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Asymptotic Confidence Intervals for the Difference and the Ratio of the Weighted Kappa Coefficients of Two Diagnostic Tests Subject to a Paired Design

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Abstract:

- The weighted kappa coefficient of a binary diagnostic test is a measure of the beyond-chance agreement between the diagnostic test and the gold standard, and depends on the sensitivity and specificity of the diagnostic test, on the disease prevalence and on the relative importance between the false negatives and the false positives. This article studies the comparison of the weighted kappa coefficients of two binary diagnostic tests subject to a paired design through confidence intervals. Three asymptotic confidence intervals are studied for the difference between the parameters and five other intervals for the ratio. Simulation experiments were carried out to study the coverage probabilities and the average lengths of the intervals, giving some general rules for application. A method is also proposed to calculate the sample size necessary to compare the two weighted kappa coefficients through a confidence interval. A program in R has been written to solve the problem studied and it is available as supplementary material. The results were applied to a real example of the diagnosis of malaria.

Keywords:

- *binary diagnostic test; paired design; weighted kappa coefficient.*

AMS Subject Classification:

- 62P10, 6207.

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1. INTRODUCTION

A diagnostic test is medical test that is applied to an individual in order to determine the presence or absence of a disease. When the result of a diagnostic test is positive (indicating the presence of the disease) or negative (indicating its absence), the diagnostic test is called a binary diagnostic test (BDT) and its accuracy is measured in terms of two fundamental parameters: sensitivity and specificity. Sensitivity (Se) is the probability of the BDT result being positive when the individual has the disease, and specificity (Sp) is the probability of the BDT result being negative when the individual does not have the disease. Sensitivity is also called true positive fraction (TPF) and specificity is also called true negative fraction (TNF), verifying that $TPF = 1 - FNF$ and that $TNF = 1 - FPF$, where FNF (FPF) is the false negative (positive) fraction. The accuracy of a BDT is assessed in relation to a gold standard (GS), which is a medical test that objectively determines whether or not an individual has the disease. When considering the losses of an erroneous classification with the BDT, the performance of the BDT is measured in terms of the weighted kappa coefficient (Kraemer *et al.*, 1990 [7]; Kraemer, 1992 [8]; Kraemer *et al.*, 2002 [9]). The weighted kappa coefficient depends on the Se and Sp of the BDT, on the disease prevalence (p) and on the relative importance between the false negatives and the false positives (weighting index c). The weighted kappa coefficient is a measure of the beyond-chance agreement between the BDT and the GS.

Furthermore, the comparison of the performance of two BDTs is an important topic in the study of Statistical Methods for Diagnosis in Medicine. The comparison of two BDTs can be made subject to two types of sample designs: unpaired design and paired design. In the book by Pepe (2003) [13] we can see a broad discussion about both types of sample designs. Summing up, subject to an unpaired design each individual is tested with a single BDT, whereas subject to a paired design each individual is tested with the two BDTs. Consequently, unpaired design consists of applying a BDT to a sample of n_1 individuals and the other BDT to another sample of n_2 individuals; paired design consists of applying both BDTs to all of the individuals of a sample sized n. The comparative studies based on a paired design are more efficient from a statistical point of view than the studies based on an unpaired design, since it minimizes the impact of the between-individual variability. Therefore, in this article we focus on paired design. Subject to this type of design, Bloch (1997) [3] has studied an asymptotic hypothesis test to compare the weighted kappa coefficients of two BDTs. Nevertheless, if the hypothesis test is significant, this method does not allow us to assess how much bigger one weighted kappa coefficient is compared to another one, and it is necessary to estimate this effect through confidence intervals (CIs). Thus, the objective of our study is to compare the weighted kappa coefficients of two BDTs through CIs. Frequentist and Bayesian CIs have been studied for the difference and for the ratio of the two weighted kappa coefficients. If a CI for the difference (ratio) does not contain the zero (one) value, then we reject the equality between the two weighted kappa coefficients and we estimate how much bigger one coefficient is than another one. Consequently, our study is an extension of the Bloch method to the situation of the CIs. We have also dealt with the problem of calculating the sample size to compare the two parameters through a CI.

The manuscript is structured in the following way. In Section 2, we explain the weighted kappa coefficient of a BDT and we relate the comparison of the weighted kappa coefficients of two BDTs with the relative true (false) positive fraction of the two BDTs.

Section 3 summarizes the Bloch method and we propose CIs for the difference and the ratio of the weighted kappa coefficients of two BDTs subject to a paired design. In Section 4, simulation experiments are carried out to study the asymptotic behaviour of the proposed CIs, and some general rules of application are given. In Section 5, we propose a method to calculate the sample size necessary to compare the two weighted kappa coefficients through a CI. In Section 6, a programme written in R is presented to solve the problems posed in this manuscript. In Section 7, the results were applied to a real example on the diagnosis of malaria, and in Section 8 the results are discussed.

2. WEIGHTED KAPPA COEFFICIENT

Let us consider a BDT that is assessed in relation to a GS. Let L (L') the loss which occurs when for a diseased (non-diseased) individual the BDT gives a negative (positive) result. Therefore, the loss L (L') is associated with a false negative (positive). If an individual (with or without the disease) is correctly diagnosed by the BDT then $L = L' = 0$. Let D be the variable that models the result of the GS: $D = 1$ when an individual has the disease and $D = 0$ when this is not the case. Let $p = P(D = 1)$ be the prevalence of the disease and $q = 1 - p$. Let T be the random variable that models the result of the BDT: $T = 1$ when the result of the BDT is positive and $T = 0$ when the result is negative. Table 1 shows the losses and the probabilities associated with the assessment of a BDT in relation to a GS, and the probabilities when the BDT and the GS are independent, i.e. when $P(T = i|D = j) = P(T = i)$. Multiplying each loss in the 2×2 table by its corresponding probability and adding up all the terms, we find $p(1 - Se)L + q(1 - Sp)L'$, a term that is defined as expected loss. Therefore, the expected loss is the loss that occurs when erroneously classifying with the BDT an individual with or without the disease.

Table 1: Losses and probabilities.

Losses (Probabilities)			
	$T = 1$	$T = 0$	Total
$D = 1$	0 (pSe)	L ($p(1 - Se)$)	L (p)
$D = 0$	L' ($q(1 - Sp)$)	0 (qSp)	L' (q)
Total	L' ($Q = pSe + q(1 - Sp)$)	L ($1 - Q = p(1 - Se) + qSp$)	$L + L'$ (1)

Probabilities when the BDT and the GS are independent			
	$T = 1$	$T = 0$	Total
$D = 1$	pQ	$p(1 - Q)$	p
$D = 0$	qQ	$q(1 - Q)$	q
Total	Q	$1 - Q$	1

Moreover, if the BDT and the GS are independent, multiplying each loss by its corresponding probability (subject to the independence between the BDT and the GS) and adding up all of the terms we find $p[p(1-Se)+qSp]L+q[pSe+q(1-Sp)]L'$, a term that is defined as random loss.

Therefore, the random loss is the loss that occurs when the BDT and the GS are independent. The independence between the BDT and the GS is equivalent to the Youden index of the BDT being equal to zero i.e. $Se + Sp - 1$, and is also equivalent to the expected loss being equal to the random loss. In terms of expected and random losses, the weighted kappa coefficient of a BDT is defined as

$$\kappa = \frac{\text{Random loss} - \text{Expected loss}}{\text{Random loss}}.$$

Substituting in this equation each loss with its expression, the weighted kappa coefficient of a BDT is expressed (Kraemer *et al.*, 1990 [7]; Kraemer, 1992 [8]; Kraemer *et al.*, 2002 [9]) as

$$\kappa(c) = \frac{pqY}{p(1-Q)c + qQ(1-c)}, \tag{2.1}$$

where $Y = Se + Sp - 1$ is the Youden index, $Q = pSe + q(1 - Sp)$ is the probability that the BDT result is positive, and $c = L/(L + L')$ is the weighting index. The weighting index c is a measure of the relative importance between the false negatives and the false positives. For example, let us consider the diagnosis of breast cancer using as a diagnostic mammography test. If the mammography test is positive in a woman that does not have cancer (false positive), the woman will be given a biopsy that will give a negative result. The loss L' is determined from the economic costs of the diagnosis and also from the risk, stress, anxiety, etc., caused to the woman. If the mammography test is negative in a woman who has breast cancer (false negative), the woman may be diagnosed at a later stage, but the cancer may spread, and the possibility of the treatment being successful will have diminished. The loss L is determined from these considerations. The losses L and L' are measured in terms of economic costs and also from risks, stress, etc., which is why in practice their values cannot be determined. Therefore, as loss L (L') cannot be determined, L (L') is substituted by the importance that a false negative (positive) has for the clinician. The value of the weighting index c will depend therefore on the relative importance between a false negative and a false positive. If the clinician is more concerned about false negatives, as in a screening test, then $0.5 < c \leq 1$. If the clinician has greater concerns about false positives, as it is the situation in which the BDT is used as a definitive test prior to a treatment that involves a risk for the individual (e.g., a definitive test prior to a surgical operation), then $0 \leq c < 0.5$. The index c is equal to 0.5 when the clinician considers that the false negatives and the false positives have the same importance, in which case $\kappa(0.5)$ is the Cohen kappa coefficient. Weighting index c quantifies the relative importance between a false negative and a false positive, but it is not a measure that quantifies how much bigger the proportion of false negatives is compared to the false positives. If $c = 0$ then

$$\kappa(0) = \frac{Sp - (1-Q)}{Q} = \frac{p(1 - FNF - FPF)}{p(1 - FNF) + qFPF}, \tag{2.2}$$

which is the chance corrected specificity according to the kappa model. If $c = 1$ then

$$\kappa(1) = \frac{Se - Q}{1 - Q} = \frac{q(1 - FNF - FPF)}{pFNF + q(1 - FPF)}, \tag{2.3}$$

which is the chance corrected sensitivity according to the kappa model. A low (high) value of $\kappa(1)$ will indicate that the value of FNF is high (low), and a low (high) value of $\kappa(0)$ will indicate that the value of FPF is high (low). The weighted kappa coefficient can be written as

$$\kappa(c) = \frac{pc(1-Q)\kappa(1) + q(1-c)Q\kappa(0)}{p(1-Q)c + qQ(1-c)}, \tag{2.4}$$

which is a weighted average of $\kappa(0)$ and $\kappa(1)$. Therefore, the weighted kappa coefficient is a measure that considers the proportion of false negatives (FNF) and the proportion of false positives (FPF). Moreover, for a set value of the c index and of the accuracy (Se and Sp) of the BDT, the weighted kappa coefficient strongly depends on the disease prevalence among the population being studied, and its value increases when the disease prevalence increases. The weighted kappa coefficient is a measure of the beyond-chance agreement between the BDT and the GS. The properties of the kappa coefficient can be seen in the manuscripts of Kraemer *et al.* (2002) [9], Roldán-Nofuentes *et al.* (2009) [15] and of Roldán-Nofuentes and Amro (2018) [16].

