Chapter 273

Confidence Intervals for One-Sample Sensitivity and Specificity

Introduction

This procedure calculates the (whole table) sample size necessary for both sensitivity and specificity confidence intervals, based on a specified sensitivity and specificity, interval width, confidence level, and prevalence.

Caution: This procedure assumes that the sensitivity and specificity of the future sample will be the same as the sensitivity and specificity that is specified. If the sample sensitivity or specificity is different from the one specified when running this procedure, the interval width may be narrower or wider than specified.

Sensitivity (True Positive Rate)

The sensitivity (or true positive rate) is the proportion of the individuals with a known positive condition for which the predicted condition is positive.

		Predicted Condition: Positive	Predicted Condition: Negative
True Condition	**Positive**	**True Positive (A)**	False Negative (C)
	Negative	False Positive (B)	True Negative (D)

Sensitivity = A / (A + C)

Specificity (True Negative Rate)

The specificity (or true negative rate) is the proportion of the individuals with a known negative condition for which the predicted condition is negative.

		Predicted Condition: Positive	Predicted Condition: Negative
True Condition	Positive	True Positive (A)	False Negative (C)
	Negative	False Positive (B)	**True Negative (D)**

Specificity = D / (B + D)

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Prevalence

The prevalence is the overall proportion of individuals with a positive condition.

		Predicted Condition: Positive	Predicted Condition: Negative
True Condition	**Positive**	**True Positive (A)**	**False Negative (C)**
	Negative	False Positive (B)	True Negative (D)

Prevalence = (A + C) / (A + B + C + D)

Technical Details

In general terms, the required sample size is determined as the larger of two (whole table) sample sizes needed for each of the sensitivity and specificity confidence intervals, including appropriate prevalence adjustments.

Sensitivity Confidence Interval Sample Size Calculation

The initial sample size calculation for the sensitivity confidence interval gives the number of individuals with a positive condition that are needed. The prevalence adjustment is used to add the number of individuals with a negative condition that are needed. The resulting sample size is the total number of individuals needed to obtain a table where the number of positive condition individuals will give the needed confidence interval width for the sensitivity.

Similarly, when calculating the confidence interval width for a given sample size, the given sample size is first used to produce the number of positive condition individuals, according to the given prevalence, and then the width based on the resulting positive condition count is then calculated.

Specificity Confidence Interval Sample Size Calculation

The initial sample size calculation for the specificity confidence interval gives the number of individuals with a negative condition that are needed. The prevalence adjustment is used to add the number of individuals with a positive condition that are needed. The resulting sample size is the total number of individuals needed to obtain a table where the number of negative condition individuals will give the needed confidence interval width for the specificity.

Similarly, when calculating the confidence interval width for a given sample size, the given sample size is first used to produce the number of negative condition individuals, according to the given prevalence, and then the width based on the resulting negative condition count is then calculated.

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Confidence Interval Formulas

Many methods have been devised for computing confidence intervals for a single proportion. Five of these methods are available in this procedure. The five confidence interval methods are

1. Exact (Clopper-Pearson)
2. Score (Wilson)
3. Score with continuity correction
4. Simple Asymptotic
5. Simple Asymptotic with continuity correction

For a comparison of methods, see Newcombe (1998a).

For each of the following methods, let *p* be the population sensitivity, and let *r* represent the number of true positives with *n* total positives. Let $\hat{p} = r / n$.

Exact (Clopper-Pearson)

Using a mathematical relationship (see Fleiss et al (2003), p. 25) between the *F* distribution and the cumulative binomial distribution, the lower and upper confidence limits of a 100(1-α)% exact confidence interval for the true proportion *p* are given by

$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}}, \frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

One-sided limits may be obtained by replacing $\alpha/2$ by α.

Score (Wilson)

The Wilson Score confidence interval, which is based on inverting the z-test for a single proportion, is calculated using

$$\frac{\left(2n\hat{p}+z_{1-\alpha/2}^2\right) \pm z_{1-\alpha/2}\sqrt{z_{1-\alpha/2}^2+4n\hat{p}(1-\hat{p})}}{2\left(n+z_{1-\alpha/2}^2\right)}$$

One-sided limits may be obtained by replacing $\alpha/2$ by α.

