

Chapter 188

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

Introduction

This module provides power analysis and sample size calculation for non-inferiority tests for vaccine efficacy (VE) using the ratio of two Poisson 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 that new vaccine (the controls). 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.

This routine is partially based on Gu et al. (2008) and on Blackwelder (1993).

The Poisson probability law gives the probability distribution of the number of events occurring in a specified interval of time or space. The Poisson distribution is often used to fit count data, such as the number of defects on an item, the number of accidents at an intersection during a year, the number of calls to a call center during an hour, or the number of diseased persons arriving at a hospital during a period of time. The Poisson distribution is also used to approximate the binomial distribution when the event probability is small.

The Poisson distribution is characterized by a single parameter which is the mean number of occurrences during the specified interval.

Test Procedure

Assume that all subjects in each group are observed for a fixed time period and the number of events, X , (outcomes or defects) is recorded. The following table presents the various terms that are used.

Group	1	2
Fixed time interval	t_1	t_2
Sample Size	N_1	N_2
Number of events	X_1	X_2
Individual event rates	λ_1	λ_2
Distribution of X	Poisson($\lambda_1 t_1$)	Poisson($\lambda_2 t_2$)

Define the ratio of event rates, RR , as

$$RR = \frac{\lambda_2}{\lambda_1}$$

Gu (2008) considered several test statistics that can be used to test hypotheses about the ratio. For example,

$$H_0 : \frac{\lambda_2}{\lambda_1} = RR_0 \text{ versus } H_a : \frac{\lambda_2}{\lambda_1} > RR_0.$$

or equivalently,

$$H_0 : RR = RR_0 \text{ versus } H_a : RR > RR_0.$$

where RR_0 is the ratio of event rates under the null hypothesis.

Vaccine Efficacy

The vaccine efficacy statistic, VE, is equal to $1 - RR$. Thus, results for the RR can be used for VE with only minor modification.

Test Statistics

Two test statistics are available in this case. The first is based on unconstrained maximum likelihood estimates

$$W_1 = \frac{X_2 - X_1 \left(\frac{\sqrt{RR_0}}{d} \right)}{\sqrt{X_2 + X_1 \left(\frac{RR_0}{d} \right)^2}}$$

with

$$d = t_1 N_1 / t_2 N_2.$$

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

The second test is based on constrained maximum likelihood estimates

$$W_2 = \frac{X_2 - X_1 \left(\frac{RR_0}{d} \right)}{\sqrt{(X_2 + X_1) \left(\frac{RR_0}{d} \right)}}$$

An equivalent pair of test statistics are available if logarithms are used. The statistical hypothesis is

$$H_0 : \ln\left(\frac{\lambda_2}{\lambda_1}\right) - \ln(RR_0) = 0 \text{ versus } H_a : \ln\left(\frac{\lambda_2}{\lambda_1}\right) - \ln(RR_0) > 0$$

or equivalently,

$$H_0 : \ln(RR) - \ln(RR_0) = 0 \text{ versus } H_a : \ln(RR) - \ln(RR_0) > 0$$

Two test statistics are available in this case as well. The first is based on unconstrained maximum likelihood estimates

$$W_3 = \frac{\ln\left(\frac{X_2}{X_1}\right) - \ln\left(\frac{RR_0}{d}\right)}{\sqrt{\frac{1}{X_2} + \frac{1}{X_1}}}$$

The second test is based on constrained maximum likelihood estimates

$$W_4 = \frac{\ln\left(\frac{X_2}{X_1}\right) - \ln\left(\frac{RR_0}{d}\right)}{\sqrt{\frac{\left(2 + \frac{d}{RR_0} + \frac{RR_0}{d}\right)}{X_1 + X_2}}}$$

After extensive simulation, they recommend the following extension of the variance-stabilized test proposed by Huffman (1984) for the case when $RR_0 / d > 1$.

$$W_5 = \frac{2 \left[\sqrt{X_2 + 3/8} - \sqrt{\frac{RR_0}{d} (X_1 + 3/8)} \right]}{\sqrt{1 + \frac{RR_0}{d}}}$$

Gu et al. (2008) show that all of these test statistics are approximately distributed as a standard normal and thus use the normal distribution as the basis of significance testing and power analysis. Their simulations support the use of W_5 .