When comparing the accuracies of two BDTs, Pepe (2003) [13] recommends using the parameters $rTPF_{12} = \frac{Se_1}{Se_2}$ and $rFPF_{12} = \frac{FPF_1}{FPF_2}$, where $FPF_h = 1 - Sp_h$, with $h = 1, 2$. If $rTPF_{12} > 1$ then the sensitivity of Test 1 is greater than that of Test 2, and if $rFPF_{12} > 1$ then the FPF of Test 1 is greater than that of Test 2 (the specificity of Test 2 is greater than that of Test 1). The comparison of the weighted kappa coefficients of two BDTs can be related to the previous measures, and these have an important effect on the comparison of $\kappa_1(c)$ and $\kappa_2(c)$. From now onwards, it is considered that $0 < Se_h < 1$, $0 < Sp_h < 1$ and $0 < p < 1$, with $h = 1, 2$. Let us consider the subindexes i and j, in such a way that if $i = 1$ ($i = 2$) then $j = 2$ ($j = 1$). It is obvious that if $rTPF_{ij} = rFPF_{ij} = 1$ then $Se_1 = Se_2$ and $Sp_1 = Sp_2$, and that therefore $\kappa_1(c) = \kappa_2(c)$ with $0 \leq c \leq 1$. Let

$$c' = \frac{(1-p)[Se_2(1-Sp_1) - Se_1(1-Sp_2)]}{p(Se_1 - Se_2) + (1-Sp_1)(Se_2 - p) - (1-Sp_2)(Se_1 - p)}. \tag{2.5}$$

In terms of $rTPF_{ij}$ and $rFPF_{ij}$ the following rules are verified to compare $\kappa_1(c)$ and $\kappa_2(c)$:

a) If $rTPF_{ij} \geq 1$ and $rFPF_{ij} < 1$, or $rTPF_{ij} > 1$ and $rFPF_{ij} \leq 1$, then $\kappa_i(c) > \kappa_j(c)$ for $0 \leq c \leq 1$.

b) If $rTPF_{ij} > 1$ and $rFPF_{ij} > 1$, then:

- **b.1**) $\kappa_i(c) > \kappa_j(c)$ if $0 < c' < c \leq 1$;
- **b.2**) $\kappa_i(c) < \kappa_j(c)$ if $0 \leq c < c' < 1$;
- **b.3**) $\kappa_i(c) = \kappa_j(c)$ if $c = c'$, with $0 < c' < 1$;
- **b.4**) $\kappa_i(c) > \kappa_j(c)$ for $0 \leq c \leq 1$ if $c' < 0$ (or $c' > 1$) and $rTPF_{ij} > rFPF_{ij} > 1$;
- **b.5**) $\kappa_i(c) < \kappa_j(c)$ for $0 \leq c \leq 1$ if $c' < 0$ (or $c' > 1$) and $rFPF_{ij} > rTPF_{ij} > 1$.

c) If $rTPF_{ij} < 1$ and $rFPF_{ij} < 1$, then:

- **c.1**) $\kappa_i(c) > \kappa_j(c)$ if $0 \leq c < c' < 1$;
- **c.2**) $\kappa_i(c) < \kappa_j(c)$ if $0 < c' < c \leq 1$;
- **c.3**) $\kappa_i(c) = \kappa_j(c)$ if $c = c'$, with $0 < c' < 1$;
- **c.4**) $\kappa_i(c) > \kappa_j(c)$ for $0 \leq c \leq 1$ if $c' < 0$ (or $c' > 1$) and $rTPF_{ij} > rFPF_{ij} > 1$;
- **c.5**) $\kappa_i(c) < \kappa_j(c)$ for $0 \leq c \leq 1$ if $c' < 0$ (or $c' > 1$) and $rFPF_{ij} > rTPF_{ij} > 1$.

The demonstrations can be seen in the Appendix A of the supplementary material. Regarding c', this is obtained solving the equation $\kappa_1(c) - \kappa_2(c) = 0$ in c. The graphs in Figure 1 show how $\kappa_1(c)$ (on a continuous line) and $\kappa_2(c)$ (on a dotted line) vary depending on the weighting index c, taking as prevalence $p = \{5\%, 25\%, 50\%, 75\%\}$, for $Se_1 = 0.80$, $Sp_1 = 0.95$, $Se_2 = 0.90$ and $Sp_2 = 0.85$. These graphs correspond to the case in which $rTPF_{12} < 1$ and $rFPF_{12} < 1$, and therefore $\kappa_1(c) > \kappa_2(c)$ when $c < c'$, and $\kappa_2(c) > \kappa_1(c)$ when $c > c'$, and c' is equal to 0.95 when $p = 5\%$, 0.75 when $p = 25\%$, 0.50 when $p = 50\%$ and 0.25 when $p = 75\%$. If the clinician considers that a false positive is 1.5 times more important than a false negative, then $c = 0.4$ and $\kappa_1(c) > \kappa_2(c)$ in the population with $p = \{5\%, 25\%, 50\%\}$ and $\kappa_2(c) > \kappa_1(c)$ in the population with $p = 75\%$. If in the population with $p = 75\%$ the clinician has a greater concern about a false positive than a false negative ($0 \leq c < 0.5$), then $\kappa_1(c) > \kappa_2(c)$ if $0 \leq c < 0.25$ and $\kappa_2(c) > \kappa_1(c)$ if $0.25 < c < 0.5$; in the populations with $p = \{5\%, 25\%, 50\%\}$, $\kappa_1(c) > \kappa_2(c)$ when $0 \leq c < 0.5$.

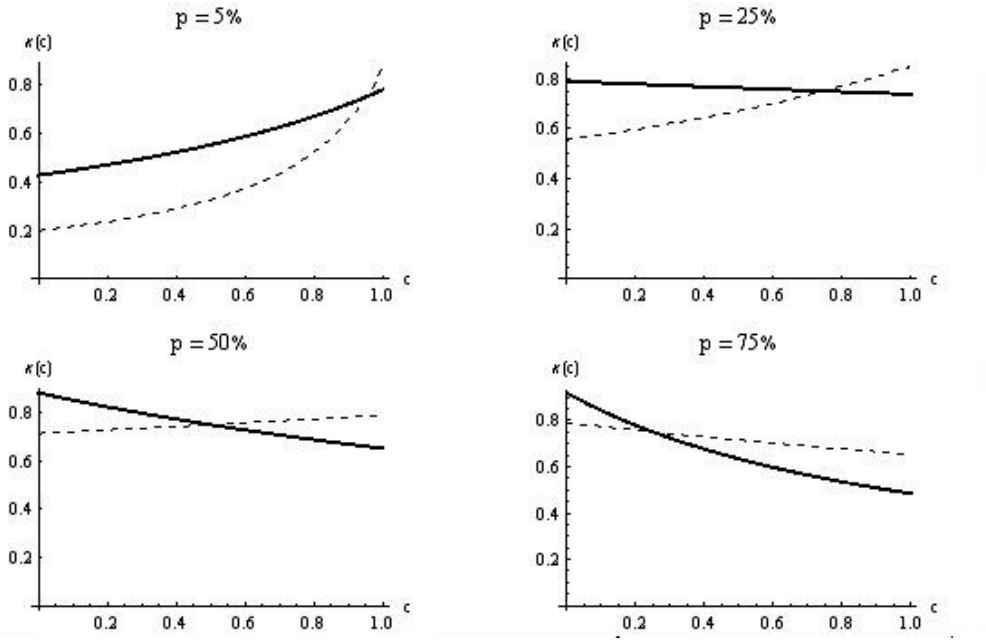

Figure 1: Weighted kappa coefficients with $rTPF_{12} < 1$ and $rFPF_{12} < 1$.

We will now study the comparison of the weighted kappa coefficients of two BDTs through CIs subject to a paired design.

3. CONFIDENCE INTERVALS

Let us consider two BDTs which are assessed in relation to the same GS. Let T_1 and T_2 be the random binary variables that model the results of each BDT respectively. Let Se_h and Sp_h be the sensitivity and specificity of the h-th BDT, with $h = 1, 2$. Table 2 (Observed frequencies) shows the frequencies that are obtained when both BDTs and the GS are applied to all the individuals in a random sample sized n. The frequencies s_{ij} and r_{ij} are the product

of a multinomial distribution whose probabilities are also shown in Table 2 (Theoretical probabilities), where $p_{ij} = P(D = 1, T_1 = i, T_2 = j)$ and $q_{ij} = P(D = 0, T_1 = i, T_2 = j)$, with $i, j = 0, 1$. Applying the Vacek (1985) [17] conditional dependency model, the probabilities p_{ij} and q_{ij} are written as

$$p_{ij} = p\left[Se_1^i(1 - Se_1)^{1-i}Se_2^j(1 - Se_2)^{1-j} + \delta_{ij}\varepsilon_1\right] \tag{3.1}$$

and

$$q_{ij} = q\left[Sp_1^{1-i}(1 - Sp_1)^i Sp_2^{1-j}(1 - Sp_2)^j + \delta_{ij}\varepsilon_0\right], \tag{3.2}$$

where ϵ_1 (ϵ_0) is the covariance or dependence factor between the two BDTs when $D = 1$ ($D = 0$), $\delta_{ij} = 1$ if $i = j$ and $\delta_{ij} = -1$ if $i \neq j$, with $i, j = 0, 1$. It is verified that

$$0 \leq \varepsilon_1 \leq \text{Min}\left\{Se_1\left(1 - Se_2\right), Se_2\left(1 - Se_1\right)\right\}$$

and

$$0 \leq \varepsilon_0 \leq \text{Min}\left\{Sp_1\left(1 - Sp_2\right), Sp_2\left(1 - Sp_1\right)\right\}.$$

If $\varepsilon_1 = \varepsilon_0 = 0$ then the two BDTs are conditionally independent on the disease. In practice, the assumption of conditional independence is not realistic, and so $\varepsilon_1 > 0$ and/or $\varepsilon_0 > 0$. Let $\pi = (p_{11}, p_{10}, p_{01}, p_{00}, q_{11}, q_{10}, q_{01}, q_{00})^{\mathsf{T}}$ be the vector of probabilities of the multinomial distribution, and it is verified that $p = \sum_{i,j=0}^{1} p_{ij}$ and $q = 1 - p = \sum_{i,j=0}^{1} q_{ij}$. The maximum likelihood estimators of these probabilities are $\hat{p}_{ij} = s_{ij}/n$ and $\hat{q}_{ij} = r_{ij}/n$.

The rules given in Section 2 about the effect of $rTPF$ and $rFPF$ on the comparison of $\kappa_1(c)$ and $\kappa_2(c)$ are theoretical rules that can be applied to the estimators, but they cannot guarantee that one weighted kappa coefficient will be higher than another. This question should be studied through hypothesis tests and confidence intervals. The Bloch method to compare the weighted kappa coefficients of two BDTs subject to a paired design is summarized below, and different CIs are proposed to compare these parameters subject to the same type of sample design.

Table 2: Observed frequencies and theoretical probabilities subject to a paired design.