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Score with Continuity Correction

The Score confidence interval with continuity correction is based on inverting the z-test for a single proportion with continuity correction. The $100(1-\alpha)\%$ limits are calculated by

$$Lower\ Limit = \frac{\left(2n\hat{p} + z_{1-\alpha/2}^2 - 1\right) - z_{1-\alpha/2}\sqrt{z_{1-\alpha/2}^2 - \{2 + (1/n)\} + 4\hat{p}\{n(1-\hat{p}) + 1\}}}{2\left(n + z_{1-\alpha/2}^2\right)}$$

$$Upper\ Limit = \frac{\left(2n\hat{p} + z_{1-\alpha/2}^2 + 1\right) + z_{1-\alpha/2}\sqrt{z_{1-\alpha/2}^2 + \{2 - (1/n)\} + 4\hat{p}\{n(1-\hat{p}) - 1\}}}{2\left(n + z_{1-\alpha/2}^2\right)}$$

One-sided limits may be obtained by replacing $\alpha/2$ by α.

Simple Asymptotic

The simple asymptotic formula is based on the normal approximation to the binomial distribution. The approximation is close only for very large sample sizes. The $100(1-\alpha)\%$ confidence limits are given by

$$\hat{p} \pm z_{1-\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$$

One-sided limits may be obtained by replacing $\alpha/2$ by α.

Simple Asymptotic with Continuity Correction

This formula is identical to the previous one, but with continuity correction. The $100(1-\alpha)\%$ confidence limits are

$$\left(\hat{p} - z_{1-\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} - \frac{1}{2n}, \hat{p} + z_{1-\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} + \frac{1}{2n}\right)$$

One-sided limits may be obtained by replacing $\alpha/2$ by α.

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Interval Widths (One-Sided vs. Two-Sided)

For two-sided intervals, the distance from the sample sensitivity to each of the limits may be different. Thus, instead of specifying the distance to the limits we specify the width of the interval, *W*.

The basic equation for determining sample size for a two-sided interval when *W* has been specified is

$$W = U - L$$

For one-sided intervals, the distance from the sample sensitivity to limit, *D*, is specified.

The basic equation for determining sample size for a one-sided upper limit when *D* has been specified is

$$D = U - \hat{p}$$

The basic equation for determining sample size for a one-sided lower limit when *D* has been specified is

$$D = \hat{p} - L$$

Each of these equations can be solved for any of the unknown quantities in terms of the others.

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Example 1 – Calculating Sample Size

Suppose a study is planned in which the researcher wishes to construct two-sided 95% exact (Clopper-Pearson) confidence intervals for the population sensitivity and specificity such that the widths of the intervals are no wider than 0.06. The anticipated sensitivity estimate is 0.7, but a range of values from 0.5 to 0.9 will be included to determine the effect of the sensitivity estimate on necessary sample size. The anticipated specificity is 0.6. Instead of examining only the interval width of 0.06, widths of 0.04, 0.08, and 0.10 will also be considered.

The goal is to determine the total sample size needed when also accounting for 20% to 60% prevalence.

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**
Confidence Interval Formula	**Exact (Clopper-Pearson)**
Interval Type	**Two-Sided**
Confidence Level (1 - Alpha)	**0.95**
Confidence Interval Width (Two-Sided)	**0.04 0.06 0.08 0.10**
Sensitivity	**0.5 to 0.9 by 0.05**
Specificity	**0.6**
Prevalence	**0.2 to 0.6 by 0.1**

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Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Confidence Interval Formula: Exact (Clopper-Pearson)
Confidence Interval Type: Two-Sided

