Chapter 109

Tests for Vaccine Efficacy with Extremely Low Incidence

Introduction

This module provides power analysis and sample size calculation for inequality tests of vaccine efficacy (VE) when the disease incidence rate is extremely low. In this case, large sample sizes are required to meet power requirements. The distribution of the number of cases in each group (vaccine and control) can be approximated by a binomial random variable.

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

$$VE = \frac{P_2 - P_1}{P_2} = 1 - \frac{P_1}{P_2}$$

where P_1 and P_2 are *attack rates* of the disease being studied among those vaccinated with a new vaccine and those receiving a standard treatment or placebo. An attack rate is the probability that a subject without the disease at the beginning of the study is infected by it during the duration of the course of the study. Hence, an analysis of vaccine effectiveness reduces to an analysis of the ratio of two proportions.

Note that because $P_1 < P_2$, the value of $VE < 1$.

Technical Details

This routine is based on Chow et al. (2018), pages 459 - 460.

Comparing Two Proportions with Low Incidence

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability (or risk) of obtaining an event of interest (testing positive for a disease) in population 1 (the treatment group) is P_1 and in population 2 (the control group) is P_2.

For sufficiently large sample sizes, the number of cases in each group is given by $\lambda_1 = N_1 P_1$ and $\lambda_2 = N_2 P_2$. The number of cases is distributed approximately as Poisson random variables. The number of cases in the vaccine group given the total number of cases is approximately distributed as a binomial random variable with rate θ, where

$$\theta = \frac{\lambda_1}{(\lambda_1 + \lambda_2)} = \frac{1 - VE}{1 - VE + R}$$

with $R = N_2/N_1$ and $VE = \left(1 - \frac{P_1}{P_2}\right)$.

Hence, testing a one-sided hypothesis about VE such as

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

is equivalent to testing the following hypothesis about θ

$$H_0: \theta \geq \theta_0 \quad \text{vs.} \quad H_1: \theta < \theta_0$$

Test Statistics

A reasonable test statistic for the testing the above hypotheses is given by

$$T = \frac{\sqrt{x_1 + x_2}\left(\hat{\theta} - \theta_0\right)}{\sqrt{\theta_0(1 - \theta_0)}}$$

where

$$\hat{\theta} = x_1/(x_1 + x_2)$$

$$\theta_0 = \frac{1 - VE_0}{1 - VE_0 + R}$$

In large samples, *T* is approximately distributed as a standard normal. The null hypothesis is rejected if $T < z_{1-\alpha}$. In this case, $\theta_0 = \frac{1}{1+R}$.

The power, assuming an alternative value of $P_1 < P_2$, is given by

$$Power = 1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\theta_0(1 - \theta_0)} - \sqrt{N_1P_1 + N_2P_2}(\theta_0 - \theta)}{\sqrt{\theta(1 - \theta)}}\right)$$

This power formula can be used directly for obtaining power or indirectly for obtaining sample size using a simple, binary search.

Note that the power formula given here uses the difference between the two terms in the numerator while the formula given on page 460 of Chow et al. (2018) uses the sum of these terms. This difference is most likely due to a difference in the definition of z_α here as the left-tail probability rather than the right-tail probability.

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 0.002. The significance level of the test is 0.025.

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.

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**
Power	**0.8**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Vaccine Efficacy Input Type	**Enter P1 and P2**
P1 (Vaccine Event Prob|H1)	**0.001 0.0015 0.002**
P2 (Control Event Probability)	**0.003**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Test Statistic: Z-Test
Groups: 1 = Vaccine, 2 = Control
Hypotheses: H0: VE ≤ 0 vs. H1: VE > 0

Power		Sample Size			Event Probability			
Target	Actual	N1	N2	N	Vaccine P1	Control P2	Vaccine Efficacy VE	Alpha
0.8	0.80001	7230	7230	14460	0.0010	0.003	0.66667	0.025
0.8	0.80000	15163	15163	30326	0.0015	0.003	0.50000	0.025
0.8	0.80001	38770	38770	77540	0.0020	0.003	0.33333	0.025

Target Power	The desired power value. Power is the probability of rejecting a false null hypothesis.
Actual Power	The calculated power obtained for the scenario on this row. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 and N2	The sample sizes of the vaccinated group and the control group, respectively.
N	The total sample size. N = N1 + N2.
P1	The event probability of the vaccinated group assumed by H1.
P2	The event probability (attack rate) of the control group.
VE	The vaccine efficacy assumed by the alternative hypothesis, H1. This is the VE value at which the power is calculated. VE = (P2 - P1)/P2.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design will be used to test vaccine efficacy (H0: VE ≤ 0 versus H1: VE > 0). The comparison will be made using a one-sided, two-sample Z-test, with a Type I error rate (α) of 0.025. To detect a vaccine efficacy of 0.66667 (vaccine and control group event probabilities of 0.001 and 0.003, respectively), with 80% power, the number of subjects needed will be 7230 in the vaccine group, and 7230 in the control group.