Observed frequencies					
	$T_1 = 1$		$T_1 = 0$		
	$T_2 = 1$	$T_2 = 0$	$T_2 = 1$	$T_2 = 0$	Total
$D = 1$	s_{11}	s_{10}	s_{01}	s_{00}	s
$D = 0$	r_{11}	r_{10}	r_{01}	r_{00}	r
Total	$s_{11} + r_{11}$	$s_{10} + r_{10}$	$s_{01} + r_{01}$	$s_{00} + r_{00}$	n

Theoretical probabilities					
	$T_1 = 1$		$T_1 = 0$		
	$T_2 = 1$	$T_2 = 0$	$T_2 = 1$	$T_2 = 0$	Total
$D = 1$	p_{11}	p_{10}	p_{01}	p_{00}	p
$D = 0$	q_{11}	q_{10}	q_{01}	q_{00}	q
Total	$p_{11} + q_{11}$	$p_{10} + q_{10}$	$p_{01} + q_{01}$	$p_{00} + q_{00}$	1

3.1. Hypothesis test

Bloch (1997) [3] studied the comparison of the weighted kappa coefficients of two BDTs subject to a paired design. In terms of probabilities (3.1) and (3.2), the weighted kappa coefficient of Test 1 is

$$\kappa_1(c) = \frac{(p_{11}+p_{10})(q_{01}+q_{00}) - (p_{01}+p_{00})(q_{10}+q_{11})}{pc\sum_{k=0}^{1}(p_{0k}+q_{0k}) + q(1-c)\sum_{k=0}^{1}(p_{1k}+q_{1k})},$$

and that of Test 2 is

$$\kappa_2(c) = \frac{(p_{11}+p_{01})(q_{10}+q_{00}) - (p_{10}+p_{00})(q_{01}+q_{11})}{pc\sum_{k=0}^{1}(p_{k0}+q_{k0}) + q(1-c)\sum_{k=0}^{1}(p_{k1}+q_{k1})}.$$

Substituting in the previous expressions the parameters by their estimators, the estimators of the weighted kappa coefficients are

$$\hat{\kappa}_1(c) = \frac{(s_{11}+s_{10})(r_{01}+r_{00}) - (s_{01}+s_{00})(r_{10}+r_{11})}{sc\sum_{k=0}^{1}(s_{0k}+r_{0k}) + r(1-c)\sum_{k=0}^{1}(s_{1k}+r_{1k})} \tag{3.3}$$

and

$$\hat{\kappa}_2(c) = \frac{(s_{11}+s_{01})(r_{10}+r_{00}) - (s_{10}+s_{00})(r_{01}+r_{11})}{sc\sum_{k=0}^{1}(s_{k0}+r_{k0}) + r(1-c)\sum_{k=0}^{1}(s_{k1}+r_{k1})}. \tag{3.4}$$

Their variances-covariance are obtained applying the delta method (see the Appendix B of the supplementary material). Subject to paired design, the covariance between the two sensitivities and between the two specificities are given by $\text{Cov}(\hat{S}e_1, \hat{S}e_2) = \frac{\varepsilon_1}{np}$ and $\text{Cov}(\hat{S}p_1, \hat{S}p_2) = \frac{\epsilon_0}{nq}$ respectively (Appendix B of the supplementary material), where ϵ_1 and ϵ_0 are the covariances between the two BDTs when $D=1$ and $D=0$ respectively. These covariances also affect the covariances between the two weighted kappa coefficients, just as can be seen in the expressions given in the Appendix B of the supplementary material. Finally, the statistic for the hypothesis test $H_0 : \kappa_1(c) = \kappa_2(c)$ vs $H_0 : \kappa_1(c) \neq \kappa_2(c)$ is

$$z = \frac{\hat{\kappa}_1(c) - \hat{\kappa}_2(c)}{\sqrt{\widehat{\text{Var}}[\hat{\kappa}_1(c)] + \widehat{\text{Var}}[\hat{\kappa}_2(c)] - 2\,\widehat{\text{Cov}}[\hat{\kappa}_1(c), \hat{\kappa}_2(c)]}} \xrightarrow[n\to\infty]{} N(0,1). \tag{3.5}$$

3.2. Confidence intervals

When two parameters are compared, the interest is generally focused on studying the difference or the ratio between them. We then compare the weighted kappa coefficients of two BDTs through CIs for the difference $\delta = \kappa_1(c) - \kappa_2(c)$ and for the ratio $\theta = \frac{\kappa_1(c)}{\kappa_2(c)}$. Through the CIs: a) the two weighted kappa coefficients are compared, in such a way that if a CI for the difference (ratio) does not contain the zero (one) value, then we reject the equality between

the weighted kappa coefficients; and b) we estimate (if the two weighted kappa coefficients are different) how much bigger one weighted kappa coefficient is than the other. Firstly, three CIs are proposed for the difference of the two weighted kappa coefficients, and secondly five CIs are proposed for the ratio.

3.2.1. CIs for the difference

For the difference of the two weighted kappa coefficients we propose the Wald, bootstrap and Bayesian CIs.

Wald CI. Based on the asymptotic normality of the estimator of $\delta = \kappa_1(c) - \kappa_2(c)$, i.e. $\hat{\delta} \to N\left[\delta, \mathrm{Var}\left(\delta\right)\right]$ when the sample size n is large, the Wald CI for the difference δ is very easy to obtain inverting the test statistic proposed by Bloch (1997) [3], therefore

$$\delta \in \hat{\kappa}_1\left(c\right) - \hat{\kappa}_2\left(c\right) \pm z_{1-\alpha/2} \sqrt{\widehat{\mathrm{Var}}\left[\hat{\kappa}_1\left(c\right)\right] + \widehat{\mathrm{Var}}\left[\hat{\kappa}_2\left(c\right)\right] - 2\,\widehat{\mathrm{Cov}}\left[\hat{\kappa}_1\left(c\right), \hat{\kappa}_2\left(c\right)\right]}, \tag{3.6}$$

where $z_{1-\alpha/2}$ is the $100\left(1-\alpha/2\right)$-th percentile of the standard normal distribution.

Bootstrap CI. The bootstrap CI is calculated generating B random samples with replacement from the sample of n individuals. In each sample with replacement, we calculate the estimators of the weighted kappa coefficients and the difference between them, i.e. $\hat{\kappa}_{i1B}\left(c\right)$, $\hat{\kappa}_{i2B}\left(c\right)$ and $\hat{\delta}_{iB} = \hat{\kappa}_{i1B}\left(c\right) - \hat{\kappa}_{i2B}\left(c\right)$, with $i = 1, ..., B$. Then, based on the B differences calculated, the average difference is estimated as $\hat{\bar{\delta}}_B = \frac{1}{B}\sum_{i=1}^{B}\hat{\delta}_{iB}$. Assuming that the bootstrap statistic $\hat{\bar{\delta}}_B$ can be transformed to a normal distribution, the bias-corrected bootstrap CI (Efron and Tibshirani, 1993 [5]) for δ is calculated in the following way. Let $A = \#\left(\hat{\delta}_{iB} < \hat{\delta}\right)$ be the number of bootstrap estimators $\hat{\delta}_{iB}$ that are lower than the maximum likelihood estimator $\hat{\delta} = \hat{\kappa}_1\left(c\right) - \hat{\kappa}_2\left(c\right)$, and let $\hat{z}_0 = \Phi^{-1}\left(A/B\right)$, where $\Phi^{-1}\left(\cdot\right)$ is the inverse function of the standard normal cumulative distribution function. Let $\alpha_1 = \Phi\left(2\hat{z}_0 - z_{1-\alpha/2}\right)$ and $\alpha_2 = \Phi\left(2\hat{z}_0 + z_{1-\alpha/2}\right)$, then the bias-corrected bootstrap CI is $\left(\hat{\delta}_B^{(\alpha_1)}, \hat{\delta}_B^{(\alpha_2)}\right)$, where $\hat{\delta}_B^{(\alpha_j)}$ is the j-th quantile of the distribution of the B bootstrap estimations of δ.

Bayesian CI. The problem is now approached from a Bayesian perspective. The number of individuals with the disease (s) is the product of a binomial distribution with parameters n and p, i.e. $s \to B(n,p)$. Conditioning on the individuals with the disease, i.e. conditioning on $D = 1$, it is verified that

$$s_{11} + s_{10} \to B\left(s, Se_1\right) \text{ and } s_{11} + s_{01} \to B\left(s, Se_2\right). \tag{3.7}$$

The number of individuals without the disease (r) is the product of a binomial distribution with parameters n and q, i.e. $r \to B(n,q)$, with $q = 1-p$. Conditioning on the individuals without the disease ($D = 0$), it is verified that

$$r_{01} + r_{00} \to B\left(r, Sp_1\right) \text{ and } r_{10} + r_{00} \to B\left(r, Sp_2\right). \tag{3.8}$$

Considering the marginal distributions of each BDT, the estimators of the sensitivity and the specificity of the Test 1, $\hat{Se}_1 = \frac{s_{11}+s_{10}}{s}$ and $\hat{Sp}_1 = \frac{r_{01}+r_{00}}{r}$, and of the Test 2, $\hat{Se}_2 = \frac{s_{11}+s_{01}}{s}$

and $\hat{S}p_2 = \frac{r_{10}+r_{00}}{r}$, are estimators of binomial proportions. In a similar way, considering the marginal distribution of the GS, the estimator of the disease prevalence, $\hat{p} = \frac{s}{n}$, is also the estimator of a binomial proportion. Therefore, for these estimators we propose conjugate beta prior distributions, which are the appropriate distributions for the binomial distributions involved, i.e.

$$\hat{S}e_h \to \text{Beta}\left(\alpha_{Se_h}, \beta_{Se_h}\right), \ \hat{S}p_h \to \text{Beta}\left(\alpha_{Sp_h}, \beta_{Sp_h}\right) \text{ and } \hat{p} \to \text{Beta}\left(\alpha_p, \beta_p\right). \tag{3.9}$$

Let $\mathbf{v} = (s_{11}, s_{10}, s_{01}, s, r_{11}, r_{10}, r_{01}, r)$ be the vector of observed frequencies, with $s_{00} = s - s_{11} - s_{10} - s_{01}$, $r = n - s$ and $r_{00} = r - r_{11} - r_{10} - r_{01}$. Then the posteriori distributions for the estimators of the sensitivities, of the specificities and of the prevalence are:

$$\begin{aligned}
\hat{S}e_1 \,|\mathbf{v} &\to \text{Beta}\left(s_{11} + s_{10} + \alpha_{Se_1}, s - s_{11} - s_{10} + \beta_{Se_1}\right), \\
\hat{S}e_2 \,|\mathbf{v} &\to \text{Beta}\left(s_{11} + s_{01} + \alpha_{Se_2}, s - s_{11} - s_{01} + \beta_{Se_2}\right), \\
\hat{S}p_1 \,|\mathbf{v} &\to \text{Beta}\left(r_{01} + r_{00} + \alpha_{Sp_1}, r - r_{01} - r_{00} + \beta_{Sp_1}\right), \\
\hat{S}p_2 \,|\mathbf{v} &\to \text{Beta}\left(r_{10} + r_{00} + \alpha_{Sp_2}, r - r_{10} - r_{00} + \beta_{Sp_2}\right), \\
\hat{p} \,|\mathbf{v} &\to \text{Beta}\left(s + \alpha_p, r + \beta_p\right).
\end{aligned} \tag{3.10}$$

Once we have defined all distributions, the posteriori distribution for the weighted kappa coefficient of each BDT, and for the difference between them, can be approximated applying the Monte Carlo method. This method consists of generating M values of the posteriori distributions given in equations (3.10). In the m-th iteration, the values generated for sensitivity $\hat{S}e_h^{(m)}$ and specificity $\hat{S}p_h^{(m)}$ of each BDT, and for the prevalence $\hat{p}^{(m)}$, are plugged in the equations

$$\hat{\kappa}_h^{(m)}(c) = \frac{\hat{p}^{(m)}\hat{q}^{(m)}\left(\hat{S}e_h^{(m)} + \hat{S}p_h^{(m)} - 1\right)}{\hat{p}^{(m)}\left(1 - \hat{Q}_h^{(m)}\right)c + \hat{q}^{(m)}\hat{Q}_h^{(m)}(1-c)}, \ h = 1, 2, \tag{3.11}$$

where $\hat{Q}_h^{(m)} = \hat{p}^{(m)}\hat{S}e_h^{(m)} + \hat{q}^{(m)}\left(1 - \hat{S}p_h^{(m)}\right)$. We then calculate the difference between the two weighted kappa coefficients in the m-th iteration: $\hat{\delta}^{(m)} = \hat{\kappa}_1^{(m)}(c) - \hat{\kappa}_2^{(m)}(c)$. As the estimator of the average difference of the weighted kappa coefficients, we calculate the average of the M estimations of difference, i.e. $\hat{\bar{\delta}} = \frac{1}{M}\sum_{m=1}^{M}\hat{\delta}^{(m)}$. Once the Monte Carlo method is applied, based on the M values $\hat{\delta}^{(m)}$ we propose the calculation of a CI based on quantiles, i.e. the $100(1-\alpha)\%$ CI for δ is

$$(q_{\alpha/2}\,, q_{1-\alpha/2}\,), \tag{3.12}$$

where q_γ is the γ-th quantile of the distribution of the M values $\hat{\delta}^{(m)}$.