			Sensitivity			Specificity			
Confidence Level	Required Sample Size N	Target Confidence Interval Width	Sample Size	C.I. Width if Sample Size = N	Value	Sample Size	C.I. Width if Sample Size = N	Value	Prevalence
0.95	12245	0.04	12245	0.040	0.50	2942	0.020	0.6	0.2
0.95	8164	0.04	8164	0.040	0.50	3362	0.026	0.6	0.3
0.95	6123	0.04	6123	0.040	0.50	3922	0.033	0.6	0.4
0.95	4898	0.04	4898	0.040	0.50	4706	0.040	0.6	0.5
0.95	5883	0.04	4082	0.033	0.50	5883	0.041	0.6	0.6
0.95	12125	0.04	12125	0.040	0.55	2942	0.020	0.6	0.2
0.95	8084	0.04	8084	0.040	0.55	3362	0.026	0.6	0.3
0.95	6063	0.04	6063	0.040	0.55	3922	0.033	0.6	0.4
0.95	4850	0.04	4850	0.040	0.55	4706	0.040	0.6	0.5
0.95	5883	0.04	4042	0.033	0.55	5883	0.041	0.6	0.6
0.95	11765	0.04	11765	0.040	0.60	2942	0.020	0.6	0.2
0.95	7844	0.04	7844	0.040	0.60	3362	0.026	0.6	0.3
0.95	5883	0.04	5883	0.040	0.60	3922	0.033	0.6	0.4
0.95	4706	0.04	4706	0.040	0.60	4706	0.040	0.6	0.5
0.95	5883	0.04	3922	0.033	0.60	5883	0.040	0.6	0.6
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Confidence Level	The proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the population sensitivity or specificity.
N	The required whole-table sample size that is needed to give the desired confidence interval width for both the sensitivity and specificity. It is the larger of the two sample sizes.
Target Confidence Interval Width	The desired distance from the lower limit to the upper limit for both the sensitivity and specificity.
Sensitivity Sample Size	The sample size needed to obtain the desired confidence interval width for sensitivity.
Sensitivity C.I. Width if Sample Size = N	The distance from the sensitivity confidence interval lower limit to the upper limit when the sample size is N.
Sensitivity Value	The assumed sample sensitivity, or true positive rate.
Specificity Sample Size	The sample size needed to obtain the desired confidence interval width for specificity.
Specificity C.I. Width if Sample Size = N	The distance from the specificity confidence interval lower limit to the upper limit when the sample size is N.
Specificity Value	The assumed sample specificity, or true negative rate.
Prevalence	The assumed overall proportion of individuals with a positive condition.

Summary Statements

A single-group diagnostic test design will be used to obtain two-sided 95% confidence intervals for the sensitivity and the specificity. The Exact (Clopper-Pearson) formula will be used to calculate the confidence interval limits. The sample sensitivity is assumed to be 0.5, the sample specificity is assumed to be 0.6, and the prevalence is assumed to be 0.2. To produce a sensitivity confidence interval with a width of no more than 0.04, 12245 subjects will be needed. To produce a specificity confidence interval with a width of no more than 0.04, 2942 subjects will be needed. The sample size required, so that both confidence intervals have widths less than 0.04, is 12245, the larger of the two sample sizes. With a sample size of 12245, the sensitivity confidence interval width is 0.04 and the specificity confidence interval width is 0.02.

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Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	12245	15307	3062
20%	8164	10205	2041
20%	6123	7654	1531
20%	4898	6123	1225
20%	5883	7354	1471
20%	12125	15157	3032
20%	8084	10105	2021
20%	6063	7579	1516
20%	4850	6063	1213
20%	5883	7354	1471
20%	11765	14707	2942
20%	7844	9805	1961
20%	5883	7354	1471
20%	4706	5883	1177
20%	5883	7354	1471
.	.	.	.
.	.	.	.
.	.	.	.

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.
N	The evaluable sample size at which the confidence interval is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated confidence interval.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' 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.)
D	The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 15307 subjects should be enrolled to obtain a final sample size of 12245 subjects.

References

Hajian-Tilaki, K. 2014. 'Sample size estimation in diagnostic test studies of biomedical informatics.' Journal of Biomedical Informatics, 48, pp. 193-204.

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

Newcombe, R. G. 1998. 'Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods.' Statistics in Medicine, 17, pp. 857-872.

These reports show the calculated sample size for each of the scenarios.

