Chapter 209

Confidence Intervals for Vaccine Efficacy using an Unmatched Case-Control Design

Introduction

This routine calculates the group sample sizes necessary to achieve a specified confidence interval width of vaccine efficacy (VE) from data collected using an unmatched case-control design. Such a design is used for retrospective studies.

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

$$VE = 1 - OR = 1 - \frac{p_1(1-p_2)}{p_2(1-p_1)}$$

where p_1 and p_2 are the *prevalence of vaccine exposure* among cases (disease) and controls (no disease), respectively.

This routine is partially based on O'Neill (1988). This paper provides a useful overview of the vaccine efficacy studies, the assumptions that are made, and discussion of when this design is useful. We highly recommend it.

Technical Details

This section will first review the details of calculating sample sizes for the odds ratio of two proportions. It will then adapt those results to calculating sample sizes for vaccine efficacy.

Comparing Two Proportions

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability of obtaining an event of interest (vaccine exposure) in population 1 (the case group) is p_1 and in population 2 (the control group) is p_2. The corresponding failure proportions are given by $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$.

The assumption is made that the responses from each group follow a binomial distribution. This means that the event probability p_i is the same for all subjects within a population and that the responses from one subject to the next are independent of one another.

Random samples of n_1 and n_2 individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows

	Cases	Controls	Total
Vaccinees	x_{11}, a	x_{12}, b	m_1
Controls	$x_{21,}c$	x_{22}, d	m_2
Totals	n_1, m	n_2, n	N

The binomial proportions are estimated from these data using the formulae

$$\hat{p}_1 = \frac{x_{11}}{n_1} \quad \text{and} \quad \hat{p}_2 = \frac{x_{12}}{n_2}$$

In this procedure, our attention will focus on using the odds ratio to compare the two binomial proportions. The odds ratio is given by $\psi = (p_1/q_1)/(p_2/q_2)$ which gives the relative change in the odds of exposure to the vaccine among the cases to the odds of the controls.

Although the odds ratio is more complicated than the simple risk ratio of the disease attack rates, it is used in this case because a direct estimate of the ratio of the attack rates is not available. In this case, it is hoped that the odds ratio of the prevalences of vaccine exposure will provide a reasonable approximation of the ratio of the attack rates of the disease in vaccinated and non-vaccinated individuals.

Confidence Intervals for the Odds Ratio

Many methods have been devised for computing confidence intervals for the odds ratio of two proportions. Eight of these methods are available in this procedure. They are

1. Exact (Conditional)
2. Score (Farrington and Manning)
3. Score (Miettinen and Nurminen)
4. Fleiss
5. Logarithm
6. Mantel-Haenszel
7. Simple
8. Simple + 1/2

Conditional Exact

The conditional exact confidence interval of the odds ratio is calculated using the noncentral hypergeometric distribution as given in Sahai and Khurshid (1995). That is, a $100(1-\alpha)\%$ confidence interval is found by searching for ψ_L and ψ_U such that

$$\frac{\sum_{k=x}^{k_2}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_L)^k}{\sum_{k=k_1}^{k_2}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_L)^k}=\frac{\alpha}{2}$$

and

$$\frac{\sum_{k=k_1}^{x}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_U)^k}{\sum_{k=k_1}^{k_2}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_U)^k}=\frac{\alpha}{2}$$

where

$$k_1=\max(0,m_1-n_1) \text{ and } k_2=\min(n_1,m_1)$$

Farrington and Manning's Score

Farrington and Manning (1990) developed a test statistic similar to that of Miettinen and Nurminen but with the factor *N*/(*N*-1) removed.

