Sample Size Estimation

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The Question

Diagnostic technology can distinguish between diseased (positive) and non-diseased (negative) blood samples.
This technology has a sensitivity of at least 99% and a specificity of at least 87%.
What is the minimum sample size needed to, with 90% probability, obtain both:

- A point estimate for the sensitivity above 98%, and
- The lower bound of a 95% confidence interval above 96%.

Notation

- n: sample size
- x: number of true positives observed.
- $\hat{p}$: point estimate for sensitivity.

Approach

The way I approached this was to:

- Choose a method for calculating the point-estimate $\hat{p}$ from the number of positive outcomes x.
- For each possible sample size n, calculate the probability that the criteria $\hat{p} > 0.98$ is satisfied.
- Plot n against the probability of satisfying the criteria $\hat{p} > 0.98$ to find the point at which the sample size is large enough that this probability is $> 90\%$. There are a few ways to do this, which I will show.

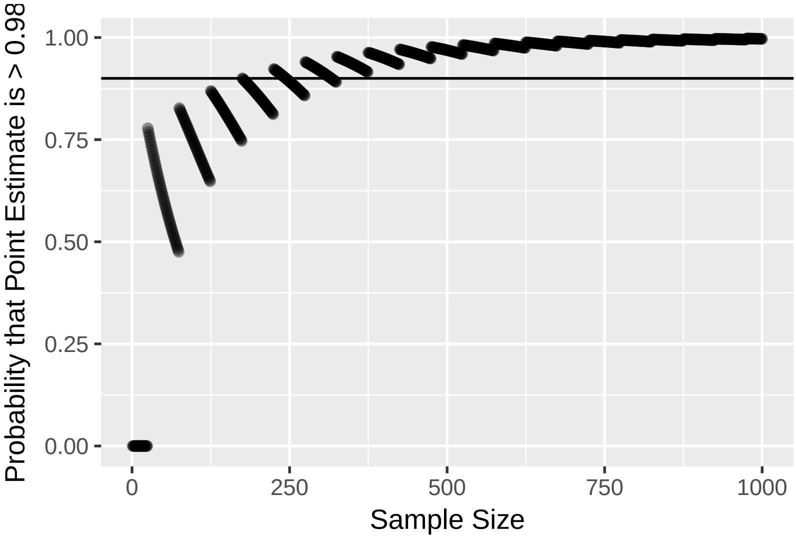
Jeffreys Point Estimate

I'll use the Jeffreys estimate:

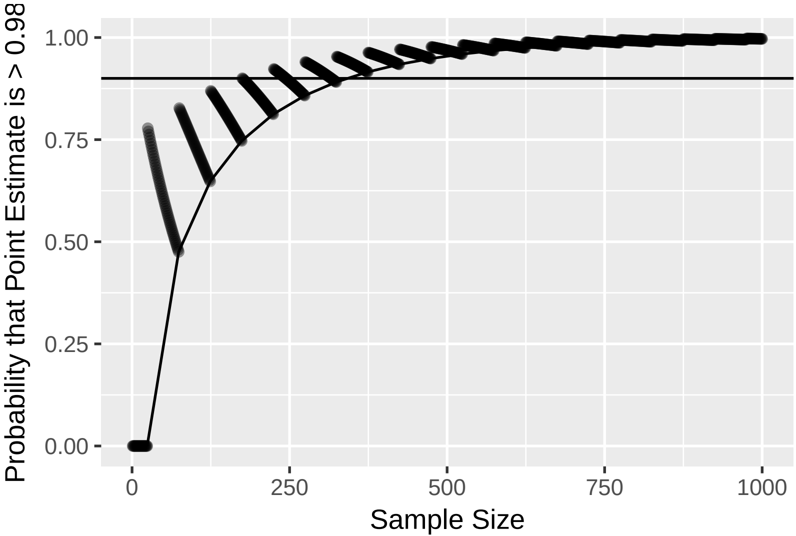
$$\hat{p} = \frac{x + 0.5}{n + 1}$$

Which is the mean of the posterior distribution when a Jeffreys prior is used. It is also a compromise between the MLE and Laplace's Law of Succession (which is the mean of the posterior when using a uniform prior).