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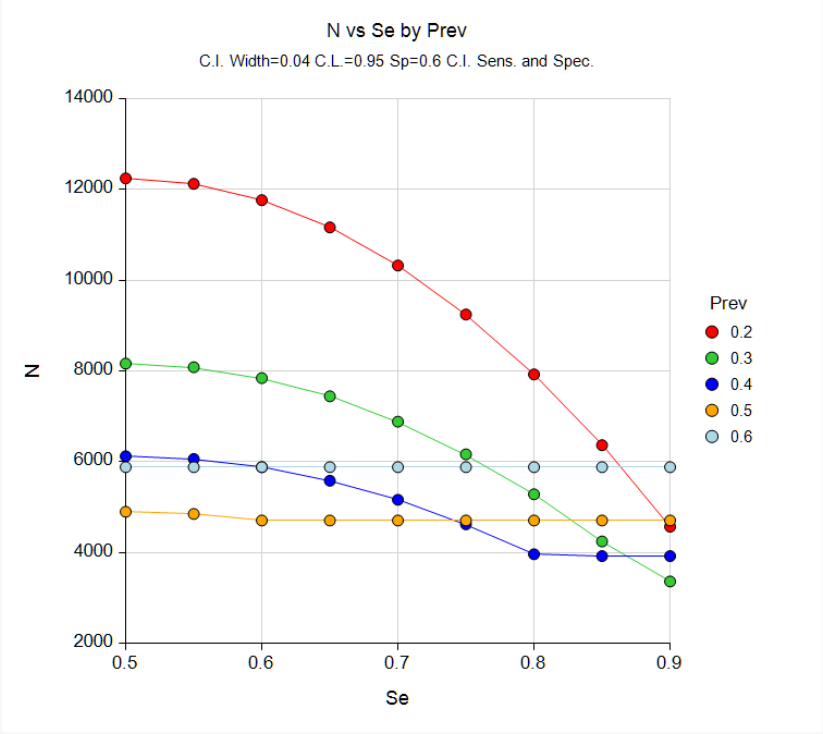
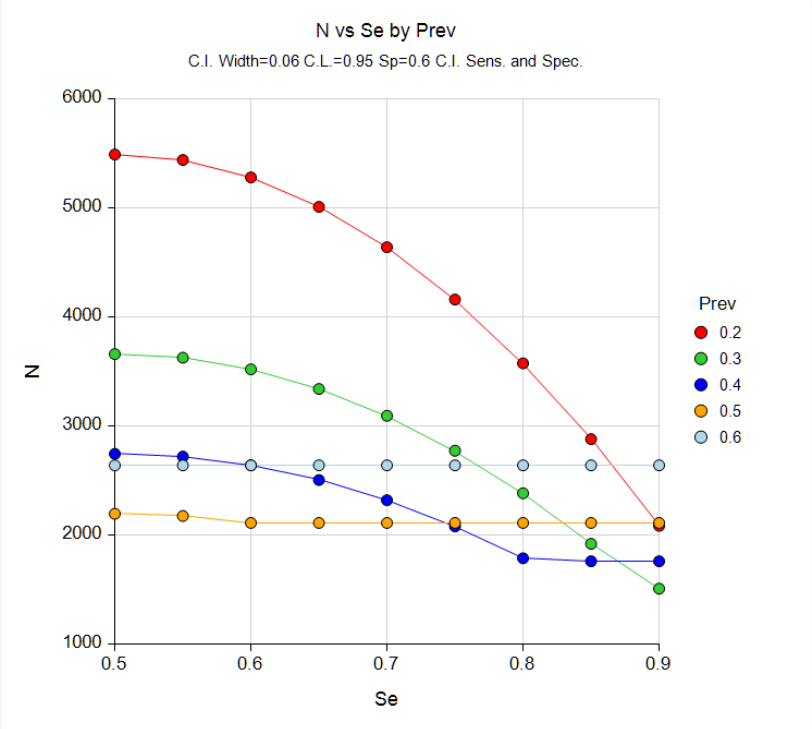
Plots Section