The formula for computing this test statistic is

$$z_{FMO}=\frac{\frac{(\hat{p}_1-\tilde{p}_1)}{\tilde{p}_1\tilde{q}_1}-\frac{(\hat{p}_2-\tilde{p}_2)}{\tilde{p}_2\tilde{q}_2}}{\sqrt{\left(\frac{1}{n_1\tilde{p}_1\tilde{q}_1}+\frac{1}{n_2\tilde{p}_2\tilde{q}_2}\right)}}$$

where the estimates $\tilde{p}_1$ and $\tilde{p}_2$ are computed as in the corresponding test of Miettinen and Nurminen (1985) as

$$\tilde{p}_1=\frac{\tilde{p}_2\psi_0}{1+\tilde{p}_2(\psi_0-1)}$$

$$\tilde{p}_2=\frac{-B+\sqrt{B^2-4AC}}{2A}$$

$$A=n_2(\psi_0-1)$$

$$B=n_1\psi_0+n_2-m_1(\psi_0-1)$$

$$C=-m_1$$

Farrington and Manning (1990) proposed inverting their score test to find the confidence interval. The lower limit is found by solving

$$z_{FMO} = |z_{\alpha/2}|$$

and the upper limit is the solution of

$$z_{FMO} = -|z_{\alpha/2}|$$

Miettinen and Nurminen's Score

Miettinen and Nurminen (1985) proposed a test statistic for testing whether the odds ratio is equal to a specified value ψ_0. Because the approach they used with the difference and ratio does not easily extend to the odds ratio, they used a score statistic approach for the odds ratio. The regular MLE's are $\hat{p}_1$ and $\hat{p}_2$. The constrained MLE's are $\tilde{p}_1$ and $\tilde{p}_2$, These estimates are constrained so that $\widetilde{\psi} = \psi_0$. A correction factor of N/(N-1) is applied to make the variance estimate less biased. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{MNO} = \frac{\frac{(\hat{p}_1 - \tilde{p}_1)}{\tilde{p}_1\tilde{q}_1} - \frac{(\hat{p}_2 - \tilde{p}_2)}{\tilde{p}_2\tilde{q}_2}}{\sqrt{\left(\frac{1}{n_1\tilde{p}_1\tilde{q}_1} + \frac{1}{n_2\tilde{p}_2\tilde{q}_2}\right)\left(\frac{N}{N-1}\right)}}$$

where

$$\tilde{p}_1 = \frac{\tilde{p}_2\psi_0}{1 + \tilde{p}_2(\psi_0 - 1)}$$

$$\tilde{p}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

$$A = n_2(\psi_0 - 1)$$

$$B = n_1\psi_0 + n_2 - m_1(\psi_0 - 1)$$

$$C = -m_1$$

Miettinen and Nurminen (1985) proposed inverting their score test to find the confidence interval. The lower limit is found by solving

$$z_{MNO} = |z_{\alpha/2}|$$

and the upper limit is the solution of

$$z_{MNO} = -|z_{\alpha/2}|$$

Iterated Method of Fleiss

Fleiss (1981) presents an improve confidence interval for the odds ratio. This method forms the confidence interval as all those values of the odds ratio which would not be rejected by a chi-square hypothesis test. Fleiss gives the following details about how to construct this confidence interval. To compute the lower limit, do the following.

1. For a trial value of ψ, compute the quantities *X, Y, W, F, U,* and *V* using the formulas

$$X = \psi(m+s) + (n-s)$$

$$Y = \sqrt{X^2 - 4ms\psi(\psi-1)}$$

$$A = \frac{X-Y}{2(\psi-1)}$$

$$B = s - A$$

$$C = m - A$$

$$D = f - m + A$$

$$W = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}$$

$$F = \left(a - A - \frac{1}{2}\right)^2 W - z_{\alpha/2}^2$$

$$T = \frac{1}{2(\psi-1)^2}\left(Y - n_{\cdot\cdot} - \frac{\psi-1}{Y}[X(m+s) - 2ms(2\psi-1)]\right)$$

$$U = \frac{1}{B^2} + \frac{1}{C^2} - \frac{1}{A^2} - \frac{1}{D^2}$$

$$V = T\left[\left(a - A - \frac{1}{2}\right)^2 U - 2W\left(a - A - \frac{1}{2}\right)\right]$$

Finally, use the updating equation below to calculate a new value for the odds ratio using the updating equation

$$\psi^{(k+1)} = \psi^{(k)} - \frac{F}{V}$$

2. Continue iterating until the value of *F* is arbitrarily close to zero.

The upper limit is found by substituting $+\frac{1}{2}$ for $-\frac{1}{2}$ in the formulas for *F* and *V*.

