Chapter 121

Tests for Vaccine Efficacy with Composite Efficacy Measure using the Ratio of Two Means

Introduction

This module provides power analysis and sample size calculation for inequality tests of vaccine efficacy (VE) when one is interested in both the incidence and severity of an infection. The burden-of-illness (BOI) score allows investigation of both disease incidence rates and disease severity and duration. See Chang et al. (1994) and Callegaro et al. (2020) for more details.

The BOI method requires that a severity-of-illness score X > 0 be assigned to individuals who develop the disease and a severity score of 0 be assigned to those not infected. Thus, a binary incidence variable and a continuous severity variable are combined to form a single burden-of-illness measurement.

Technical Details

This routine is based on Callegaro et al. (2020).

In the discussion that follows, the subscripts 1 and 2 refer to the new vaccine group and the control (or placebo) group, respectively. Let N_1 and N_2 are the sample sizes of the two groups.

A post-infection variable X records a BOI score. If a subject is not infected, their BOI score is 0. The BOI score measures various attributes of the infection such as amount of pain, duration, etc. Often, X is an ordinal variable taking on values from 1 to 7 or 1 to 10.

Test Statistics

A reasonable composite index of is the following vaccine efficacy statistic

$$\widehat{VE_{BOI}} = 1 - \frac{\bar{X}_1}{\bar{X}_2}$$

where $\bar{X}_1$ and $\bar{X}_2$ are the group means of X.

In a fixed time design, which is terminated after a preset elapsed time, the following results are obtained.

$$\mathrm{E}(\bar{X}_j) = P_j\mu_j, \qquad j = 1,2$$

$$\mathrm{V}(\bar{X}_j) = P_j\{\sigma_j^2 + (1-P_j)\mu_j^2\}/N_j$$

where P_j is the probability of infection, μ_j is the expectation of X of those infected in group j, σ_j is the standard deviation of X for those infected in group j.

It follows from the delta method that

$$Var\left(\frac{\bar{X}_1}{\bar{X}_2}\right) = \left(\frac{P_1\mu_1}{P_2\mu_2}\right)^2\left(\frac{P_1\{\sigma_1^2 + (1-P_1)\mu_1^2\}}{N_1(P_1\mu_1)^2} + \frac{P_2\{\sigma_2^2 + (1-P_2)\mu_2^2\}}{N_2(P_2\mu_2)^2}\right)$$

Using this result, a test statistic Z is developed as follows

$$Z = \frac{\log(\widehat{RR})}{\sqrt{\widehat{\mathrm{Var}}\left(\log(\widehat{RR})\right)}}$$

where $\widehat{RR} = \left(\frac{\bar{X}_1}{\bar{X}_2}\right)$. Note that $VE_{BOI} = 1 - RR$, where $RR = \left(\frac{P_1\mu_1}{P_2\mu_2}\right)$.

This leads to

$$E(Z) = \frac{\log(RR)}{\sqrt{\frac{P_1\{\sigma_1^2 + (1-P_1)\mu_1^2\}}{N_1(P_1\mu_1)^2} + \frac{P_2\{\sigma_2^2 + (1-P_2)\mu_2^2\}}{N_2(P_2\mu_2)^2}}}$$

Power Calculation

The asymptotic power of this test statistic for a two-sided inequality test is given by

$$Power = \Phi\left(E(Z) - z_{1-\alpha/2}\right)$$

Sample Size Calculation

Sample size is found using a binary search on this power formula.

Example 1 – Finding Sample Size

A two-arm parallel study is being planned to substantiate that a new vaccine controls a certain disease better than a control. The disease rate in the control group is 0.003. The disease rate in the treatment group is anticipated to be between 0.001 and 0.0015. The significance level of the test is 0.05.

Previous trials have obtained an average BOI score in the control group of 11.9 and standard deviation of 1.87. Three BOI scores in the vaccine group will be considered: 9, 10, and 11. Their standard deviation will be set to 1.7.

