1 (Actual Vaccine Efficacy) | **0.6 0.7 0.8** |
| λ1 (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 | Incidence Rate | | | Vaccine Efficacy | | Dispersion | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Time | Cntl | Sup Vax | Act Vax | Sup | Act | | |
| Power | N1 | N2 | N | μ(t) | λ1 | λ2.0 | λ2.1 | VE0 | VE1 | φ | Alpha |
| 0.80002 | 1617 | 1617 | 3234 | 1 | 0.1 | 0.06 | 0.04 | 0.4 | 0.6 | 1 | 0.025 |
| 0.80012 | 620 | 620 | 1240 | 1 | 0.1 | 0.06 | 0.03 | 0.4 | 0.7 | 1 | 0.025 |
| 0.80017 | 289 | 289 | 578 | 1 | 0.1 | 0.06 | 0.02 | 0.4 | 0.8 | 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.

# Superiority by a Margin Tests for Vaccine Efficacy using the Ratio of Two Negative Binomial Rates

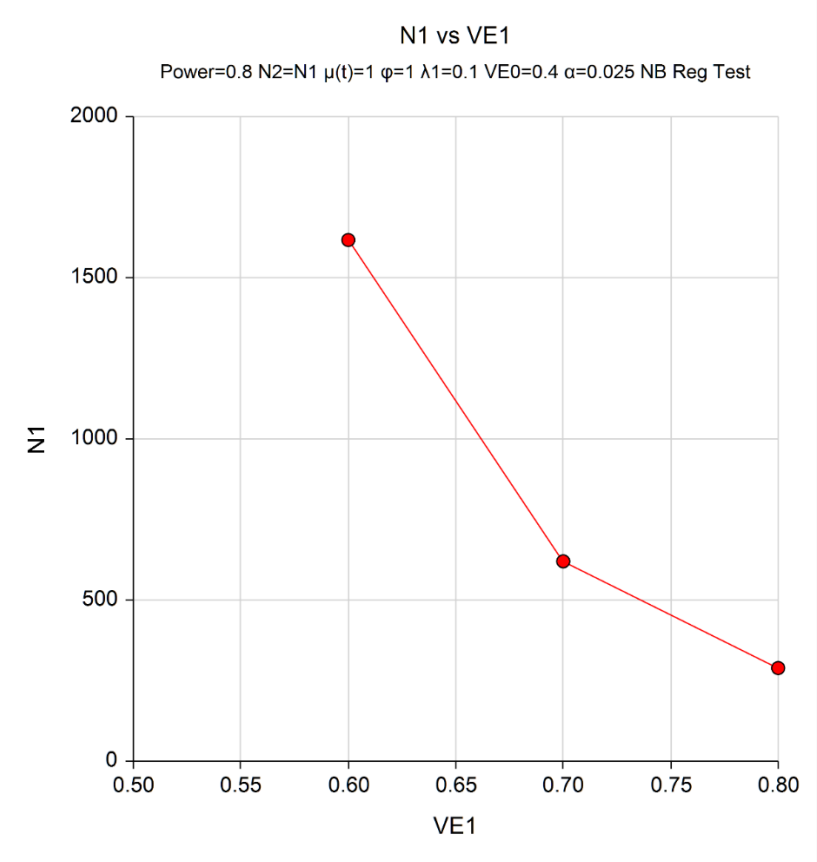
**Report Definitions**
Power is the probability of rejecting the null hypothesis when it is false.
N1 and N2 are the number of subjects in groups 1 and 2, respectively.
N is the total sample size. N = N1 + N2.
μ(t) is the average exposure (observation) time across subjects in both groups.
λ1 is the event rate per time unit in Group 1 (control).
λ2.0 is the incidence rate per unit in vaccine group under the null hypothesis. This may be thought of as a superiority bound for the incidence rate.
λ2.1 is the incidence rate per unit in vaccine group under the alternative hypothesis.
VE1 is the vaccine efficacy under the alternative hypothesis. VE1 = 1 - λ2.1 / λ1.
VE0 is the vaccine efficacy under the null hypothesis. This may be thought of as the superiority bound for vaccine efficacy.
φ is the negative binomial dispersion parameter. Overdispersion is modelled by setting φ > 1.
Alpha is the probability of rejecting the null hypothesis when it is true.

**Summary Statements**
A superiority by a margin test of vaccine efficacy (VE) of H0: VE ≤ VE0 versus H1: VE > VE0 (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 1617 and 1617 subjects with average exposure time 1 achieve 80% power to detect a vaccine efficacy of 0.6 above the superiority bound of 0.4. The incidence rate of the control group (λ1) is 0.1, the superiority bound (λ2.0) is 0.06, and the alternative hypothesis (λ2.1) is 0.04. 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 a Previously Validated Procedure

We will validate this procedure using the *Superiority by a Margin Tests for the Ratio of Two Negative Binomial Rates* procedure which has been previously validated. In that procedure, enter and run the following settings.

The desired power is 0.8 and the significance level will be 0.025. The variance calculation method used will be the restricted MLE. 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 value of R0 is 0.6 (VE0 = 0.4) and the ratio of event rates is 0.4 (VE1 = 0.6). The sample size is determined to be 1617 in each group.

## 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**.

| Option | Value |
|---|---|
| **Design Tab** | |
| Solve For | **Sample Size** |
| Variance Calculation Method | **Restricted Maximum Likelihood Estimation** |
| Power | **0.8** |
| Alpha | **0.025** |
| μ(t) (Average Exposure Time) | **1** |
| Group Allocation | **Equal (N1 = N2)** |
| Vaccine Efficacy Input Type | **Enter VE0 and VE1** |
| VE0 (Superiority Vaccine Efficacy) | **0.4** |
| VE1 (Actual Vaccine Efficacy) | **0.6** |
| λ1 (Control Group Incidence Rate) | **0.1** |
| φ (Dispersion) | **1** |

## 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cntl | Sup Vax | Act Vax | Sup | Act | | |
| Power | N1 | N2 | N | μ(t) | λ1 | λ2.0 | λ2.1 | VE0 | VE1 | φ | Alpha |
| 0.80002 | 1617 | 1617 | 3234 | 1 | 0.1 | 0.06 | 0.04 | 0.4 | 0.6 | 1 | 0.025 |

The value of N1 = 1617 matches the previous procedure, so this procedure is validated.