Confidence limits for the *relative risk* can be calculated using the expected counts *A, B, C,* and *D* from the last iteration of the above procedure. The lower limit of the relative risk

$$\phi_{lower} = \frac{A_{lower} n}{B_{lower} m}$$

$$\phi_{upper} = \frac{A_{upper} n}{B_{upper} m}$$

Mantel-Haenszel

The common estimate of the logarithm of the odds ratio is used to create this estimator. That is

$$\ln(\hat{\psi}) = \ln\left(\frac{ad}{bc}\right)$$

The standard error of this estimator is estimated using the Robins, Breslow, Greenland (1986) estimator which performs well in most situations. The standard error is given by

$$se\left(\ln(\hat{\psi})\right) = \sqrt{\frac{A}{2C} + \frac{AD + BC}{2CD} + \frac{B}{2D}}$$

where

$$A = \frac{a + d}{N}$$

$$B = \frac{b + c}{N}$$

$$C = \frac{ad}{N}$$

$$D = \frac{bc}{N}$$

The confidence limits are calculated as

$$\hat{\psi}_{lower} = \exp\left(\ln(\hat{\psi}) - z_{1-\frac{\alpha}{2}} se\left(\ln(\hat{\psi})\right)\right)$$

$$\hat{\psi}_{upper} = \exp\left(\ln(\hat{\psi}) + z_{1-\alpha/2} se\left(\ln(\hat{\psi})\right)\right)$$

Simple, Simple + ½, and Logarithm

The simple estimate of the odds ratio uses the formula

$$\hat{\psi} = \frac{\hat{p}_1\hat{q}_2}{\hat{p}_2\hat{q}_1}$$

$$= \frac{ad}{bc}$$

The standard error of this estimator is estimated by

$$se(\hat{\psi}) = \hat{\psi}\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

Problems occur if any one of the quantities *a*, *b*, *c*, or *d* are zero. To correct this problem, many authors recommend adding one-half to each cell count so that a zero cannot occur. Now, the formulas become

$$\hat{\psi}' = \frac{(a+0.5)(d+0.5)}{(b+0.5)(c+0.5)}$$

and

$$se(\hat{\psi}') = \hat{\psi}'\sqrt{\frac{1}{a+0.5}+\frac{1}{b+0.5}+\frac{1}{c+0.5}+\frac{1}{d+0.5}}$$

The distribution of these direct estimates of the odds ratio do not converge to normality as fast as does their logarithm, so the logarithm of the odds ratio is used to form confidence intervals. The formula for the standard error of the log odds ratio is

$$L' = \ln(\hat{\psi}')$$

and

$$se(L') = \sqrt{\frac{1}{a+0.5}+\frac{1}{b+0.5}+\frac{1}{c+0.5}+\frac{1}{d+0.5}}$$

A $100(1-\alpha)\%$ confidence interval for the log odds ratio is formed using the standard normal distribution as follows

$$\hat{\psi}_{lower} = \exp\left(L' - z_{1-\alpha/2}se(L')\right)$$

$$\hat{\psi}_{upper} = \exp\left(L' + z_{1-\alpha/2}se(L')\right)$$

See Fleiss et al (2003) for more details.

Sample Size Comparison

It is instructive to see the impact of the choice of calculation method on computed sample size. In the following table, we present the necessary sample size for the validation example for each method.

Method	N1 + N2	Increase Over Minimum
Exact (Conditional)	1445	185
Score (Farrington & Manning)	1370	110
Score (Miettinen & Nurminen)	1370	110
Fleiss	1555	295
Logarithm	1440	180
Mantel-Haenszel	1405	145
Simple	1260	0
Simple + 1/2	1310	50

Sample Size Estimation

Sample size estimation is relatively straight forward. For each method, anticipated (planned) values of the two proportions are substituted for the estimated values given by the above formulas, along with the sample sizes of each of the groups and the confidence level. The width between the two limits becomes the measure of precision. The narrower the confidence interval, the more precise it is.

