

Chapter 239

Non-Inferiority Tests for Vaccine Efficacy using the Ratio of Two Poisson Rates in a Cluster-Randomized Design

Introduction

This procedure calculates power and sample size for non-inferiority tests of vaccine efficacy using the ratio of two rates in a cluster-randomized design in which the outcome variable is a count. It uses the work of Wang, Zhang, and Ahn (2018) which give the power for the case of varying cluster sizes. The analysis uses a simple z-test comparing the two rates.

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

$$VE = \frac{\lambda_2 - \lambda_1}{\lambda_2} = 1 - \frac{\lambda_1}{\lambda_2}$$

where λ_1 and λ_2 are *incidence rates* of the disease being studied among those vaccinated with a certain vaccine and those not vaccinated with that vaccine. 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.

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are put into the treatment group or the control group. Generally speaking, the larger the cluster sizes and the higher the correlation among subjects within the same cluster, the larger will be the overall sample size necessary to detect an effect with the same power.

Hypotheses

When higher rates are worse such as in this procedure, the non-inferiority test hypotheses are

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

Technical Details

The following discussion summarizes the results in Wang, Zhang, and Ahn (2018).

Suppose you are interested in comparing the incidence rates of two groups (treatment and control) with a non-inferiority test. Further suppose that the response is known to be related to other covariates (such as age, race, or gender) and so their impact needs to be adjusted for. This may be accomplished by stratifying on the covariates and forming hypotheses about a common mean difference across all clusters and strata. Often, the stratification is based on cluster size, but this is not required.

Let Y_{jki} be the count outcome of the i th ($i = 1, \dots, M_{jk}$) subject in the k th ($k = 1, \dots, K_j$) cluster of the j th ($j = 1, 2$) group. Assuming that Y_{jki} follows a Poisson model with

$$\lambda_j = E(Y_{jki}) = \text{Var}(Y_{jki})$$

and a common intraclass correlation coefficient (ICC) $\rho = \text{corr}(Y_{jki}, Y_{jki'})$ for $i \neq i'$.

Test Statistic

An unbiased estimator of λ_j is

$$\hat{\lambda}_j = \frac{\sum_{k=1}^{K_j} \sum_{i=1}^{M_{jk}} Y_{jki}}{\sum_{k=1}^{K_j} M_{jk}}$$

with estimated variance

$$s_j^2 = \frac{\hat{\lambda}_j \sum_{k=1}^{K_j} M_{jk} [1 + (M_{jk} - 1)\hat{\rho}]}{\left(\sum_{k=1}^{K_j} M_{jk}\right)^2}$$

Using a one-sided hypothesis $H_0: \lambda_1 = \lambda_2$ versus $H_1: \lambda_1 < \lambda_2$, H_0 is rejected if

$$\frac{\hat{\lambda}_1 - \hat{\lambda}_2}{\sqrt{s_1^2 + s_2^2}} > z_{1-\alpha}$$

Sample Size and Power

Wang, Zhang, and Ahn (2018) provide the following formula for estimating K_2 (the number of clusters in the control group) when there are an unequal number of clusters in each group.

$$K_2 = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\frac{\lambda_1}{R} + \lambda_2\right)}{(\lambda_1 - \lambda_2)^2} \left[(1 - \rho) \frac{1}{\theta} + \rho + \rho\gamma^2 \right]$$

where $R = K_1/K_2$, $M = E(M_{jk})$, $\tau^2 = \text{Var}(M_{jk})$, and $\gamma = \tau/M$. Here M is the average cluster size of all clusters in the study and γ is the coefficient of variation of the cluster sizes. Note that $z_x = \Phi(x)$ is the standard normal distribution function.

This equation can easily be rearranged to provide a formula for power $(1 - \beta)$.

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Example 1 – Finding the Number of Clusters

A non-inferiority study is being planned to investigate whether a new intervention will decrease the incidence rate of a certain disease over the rate achieved by the current intervention. The response is a count. For a number of reasons, the researchers decide to administer the intervention to whole clusters (clinics) rather than randomize the treatment to individuals. The number of clinics receiving each treatment will be balanced.

