

## Chapter 104

# Superiority by a Margin Tests for Vaccine Efficacy with Extremely Low Incidence

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### Introduction

This module provides power analysis and sample size calculation for superiority by a margin 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  $VE < 1$ .

Perhaps an example will set the stage for the discussion of the terminology that follows. Suppose that the population of interest has a disease incidence rate of 0.002. A promising new vaccine has been developed to the point where it can be tested. The researchers wish to show that the incidence rate in a group treated with this new vaccine will be reduced to at least 0.0015. That is, they want to show that the efficacy of the new vaccine is at least  $1 - 0.0015/0.002 = 0.25$ .

## Technical Details

This procedure 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  $\lambda_1 = N_1P_1$  and  $\lambda_2 = N_2P_2$ . 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  $\theta$ , where

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

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

The one-sided, superiority by a margin hypotheses in terms of VE may be written as

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

An equivalent test about  $\theta$  is

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

### Test Statistics

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

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

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  $T < z_{1-\alpha}$ .

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  $z_\alpha$  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 0.004. The superiority boundary is set at 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 researchers would like to determine the required sample size needed to achieve a power of 0.80.

### 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Power.....	<b>0.8</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Vaccine Efficacy Input Type .....	<b>Enter P1.0, P1.1, and P2</b>
P1.0 (Superiority Vaccine Event Prob) ...	<b>0.003</b>
P1.1 (Actual Vaccine Event Prob) .....	<b>0.001 0.0015 0.002</b>
P2 (Control Event Probability) .....	<b>0.004</b>

### Annotated Output

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

#### Numeric Results

##### Numeric Results

Test Statistic: Z Test

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

Target Power	Actual Power	N1	N2	N	Event Probability			Vaccine Efficacy		Alpha
					Cntl P2	Sup Vax P1.0	Act Vax P1.1	Sup VE0	Act VE1	
0.8	0.80006	6536	6536	13072	0.004	0.003	0.0010	0.25	0.750	0.025
0.8	0.80001	13538	13538	27076	0.004	0.003	0.0015	0.25	0.625	0.025
0.8	0.80000	34321	34321	68642	0.004	0.003	0.0020	0.25	0.500	0.025

##### 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.

Blackwelder, William C. 1993. 'Sample Size and Power for Prospective Analysis of Relative Risk.' Statistics in Medicine, Vol. 12, 691-698.

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

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### Report Definitions

Target Power is the desired power value. Power is the probability of rejecting a false null hypothesis.  
 Actual Power is 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 are the sample sizes of the vaccinated group and the control group, respectively.  
 N is the total sample size, N1 + N2.  
 P1.0 is the smallest value of the event probability for vaccinated group that still yields a superiority conclusion.  
 P1.1 is the event probability of the vaccinated group assumed by H1.  
 P2 is the event probability (attack rate) of the control group.  
 VE0 is the vaccine efficacy assumed by the null hypothesis, H0. This is the superiority boundary of VE.  $VE0 = 1 - P1.0/P2$ .  
 VE1 is 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 is the probability of rejecting a true null hypothesis.

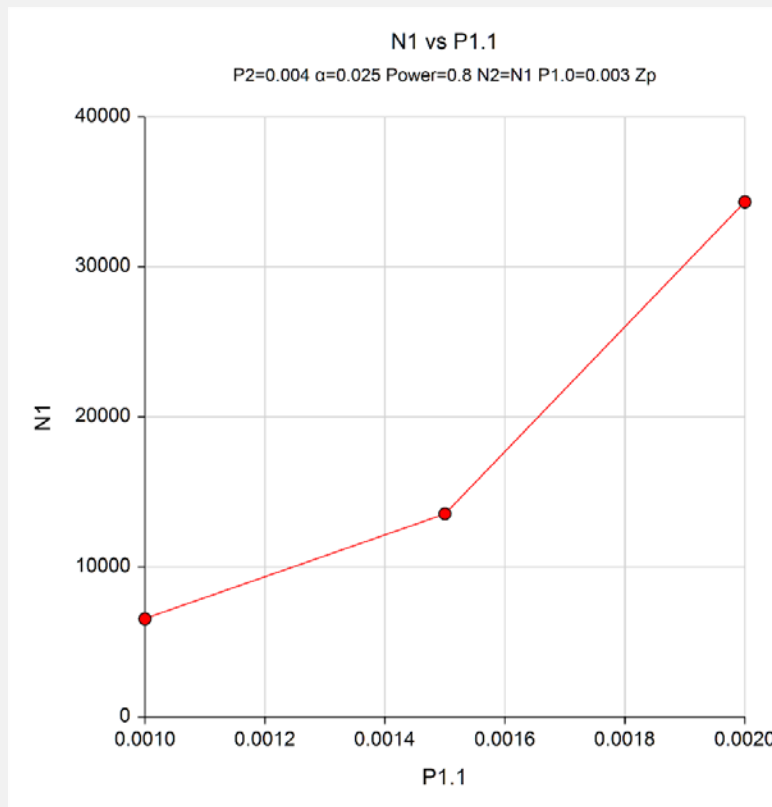
### Summary Statements

Sample sizes of 6536 in the vaccine group and 6536 in the control group achieve 80% power to detect a vaccine efficacy of 0.75. The significance level of the test is 0.025. The control group event probability is 0.004. The vaccine group event probability at the superiority limit is 0.003. The power was computed for the case when the actual vaccine group event probability is 0.001. The test statistic used is the one-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 P1.1.

## Example 2 – Validation using Hand Calculations

We could not find a validation example in the literature so we will validate the procedure using hand calculations. 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 0.004. The superiority boundary is set at 0.003. The disease rate in the treatment group is anticipated to be 0.001. The significance level of the test is 0.025 and the power is 0.80. The sample size per group is 6536.

We will validate this procedure by calculating the power and showing that the power is indeed 0.80.

$$\begin{aligned}
 \text{Power} &= 1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\theta_0(1-\theta_0)} - \sqrt{N_1P_1 + N_2P_2}(\theta_0 - \theta)}{\sqrt{\theta(1-\theta)}}\right) \\
 &= 1 - \Phi\left(\frac{1.959964\sqrt{0.428571(0.571429)} - \sqrt{6536(0.001 + 0.004)}(0.428571 - 0.2)}{\sqrt{0.2(1-0.2)}}\right) \\
 &= 1 - \Phi\left(\frac{0.969931 - 1.306659}{0.4}\right) \\
 &= 1 - \Phi(-0.84182) \\
 &= 0.80006
 \end{aligned}$$

### 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
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alpha.....	<b>0.025</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
Sample Size Per Group.....	<b>6536</b>
Vaccine Efficacy Input Type .....	<b>Enter P1.0, P1.1, and P2</b>
P1.0 (Superiority Vaccine Event Prob)...	<b>0.003</b>
P1.1 (Actual Vaccine Event Prob) .....	<b>0.001</b>
P2 (Control Event Probability) .....	<b>0.004</b>

### Output

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

#### Numeric Results

Numeric Results									
Test Statistic: Z Test									
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0									
Power	N1	N2	N	Event Probability			Vaccine Efficacy		Alpha
				Cntl P2	Sup Vax P1.0	Act Vax P1.1	Sup VE0	Act VE1	
0.80006	6536	6536	13072	0.004	0.003	0.001	0.25	0.75	0.025

PASS has also calculated the power as 0.80006, so the procedure is validated.