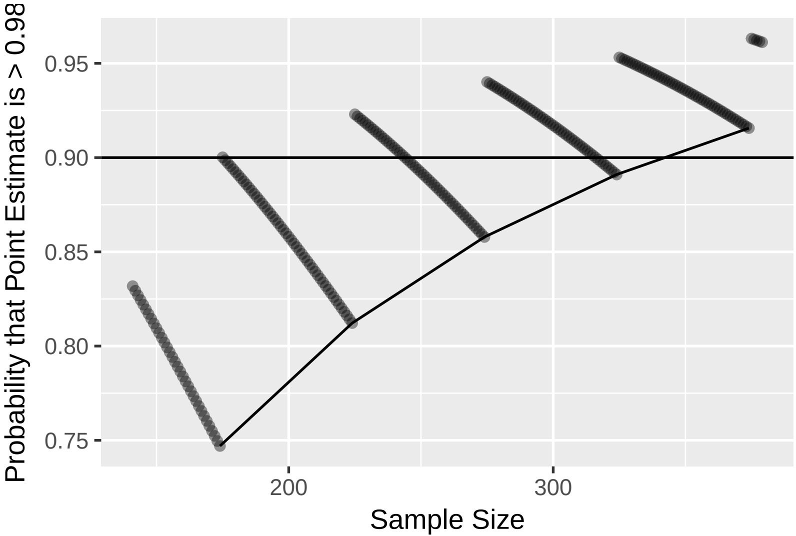
Jeffreys Point Estimate



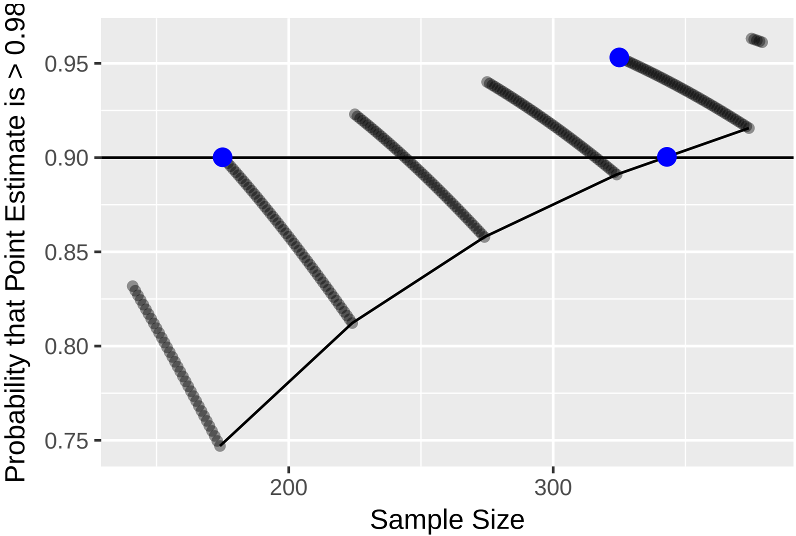
Jeffreys Point Estimate



Jeffreys Point Estimate



Jeffreys Point Estimate



Jeffreys Point Estimate

These three different approaches each give us a sample size estimate to varying degrees of conservativeness:

First	Strict Min	Interpolation
175	325	343

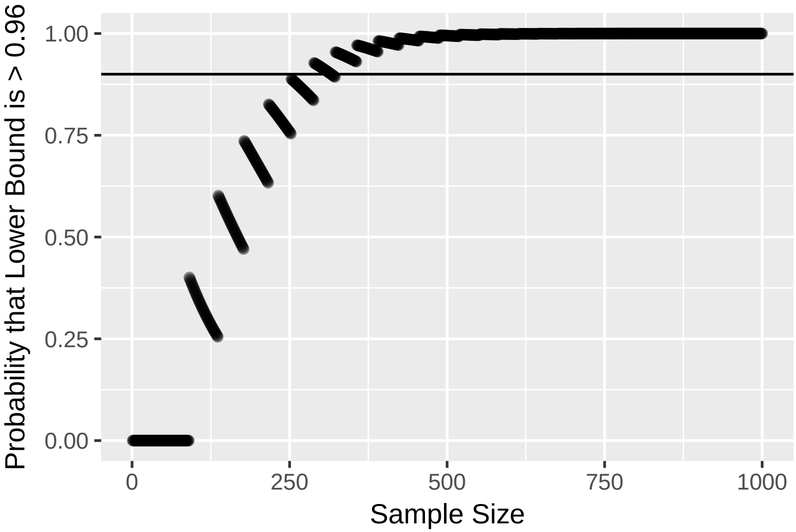
Clopper-Pearson Exact Interval

I'll use the Clopper-Pearson Exact confidence interval, which has lower bound p_0 as the solution to