The average number of subjects per clinic is 20. The coefficient of variation of the cluster sizes is 0.4.

Prior studies have obtained an incidence rate of 0.05 for the current treatment and an ICC of 0.01. The value of VE0 is set to -0.6. The researchers want to see the sample sizes needed for VE1 = 0, 0.2, 0.4, and 0.6.

The one-sided significance level is set to 0.025 and the power is set to 0.8.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load this procedure. 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	K1 (Number of Clusters in Group 1)
Power.....	0.80
Alpha.....	0.025
K2 (Clusters in Group 2).....	K1
M (Average of Cluster Sizes).....	20
CV (Coef of Variation of Cluster Sizes)	0.4
Vaccine Efficacy Input Type	Vaccine Efficacies (VE0 and VE1)
VE0 (Non-Inferiority Vaccine Efficacy)	-0.6
VE1 (Actual Vaccine Efficacy)	0 0.2 0.4 0.6
λ_2 (Incidence Rate of Control Group).....	0.05
ρ (Intracluster Correlation, ICC).....	0.01

Annotated Output

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

Numeric Results

Numeric Results												
Hypothesis: $H_0: VE \leq VE_0$ vs. $H_1: VE > VE_0$												
	Sample Size	Clusters		Cluster Size		Incidence Rates			Vaccine Efficacy			
		Grp 1	Grp 2	Ave	COV	N.I.	Act	Cntl	N.I.	Act	ICC	
Power	N	K1	K2	M	CV	$\lambda_{1.0}$	$\lambda_{1.1}$	λ_2	VE0	VE1	ρ	Alpha
0.80409	2800	70	70	20	0.4	0.08	0.05	0.05	-0.6	0.0	0.01	0.025
0.80035	2560	64	64	20	0.4	0.08	0.04	0.05	-0.6	0.2	0.01	0.025
0.80257	2360	59	59	20	0.4	0.08	0.03	0.05	-0.6	0.4	0.01	0.025
0.80520	2160	54	54	20	0.4	0.08	0.02	0.05	-0.6	0.6	0.01	0.025

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References

- 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.
- Wang, J., Zhang, S., and Ahn, C. 2018. 'Sample size calculation for count outcomes in cluster randomization trials with varying cluster sizes.' *Communications in Statistics--Theory and Methods*, DOI: 10.1080/03610926.2018.1532004.

Report Definitions

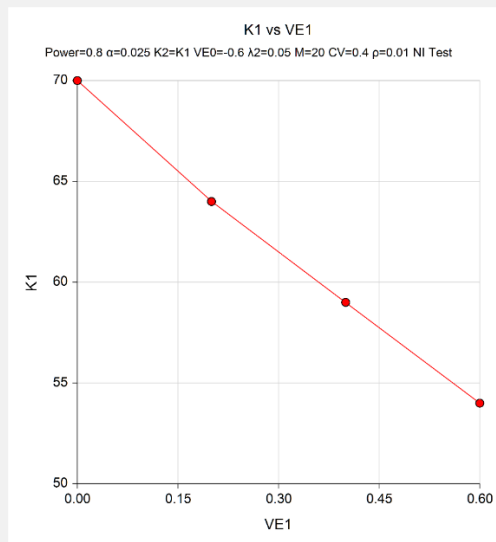
- Power is the probability of rejecting a false null hypothesis. It should be close to one.
- N is the total sample size, i.e., the total number of subjects from all clusters.
- K1 is the number of clusters assigned to group 1, the treatment group.
- K2 is the number of clusters assigned to group 2, the control group.
- M is the average cluster size. It is the anticipated average number of subjects per cluster.
- CV is the coefficient of variation of the cluster sizes. It is the standard deviation of cluster sizes divided by the average cluster size.
- $\lambda_{1.0}$ is the non-inferiority bound on incidence rate in the treatment group.
- $\lambda_{1.1}$ is the actual incidence rate of the treatment group at which the power is computed.
- λ_2 is the incidence rate in the control group.
- VE0 is the vaccine efficacy assumed by the null hypothesis. This is the non-inferiority boundary. $VE0 = 1 - \lambda_{1.0} / \lambda_2$.
- VE1 is the vaccine efficacy assumed by the alternative hypothesis. This is the VE at which the power is computed. $VE1 = 1 - \lambda_{1.1} / \lambda_2$.
- ρ is the intracluster correlation coefficient. This is the correlation between any two subjects within a particular cluster.
- Alpha is the probability of rejecting a true null hypothesis.