Assumptions

The assumptions of the two-sample *Poisson* test are:

1. The data in each group are counts (discrete) that follow the Poisson distribution.
2. Each sample is a simple random sample from its population. Unlike most designs, in this design the sample size involves a fixed time parameter. That is, instead of specifying the number of people in a study, the number of man-hours is what is important. Hence, a sample size of 10 hours could be achieved by ten people being observed for one hour or two people being observed for five hours.

Technical Details

Computing Power

Rather than present the results in terms of VE, it will be more convenient to present the results in terms of $RR = 1 - VE$.

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

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

Substituting $1 - RR$ for VE, this becomes

$$H_0: (1 - RR) \leq (1 - RR_0) \text{ vs } H_a: (1 - RR) > (1 - RR_0).$$

or simply

$$H_0: RR \geq RR_0 \text{ vs } H_a: RR < RR_0.$$

Thus, this procedure is based on a one-sided hypothesis test of the rate ratio. Using the test statistics defined above, the power is as follows.

1. **Find the critical value.** Choose the critical value $z_{1-\alpha}$ using the standard normal distribution so that the probability of rejecting H_0 when it is true is α .
2. **Compute the power.** Compute the power for each test as follows. Assume that under the alternative hypothesis, the value of RR is given by RR_a .

For W_1 , W_3 , and W_4 , the power is given by

$$Power(W_i) = \Phi\left(\frac{z_\alpha \sigma_i - \mu_i}{\sigma_i}\right)$$

where

$$\Phi(z) = \int_{-\infty}^z Normal(0,1)$$

$$\mu_1 = \left(\frac{RR_a}{d} - \frac{RR_0}{d}\right) t_1 N_1 \lambda_1, \quad \sigma_1^2 = \left(\frac{dRR_a + RR_0^2}{d^2}\right) t_1 N_1 \lambda_1$$

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

$$\mu_3 = \ln\left(\frac{RR_a}{RR_0}\right), \quad \sigma_3^2 = \frac{d + RR_a}{t_1 N_1 \lambda_1 RR_a}$$

$$\mu_4 = \ln\left(\frac{RR_a}{RR_0}\right), \quad \sigma_4^2 = \frac{\left(2 + \frac{d}{RR_0} + \frac{RR_0}{d}\right)}{t_1 N_1 \lambda_1 \left(1 + \frac{RR_a}{d}\right)}$$

For W_2 the power is computed using

$$Power(W_i) = \Phi\left(\frac{Ez_\alpha - F}{G}\right)$$

where

$$E = \sqrt{\left(\frac{RR_0}{RR_a}\right)^2 + \frac{RR_0^2}{RR_a d}}, \quad F = \left(1 - \frac{RR_0}{RR_a}\right) \sqrt{\frac{\lambda_1 t_1 N_1 RR_0}{d}},$$

$$G = \sqrt{\frac{RR_0}{RR_a} \left(1 + \frac{RR_0^2}{d RR_a}\right)}$$

For W_3 the power is computed using

$$Power(W_i) = 1 - \Phi\left(\frac{|A|\sqrt{B} - z_\alpha C}{D}\right)$$

where

$$A = 2\left(1 - \sqrt{\frac{RR_0}{RR_a}}\right), \quad B = \lambda_1 t_1 N_1 + 3/8,$$

$$C = \sqrt{\frac{RR_0 + d}{RR_a}}, \quad D = \sqrt{\frac{RR_a + d}{RR_a}}$$

Computing Sample Size

The sample size is computed using a simple binary search algorithm with the above power functions.