To find an appropriate sample size for a given set of parameters, a binary search is conducted for the smallest sample size that meets the width requirements.

Confidence Level

The confidence level, 1 – α, has the following interpretation. If thousands of random samples of size n_1 and n_2 are drawn from populations 1 and 2, respectively, and a confidence interval for the true difference/ratio/odds ratio of proportions is calculated for each pair of samples, the proportion of those intervals that will include the true difference/ratio/odds ratio of proportions is 1 – α.

Adapting the Odds Ratio to Vaccine Efficacy Studies

A traditional index of the protective efficacy of a vaccine is called the vaccine efficacy (VE). It is calculated as

$$VE = 1 - OR = 1 - \frac{p_1(1-p_2)}{p_2(1-p_1)}$$

Note that VE is a simple transformation of the odds ratio made by subtracting it from one. Thus, the confidence interval methods described above can be adapted for computing sample sizes for vaccine efficacy studies. O'Neill (1988) gives the details using the Mantel-Haenszel method.

Relative Width

Although negative values are possible, *VE* is usually restricted to being greater than zero for planning purposes. Some authors prefer to use the following relative width (*RW*) in planning. The formula for *RW* is

$$RW = \frac{Width}{VE}$$

If *RW* is specified, the above relationship can be used to find the corresponding value of the *width*.

Example 1 – Calculating Sample Size

Suppose a study is planned in which the researcher wishes to construct a two-sided 95% confidence interval for vaccine efficacy (VE) such that the width of the interval is no wider than 0.2. Additional widths of 0.15 and 0.25 are also to be investigated. The confidence interval method to be used is the Mantel-Haenszel method. The confidence level is set to 0.95. VE is set at 0.7 and 0.8. P2 is 0.06.

The goal is to determine the necessary sample size.

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**
Method	**Mantel-Haenszel**
Interval Type	**Two-Sided**
Confidence Level (1 - α)	**0.95**
Group Allocation	**Equal (N1 = N2)**
Precision Input Type	**Absolute**
W (Confidence Interval Width)	**0.15 0.2 0.25**
Vaccine Efficacy Input Type	**Enter VE and P2**
VE (Vaccine Efficacy)	**0.7 0.8**
P2 (Prevalence of Vaccine in Controls)	**0.06**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Interval Type: Two-Sided
Confidence Interval Method: Mantel-Haenszel

Confidence Level 1 - α	Sample Size Case N1	Control N2	Total N	Confidence Interval Width Target W_T	Actual W_A	Relative RW	Vaccine Prevalence Case P1	Control P2	Vaccine Efficacy VE	Confidence Interval Limits of VE Lower LCL	Upper UCL
0.95	4515	4515	9030	0.15	0.14999	0.21428	0.01879	0.06	0.7	0.61577	0.76576
0.95	2579	2579	5158	0.20	0.19998	0.28569	0.01879	0.06	0.7	0.58379	0.78377
0.95	1682	1682	3364	0.25	0.24998	0.35711	0.01879	0.06	0.7	0.55002	0.79999
0.95	2802	2802	5604	0.15	0.14998	0.18748	0.01261	0.06	0.8	0.71141	0.86139
0.95	1628	1628	3256	0.20	0.19993	0.24992	0.01261	0.06	0.8	0.67644	0.87638
0.95	1082	1082	2164	0.25	0.24997	0.31247	0.01261	0.06	0.8	0.63917	0.88914

1 - α The Confidence Level. The proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the true value of VE.
N1 The number of subjects sampled from the population of cases.
N2 The number of subjects sampled from the population of controls.
N The total sample size. N = N1 + N2.
W_T The target width of the confidence interval of VE.
W_A The actual width of the confidence interval of VE that was computed by the procedure.
RW The relative width of the confidence interval. RW = Width / VE.
P1 The probability of having been vaccinated (vaccine prevalence) in the case group.
P2 The probability of having been vaccinated (vaccine prevalence) in the control group.
VE The index of vaccine efficacy. It represents the proportion of cases of disease prevented by the vaccine. It is calculated using VE = 1 - OR, where OR is the odds ratio of the prevalences of cases to controls.
LCL The lower confidence interval limit of VE.
UCL The upper confidence interval limit of VE.