Summary Statements

A cluster-randomized, non-inferiority design consists of 70 treatment clusters and 70 control clusters. Each cluster is assumed to have an average of 20 subjects per cluster. The outcome of the study will be analyzed by comparing the vaccine efficacy to a non-inferiority bound. Higher values of these incidence rates are assumed to be worse. The expected sample size of 2800 subjects achieves 80% power to reject inferiority when the actual vaccine efficacy is 0. The non-inferiority bound of the vaccine efficacy is -0.6. The incidence rate of the control group 0.05. The incidence rate of the treatment group assumed by the alternative hypothesis is 0.05. The incidence rate of the treatment group which is the non-inferiority bound is 0.08. The intracluster correlation coefficient is 0.01. The significance level of the test is 0.025. The individual cluster sizes (the number of subjects per cluster) are assumed to vary according to a discrete distribution with mean 20 and coefficient of variation 0.4.

Chart Section

Chart Section



The values from the Numeric Results report are displayed in this plot.

Example 2 – Validation using a Previously Validated Procedure

We could not find a validation example in the literature so we will use a previously validated procedure in **PASS** to validate this procedure.

Suppose in a non-inferiority design, higher rates are worse, power = 0.9, alpha = 0.025, K2 = K1, M = 50, CV = 0.2, $\lambda_{1.0} = 0.6$, $\lambda_{1.1} = 0.5$, $\lambda_2 = 0.5$, and $\rho = 0.002$. Solve for K1.

This scenario can be solved using the procedure “Tests for the Difference Between Two Poisson Rates in a Cluster-Randomized Design” with the following settings.

Set the alternative hypothesis to “One-Sided ($H_1: \delta > 0$)”, power = 0.9, alpha = 0.025, K2 = K1, M = 50, CV = 0.2, $\lambda_1 = 0.6$, $\lambda_2 = 0.5$, and $\rho = 0.002$. The solution is K1 = K2 = 26.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load this procedure. 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	K1 (Number of Clusters in Group 1)
Power.....	0.9
Alpha.....	0.025
K2 (Clusters in Group 2).....	K1
M (Average of Cluster Sizes).....	50
CV (Coef of Variation of Cluster Sizes)	0.2
Vaccine Efficacy Input Type	Incidence Rates ($\lambda_{1.0}$ and $\lambda_{1.1}$)
$\lambda_{1.0}$ (Non-Inferiority Incidence Rate).....	0.6
$\lambda_{1.1}$ (Actual Incidence Rate)	0.5
λ_2 (Incidence Rate of Control Group).....	0.5
ρ (Intracluster Correlation, ICC).....	0.002

Output

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

Numeric Results

Numeric Results													
Hypothesis: $H_0: VE \leq VE_0$ vs. $H_1: VE > VE_0$													
Power	Sample Size N	Clusters		Cluster Size		Incidence Rates			Vaccine Efficacy		ICC ρ	Alpha	
		Grp 1 K1	Grp 2 K2	Ave M	COV CV	N.I. $\lambda_{1.0}$	Act $\lambda_{1.1}$	Cntl λ_2	N.I. VE0	Act VE1			
0.90572	2600	26	26	50	0.2	0.6	0.5	0.5	-0.2	0	0.002	0.025	

PASS has also obtained K1 = K2 = 26. Thus, the procedure is validated.