The sample sizes will be equal in each arm. The current analysis is to determine the required sample size to achieve a power of 0.80 when using a two-sided test.

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 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**
Alternative Hypothesis	**Two-Sided**
Power	**0.8**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
P1 (Vaccine Event Prob|H1)	**0.001 0.0015**
P2 (Control Event Probability)	**0.003**
μ1 (Mean of Vaccine Group)	**9 10 11**
μ2 (Mean of Control Group)	**11.9**
Std Dev Input Type	**Unequal**
σ1 (Std Dev of Vaccine Group)	**1.7**
σ2 (Std Dev of Control Group)	**1.87**

Annotated Output

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

Numeric Results

Numeric Results

Test Statistic: Z Test
Hypothesis: Two-Sided

				Event Probability		Mean		Standard Deviation		Vaccine Efficacy		
				Vax	Cntl	Vax	Cntl	Vax	Cntl	Scores	Probs	
Power	N1	N2	N	P1	P2	μ1	μ2	σ1	σ2	VE$_{BOI}$	VE	Alpha
0.8001	5686	5686	11372	0.0010	0.003	9	11.9	1.7	1.87	0.748	0.667	0.05
0.8000	6633	6633	13266	0.0010	0.003	10	11.9	1.7	1.87	0.720	0.667	0.05
0.8000	7722	7722	15444	0.0010	0.003	11	11.9	1.7	1.87	0.692	0.667	0.05
0.8000	8549	8549	17098	0.0015	0.003	9	11.9	1.7	1.87	0.622	0.500	0.05
0.8000	10706	10706	21412	0.0015	0.003	10	11.9	1.7	1.87	0.580	0.500	0.05
0.8000	13469	13469	26938	0.0015	0.003	11	11.9	1.7	1.87	0.538	0.500	0.05

References
Callegaro, A., Curran, D., and Matthews, S. 2020. 'Burden-of-illness vaccine efficacy'. Pharmaceutical Statistics. Volume 19, Issue 5. Pages 636-645. https://doi.org/10.1002/pst.2020
Chang, M.N., Guess, H.A., and Heyse, J.F. 1994. 'Reduction in Burden of Illness: A New Efficacy Measure for Prevention Trials'. Statistics in Medicine. Vol 13. Pages 1807-1814. https://doi.org/10.1002/sim.4780131803
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Nauta, Jozef. 2020. Statistics in Clinical and Observational Vaccine Studies, 2nd Edition. Springer. Cham, Switzerland.

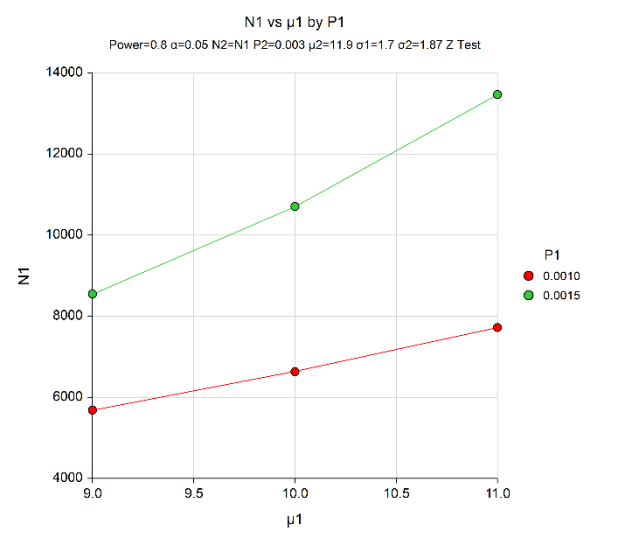
Report Definitions
Power is the probability of rejecting a false null hypothesis.
N1 and N2 are the sample sizes of the vaccine group and the control group, respectively.
N is the total sample size, N1 + N2.
P1 is the event probability of the vaccine group assumed by H1.
P2 is the event probability (attack rate) of the control group.
μ1 is the mean BOI score of those infected in the vaccine group.
μ2 is the mean BOI score of those infected in the control group.
σ1 is the standard deviation of the BOI scores of those infected in the vaccine group.
σ2 is the standard deviation of the BOI scores of those infected in the control group.
VEBOI is the BOI score vaccine efficacy assumed by the alternative hypothesis, H1. VEBOI = 1 - (P1 μ1) / (P2 μ2).
VE is the vaccine efficacy assumed by the alternative hypothesis, H1. VE = 1 - P1 / P2.
Alpha is the probability of rejecting a true null hypothesis.