Summary Statements

An unmatched case-control design will be used to obtain a two-sided 95% confidence interval for the vaccine efficacy (1 - odds[Cases] / odds[Controls]). The prevalence of vaccine exposure among the controls is assumed to be 0.06 and the prevalence of vaccine exposure among the cases is assumed to be 0.01879, corresponding to a vaccine efficacy of 0.7. The Mantel-Haenszel method will be used to compute the confidence interval limits. To produce a confidence interval width of 0.15, the number of subjects needed will be 4515 in the case group and 4515 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%	4515	4515	9030	5644	5644	11288	1129	1129	2258
20%	2579	2579	5158	3224	3224	6448	645	645	1290
20%	1682	1682	3364	2103	2103	4206	421	421	842
20%	2802	2802	5604	3503	3503	7006	701	701	1402
20%	1628	1628	3256	2035	2035	4070	407	407	814
20%	1082	1082	2164	1353	1353	2706	271	271	542

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, 5644 subjects should be enrolled in Group 1, and 5644 in Group 2, to obtain final group sample sizes of 4515 and 4515, respectively.

References

O'Neill, Robert T. 1988. 'On Sample Sizes to Estimate the Protective Efficacy of a Vaccine'. Statistics in Medicine, Volume 7, Pages 1279-1288.

Farrington, C. P. and Manning, G. 1990. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statistics in Medicine, Vol. 9, pages 1447-1454.

Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.

Miettinen, O.S. and Nurminen, M. 1985. 'Comparative analysis of two rates.' Statistics in Medicine 4: 213-226.

Robbins, Breslow, and Greenland. 1986. 'Estimators of the Mantel-Haenszel Variance Consistent in both Sparse Data and Large-Strata Limiting Models.' Biometrics, Volume 42, 311-323.

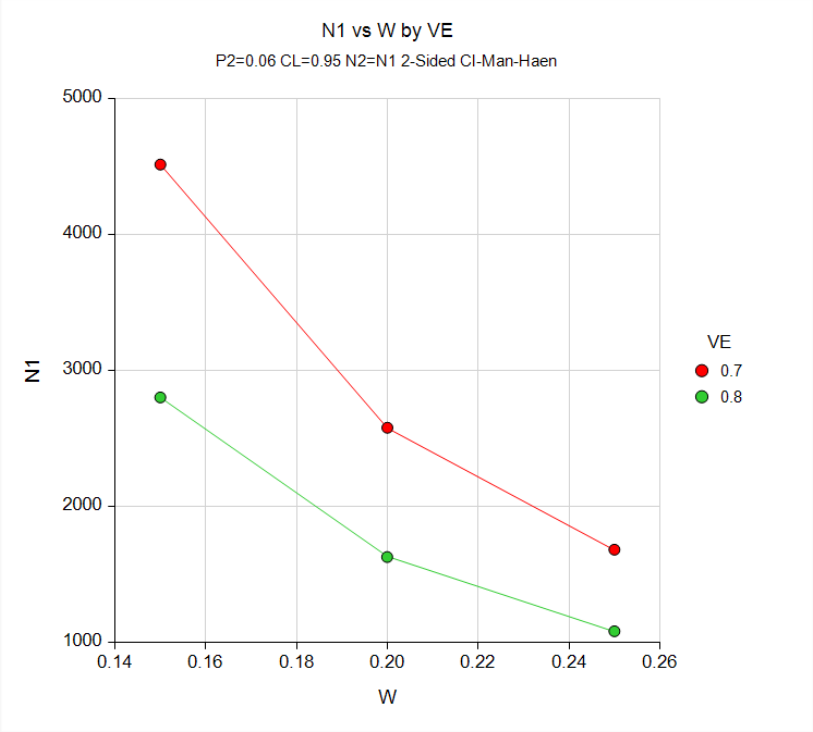
Sahai, H. and Khurshid, A. 1995. Statistics in Epidemiology. CRC Press. Boca Raton, Florida.