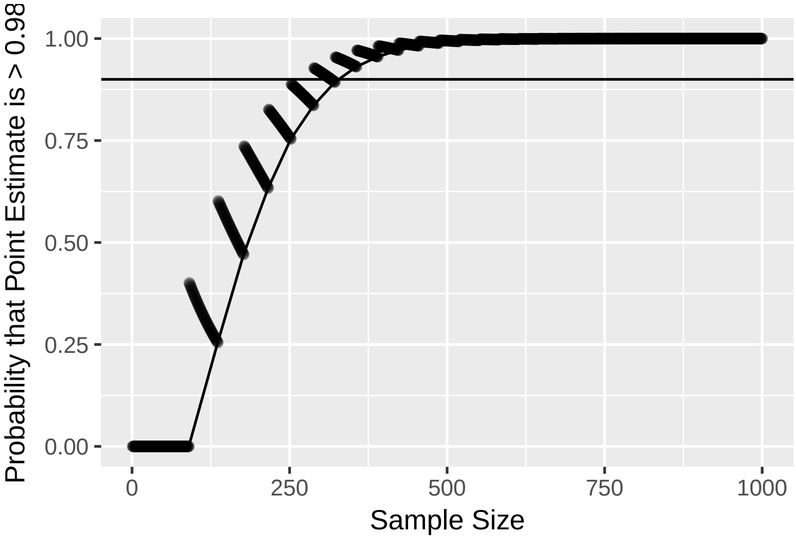
$$\sum_{k=x}^{n} \binom{n}{k} p_0^k (1 - p_0)^{n-k} = \alpha/2$$

where α is the required significance level, in this case 0.05. This lower bound can neatly be calculated as the $\alpha/2$ quantile of a beta distribution with shape parameters x and $n - x + 1$ (Agresti and Coull [1998]).

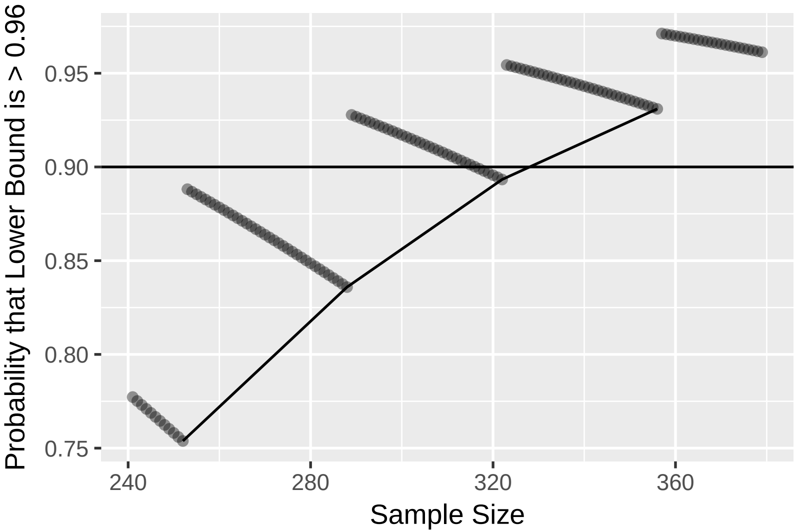
Clopper-Pearson Exact Interval



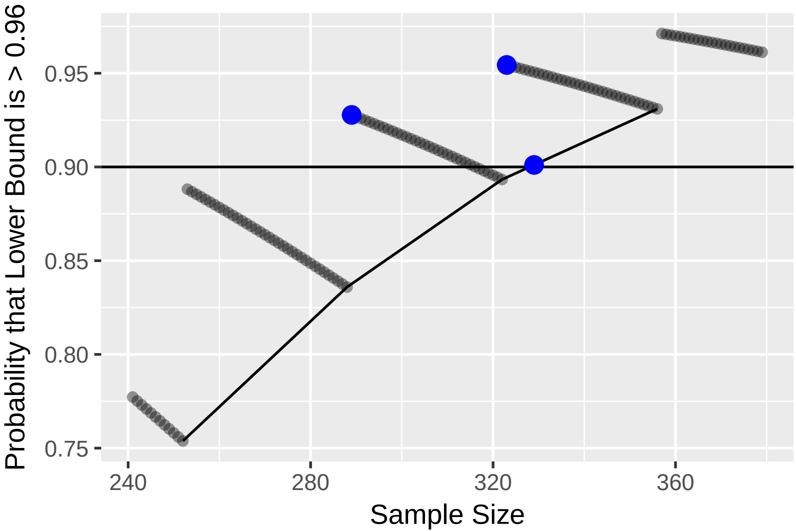
Clopper-Pearson Exact Interval



Clopper-Pearson Exact Interval



Clopper-Pearson Exact Interval



Sample Size Reccomendation

The sample size estimates for the point estimate criteria were:

First	Strict Min	Interpolation
175	325	343

and the equivalent estimates for the confidence interval criteria are:

First	Strict Min	Interpolation
289	323	329

Based on these calculations, the most conservative estimate would be $n = 343$, although I would still consider $n = 325$ quite reasonable and still quite conservative.

Assumptions

- Results will be distributed according to a Binomial distribution.
- Cannot use prior knowledge about the sensitivity to inform our calculations.

Additional Considerations

- As is, these criteria could be manipulated:
  - There is no criteria requiring a certain level of specificity.
  - There is no criteria that prior knowledge cannot be used in calculation of confidence intervals and point estimates.
- Knowledge about the cost per sample, and the consequences of failing to meet the criteria, could be used to optimise the choice of sample size.