3.2.2. CIs for the ratio

We propose five CIs for the ratio of the two weighted kappa coefficients: Wald, logarithmic, Fieller, bootstrap and Bayesian CIs.

Wald CI. Assuming the asymptotic normality of the estimator of $\theta = \kappa_1(c)/\kappa_2(c)$, i.e. $\hat{\theta} \to N[\theta, \text{Var}(\theta)]$ when the sample size n is large, the Wald CI for θ is

$$\theta \in \hat{\theta} \pm z_{1-\alpha/2} \sqrt{\widehat{\text{Var}}(\hat{\theta})}, \tag{3.13}$$

where $\widehat{\text{Var}}(\hat{\theta})$ is obtained applying the delta method (Agresti, 2002 [1]), and whose expression is

$$\widehat{\text{Var}}\left(\hat{\theta}\right) \approx \frac{\hat{\kappa}_2^2(c)\,\widehat{\text{Var}}\left[\hat{\kappa}_1(c)\right] + \hat{\kappa}_1^2(c)\,\widehat{\text{Var}}\left[\hat{\kappa}_2(c)\right] - 2\hat{\kappa}_1(c)\,\hat{\kappa}_2(c)\,\widehat{\text{Cov}}\left[\hat{\kappa}_1(c), \hat{\kappa}_2(c)\right]}{\hat{\kappa}_2^4(c)}.$$

Expressions of the variances-covariance can be seen in the Appendix B of the supplementary material.

Logarithmic CI. Assuming the asymptotic normality of the Napierian logarithm of the $\hat{\theta}$, i.e. $\ln(\hat{\theta}) \to N(\ln(\theta), \text{Var}[\ln(\theta)])$ when the sample size n is large, an asymptotic CI for $\ln(\theta)$ is

$$\ln(\theta) \in \ln(\hat{\theta}) \pm z_{1-\alpha/2} \sqrt{\widehat{\text{Var}}[\ln(\hat{\theta})]}.$$

Taking exponential, the logarithmic CI for θ is

$$\theta \in \hat{\theta} \times \exp\left\{\pm z_{1-\alpha/2} \sqrt{\widehat{\text{Var}}[\ln(\hat{\theta})]}\right\}, \tag{3.14}$$

where $\widehat{\text{Var}}[\ln(\hat{\theta})]$ is obtained applying the delta method (see the Appendix B of the supplementary material), i.e.

$$\widehat{\text{Var}}[\ln(\hat{\theta})] \approx \frac{\widehat{\text{Var}}\left[\hat{\kappa}_1(c)\right]}{\hat{\kappa}_1^2(c)} + \frac{\widehat{\text{Var}}\left[\hat{\kappa}_2(c)\right]}{\hat{\kappa}_2^2(c)} - \frac{2\,\widehat{\text{Cov}}\left[\hat{\kappa}_1(c), \hat{\kappa}_2(c)\right]}{\hat{\kappa}_1(c)\,\hat{\kappa}_2(c)}.$$

Fieller CI. The Fieller method (1940) [6] is a classic method to obtain a CI for the ratio of two parameters. This method requires us to assume that the estimators are distributed according to a normal bivariate distribution, i.e. $\left(\hat{\kappa}_1(c), \hat{\kappa}_2(c)\right)^{\mathsf{T}} \to N\left[\boldsymbol{\kappa}(c), \sum_{\boldsymbol{\kappa}(c)}\right]$ when the sample size n is large, where

$$\boldsymbol{\kappa}(c) = \left(\kappa_1(c), \kappa_2(c)\right)^{\mathsf{T}}$$

and

$$\sum_{\boldsymbol{\kappa}(c)} = \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{pmatrix} = \begin{pmatrix} \text{Var}\left[\kappa_1(c)\right] & \text{Cov}\left[\kappa_1(c), \kappa_2(c)\right] \\ \text{Cov}\left[\kappa_1(c), \kappa_2(c)\right] & \text{Var}\left[\kappa_2(c)\right] \end{pmatrix}.$$

Applying the Fieller method it is verified that

$$\hat{\kappa}_1(c) - \theta\hat{\kappa}_2(c) \xrightarrow[n\to\infty]{} N\left(0, \sigma_{11} - 2\theta\sigma_{12} + \theta^2\sigma_{22}\right).$$

The Fieller CI is obtained by searching for the set of values for that satisfy the inequality

$$\frac{\left[\hat{\kappa}_1(c) - \theta\hat{\kappa}_2(c)\right]^2}{\hat{\sigma}_{11} - 2\theta\hat{\sigma}_{12} + \theta^2\hat{\sigma}_{22}} < z_{1-\alpha/2}^2.$$

Finally, the Fieller CI for $\theta = \kappa_1(c)/\kappa_2(c)$ is

$$\theta \in \frac{\hat{\omega}_{12} \pm \sqrt{\hat{\omega}_{12}^2 - \hat{\omega}_{11}\hat{\omega}_{22}}}{\hat{\omega}_{22}}, \tag{3.15}$$

where $\hat{\omega}_{ij} = \hat{\kappa}_i(c) \times \hat{\kappa}_j(c) - \hat{\sigma}_{ij} z_{1-\alpha/2}^2$ with $i, j = 1, 2$, and verifying that $\hat{\omega}_{12} = \hat{\omega}_{21}$. This interval is valid when $\hat{\omega}_{12}^2 > \hat{\omega}_{11}\hat{\omega}_{22}$ and $\hat{\omega}_{22} \neq 0$.

Bootstrap CI. The bootstrap CI for θ is calculated in a similar way to that of the bootstrap interval explained in Section 3.1 but considering θ instead of δ. In each sample with replacement obtained we calculate the estimators of the weighted kappa coefficients and the ratio between them, i.e. $\hat{\kappa}_{i1B}(c)$, $\hat{\kappa}_{i2B}(c)$ and $\hat{\theta}_{iB} = \hat{\kappa}_{i1B}(c)/\hat{\kappa}_{i2B}(c)$, with $i = 1, ..., B$. Then, based on the B ratios calculated we estimate the average ratio as $\hat{\bar{\theta}}_B = \frac{1}{B}\sum_{i=1}^{B}\hat{\theta}_{iB}$. Assuming that the statistic $\hat{\bar{\theta}}_B$ can be transformed to a normal distribution, the bias-corrected bootstrap CI (Efron and Tibshirani, 1993 [5]) for θ is obtained in a similar way to how the bootstrap CI for δ is calculated, considering now that $A = \#\left(\hat{\theta}_{iB} < \hat{\theta}\right)$. Finally, the bias-corrected bootstrap CI is $\left(\hat{\theta}_B^{(\alpha_1)}, \hat{\theta}_B^{(\alpha_2)}\right)$, where $\hat{\theta}_B^{(\alpha_j)}$ is the j-th quantile of the distribution of the B bootstrap estimations of θ.

Bayesian CI. The Bayesian CI for θ is also calculated in a similar way to that of the bayesian CI presented in Section 3.1. Considering the same distributions given in equations (3.9) and (3.10), in the m-th iteration of the Monte Carlo method we calculate the ratio $\hat{\theta}^{(m)} = \hat{\kappa}_1^{(m)}(c)/\hat{\kappa}_2^{(m)}(c)$ and as an estimator we calculate $\hat{\bar{\theta}} = \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}^{(m)}$. Finally, based on the M values $\hat{\theta}^{(m)}$ we calculate the CI based on quantiles.

The five previous CIs are for the ratio $\theta = \kappa_1(c)/\kappa_2(c)$. If we want to calculate the CI for the ratio $\kappa_2(c)/\kappa_1(c)$ $(= \theta' = 1/\theta)$, then the logarithmic, Fieller, bootstrap and Bayesian CIs are obtained by calculating the inverse of each boundary of the corresponding CI for $\theta = \kappa_1(c)/\kappa_2(c)$. Nevertheless, the Wald CI for θ' is obtained from the Wald CI for θ dividing each boundary by $\hat{\theta}^2$, i.e. if (L_θ, U_θ) is the Wald CI for $\theta = \kappa_1(c)/\kappa_2(c)$ then the Wald CI for $\theta' = \kappa_2(c)/\kappa_1(c)$ is $\left(L_\theta/\hat{\theta}^2\,, U_\theta/\hat{\theta}^2\right)$.

4. SIMULATION EXPERIMENTS

Monte Carlo simulation experiments were carried out to study the coverage probability (CP) and the average length (AL) of each of the CIs presented in Section 3.2. For this purpose, we generated $N = 10,000$ random samples with multinomial distribution sized $n = \{25, 50, 100, 200, 300, 400, 500, 1000\}$. The random samples were generated setting the values of the weighted kappa coefficients, following these Steps:

1. For the disease prevalence, we took the values $p = \{5\%, 10\%, 25\%, 50\%\}$.
2. For the weighting index, we took a small, intermediate and high value: $c = \{0.1, 0.5, 0.9\}$.
3. As values of the weighted kappa coefficients with $c = 0$ and $c = 1$, we took the following values: $\kappa_h(0), \kappa_h(1) = \{0.01, 0.02, ..., 0.98, 0.99\}$.
4. Next, using all of the values set previously, we calculated the sensitivity and the specificity of each diagnostic test solving the equations

$$Se_h = \frac{[q\kappa_h(0) + p]\,\kappa_h(1)}{q\kappa_h(0) + p\kappa_h(1)} \text{ and } Sp_h = \frac{[p\kappa_h(1) + q]\,\kappa_h(0)}{q\kappa_h(0) + p\kappa_h(1)},$$

considering, quite logically, only those cases in which the Youden index is higher than 0, i.e. $Y_h = Se_h + Sp_h - 1 > 0$.

5. The values of $\kappa_h(c)$ were calculated applying the equation

$$\kappa_h(c) = \frac{pc(1-Q_h)\kappa_h(1) + q(1-c)Q_h\kappa_h(0)}{pc(1-Q_h) + q(1-c)Q_h},$$

where $Q_h = pSe_h + q(1-Sp_h)$.

6. As values of the weighted kappa coefficients we considered $\kappa_h(c) = \{0.2, 0.4, 0.6, 0.8\}$, and from these we calculated δ and θ. In order to be able to compare the coverage probabilities of the CIs for δ and for θ, $\kappa_1(c)$ and $\kappa_2(c)$ must be the same for δ and θ.