Plots





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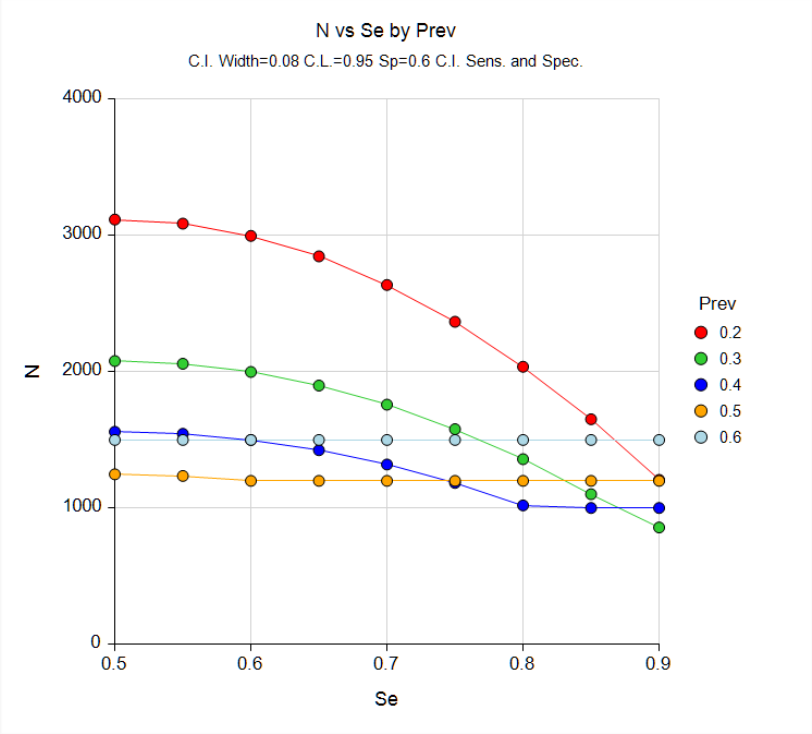
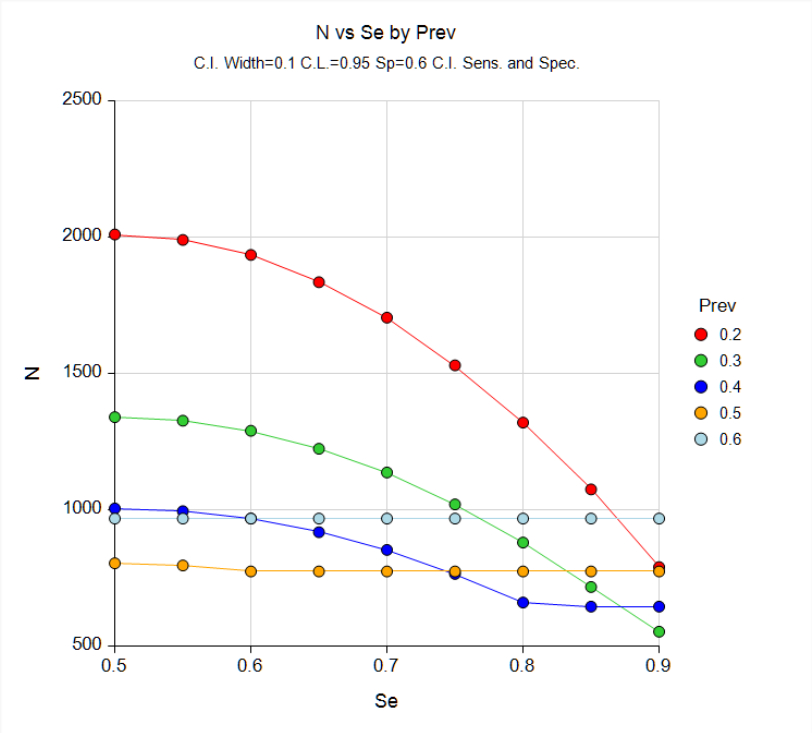
Confidence Intervals for One-Sample Sensitivity and Specificity