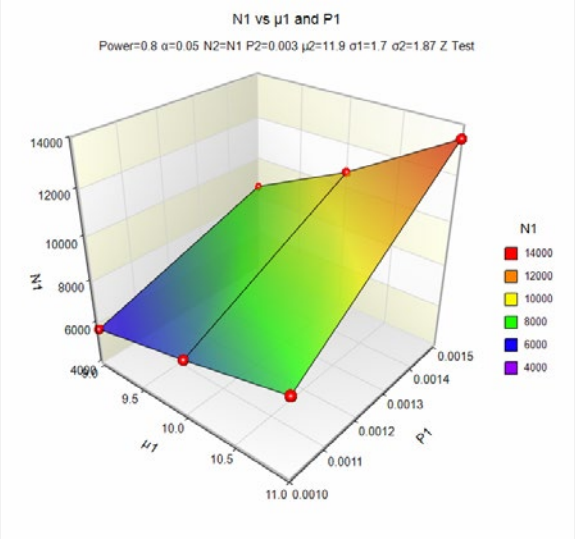
Summary Statements
Sample sizes of 5686 in the vaccine group and 5686 in the control group achieve 80% power to detect a burden-of-illness (BOI) vaccine efficacy of 0.748. The significance level of the two-sided test is 0.05. The control group event probability is 0.003. The means of the vaccine and control groups are 9 and 11.9. The standard deviations of the vaccine and control groups are 1.7 and 1.87. The power was computed for the case when the actual vaccine group event probability is 0.001. The test statistic used is the two-sided Z Test.

This report shows the values of each of the parameters, one scenario per row.

Chart Section

Chart Section





The values from the table are displayed in the above chart. This chart gives a quick look at the sample sizes that are required for various values of μ1 and P1.

Example 2 – Validation using Callegaro et al. (2020)

Callegaro et al. (2020) Table 5 presents the results of an extensive simulation study. We will use the ninth row of this table to validate this procedure. Note that since this is a simulation study, our analytic results will not match those from the article exactly.

The settings for this example are N1 = N2 = 858, P1 = 0.105, P2 = 0.15, μ1 = 3.7, μ2 = 4.5, σ = 1.5, and α= 0.05 (two-sided). The resulting power is 0.980.

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 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	**Power**
Alternative Hypothesis	**Two-Sided**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**858**
P1 (Vaccine Event Prob|H1)	**0.105**
P2 (Control Event Probability)	**0.15**
μ1 (Mean of Vaccine Group)	**3.7**
μ2 (Mean of Control Group)	**4.5**
Std Dev Input Type	**Equal**
σ (Std Dev of Both Groups)	**1.5**

Output

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

Numeric Results

Numeric Results
Test Statistic: Z Test
Hypothesis: Two-Sided

				Event Probability		Mean		Standard Deviation		Vaccine Efficacy		
				Vax	Cntl	Vax	Cntl	Vax	Cntl	Scores	Probs	
Power	N1	N2	N	P1	P2	μ1	μ2	σ1	σ2	VE$_{BOI}$	VE	Alpha
0.9785	858	858	1716	0.105	0.15	3.7	4.5	1.5	1.5	0.424	0.3	0.05

PASS has calculated the power as 0.9785 which is close to the simulated value of 0.980. Thus, the procedure is validated.