Following the idea of Cicchetti (2001) [4], simulations were carried out for values of $\kappa_h(c)$ with different levels of significance: poor ($\kappa_h(c) < 0.40$), fair ($0.40 \leq \kappa_h(c) \leq 0.59$), good ($0.60 \leq \kappa_h(c) \leq 0.74$) and excellent ($0.75 \leq \kappa_h(c) \leq 1$). As values of the dependence factors ε_1 and ε_0 we took intermediate values (50% of the maximum value of each ε_i) and high values (80% of the maximum value of each ε_i), i.e. $\varepsilon_1 = f \times \text{Min}\{Se_1(1-Se_2), Se_2(1-Se_1)\}$ and $\varepsilon_0 = f \times \text{Min}\{Sp_1(1-Sp_2), Sp_2(1-Sp_1)\}$, where $f = \{0.50,\ 0.80\}$. Probabilities of the multinomial distributions, equations (3.1) and (3.2), were calculated from values of the weighted kappa coefficients, and not setting the values of the sensitivities and specificities. In each scenario considered, for each one of the N random samples we calculated all the CIs proposed in Section 3.2. For the bayesian CIs we considered as prior distribution a Beta$(1,1)$ distribution for all of the estimators (sensitivities, specificities and prevalence). This distribution is a non-informative distribution and is flat for all possible values of each sensitivity, specificity and prevalence, and has a minimum impact on each posteriori distribution. For the bootstrap method, for each one of the N random samples we also generated $B = 2,000$ samples with replacement; and for the Bayesian method, for each one of the N random samples we also generated another $M = 10,000$. Moreover, the simulation experiments were designed in such a way that in all of the random samples generated we can estimate the weighted kappa coefficients and their variances-covariance, in order to be able to calculate all of the intervals proposed in Section 3.2. As the confidence level, we took 95%.

The comparison of the asymptotic behaviour of the CIs was made following a similar procedure to that used by other authors (Price and Bonett, 2004 [14]; Martín-Andrés and Alvarez-Hernández, 2014a [10], 2014b [11]; Montero-Alonso and Roldán-Nofuentes, 2019 [12]). This procedure consists of determining if the CI "fails" for a confidence of 95%, which happens if the CI has a $CP \leq 93\%$. The selection of the CI with the best asymptotic behaviour (for the difference and for the ratio) was made following the following Steps: 1) Choose the CIs with the least failures ($CP > 93\%$), and 2) Choose the CIs which are the most accurate, i.e. those which have the lowest AL. In the Appendix C of the supplementary material this method is justified.

4.1. CIs for the difference δ

Tables 3 and 4 show some of the results obtained (CPs and ALs) for $\delta = \{-0.6, -0.4, -0.2, 0\}$, indicating in each case the scenarios ($\kappa_h(c)$, Se_h, Sp_h and p) in which these values were obtained, and for intermediate values of the dependence factors ϵ_1 and ϵ_0. These tables indicate the failures in bold type and it was considered that $\kappa_1(c) \leq \kappa_2(c)$.

Table 3: Coverage probabilities (CPs) and average lengths (ALs) of the CIs for the difference δ of the two weighted kappa coefficients (I).

$\kappa_1(0.1) = 0.2,\ \kappa_2(0.1) = 0.8,\ \delta = -0.6$
$Se_1 = 0.484,\ Sp_1 = 0.684,\ Se_2 = 0.852,\ Sp_2 = 0.911$
$\varepsilon_1 = 0.0359,\ \varepsilon_0 = 0.0306,\ p = 50\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.335**	0.866	**0**	0.643	**0.287**	0.923
50	**0.737**	0.646	**0.038**	0.589	**0.762**	0.690
100	**0.912**	0.470	**0.750**	0.473	0.937	0.501
200	0.958	0.337	0.952	0.354	0.968	0.364
300	0.972	0.276	0.980	0.295	0.982	0.301
400	0.960	0.239	0.969	0.258	0.971	0.262
500	0.955	0.214	0.972	0.231	0.975	0.236
1000	0.937	0.152	0.963	0.164	0.965	0.168

$\kappa_1(0.9) = 0.2,\ \kappa_2(0.9) = 0.8,\ \delta = -0.6$
$Se_1 = 0.28,\ Sp_1 = 0.92,\ Se_2 = 0.82,\ Sp_2 = 0.98$
$\epsilon_1 = 0.0252,\ \epsilon_0 = 0.0092,\ p = 10\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.114**	0.999	**0**	0.651	**0.033**	0.987
50	**0.566**	0.863	**0**	0.640	**0.280**	0.838
100	**0.760**	0.682	**0.031**	0.614	**0.600**	0.667
200	**0.885**	0.503	**0.487**	0.490	**0.815**	0.503
300	0.934	0.411	**0.733**	0.402	**0.886**	0.418
400	0.935	0.354	**0.823**	0.347	**0.903**	0.365
500	0.947	0.314	**0.892**	0.309	0.937	0.326
1000	0.947	0.220	0.938	0.218	0.947	0.233

$\kappa_1(0.1) = 0.4,\ \kappa_2(0.1) = 0.8,\ \delta = -0.4$
$Se_1 = 0.804,\ Sp_1 = 0.887,\ Se_2 = 0.82,\ Sp_2 = 0.98$
$\epsilon_1 = 0.0723,\ \epsilon_0 = 0.0089,\ p = 10\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.847**	0.812	**0.473**	0.671	**0.920**	0.899
50	**0.856**	0.715	**0.602**	0.608	**0.910**	0.764
100	**0.924**	0.534	**0.847**	0.528	0.953	0.580
200	0.968	0.373	0.955	0.423	0.978	0.426
300	0.957	0.302	0.986	0.367	0.976	0.369
400	0.951	0.261	0.992	0.313	0.978	0.315
500	0.955	0.232	0.994	0.259	0.979	0.262
1000	0.941	0.164	0.994	0.202	0.967	0.204

$\kappa_1(0.5) = 0.4,\ \kappa_2(0.5) = 0.8,\ \delta = -0.4$
$Se_1 = 0.76,\ Sp_1 = 0.72,\ Se_2 = 0.85,\ Sp_2 = 0.95$
$\epsilon_1 = 0.0570,\ \epsilon_0 = 0.0180,\ p = 25\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.894**	0.810	**0.004**	0.613	0.962	0.858
50	0.935	0.580	**0.516**	0.516	0.961	0.641
100	0.945	0.397	**0.824**	0.379	0.970	0.458
200	0.946	0.275	**0.928**	0.271	0.971	0.320
300	0.952	0.221	0.934	0.220	0.974	0.259
400	0.940	0.191	0.938	0.192	0.963	0.224
500	0.948	0.171	0.942	0.170	0.979	0.200
1000	0.945	0.120	0.944	0.119	0.979	0.140

Table 4: Coverage probabilities (CPs) and average lengths (ALs) of the CIs for the difference δ of the two weighted kappa coefficients (II).

$\kappa_1(0.9) = 0.6,\ \kappa_2(0.9) = 0.8,\ \delta = -0.2$
$Se_1 = 0.62,\ Sp_1 = 0.98,\ Se_2 = 0.911,\ Sp_2 = 0.937$
$\varepsilon_1 = 0.0277,\ \varepsilon_0 = 0.0094,\ p = 5\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	1	1.009	**0.757**	0.724	1	1.018
50	0.996	0.913	**0.829**	0.659	0.999	0.916
100	0.993	0.823	**0.928**	0.580	0.998	0.801
200	0.934	0.642	**0.763**	0.535	0.986	0.649
300	0.922	0.533	**0.745**	0.483	0.964	0.551
400	0.941	0.456	**0.794**	0.434	0.971	0.481
500	0.933	0.404	**0.799**	0.393	0.962	0.430
1000	0.948	0.282	**0.913**	0.282	0.967	0.305

$\kappa_1(0.1) = 0.6,\ \kappa_2(0.1) = 0.8,\ \delta = -0.2$
$Se_1 = 0.195,\ Sp_1 = 0.995,\ Se_2 = 0.477,\ Sp_2 = 0.987$
$\varepsilon_1 = 0.0509,\ \varepsilon_0 = 0.0026,\ p = 25\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	1	0.928	1.000	0.644	1	0.981
50	0.999	0.787	1.000	0.613	1	0.866
100	0.994	0.604	0.999	0.581	0.999	0.692
200	0.985	0.429	0.997	0.464	0.998	0.505
300	0.981	0.347	0.991	0.393	0.994	0.411
400	0.973	0.297	0.986	0.346	0.992	0.352
500	0.967	0.263	0.984	0.311	0.989	0.311
1000	0.957	0.182	0.988	0.222	0.987	0.213

$\kappa_1(0.5) = 0.4,\ \kappa_2(0.5) = 0.4,\ \delta = 0$
$Se_1 = 0.76,\ Sp_1 = 0.72,\ Se_2 = 0.40,\ Sp_2 = 0.943$
$\varepsilon_1 = 0.0480,\ \varepsilon_0 = 0.0206,\ p = 25\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	0.990	0.811	0.988	0.624	0.999	0.826
50	0.978	0.683	0.998	0.598	0.994	0.691
100	0.962	0.499	0.967	0.466	0.985	0.522
200	0.955	0.353	0.963	0.340	0.981	0.381
300	0.944	0.288	0.943	0.280	0.965	0.314
400	0.960	0.250	0.962	0.244	0.980	0.274
500	0.946	0.223	0.945	0.219	0.966	0.246
1000	0.951	0.158	0.951	0.155	0.972	0.175

$\kappa_1(0.9) = 0.4,\ \kappa_2(0.9) = 0.4,\ \delta = 0$
$Se_1 = 0.943,\ Sp_1 = 0.229,\ Se_2 = 0.70,\ Sp_2 = 0.70$
$\varepsilon_1 = 0.0200,\ \varepsilon_0 = 0.0343,\ p = 50\%$

n	Wald		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**
25	1	0.936	1	0.735	1	0.950
50	0.997	0.788	0.997	0.717	1	0.786
100	0.992	0.602	0.982	0.578	0.997	0.617
200	0.980	0.435	0.981	0.432	0.990	0.461
300	0.959	0.356	0.965	0.358	0.973	0.382
400	0.951	0.307	0.958	0.311	0.972	0.332
500	0.956	0.274	0.958	0.278	0.969	0.297
1000	0.956	0.193	0.958	0.196	0.970	0.210

If it is considered that $\kappa_1(c) > \kappa_2(c)$, the CPs are the same and the conclusions too. From the results, the following conclusions are obtained:

a) Wald CI. For $\delta = \{-0.6, -0.4\}$ the Wald CI fails for a small ($n \leq 50$) and a moderate sample size ($n = 100$), and for a large sample size ($n \geq 200$) the Wald CI does not fail. For $\delta = \{-0.2, 0\}$ the Wald CI does not fail.

b) Bootstrap CI. In very general terms, for $\delta = \{-0.6, -0.4\}$ this CI fails when $n \leq 100$, and for $n \geq 200$ this interval does not fail. For $\delta = -0.2$ this CI fails for almost all the sample sizes, and for $\delta = 0$ does not fail. When this CI does not fail, the AL is slightly lower than the Wald CI for $\delta = \{-0.2, 0\}$, and slightly higher for $\delta = \{-0.6, -0.4\}$ and $n \geq 200$.

c) Bayesian CI. In very general terms, for $\delta = \{-0.6, -0.4\}$ this CI fails when $n \leq 50$, whereas for $n \geq 100$ this CI does not fail. For $\delta = \{-0.2, 0\}$ this CI does not fail. Regarding the AL, in the situations in which it does not fail, the AL is slightly higher than the ALs of the Wald CI and of the bootstrap CI.