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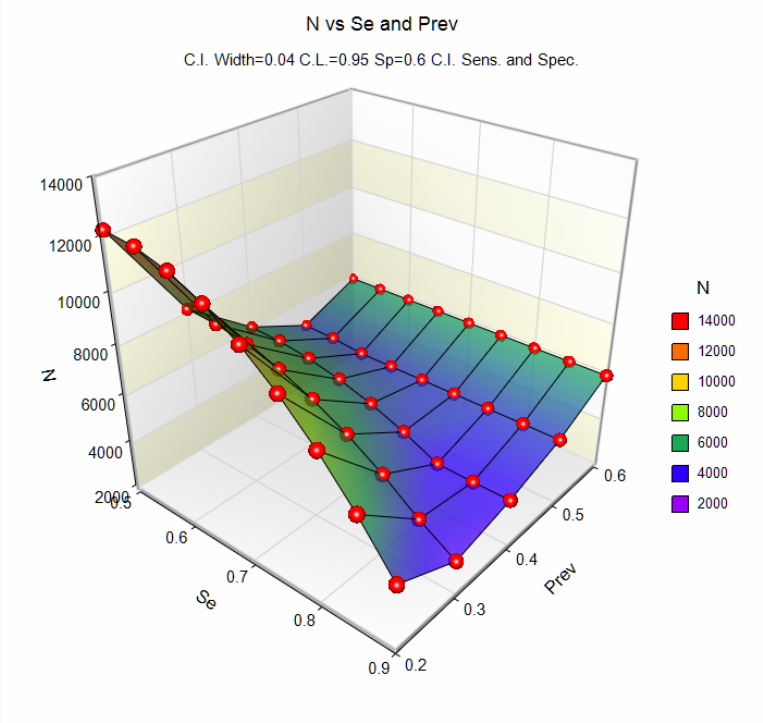
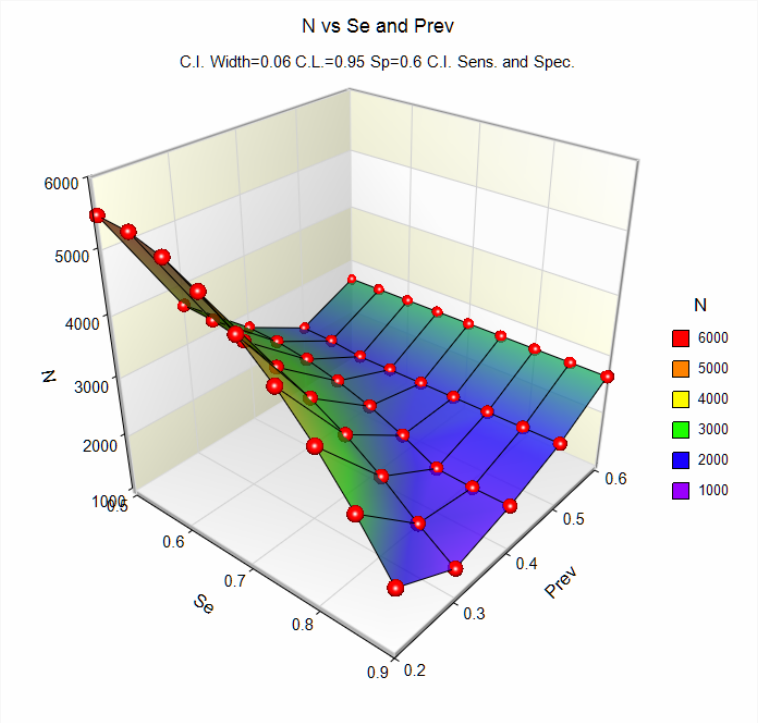
Confidence Intervals for One-Sample Sensitivity and Specificity