Questions?

Other Point Estimates

There are a number of different methods for point estimation:

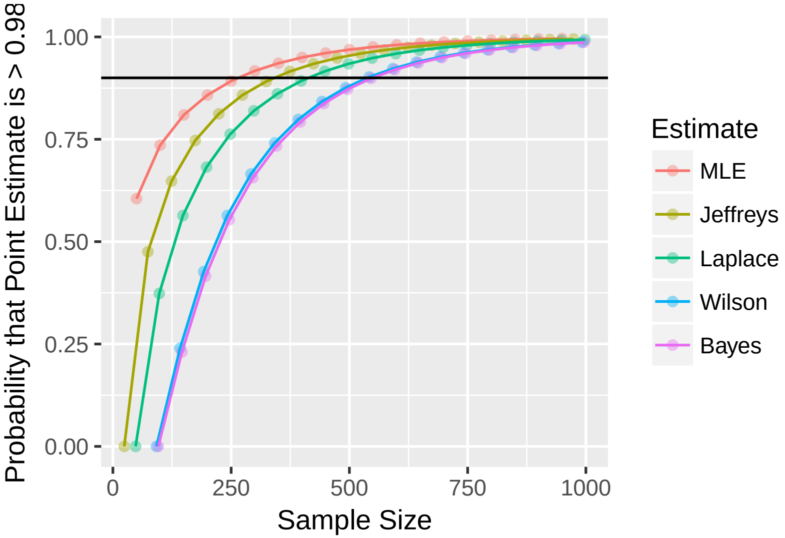
- MLE: $\hat{p} = \frac{x}{n}$,
- Jeffreys: $\hat{p} = \frac{x+0.5}{n+1}$,
- Laplace: $\hat{p} = \frac{x+1}{n+2}$,
- Bayes: $\hat{p} = \frac{x+2}{n+4}$,
- Wilson: $\hat{p} = \frac{x+\frac{z^2}{2}}{n+z^2}$ (Wilson [1927]),

and more. Chew [1971] offer a good review of point estimates for a binomial proportion.

Point Estimate Summary

	First	Strict Min	Interpolation
MLE	1	251	266
Jeffreys	175	325	343
Laplace	299	399	414
Wilson	443	493	539
Bayes	447	547	549

Point Estimate Summary



Confidence Intervals

There are many methods for confidence interval estimation as well, including:

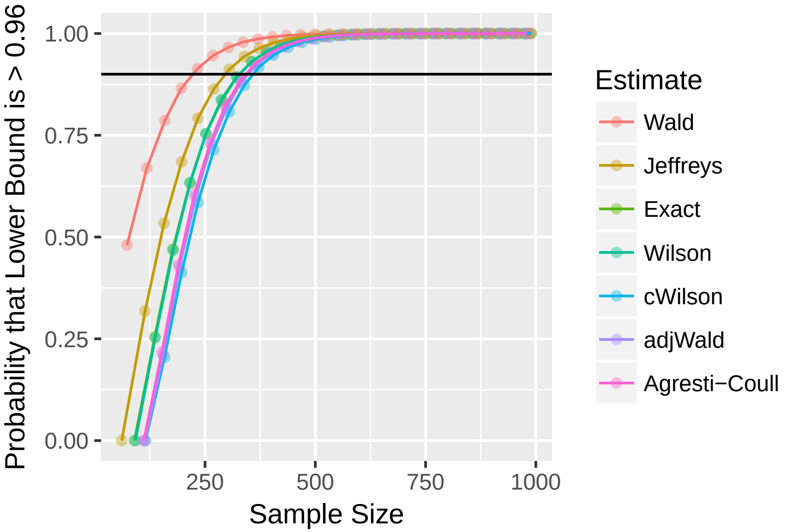
- Exact (Clopper and Pearson [1934])
- Wilson Score (Wilson [1927])
- Continuity-Corrected Wilson Score
- Wald
- Adjusted Wald (Agresti and Coull [1998])
- Jeffreys

and more. Agresti and Coull [1998] offer a good review of interval estimation methods for a binomial proportion.

Confidence Interval Summary

	First	Strict Min	Interpolation
Exact	289	323	329
Wilson	288	323	329
cWilson	306	340	360
Agresti-Coull	297	331	343
Wald	1	197	223
adjWald	300	333	348
Jeffreys	235	271	297

Confidence Interval Summary



Colophon

These slides where written using LaTeXin Rstudio. knitr was used to embed the R code that performed the analysis and generated the plots for this presentation. The complete source is available my github. This colophon was inspired by that in the book R packages by Hadley Wickham.

Bibliography

Alan Agresti and Brent A Coull. Approximate is better than "exact" for interval estimation of binomial proportions. *The American Statistician*, 52(2):119–126, 1998.

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