Similar conclusions are obtained when the dependence factors take high values. Therefore, regarding the effect of the dependence factors ϵ_i on the asymptotic behaviour of the CIs, in general terms they do not have a clear effect on the CPs of the CIs.

4.2. CIs for the ratio θ

Tables 5 and 6 show some of the results obtained for $\theta = \{0.25, 0.50, 0.75, 1\}$, considering the same scenarios as in Tables 3 and 4. As in the case of the previous CIs, it was considered that $\kappa_1(c) \leq \kappa_2(c)$, and the same conclusions are obtained if $\kappa_1(c) > \kappa_2(c)$. From the results, the following conclusions are obtained:

a) Wald CI. The Wald CI fails when $\theta = 0.25$ and the sample size is small ($n \leq 50$) or moderate ($n = 100$), and this CI does not fail for the rest of the values of θ and sample sizes.

b) Logarithmic CI. This CI fails when $\theta = \{0.25, 0.50\}$ and $n \leq 200 - 300$ depending on the value of θ. For $\theta = 0.75$ this CI fails for some large sample sizes, and for $\theta = 1$ it does not fail. This CI fails more than the Wald CI, and in the situations in which it does not fail, its AL is slightly higher than that of the Wald CI.

c) Fieller CI. This CI fails when $\theta = \{0.25, 0.5\}$ and $n \leq 50$, and it does not fail for the rest of the values of θ and sample sizes. In general terms, when there are no failures, its AL is similar to that of the Wald and logarithmic CIs.

d) Bootstrap CI. This CI has numerous failures when $\theta = \{0.25, 0.50, 0.75\}$, whereas for $\theta = 1$ it does not fail. When $\theta = 1$, its AL is greater than that of the Wald and logarithmic CIs, especially when $n \leq 400$, and its AL is also slightly lower than that of the Fieller CI.

e) Bayesian CI. This CI only fails when $\theta = 0.25$ and $n \leq 50$. When this CI does not fail, its AL is, in general terms, somewhat larger than that of the rest of the CIs.

Similar conclusions are obtained when the dependence factors take high values. Therefore, regarding the effect of the dependence factors on the CIs, in general terms they do not have a clear effect on the CPs of the CIs.

Table 5: Coverage probabilities (CPs) and average lengths (ALs) of the CIs for the ratio θ of the two weighted kappa coefficients (I).

$\kappa_1(0.1) = 0.2,\ \kappa_2(0.1) = 0.8,\ \theta = 0.25$
$Se_1 = 0.484,\ Sp_1 = 0.684,\ Se_2 = 0.852,\ Sp_2 = 0.911$
$\varepsilon_1 = 0.0359,\ \varepsilon_0 = 0.0306,\ p = 50\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.823**	1.351	**0.088**	1.517	**0.700**	1.950	**0.368**	2.260	**0.884**	2.704
50	**0.837**	0.803	**0.532**	0.886	**0.828**	0.851	**0.634**	0.882	**0.905**	0.965
100	0.931	0.551	**0.832**	0.608	0.942	0.565	**0.889**	0.569	0.954	0.585
200	0.957	0.389	**0.920**	0.422	0.962	0.392	0.952	0.388	0.970	0.402
300	0.970	0.318	0.933	0.340	0.974	0.319	0.969	0.316	0.984	0.328
400	0.960	0.277	0.936	0.293	0.967	0.278	0.962	0.276	0.976	0.285
500	0.957	0.248	0.944	0.260	0.967	0.248	0.969	0.247	0.975	0.256
1000	0.945	0.175	0.963	0.179	0.944	0.176	0.943	0.175	0.953	0.182

$\kappa_1(0.9) = 0.2,\ \kappa_2(0.9) = 0.8,\ \theta = 0.25$
$Se_1 = 0.28,\ Sp_1 = 0.92,\ Se_2 = 0.82,\ Sp_2 = 0.98$
$\epsilon_1 = 0.0252,\ \epsilon_0 = 0.0092,\ p = 10\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.885**	1.760	**0.002**	2.029	**0.566**	3.567	**0.011**	3.175	**0.866**	3.851
50	**0.916**	1.249	**0.259**	1.415	**0.765**	1.660	**0.040**	1.722	**0.767**	1.816
100	0.936	0.846	**0.636**	0.947	**0.884**	0.939	**0.363**	1.048	**0.843**	0.986
200	0.958	0.560	**0.835**	0.617	0.945	0.581	**0.807**	0.607	0.932	0.594
300	0.967	0.440	**0.900**	0.479	0.960	0.450	**0.902**	0.456	0.948	0.459
400	0.965	0.373	0.931	0.402	0.959	0.379	0.932	0.380	0.943	0.387
500	0.971	0.327	0.936	0.349	0.971	0.331	0.942	0.330	0.960	0.339
1000	0.950	0.227	0.941	0.235	0.950	0.228	0.949	0.227	0.955	0.234

$\kappa_1(0.1) = 0.4,\ \kappa_2(0.1) = 0.8,\ \theta = 0.5$
$Se_1 = 0.804,\ Sp_1 = 0.887,\ Se_2 = 0.82,\ Sp_2 = 0.98$
$\epsilon_1 = 0.0723,\ \epsilon_0 = 0.0089,\ p = 10\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**
25	**0.918**	1.141	**0.835**	1.259	**0.893**	2.824	**0.543**	1.157	**0.906**	2.310
50	0.959	1.021	**0.859**	1.119	0.939	1.518	**0.897**	1.140	0.978	1.710
100	0.961	0.619	**0.922**	0.655	0.949	0.693	**0.880**	0.670	0.975	0.828
200	0.962	0.395	0.947	0.406	0.959	0.409	**0.914**	0.400	0.977	0.470
300	0.955	0.315	0.951	0.320	0.956	0.321	**0.928**	0.312	0.976	0.363
400	0.953	0.271	0.949	0.274	0.952	0.274	0.935	0.265	0.975	0.308
500	0.951	0.240	0.950	0.242	0.953	0.242	0.932	0.234	0.971	0.271
1000	0.939	0.169	0.943	0.170	0.939	0.170	0.934	0.163	0.963	0.189

$\kappa_1(0.5) = 0.4,\ \kappa_2(0.5) = 0.8,\ \theta = 0.5$
$Se_1 = 0.76,\ Sp_1 = 0.72,\ Se_2 = 0.85,\ Sp_2 = 0.95$
$\epsilon_1 = 0.0570,\ \epsilon_0 = 0.0180,\ p = 25\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**	**CP**	**AL**
25	0.997	1.328	**0.918**	1.493	0.966	2.222	**0.901**	2.463	0.999	2.825
50	0.983	0.780	**0.924**	0.848	0.966	0.855	**0.925**	0.894	0.995	1.057
100	0.977	0.488	0.957	0.510	0.969	0.501	0.952	0.498	0.990	0.586
200	0.958	0.323	0.956	0.329	0.957	0.327	0.940	0.320	0.981	0.372
300	0.958	0.257	0.954	0.260	0.957	0.259	0.945	0.252	0.978	0.292
400	0.948	0.221	0.947	0.222	0.948	0.221	0.936	0.215	0.966	0.249
500	0.954	0.196	0.953	0.197	0.954	0.196	0.943	0.190	0.972	0.220
1000	0.944	0.137	0.951	0.137	0.945	0.137	0.933	0.132	0.968	0.152

Table 6: Coverage probabilities (CPs) and average lengths (ALs) of the CIs for the ratio θ of the two weighted kappa coefficients (II).

$\kappa_1(0.9) = 0.6,\ \kappa_2(0.9) = 0.8,\ \theta = 0.75$
$Se_1 = 0.62,\ Sp_1 = 0.98,\ Se_2 = 0.911,\ Sp_2 = 0.936$
$\epsilon_1 = 0.0277,\ \epsilon_0 = 0.0094,\ p = 5\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	1	1.514	1	1.679	1	2.689	0.999	2.578	1	3.538
50	0.999	1.409	0.994	1.487	0.993	1.972	0.979	2.311	1	2.392
100	0.999	1.323	0.993	1.451	0.993	1.899	0.975	1.425	1	1.980
200	0.971	0.909	0.933	0.965	0.940	1.037	0.965	0.998	0.991	1.173
300	0.946	0.709	0.916	0.738	0.939	0.767	0.958	0.784	0.973	0.854
400	0.955	0.583	0.933	0.599	0.944	0.601	0.959	0.620	0.977	0.679
500	0.943	0.506	0.925	0.516	0.931	0.516	0.961	0.551	0.969	0.579
1000	0.947	0.341	0.945	0.344	0.943	0.344	0.969	0.375	0.969	0.377

$\kappa_1(0.1) = 0.6,\ \kappa_2(0.1) = 0.8,\ \theta = 0.75$
$Se_1 = 0.195,\ Sp_1 = 0.995,\ Se_2 = 0.477,\ Sp_2 = 0.987$
$\epsilon_1 = 0.0509,\ \epsilon_0 = 0.0026,\ p = 25\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	1	1.687	1	1.924	1	4.747	1	2.676	1	4.561
50	1	1.266	1	1.400	1	2.837	1	1.609	1	2.308
100	0.999	0.865	0.997	0.923	0.997	0.946	0.998	0.945	1	1.188
200	0.992	0.565	0.990	0.583	0.986	0.579	0.975	0.618	0.997	0.700
300	0.971	0.444	0.990	0.452	0.976	0.449	0.958	0.493	0.992	0.536
400	0.971	0.375	0.985	0.380	0.972	0.378	0.960	0.420	0.989	0.448
500	0.966	0.328	0.976	0.331	0.971	0.331	0.964	0.371	0.987	0.390
1000	0.955	0.223	0.965	0.224	0.960	0.224	0.976	0.255	0.986	0.258

$\kappa_1(0.5) = 0.4,\ \kappa_2(0.5) = 0.4,\ \theta = 1$
$Se_1 = 0.76,\ Sp_1 = 0.72,\ Se_2 = 0.40,\ Sp_2 = 0.943$
$\epsilon_1 = 0.0480,\ \epsilon_0 = 0.0206,\ p = 25\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	0.979	1.627	0.999	1.835	0.990	5.762	0.977	2.244	0.999	3.650
50	0.953	1.525	0.991	1.708	0.977	3.028	0.981	2.173	0.995	2.728
100	0.941	1.350	0.983	1.467	0.962	2.342	0.956	1.703	0.984	2.051
200	0.953	0.972	0.971	1.014	0.955	1.212	0.960	1.091	0.979	1.251
300	0.950	0.770	0.953	0.790	0.944	0.851	0.941	0.825	0.965	0.931
400	0.955	0.658	0.969	0.670	0.960	0.705	0.959	0.694	0.980	0.776
500	0.951	0.582	0.954	0.590	0.947	0.612	0.943	0.607	0.965	0.678
1000	0.952	0.403	0.955	0.406	0.951	0.413	0.950	0.410	0.972	0.458