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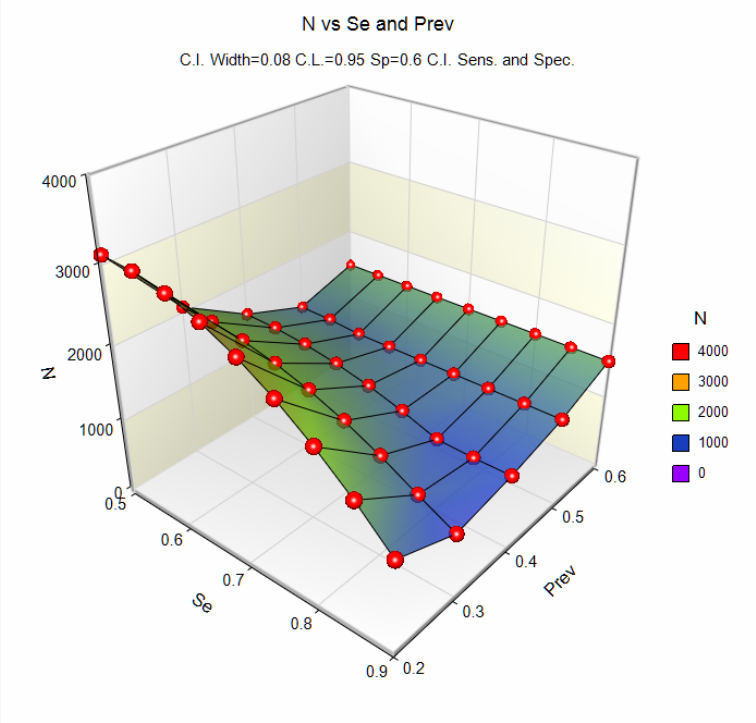
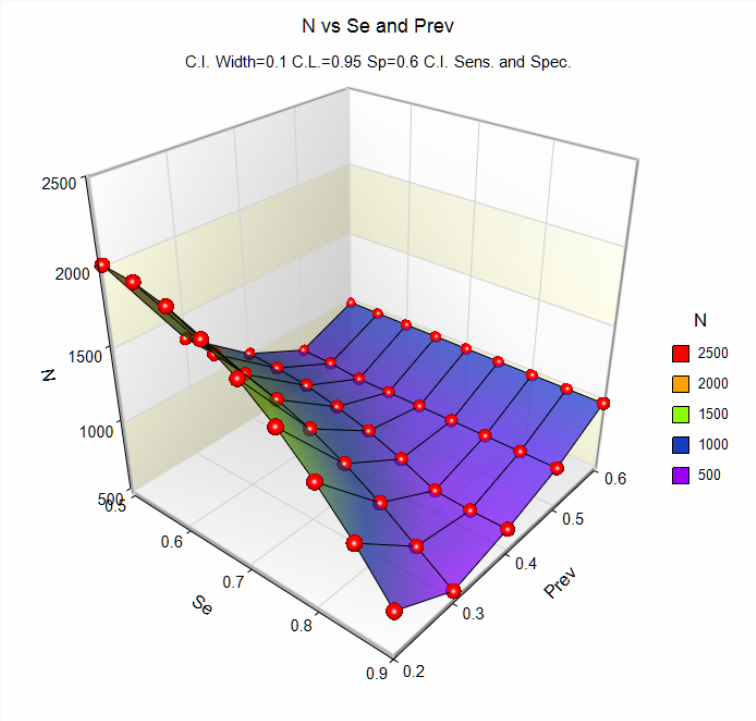
Confidence Intervals for One-Sample Sensitivity and Specificity





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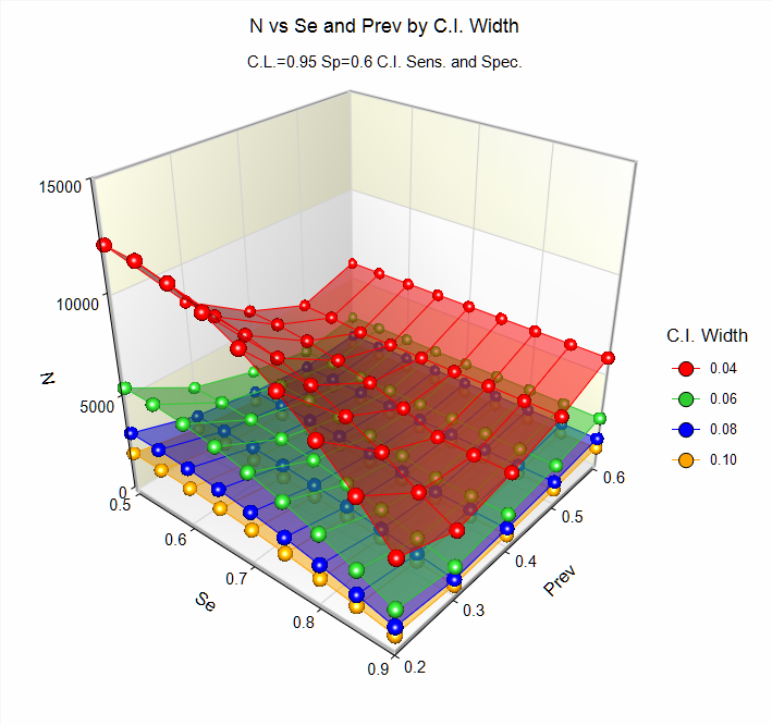

