Chapter 189

Superiority by a Margin Tests for Vaccine Efficacy using the Ratio of Two Poisson 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 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 and those not vaccinated. 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 $\lambda_2 < \lambda_1$, the value of $VE < 1$.

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,

$$H_0\colon \frac{\lambda_2}{\lambda_1} = RR_0 \quad \text{vs.} \quad H_a\colon \frac{\lambda_2}{\lambda_1} > RR_0\,.$$

or equivalently,

$$H_0\colon RR = RR_0 \quad \text{vs.} \quad H_a\colon RR > RR_0$$

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

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

where

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

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

$$H_0\colon \ln\left(\frac{\lambda_2}{\lambda_1}\right) - \ln(RR_0) = 0 \quad \text{vs.} \quad H_a\colon \ln\left(\frac{\lambda_2}{\lambda_1}\right) - \ln(RR_0) > 0$$

or equivalently,

$$H_0\colon \ln(RR) - \ln(RR_0) = 0 \quad \text{vs.} \quad H_a\colon \ln(RR) - \ln(RR_0) > 0$$

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 superiority by a margin test can be written as

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

Substituting 1 – *RR* for *VE*, this becomes

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

or simply

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

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

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

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

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

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

For W_2, the power is computed using

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

where

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

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

For W_5, the power is computed using

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

where

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

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

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 0.005. How large of a sample is needed to detect a change in vaccine efficacy from 0.4 to 0.6, 0.7, 0.8. 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

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

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 (Superiority Vaccine Efficacy)	**0.4**
VE1 (Actual Vaccine Efficacy)	**0.6 0.7 0.8**
λ1 (Control Group Incidence Rate)	**0.005**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Test Statistic: W5 = Variance Stabilized
Groups: 1 = Control, 2 = Vaccine
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

						Incidence Rate					
	Sample Size			Exposure Time			Vaccine		Vaccine Efficacy		
Power	N1	N2	N	Control t1	Vaccine t2	Control λ1	Superiority λ2.0	Actual λ2.1	Superiority VE0	Actual VE1	Alpha
0.80000	16835	16835	33670	2	2	0.005	0.003	0.0020	0.4	0.6	0.025
0.80005	7024	7024	14048	2	2	0.005	0.003	0.0015	0.4	0.7	0.025
0.80002	3688	3688	7376	2	2	0.005	0.003	0.0010	0.4	0.8	0.025

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1, N2 The number of subjects in the control and vaccine groups, respectively.
N The total sample size. N = N1 + N2.
t1, t2 The exposure (observation) times in groups 1 and 2, respectively.
λ1 The incidence rate per unit in the control group. This is often the baseline event rate.
λ2.0 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 The incidence rate per unit in vaccine group under the alternative hypothesis.
VE1 The vaccine efficacy under the alternative hypothesis. VE1 = 1 - λ2.1 / λ1.
VE0 The vaccine efficacy under the null hypothesis. This may be thought of as the superiority bound for vaccine efficacy.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design will be used to test whether the Group 2 (vaccine) Poisson rate (λ2) is superior to the Group 1 (control) Poisson rate (λ1) by a margin, by testing whether the vaccine efficacy (VE = 1 - λ2 / λ1) is greater than 0.4 (H0: VE ≤ 0.4 versus H1: VE > 0.4). The comparison will be made using a one-sided, two-sample test with the 'W5 = Variance Stabilized' test statistic and a Type I error rate (α) of 0.025. The incidence rate of the control group (λ1) is assumed to be 0.005. To detect a vaccine efficacy of 0.6 with 80% power, the number of subjects needed will be 16835 in the control group, with exposure time 2, and 16835 in the vaccine group, with exposure time 2.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	16835	16835	33670	21044	21044	42088	4209	4209	8418
20%	7024	7024	14048	8780	8780	17560	1756	1756	3512
20%	3688	3688	7376	4610	4610	9220	922	922	1844

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N1, N2, and N	The evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.
N1', N2', and N'	The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D1, D2, and D	The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements

Anticipating a 20% dropout rate, 21044 subjects should be enrolled in Group 1, and 21044 in Group 2, to obtain final group sample sizes of 16835 and 16835, respectively.