$\kappa_1(0.9) = 0.4,\ \kappa_2(0.9) = 0.4,\ \theta = 1$
$Se_1 = 0.943,\ Sp_1 = 0.229,\ Se_2 = 0.70,\ Sp_2 = 0.70$
$\epsilon_1 = 0.0200,\ \epsilon_0 = 0.0343,\ p = 50\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	1	1.857	1	2.233	1	4.483	1	2.595	1	4.216
50	0.999	1.762	0.999	2.134	0.997	3.455	0.979	1.943	1	3.294
100	0.995	1.685	0.997	1.876	0.992	2.338	0.974	1.770	0.997	2.396
200	0.983	1.195	0.988	1.278	0.980	1.345	0.980	1.268	0.990	1.445
300	0.964	0.943	0.982	0.986	0.959	1.003	0.965	0.989	0.971	1.093
400	0.957	0.803	0.976	0.828	0.951	0.838	0.957	0.839	0.971	0.913
500	0.954	0.709	0.970	0.726	0.956	0.733	0.960	0.739	0.970	0.801
1000	0.956	0.491	0.964	0.496	0.956	0.499	0.959	0.505	0.969	0.545

4.3. CIs with a small sample

The results of the simulation experiments have shown that the CIs may fail when the sample size is small ($n = 25 - 50$). A classic solution to this problem is adding the correction 0.5 to each observed frequency, as is frequent in the analysis of 2×2 tables. To assess this procedure, the same simulation experiments as before were carried out for $n = \{25, 50, 100\}$ adding the value 0.5 to all of the observed frequencies s_{ij} and r_{ij}. Table 7 shows some of the results obtained for the CIs for the ratio θ. The results for the difference δ are not shown since, although this method improves the CP of the CIs, these intervals continue to fail when they failed without adding the correction. The results for $n = 100$ are not shown either, since these are very similar to those obtained without adding the correction. As conclusions, in general terms, it holds that: a) the Wald CI for θ does not fail, its CP is 100% or very close to 100%, and its AL is lower than the rest of the intervals when these do not fail; b) the logarithmic, Fieller, Bootstrap and Bayesian CIs may continue to fail when $\theta = 0.25$. Consequently, when the sample size is small one must use the Wald CI for θ adding the value 0.5 to all of the observed frequencies.

Table 7: Coverage probabilities (CPs) and average lengths (ALs) of the CIs for θ with small samples.

$\kappa_1\,(0.9) = 0.2,\ \kappa_2\,(0.9) = 0.8,\ \theta = 0.25$
$Se_1 = 0.28,\ Sp_1 = 0.92,\ Se_2 = 0.82,\ Sp_2 = 0.98$
$\epsilon_1 = 0.0252,\ \epsilon_0 = 0.00092,\ p = 10\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	0.999	1.808	0.008	1.960	0.653	3.014	0.145	2.150	0.783	3.531
50	0.940	1.287	0.262	1.464	0.768	1.710	0.556	1.440	0.768	1.813

$\kappa_1\,(0.5) = 0.4,\ \kappa_2\,(0.5) = 0.8,\ \theta = 0.5$
$Se_1 = 0.76,\ Sp_1 = 0.72,\ Se_2 = 0.85,\ Sp_2 = 0.95$
$\epsilon_1 = 0.0570,\ \epsilon_0 = 0.0180,\ p = 25\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	1	1.458	0.961	1.659	0.984	2.332	0.940	1.897	1	3.118
50	0.992	0.836	0.960	0.913	0.982	0.932	0.962	0.869	0.997	1.141

$\kappa_1\,(0.9) = 0.6,\ \kappa_2\,(0.9) = 0.8,\ \theta = 0.75$
$Se_1 = 0.62,\ Sp_1 = 0.98,\ Se_2 = 0.911,\ Sp_2 = 0.936$
$\epsilon_1 = 0.0277,\ \epsilon_0 = 0.0094,\ p = 5\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	1	1.812	1	2.073	1	3.554	1	2.425	1	4.053
50	1	1.593	1	1.789	1	2.564	0.999	2.067	1	2.682

$\kappa_1\,(0.9) = 0.4,\ \kappa_2\,(0.9) = 0.4,\ \theta = 1$
$Se_1 = 0.943,\ Sp_1 = 0.229,\ Se_2 = 0.70,\ Sp_2 = 0.70$
$\epsilon_1 = 0.0200,\ \epsilon_0 = 0.0343,\ p = 50\%$

n	Wald		Logarit.		Fieller		Bootstrap		Bayesian	
	CP	AL	CP	AL	CP	AL	CP	AL	CP	AL
25	1	1.896	1	2.140	1	4.727	1	2.571	1	4.234
50	1	1.798	1	1.991	1	3.211	1	2.418	1	3.242

4.4. Rules of application

The CIs for the difference and for the ratio of the two weighted kappa coefficients compare both parameters, and therefore we can decide which method is preferable to make this comparison. Once we have studied the coverage probabilities and the average lengths of the CIs for $\delta = \kappa_1(c) - \kappa_2(c)$ and for $\theta = \kappa_1(c)/\kappa_2(c)$, from the results obtained some general rules of application can be given for the CIs in terms of sample size. These rules are based on the failures and on the coverage probabilities, since the average lengths of the CIs for the difference and for the ratio cannot be compared as they are different intervals. In terms of sample size n:

a) If n is small ($n < 100$), use the Wald CI for θ increasing the frequencies s_{ij} and r_{ij} in 0.5.

b) If $100 \leq n \leq 400$, use the Wald CI for the ratio θ without adding 0.5.

c) If $n \geq 500$, use any of the CIs (for the difference or for the ratio) proposed in Section 3.2 without adding 0.5.

In general terms, if the sample size is small, the Wald CI calculated adding 0.5 to each observed frequency does not fail. In this situation, its AL increases in relation to the Wald CI without adding 0.5, but its CP also increases meaning that the interval does not fail. When $100 \leq n \leq 400$ the CI that behaves best (fewest failures and its CP shows better fluctuations around 95%) is the Wald CI for the ratio θ. When the sample size is very large ($n \geq 500$), there is no important difference between the asymptotic behaviour of the proposed CIs, and therefore any one of them can be used. When the sample size is small, ($n \leq 50$) the CIs may fail, especially when the difference between the two weighted kappa coefficients is not small.

5. SAMPLE SIZE

The determination of the sample size to compare parameters of two BDTs is a topic of interest. We then propose a method to calculate the sample size to estimate the ratio θ between two weighted kappa coefficients with a precision ϕ and a confidence $100(1-\alpha)\%$. This method is based on the Wald CI for θ, which is, in general terms, the interval with the best asymptotic behaviour. Furthermore, this method requires a pilot sample (or another previous study) from which we calculate estimations of all of the parameters (Se_h, Sp_h, ϵ_1, ϵ_0 and p, and consequently of $\kappa_h(c)$) and the Wald CI for θ. If the pilot sample size is not small and the Wald CI for θ calculated from this sample contains the value 1, it makes no sense to determine the sample size necessary to estimate how much bigger one weighted kappa coefficient is than the other one, as the equality between both is not rejected. Nevertheless, if the pilot sample is small and the Wald CI (adding 0.5) contains the value 1, it may be useful to calculate the sample size to estimate the ratio θ. In this situation, the Wald CI (adding 0.5) will be very wide (as the pilot sample is small) and may contain the value 1 even if $\kappa_1(c)$ and $\kappa_2(c)$ are different. Let us considerer that $\kappa_2(c) \geq \kappa_1(c)$ and therefore $\theta \leq 1$, and let ϕ be the precision set by the researcher. As it has been assumed that $\theta \leq 1$, then ϕ must be lower than one, and if we want to have a high level of precision then ϕ must be a small value.

On the other and, based on the asymptotic normality of $\hat{\theta} = \hat{\kappa}_1(c)/\hat{\kappa}_2(c)$ it is verified that $\hat{\theta} \in \theta \pm z_{1-\alpha/2}\sqrt{\text{Var}(\hat{\theta})}$, i.e. the probability of obtaining an estimator $\hat{\theta}$ is in this interval with a probability $100(1-\alpha)\%$. Setting a precision ϕ, we can then calculate the sample size n from

$$\phi = z_{1-\alpha/2}\sqrt{\text{Var}(\hat{\theta})}, \tag{5.1}$$

where

$$\text{Var}\left(\hat{\theta}\right) \approx \frac{\kappa_2^2(c)\,\text{Var}\left[\hat{\kappa}_1(c)\right] + \kappa_1^2(c)\,\text{Var}\left[\hat{\kappa}_2(c)\right] - 2\kappa_1(c)\,\kappa_2(c)\,\text{Cov}\left[\hat{\kappa}_1(c), \hat{\kappa}_2(c)\right]}{\kappa_2^4(c)}.$$

In the Appendix B of the supplementary material, we can see how this expression is obtained. This variance depends on the weighted kappa coefficients and on their respective variances and covariance. Furthermore, the variances $\text{Var}[\hat{\kappa}_h(c)]$ and the covariance $\text{Cov}[\hat{\kappa}_1(c), \hat{\kappa}_2(c)]$ (their expressions can be seen in the Appendix B of the supplementary material) depend, among other parameters, on the sample size n. Consequently, it is possible to use this relation to calculate the sample size to estimate the ratio θ. Substituting in the equation of $\text{Var}(\hat{\theta})$ the variances and the covariance with its respective expressions, substituting the parameters with their estimators and clearing n in equation (5.1), it is obtained that

$$\begin{aligned} n = \frac{z_{1-\alpha/2}^2\,\hat{\theta}^2}{\phi^2\hat{p}^3\hat{q}^3} \Bigg\{ \sum_{h=1}^{2} \left[\frac{\hat{a}_{h1}^2 \hat{Se}_h \left(1-\hat{Se}_h\right)\hat{q} + \hat{a}_{h2}^2 \hat{Sp}_h \left(1-\hat{Sp}_h\right)\hat{p} + \hat{a}_{h3}^2 \hat{p}^2\hat{q}^2}{\hat{Y}_h^2} \right] \\ - \frac{2}{\hat{Y}_1\hat{Y}_2}\left[\hat{a}_{11}\hat{a}_{21}\hat{\varepsilon}_1\hat{q} + \hat{a}_{12}\hat{a}_{22}\hat{\varepsilon}_0\hat{p} + \hat{a}_{13}\hat{a}_{23}\hat{p}^2\hat{q}^2\right] \Bigg\}, \end{aligned} \tag{5.2}$$

where $\hat{a}_{h1} = \hat{p}\hat{q} - \hat{p}\,(\hat{q}-c)\,\hat{\kappa}_h(c)$, $\hat{a}_{h2} = \hat{a}_{h1} + (\hat{q}-c)\,\hat{\kappa}_h(c)$ and $\hat{a}_{h3} = (1-2\hat{p})\,\hat{Y}_h - \left[(1-c-2\hat{p})\,\hat{Y}_h + \hat{Sp}_h + c - 1\right]\hat{\kappa}_h(c)$, with $h = 1, 2$. This method requires us to know $\hat{Se}_h$, $\hat{Sp}_h$, $\hat{\epsilon}_1$, $\hat{\epsilon}_0$ and $\hat{p}$ (and therefore $\hat{\kappa}_h(c)$), for example obtained from a pilot sample or from previous studies. The procedure to calculate the sample size consists of the following Steps:

1. Take pilot samples sized n' (in general terms, $n' \geq 100$ to be able to calculate the Wald CI without adding 0.5 or use the Wald CI adding 0.5 to the frequencies if n is small), and from this sample calculate $\hat{Se}_h$, $\hat{Sp}_h$, $\hat{\epsilon}_1$, $\hat{\epsilon}_0$, $\hat{p}$ and $\hat{\kappa}_h(c)$, and a then calculate the Wald CI for θ. If the Wald CI calculated has a precision ϕ, i.e. if $\frac{\text{Upper limit}-\text{Lower limit}}{2} \leq \phi$, then with the pilot sample the precision has been reached and the process has finished (θ has been estimated with a precision ϕ to a confidence $100(1-\alpha)\%$); if this is not the case, go to the following Step.