These plots show the sample size versus the sample sensitivity and prevalence for the four confidence interval widths. It can be seen in the plots where the sample size depends on the sensitivity, and where it depends on the specificity.

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Example 2 – Validation for Sensitivity Confidence Interval using Hajian-Tilaki (2014)

Hajian-Tilaki (2014), page 195, gives an example of a calculation for a simple asymptotic two-sided confidence interval for a single sensitivity when the confidence level is 95%, the sensitivity is 0.8, the prevalence is 0.1, and the margin of error is 7% (With a margin of error (precision) of 7%, the width is 0.14). The necessary sample size is calculated to be 1254.

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**
Confidence Interval Formula	**Simple Asymptotic**
Interval Type	**Two-Sided**
Confidence Level (1 - Alpha)	**0.95**
Confidence Interval Width (Two-Sided)	**0.14**
Sensitivity	**0.8**
Specificity	**0.8**
Prevalence	**0.1**

Output

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

Numeric Results

Solve For: Sample Size
Confidence Interval Formula: Simple Asymptotic
Confidence Interval Type: Two-Sided

			Sensitivity			Specificity			
Confidence Level	Required Sample Size N	Target Confidence Interval Width	Sample Size	C.I. Width if Sample Size = N	Value	Sample Size	C.I. Width if Sample Size = N	Value	Prevalence
0.95	1260	0.14	1260	0.14	0.8	140	0.047	0.8	0.1

PASS calculates the necessary sample size to be 1260. The sample size calculated in **PASS** is slightly different from the article. In the article the sample sizes are calculated directly, while **PASS** calculates the sample size needed before prevalence is taken into account, and then adjusts for the prevalence. With a sample size of 1254, the number of positives would be 125.4, which should be rounded up to 126. Adjusting 126 for prevalence gives 1260.

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Example 3 – Validation for Specificity Confidence Interval using Hajian-Tilaki (2014)

Hajian-Tilaki (2014), page 196, gives an example of a calculation for a simple asymptotic two-sided confidence interval for a single specificity when the confidence level is 95%, the specificity is 0.8, the prevalence is 0.1, and the margin of error is 3% (With a margin of error (precision) of 3%, the width is 0.06). The necessary sample size is calculated to be 759.

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 3** 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**
Confidence Interval Formula	**Simple Asymptotic**
Interval Type	**Two-Sided**
Confidence Level (1 - Alpha)	**0.95**
Confidence Interval Width (Two-Sided)	**0.06**
Sensitivity	**0.8**
Specificity	**0.8**
Prevalence	**0.1**

Output

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

Numeric Results

Solve For: Sample Size
Confidence Interval Formula: Simple Asymptotic
Confidence Interval Type: Two-Sided

			Sensitivity			Specificity			
Confidence Level	Required Sample Size N	Target Confidence Interval Width	Sample Size	C.I. Width if Sample Size = N	Value	Sample Size	C.I. Width if Sample Size = N	Value	Prevalence
0.95	6830	0.06	6830	0.06	0.8	759	0.02	0.8	0.1

PASS also calculates the necessary sample size to be 759. For some entries in the table, the sample size calculated in **PASS** is slightly different from the article. In the article the sample sizes are calculated directly, while **PASS** calculates the sample size needed before prevalence is taken into account, and then adjusts for the prevalence.

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