

Chapter 111

Non-Inferiority Tests for Vaccine Efficacy with Extremely Low Incidence

Introduction

This module provides power analysis and sample size calculation for non-inferiority 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 0.004. 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 no worse than 0.005.

Relative Vaccine Efficacy

Often, the goal of the study is to show that the attack rate of a new vaccine is no worse than that of the current standard vaccine. For example, the standard vaccine might have serious side effects, be expensive to produce, etc. In this case, the trial is conducted to show that the new vaccine is an attractive replace for the standard vaccine. In this case, the control group does not receive a placebo. Rather, it receives the standard vaccine. In this case, the quantity of interest is called the *relative vaccine efficacy* (rVE). It is calculated as

$$rVE = \frac{p_2 - p_1}{p_2} = 1 - \frac{p_1}{p_2}$$

where now p_2 is the attack rate for those receiving the standard vaccine.

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 $\lambda_1 = N_1 P_1$ 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

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

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

The one-sided, non-inferiority 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 θ is

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

Non-Inferiority Bound

The idea of a non-inferiority test is that a new treatment is no worse than the treatment it is being compared to. To allow the comparison to be made, you must determine a non-inferiority boundary. In this procedure, that means that p_1 can only be slightly larger than p_2 . When $p_1 > p_2$, the risk ratio will be greater than one so that the value of VE will be negative. See Nauta (2020) page 94 for a discussion and example of this.

Hence, one task that will have to be completed is to determine how much worse the new vaccine can be without causing it to be rejected.

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

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

$$Power = 1 - \Phi \left(\frac{z_{1-\alpha} \sqrt{\theta_0(1-\theta_0)} - \sqrt{N_1 P_1 + N_2 P_2} (\theta_0 - \theta)}{\sqrt{\theta(1-\theta)}} \right)$$

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 no worse than a control. The disease rate in the control group is 0.004. The non-inferiority boundary is set at 0.005. The disease rate in the treatment group is anticipated to be between 0.002 and 0.003. 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>
Design Tab	
Solve For	Sample Size
Power	0.80
Alpha	0.025
Group Allocation	Equal (N1 = N2)
Vaccine Efficacy Input Type	Enter P1.0, P1.1, and P2
P1.0 (Non-Inferiority Vaccine Event Prob)	0.005
P1.1 (Actual Vaccine Event Prob)	0.002 0.003
P2 (Control Event Probability)	0.004

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
					Ctrl P2	N.I. Vax P1.0	Act Vax P1.1	N.I. VE0	Act VE1	
0.8	0.80002	6341	6341	12682	0.004	0.005	0.002	-0.25	0.50	0.025
0.8	0.80002	17128	17128	34256	0.004	0.005	0.003	-0.25	0.25	0.025

References

Chow, S.C., Shao, J., Wang, H., and Lohknygina, 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 largest value of the event probability for vaccinated group that still yields a non-inferiority 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 non-inferiority 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.

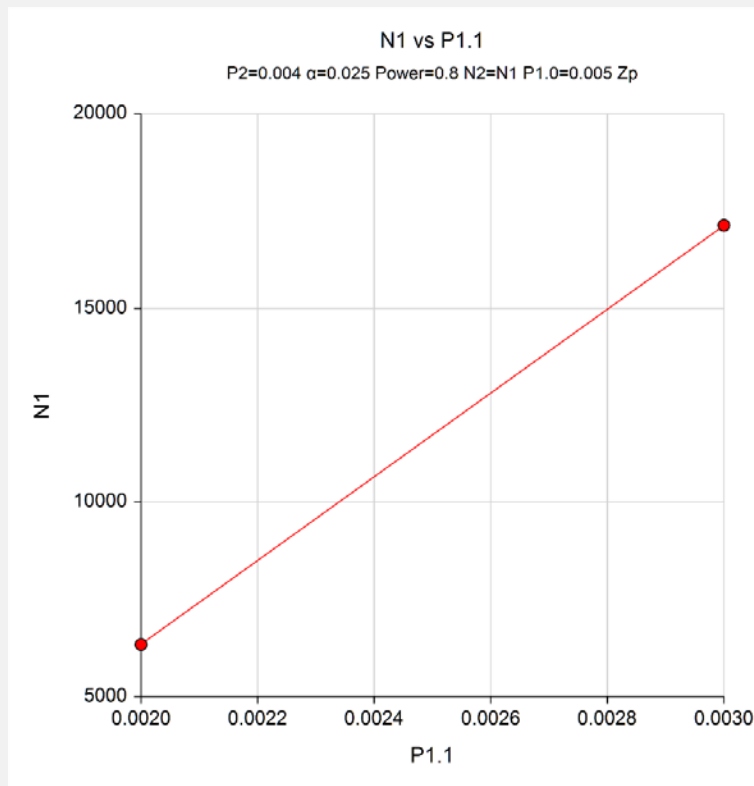
Summary Statements

Sample sizes of 6341 in the vaccine group and 6341 in the control group achieve 80% power to detect a vaccine efficacy of 0.5. The significance level of the test is 0.025. The control group event probability is 0.004. The vaccine group event probability at the non-inferiority limit is 0.005. The power was computed for the case when the actual vaccine group event probability is 0.002. 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 the two values of P1.1.

Example 2 – Validation using a Previously Validated PASS Procedure

We could not find a validation example in the literature so we will validate the procedure using the *Superiority by a Margin Tests for Vaccine Efficacy with Extremely Low Incidence* procedure. That procedure using the same power calculations as this procedure, so it can be used to validate this procedure.

Suppose a two-arm parallel study is being planned to substantiate that a new vaccine controls a certain disease no worse than a control. The disease rate in the control group is 0.004. The non-inferiority boundary is set at 0.005. The disease rate in the treatment group is anticipated to be 0.002. The significance level of the test is 0.025. Using a sample size of 6341 in each arm, the power was found to be 0.80002.

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**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Power
Alpha.....	0.025
Group Allocation	Equal (N1 = N2)
Sample Size Per Group.....	6341
Vaccine Efficacy Input Type	Enter P1.0, P1.1, and P2
P1.0 (Non-Inferiority Vaccine Event Prob)	0.005
P1.1 (Actual Vaccine Event Prob)	0.002
P2 (Control Event Probability)	0.004

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	Event Probability			Vaccine Efficacy		Alpha			
	N1	N2	N	Cntl P2	N.I. Vax P1.0		Act Vax P1.1	N.I. VE0	Act VE1
0.80002	6341	6341	12682	0.004	0.005	0.002	-0.25	0.5	0.025

PASS has calculated the power as 0.80002, so the procedure is validated.