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# Confidence limits for prevalence of disease adjusted for estimated sensitivity and specificity

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ABSTRACT

Prevalence of a disease is usually assessed by diagnostic tests that may produce false results. Rogan and Gladen (1978) described a method to estimate the true prevalence correcting for sensitivity and specificity of the diagnostic procedure, and Reiczigel et al. (2010) provided exact confidence intervals for the true prevalence assuming sensitivity and specificity were known. In this paper we propose a new method to construct approximate confidence intervals for the true prevalence when sensitivity and specificity are estimated from independent samples. To improve coverage we applied an adjustment similar to that described in Agresti and Coull (1998). According to an extensive simulation study the new confidence intervals maintain the nominal level fairly well even for sample sizes as small as 30; minimum coverage is above 88%, 93%, and 98% at nominal 90%, 95%, and 99%, respectively. We illustrate the advantages of the proposed method with real-life applications.



## 1. Introduction

Prevalence estimates accompanied by standard errors and/or confidence intervals are among the most basic tasks in epidemiological studies. In many published analyses of survey data it is implicitly assumed that the diagnostic test has a sensitivity and specificity of 1. However, this assumption is often unrealistic. Rogan and Gladen (1978) proposed corrected point estimates for prevalence with asymptotic standard errors taking into account sensitivity and specificity of the diagnostic test. Reiczigel et al. (2010) presented a method to construct exact two-sided confidence intervals assuming that sensitivity and specificity were known.

When sensitivity and specificity are not known a priori but estimated from a sample, the uncertainty of their estimates will increase the variance of the prevalence estimate, and this must be taken into account in the confidence interval construction. In many publications there is no information about the sample size for determination of sensitivity and specificity, or just some references are given to other studies (Boadella et al., 2012; Pinho et al., 2013; Sarrazin et al., 2013). It is often the case that samples of 100 or even less are used for estimating sensitivity and specificity (for a literature summary see e.g. Farnham et al., 2012). In these cases ignoring the uncertainty in sensitivity and specificity estimates leads to unduly small standard errors and/or too narrow confidence intervals.

Several authors have studied estimation of prevalence under various assumptions about sensitivity and specificity. Greiner and Gardner (2000a,b) describe various study designs for this problem. Messam et al. (2008) review frequentist as well as Bayesian methods to estimate prevalence while controlling for diagnostic parameters of the test. Most of these approaches assume that there is a gold standard test to determine the true disease status. Some other models are able to work without this assumption (Hui and Walter, 1980; Enøe et al., 2000; Toft et al., 2005).

Rogan and Gladen (1978) also calculated the variance of the prevalence estimate for this setting but their confidence interval using a normal approximation performs poorly (see Greiner and Gardner, 2000a). Since the exact

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computation as in Reiczigel et al. (2010) seemed to be computationally infeasible with two nuisance parameters, we adopted the "add 2 successes and 2 failures" method proposed by Agresti and Coull (1998) and found that this made the method quite acceptable. Although the new CI is not exact, it maintains the nominal level fairly well even for moderate sample sizes. (The nominal confidence level is the prescribed or anticipated probability that the CI covers the true parameter value.)

In the rest of this paper we describe the proposed method and carry out a simulation study to assess the actual coverage probability of the CI for various values of sensitivity, specificity and prevalence. (The actual coverage probability is the probability that the CI indeed covers the true parameter value, in this case true prevalence.) To illustrate how the new method works, and to demonstrate why it is important to account for the uncertainty of the sensitivity and specificity estimates, we apply the method to real-life examples taken from other papers. Detailed simulation results, an Excel file and an R function for the proposed procedure can be found at http://www.univet.hu/users/jreiczig/prevalence-with-se-sp.html.

## 2. Methods

We assume that we have three independent samples:

- the first one consists of subjects who are known to have the disease (this will be used to estimate the sensitivity of the diagnostic test),
- the second one consists of subjects who don't have the disease (this will be used to estimate the specificity of the diagnostic test),
- the third one is a random sample from the target population, examined by the diagnostic test (true disease statuses of the subjects are unknown, just their test results – positive or negative – are known).