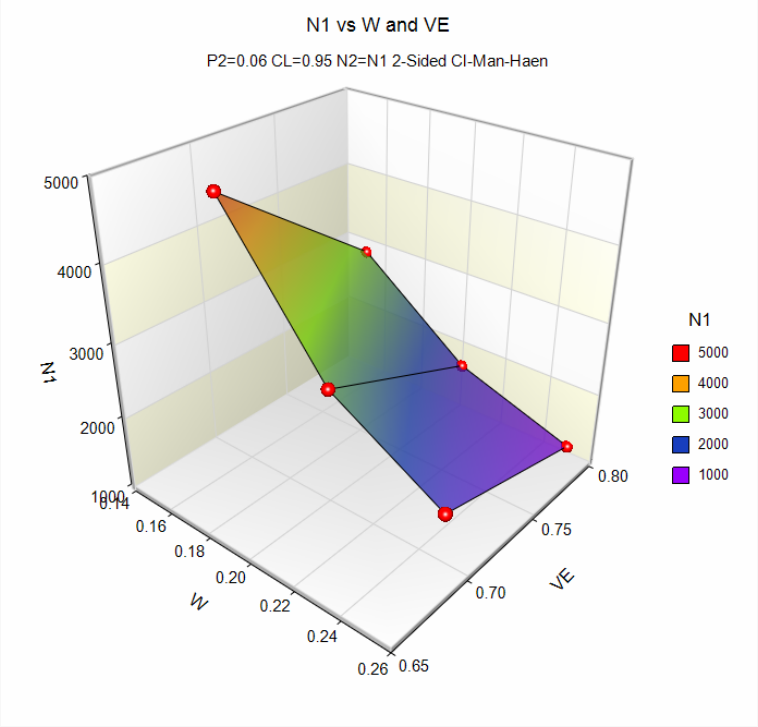
Schlesselman, James. 1982. Case-Control Studies: Design, Conduct, Analysis. Oxford University Press. New York.

This report shows the calculated sample sizes for each of the scenarios.

Plots Section

Plots





These plots show the group sample size versus the confidence interval width for the two VE values.

Example 2 – Validation using O'Neill (1988)

O'Neill (1988) page 1286 gives an example of a sample size calculation for a confidence interval for VE when the confidence level is 95%, VE is 0.8, P2 is 0.2, and the desired width is 0.24. The confidence interval method is Mantel-Haenszel. The design calls for 4 controls for each case. The sample size given for this scenario is 280.

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**
Method	**Mantel-Haenszel**
Interval Type	**Two-Sided**
Confidence Level (1 - α)	**0.95**
Group Allocation	**Enter R = N2/N1, solve for N1 and N2**
R (Group Sample Size Ratio)	**4**
Precision Input Type	**Absolute**
W (Confidence Interval Width)	**0.240**
Vaccine Efficacy Input Type	**Enter VE and P2**
VE (Vaccine Efficacy)	**0.8**
P2 (Prevalence of Vaccine in Controls)	**0.2**

Output

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

Numeric Results

Solve For: Sample Size
Interval Type: Two-Sided
Confidence Interval Method: Mantel-Haenszel

Confidence Level 1 - α	Sample Size: Case N1	Control N2	Total N	Target R	Confidence Interval Width: Target W_T	Actual W_A	Relative RW	Vaccine Prevalence: Case P1	Control P2	Vaccine Efficacy VE	Confidence Interval Limits of VE: Lower LCL	Upper UCL
0.95	281	1124	1405	4	0.24	0.23969	0.29961	0.04762	0.2	0.8	0.647	0.88669

PASS has also computed an N1 of 281 which is just slightly above the 280 in the article. This difference arises because of rounding. The procedure is validated.