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%	7230	7230	14460	9038	9038	18076	1808	1808	3616
20%	15163	15163	30326	18954	18954	37908	3791	3791	7582
20%	38770	38770	77540	48463	48463	96926	9693	9693	19386

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, 9038 subjects should be enrolled in Group 1, and 9038 in Group 2, to obtain final group sample sizes of 7230 and 7230, respectively.

References

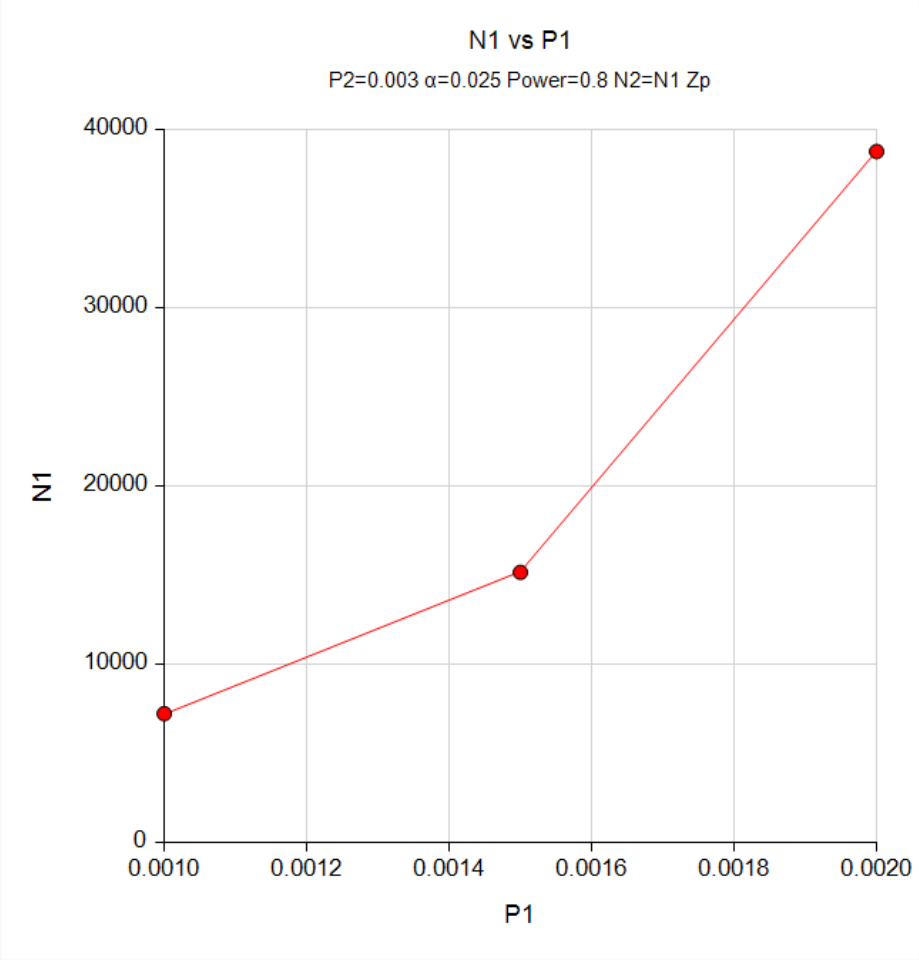
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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

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

Plots Section

Plots



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 P1.

Example 2 – Validation using Chow et al. (2018)

Chow et al. (2018) page 460 presents an example which will be used to validate this procedure. In this example, 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 0.002. The disease rate in the treatment group is anticipated to be 0.001. The significance level of the test is 0.05 and the power is 0.80. The anticipated sample size is 17837 per group.

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**
Power	**0.8**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
Vaccine Efficacy Input Type	**Enter P1 and P2**
P1 (Vaccine Event Prob|H1)	**0.001**
P2 (Control Event Probability)	**0.002**

Output

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

Numeric Results

Solve For: Sample Size
Test Statistic: Z-Test
Groups: 1 = Vaccine, 2 = Control
Hypotheses: H0: VE ≤ 0 vs. H1: VE > 0

Power		Sample Size			Event Probability			
Target	Actual	N1	N2	N	Vaccine P1	Control P2	Vaccine Efficacy VE	Alpha
0.8	0.80001	17837	17837	35674	0.001	0.002	0.5	0.05

PASS has also calculated the sample size to be 17,837 per group. Thus, the procedure is validated.