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.

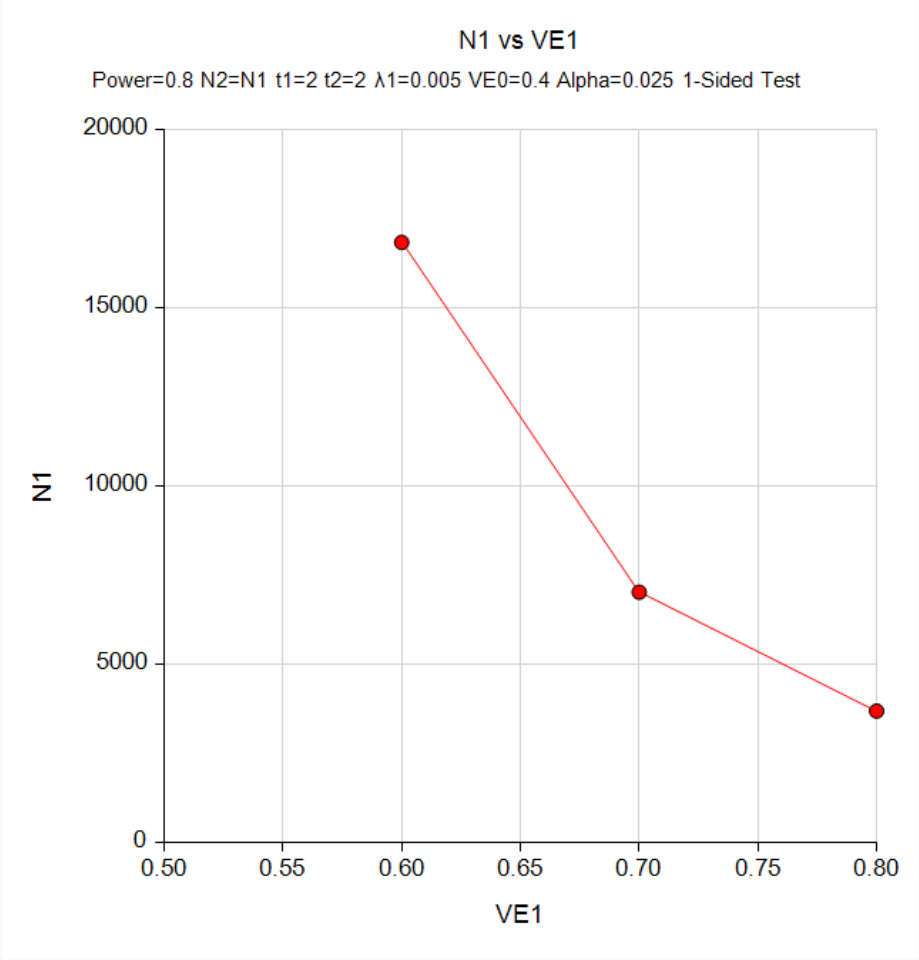
Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2009. Sample Size Tables for Clinical Studies, 3rd Edition. Wiley-Blackwell. Chichester, UK.

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

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.

Plots Section

Plots



This plot shows the relationship between sample size and VE1.

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

We could not find a superiority by a margin example, so instead we will use one of the examples from Gu et al. (2008), page 295, where incidence rates are not given in a superiority arrangement. However, it does allow us to validate the procedure. In the example the settings are power = 0.9, alpha = 0.05, t1 = t2 = 2, N1 = 2 N2, VE0 = 0, VE1 = -3, and λ1 = 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

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

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 λ1**
VE0 (Superiority Vaccine Efficacy)	**0**
VE1 (Actual Vaccine Efficacy)	**-3**
λ1 (Control Group Incidence Rate)	**0.0005**

Output

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

Numeric Results

Solve For: Sample Size
Test Statistic: W5 = Variance Stabilized
Groups: 1 = Control, 2 = Vaccine
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

	Sample Size			Allocation	Exposure Time		Incidence Rate			Vaccine Efficacy		
								Vaccine				
Power	N1	N2	N	Ratio R	Control t1	Vaccine t2	Control λ1	Superiority λ2.0	Actual λ2.1	Superiority VE0	Actual VE1	Alpha
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.