Our aim is to construct a confidence interval for the population prevalence. Let us denote the unknown true sensitivity, specificity, apparent and true prevalence by $Se$, $Sp$, $Ap$ and $P$, the corresponding estimated quantities by $\widehat{Se}$, $\widehat{Sp}$, $\widehat{AP}$ and $\widehat{P}$, and the sample sizes by $n_{Se}$, $n_{Sp}$, $n_P$. Note that apparent prevalence $AP$ is the proportion of test positives in the target population, thus the number of test positives in the sample follows a binomial distribution with parameters $n_P$ and $AP$. True prevalence is expressed as

$$P = \frac{AP + Sp - 1}{Se + Sp - 1} \tag{1}$$

resulting in the following point estimate of $P$ (Rogan and Gladen, 1978)

$$\widehat{P} = \frac{\widehat{AP} + \widehat{Sp} - 1}{\widehat{Se} + \widehat{Sp} - 1} \tag{2}$$

Asymptotic variance of $\widehat{P}$ can be obtained by Taylor series expansion of (2) as described in Rogan and Gladen (1978). This is actually the application of the so-called delta method; see e.g. Agresti (2002). The resulting variance estimate is

$$var(\widehat{P}) = \frac{var(\widehat{AP}) + \widehat{P}^2 var(\widehat{Se}) + (1-\widehat{P})^2 var(\widehat{Sp})}{(\widehat{Se} + \widehat{Sp} - 1)^2} \tag{3}$$

or by substituting the binomial variances in (3)

$$var(\widehat{P}) = \frac{\widehat{AP}(1-\widehat{AP})/n_p + \widehat{P}^2\widehat{Se}(1-\widehat{Se})/n_{Se} + (1+\widehat{P})^2\widehat{Sp}(1-\widehat{Sp})/n_{Sp}}{(\widehat{Se} + \widehat{Sp} - 1)^2} \tag{4}$$

Note that the variance estimate of $\widehat{P}$ in (3) equals the variance estimate of $\widehat{AP}$ if and only if $\widehat{Se}$ and $\widehat{Sp}$ are known (rather than estimates), and $Se = Sp = 1$. In all other cases $\mathrm{var}(\widehat{P}) > \mathrm{var}(\widehat{AP})$ holds.

Using these results, the simplest, so-called Wald confidence limits for the true prevalence based on normal approximation are defined by the formula

$$\widehat{P} \pm Z_{crit} \cdot var(\widehat{P})^{1/2} \tag{5}$$

with values less than 0 or greater than 1 replaced by 0 or 1. Here $Z_{crit}$ is the critical value of the standard normal distribution belonging to the prescribed confidence level. Note that the asymptotic variance tends to be close to the true variance if all three sample sizes are large and all three binomial probabilities are relatively far from their boundary values of 0 and 1. However, in many practical situations the prevalence is low and sensitivity and specificity are close to 1. In such cases formula (4) results in a variance near 0, and the coverage probability of the CI falls far below the nominal level.

To obtain better coverage the numerator and denominator of $\widehat{AP}$ are adjusted by adding $Z^2_{crit}/2$ and $Z^2_{crit}$ to them. Agresti and Coull (1998) demonstrated that this method considerably improves the coverage of the confidence interval for a binomial proportion. Formally, if

$$n'_P = n_P + Z^2_{crit} \tag{6}$$

$$AP' = \frac{n_P \cdot \widehat{AP} + Z^2_{Crit}/2}{n_P + Z^2_{Crit}} \tag{7}$$

then the adjusted confidence interval for $AP$ is

$$AP' \pm Z_{crit} \cdot \left( AP' \frac{1 - AP'}{n'_p} \right)^{1/2} \tag{8}$$

In the important special case when true sensitivity $Se$ and specificity $Sp$ are presumed known the Agresti–Coull confidence interval for $AP$ can be transformed to a confidence interval for the true prevalence $P$ by (1)

$$P' \pm Z_{crit} / (Se + Sp - 1) \cdot \left( AP' \left(1 - AP'\right) / n'_P \right)^{1/2} \tag{9}$$

where

$$P' = \frac{AP' + Sp - 1}{Se + Sp - 1} \tag{10}$$