Example 1 – Finding the Sample Size

In the following example, an epidemiologist wishes to evaluate a new vaccine using a two-group cohort study in which the control group receives the standard treatment. The incidence rate in the control group is 0.01. How large of a sample is needed to detect a change in vaccine efficacy from -0.5 to 0, 0.1, or 0.2. Assume that 80% power is required and $\alpha = 0.025$. Assume that each subject will be observed for two years and that the design calls for an equal number of subjects in both groups.

The variance stabilized technique, test W5, will be used for the analysis.

Setup

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

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Test Statistic	W5 = Variance Stabilized
Power.....	0.80
Alpha.....	0.025
t1 (Exposure Time of Control Group)	2
t2 (Exposure Time of Vaccine Group)	2
Group Allocation	Equal (N1 = N2)
Vaccine Efficacy Input Type	Enter VE0, VE1, and λ1
VE0 (Non-Inferiority Vaccine Efficacy) ...	-0.5
VE1 (Actual Vaccine Efficacy)	0 0.1 0.2
λ 1 (Control Group Incidence Rate).....	0.01

Annotated Output

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

Numeric Results

Numeric Results

Hypothesis: H0: VE ≤ VE0 vs. H1: VE > VE0
 Test Statistic: W5 = Variance Stabilized

Power	Exposure			Event Rate			Vaccine Efficacy			Alpha	
	N1	N2	N	Time		N.I. Vax λ 2.0	Act Vax λ 2.1	Efficacy			
				Cntl t1	Vax t2			N.I. VE0	Act VE1		
0.80002	5120	5120	10240	2	2	0.01	0.015	0.010	-0.5	0.0	0.025
0.80002	3445	3445	6890	2	2	0.01	0.015	0.009	-0.5	0.1	0.025
0.80007	2449	2449	4898	2	2	0.01	0.015	0.008	-0.5	0.2	0.025

References

Gu, K., Ng, H.K.T., Tang, M.L., and Schucany, W. 2008. 'Testing the Ratio of Two Poisson Rates.' Biometrical Journal, 50, 2, 283-298.

Huffman, Michael. 1984. 'An Improved Approximate Two-Sample Poisson Test.' Applied Statistics, 33, 2, 224-226.

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.

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

Report Definitions

Power is the probability of rejecting the null hypothesis when it is false. It should be close to one.

N1 and N2 are the number of subjects in the control and vaccine groups, respectively.

N is the total sample size. $N = N1 + N2$.

t1 and t2 are the exposure (observation) times in groups 1 and 2, respectively.

$\lambda1$ is the incidence rate per unit in the control group. This is often the baseline event rate.

$\lambda2.0$ 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.

$\lambda2.1$ is the incidence rate per unit in vaccine group under the alternative hypothesis.

VE1 is the vaccine efficacy under the alternative hypothesis. $VE1 = 1 - \lambda2.1 / \lambda1$.

VE0 is the vaccine efficacy under the null hypothesis. This may be thought of as the non-inferiority bound for vaccine efficacy.

Alpha is the probability of rejecting the null hypothesis when it is true. It should be small.

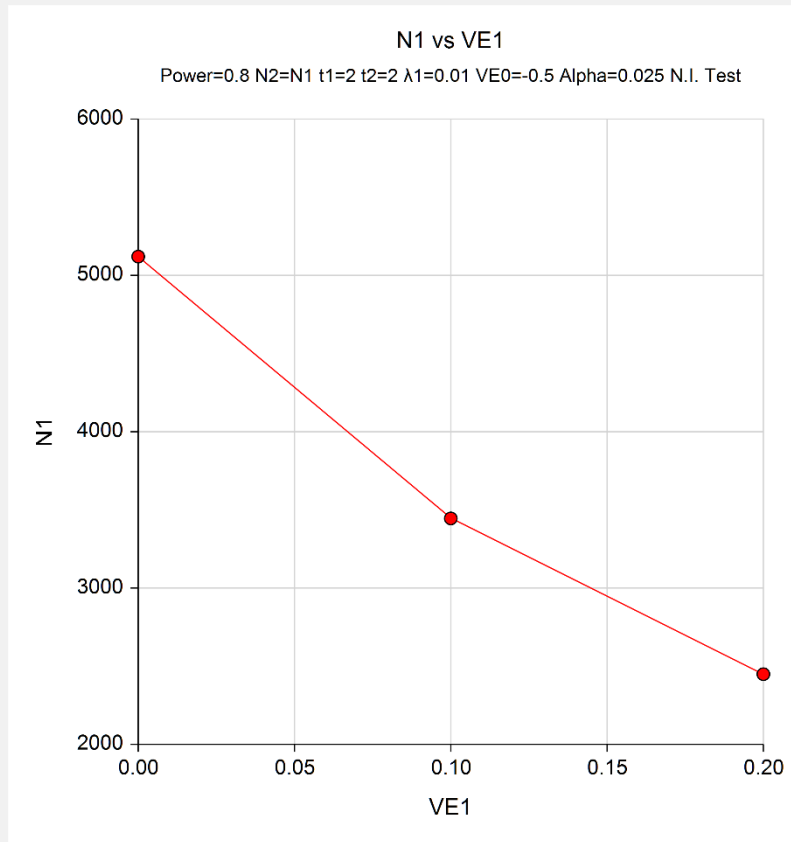
Summary Statements

For a non-inferiority test of vaccine efficacy (VE) of $H0: VE \leq VE0$ versus $H1: VE > VE0$ using the W5 = Variance Stabilized test statistic, samples of 5120 subjects in the control group with exposure time of 2 and 5120 subjects in vaccine group with exposure time of 2 achieve 80.002% power to detect a vaccine efficacy of 0 above the non-inferiority bound of -0.5. The incidence rate of the control group ($\lambda1$) is 0.01, the non-inferiority bound ($\lambda2.0$) is 0.015, and the alternative hypothesis ($\lambda2.1$) is 0.01. The significance level (alpha) is 0.025.

This report shows the values of each of the parameters, one scenario per row. The values of power and beta were calculated from the other parameters.

Chart Section

Chart Section



This plot shows the relationship between sample size and VE1.

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

Example 2 – Validation using Gu et al. (2008)

We will use one of the examples from Gu et al. (2008) page 295. In the example the settings are power = 0.9, alpha = 0.05, $t_1 = t_2 = 2$, $N_1 = 2 N_2$, $VE_0 = 0$, $VE_1 = -3$, and $\lambda_1 = 0.0005$.

In their Table 6, they list the sample size for $p_5^{(A)}$ in this scenario as 8627. However, this number is inaccurate because of the two-decimal place rounding that was done during their calculation. In a private communication, they agreed that the more accurate number is 8590.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may 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
Test Statistic	W5 = Variance Stabilized
Power.....	0.9
Alpha.....	0.05
t1 (Exposure Time of Control Group)	2
t2 (Exposure Time of Vaccine Group)	2
Group Allocation	Enter R = N2/N1, solve for N1 and N2
R (Group Sample Size Ratio)	0.5
Vaccine Efficacy Input Type	Enter VE0, VE1, and λ_1
VE0 (Non-Inferiority Vaccine Efficacy) ...	0
VE1 (Actual Vaccine Efficacy)	-3
λ_1 (Control Group Incidence Rate).....	0.0005

Output

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

Numeric Results

Numeric Results												
Hypothesis: $H_0: VE \leq VE_0$ vs. $H_1: VE > VE_0$												
Test Statistic: W5 = Variance Stabilized												
Power	N1	N2	N	R	Exposure Time		Event Rate			Vaccine Efficacy		Alpha
					Cntl t1	Vax t2	Cntl λ_1	N.I. Vax $\lambda_{2.0}$	Act Vax $\lambda_{2.1}$	N.I. VE0	Act VE1	
0.90001	8590	4295	12885	0.5	2	2	0.0005	0.0005	0.002	0	-3	0.05

These results match the more accurate value of 8590.