2. From the estimations obtained in Step 1, calculate the new sample size n applying equation (5.2).

3. Take the sample of n individuals ($n - n'$ is added to the pilot sample), and from the new sample we calculate $\hat{Se}_h$, $\hat{Sp}_h$, $\hat{\epsilon}_1$, $\hat{\epsilon}_0$, $\hat{p}$, $\hat{\kappa}_h(c)$ and the Wald CI for θ. If the Wald CI calculated has a precision ϕ, then with the new sample the precision has been reached and the process has finished. If the Wald CI does not have the required precision, then this new sample is considered as a pilot sample and the process starts again at Step 1. In this situation, the new sample has a size n calculated in Step 2, i.e. we add $n - n'$ individuals to the initial pilot sample (sized n'). Therefore, the process starts again at Step 1 considering the new sample as the pilot sample and from this sample we calculate the values of the estimators and the Wald CI.

The method to calculate the sample size is an iterative method which depends on the pilot sample and which does not guarantee that θ will be estimated with the required precision. Each time that the previous process (Steps 1–3) is repeated, we calculate (starting from an initial sample) the new sample size to estimate θ, i.e. we calculate the number of individuals that must be added to the initial sample to obtain a new sample. Therefore, this process adjusts the size of the initial pilot sample, adding (in each iteration of the process: Steps 1–3) the number of individuals necessary to obtain the right sample size to estimate θ with the precision required. The programme in R described in the Section 6 allows us to calculate the sample size to estimate θ.

If the Wald CI for θ is higher than one, the BDTs can always be permuted and θ will then be lower than one. Another alternative consists of setting a value for a precision ϕ', in a similar way to the previous situation when $\theta \leq 1$, and then apply the equation (5.2) with $\phi = \hat{\theta}^2\phi'$, where $\hat{\theta} = \hat{\kappa}_1(c)/\hat{\kappa}_2(c) \leq 1$. This is due to the fact that if (L_θ, U_θ) is the Wald CI for $\theta = \kappa_1(c)/\kappa_2(c) \leq 1$ then the Wald CI for $\theta' = 1/\theta = \kappa_2(c)/\kappa_1(c)$ is $\left(L_\theta/\hat{\theta}^2 \ , \ U_\theta/\hat{\theta}^2\right)$. It is easy to check that the calculated value of the sample size n is the same both if $\theta \leq 1$ (with precision ϕ) and if $\theta > 1$ (with precision $\phi = \hat{\theta}^2\phi'$).

Simulation experiments were carried out to study the effect that the pilot sample has on the calculation of the sample size. These experiments consisted of generating $N = 10,000$ random samples of multinomial distributions considering the same scenarios as those given in Tables 5 and 6. The equation of the sample size depends on the values of the estimators, which in turn depend on the pilot sample. Consequently, the pilot sample may have an effect on the sample size calculated. To study this effect, the simulation experiments consisted of the following Steps:

1. Calculate the sample size n from the values of the parameters set in the different scenarios considered. Therefore, equation (5.2) was applied using the values of the parameters (instead of their estimators).
2. Generate the N multinomial random samples sized n calculating the probabilities from equations (3.1) and (3.2), using the values of the previous parameters, and as ε_i we considered low values (25%), intermediate values (50%) and high values (80%). From each one of the N random samples, $\hat{Se}_h$, $\hat{Sp}_h$, $\hat{\varepsilon}_1$, $\hat{\varepsilon}_0$ and $\hat{p}$ (and therefore $\hat{\kappa}_h(c)$) were calculated, and then we calculated the sample size n'_i applying equation (5.2).
3. For each scenario, the average sample size and the relative bias were calculated, i.e. $\bar{n} = \sum n'_i/N$ and $RB\,(n') = (\bar{n} - n)/n$.

Table 8 shows some of the results obtained. The relative biases are very small, which indicates that the equation of the calculation of the sample size provides robust values, and therefore the choice of the pilot sample does not have an important effect on the calculation of the sample size.

Table 8: Effect of the pilot sample on the sample size.

$\kappa_1\,(0.1) = 0.2\ \kappa_2\,(0.1) = 0.8\ \theta = 0.25$ $Se_1 = 0.484\ Sp_1 = 0.684\ Se_2 = 0.852\ Sp_2 = 0.911\ p = 50\%$						
	$\epsilon_1 = 0.0179\ \epsilon_0 = 0.0153$		$\epsilon_1 = 0.0359\ \epsilon_0 = 0.0306$		$\epsilon_1 = 0.0574\ \epsilon_0 = 0.0489$	
	$\phi = 0.05$	$\phi = 0.10$	$\phi = 0.05$	$\phi = 0.10$	$\phi = 0.05$	$\phi = 0.10$
Sample size	3170	793	3066	767	2942	736
Average sample size	3173	795	3068	769	2946	738
Relative bias (%)	0.095	0.252	0.065	0.261	0.136	0.272

$\kappa_1\,(0.9) = 0.2\ \kappa_2\,(0.9) = 0.8\ \theta = 0.25$ $Se_1 = 0.28\ Sp_1 = 0.92\ Se_2 = 0.82\ Sp_2 = 0.98\ p = 10\%$						
	$\epsilon_1 = 0.0126\ \epsilon_0 = 0.0046$		$\epsilon_1 = 0.0252\ \epsilon_0 = 0.0092$		$\epsilon_1 = 0.0403\ \epsilon_0 = 0.0147$	
	$\phi = 0.05$	$\phi = 0.10$	$\phi = 0.05$	$\phi = 0.10$	$\phi = 0.05$	$\phi = 0.10$
Sample size	5104	1276	4947	1237	4758	1190
Average sample size	5113	1287	4948	1246	4759	1218
Relative bias (%)	0.18	0.83	0.02	0.73	0.02	2.35

6. PROGRAMME citwkc

A programme has been written in R and called "citwkc" (Confidence Intervals for Two Weighted Kappa Coefficients) which allows us to calculate the CIs proposed in Section 3 and the sample size proposed in Section 5. The programme runs with the command

$$\text{citwkc}\Big(s_{11},\ s_{10},\ s_{01},\ s_{00},\ r_{11},\ r_{10},\ r_{01},\ r_{00},\ \mathit{cindex},\ \mathit{preci}=0,\ \mathit{conf}=0.95\Big),$$

where *cindex* is the weighting index, *preci* is the precision that is needed to calculate the sample size and *conf* is the level of confidence (by default 95%). By default $\mathit{preci} = 0$, and the programme does not calculate the sample size, and only calculates it when $\mathit{preci} > 0$. In this situation ($\mathit{preci} > 0$), the programme checks if it is necessary to calculate the sample size. The programme checks that the values of the frequencies and of the parameters are viable (e.g. that there are no negative values, frequencies with decimals, etc,), and also checks that it is possible to estimate all of the parameters and their variances-covariances. For the intervals obtained applying the bootstrap method, 2,000 samples with replacement are generated, and for the Bayesian intervals 10,000 random samples are generated. The results obtained on running the programme are saved in file called "`Results_citwkc.txt`" in the same folders from where the programme is run. The program is available for free at URL:

`https://www.ugr.es/local/bioest/software/cmd.php?seccion=mdb`

7. APPLICATION

The results obtained have been applied to the study by Batwala *et al.* (2010) [2] on the diagnosis of malaria. Batwala *et al.* have applied the Expert Microscopy Test and the HRP2-Based Rapid Diagnostic Test to a sample of 300 individuals using the PCR as the GS. The observed frequencies of this study are shown in Table 9, where the T_1 models the result of the Expert Microscopy Test, T_2 models the result of the HRP2-Based Rapid Diagnostic Test and D models the result of the PCR. In this example, $\hat{S}e_1 = 46.07\%$, $\hat{S}p_1 = 97.16\%$, $\hat{S}e_2 = 91.01\%$ and $\hat{S}p_2 = 86.26\%$, and therefore $r\widehat{TPF}_{12} = 0.506$ and $r\widehat{FPF}_{12} = 0.207$. Applying the equation (2.5) it holds that $c' = 0.1902$. As $r\widehat{TPF}_{12} < 1$ and $r\widehat{FPF}_{12} < 1$, applying the rule c) given in Section 2, it holds that $\hat{\kappa}_1(c) > \hat{\kappa}_2(c)$ for $0 \leq c < 0.1902$ and that $\hat{\kappa}_1(c) < \hat{\kappa}_2(c)$ for $0.1902 < c \leq 1$. Applying the rules given in Section 4, as $n = 300 < 400$ then it is necessary to use the Wald CI for the ratio θ. Table 10 shows the values of $\hat{\kappa}_h(c)$, $\hat{\delta}$, $\hat{\theta}$ and the 95% CIs for θ when $c = \{0.1, 0.1902, 0.2, ..., 0.8, 0.9\}$. The results were obtained running the programme "citwkc" with the command "citwkc $(41, 0, 40, 8, 5, 1, 24, 181, c)$" taking $c = \{0.1, 0.1902, 0.2, ..., 0.8, 0.9\}$.

Table 9: Observed frequencies of the study of Batwala *et al.*.

Frequencies					
	$T_1 = 1$		$T_1 = 0$		
	$T_2 = 1$	$T_2 = 0$	$T_2 = 1$	$T_2 = 0$	Total
$D = 1$	41	0	40	8	89
$D = 0$	5	1	24	181	211
Total	46	1	64	189	300

Table 10: CIs for the ratio $\theta = \kappa_1(c)/\kappa_2(c)$.

c	$\hat{\kappa}_1(c)$	$\hat{\kappa}_2(c)$	$\hat{\delta}$	Wald	Logarithmic	Fieller	Bootstrap	Bayesian
0.1	0.726	0.642	1.131	0.925 , 1.335	0.943 , 1.355	0.940 , 1.357	0.926 , 1.344	0.883 , 1.393
0.1902	0.659	0.659	1	0.811 , 1.189	0.828 , 1.208	0.823 , 1.206	0.817 , 1.204	0.776 , 1.234
0.2	0.653	0.661	0.988	0.800 , 1.174	0.817 , 1.194	0.812 , 1.192	0.808 , 1.192	0.766 , 1.219
0.3	0.593	0.681	0.871	0.695 , 1.046	0.711 , 1.065	0.704 , 1.059	0.701 , 1.065	0.673 , 1.083
0.4	0.543	0.701	0.775	0.609 , 0.939	0.625 , 0.958	0.615 , 0.948	0.615 , 0.952	0.593 , 0.971
0.5	0.501	0.723	0.693	0.537 , 0.847	0.553 , 0.866	0.541 , 0.854	0.541 , 0.857	0.525 , 0.877
0.6	0.464	0.747	0.621	0.476 , 0.768	0.492 , 0.786	0.479 , 0.772	0.481 , 0.776	0.468 , 0.799
0.7	0.433	0.772	0.561	0.425 , 0.698	0.440 , 0.716	0.426 , 0.701	0.430 , 0.707	0.418 , 0.727
0.8	0.406	0.799	0.508	0.380 , 0.637	0.395 , 0.654	0.381 , 0.639	0.384 , 0.644	0.375 , 0.667
0.9	0.382	0.827	0.462	0.341, 0.582	0.356 , 0.599	0.342 , 0.584	0.347 , 0.594	0.339 , 0.611

For $c = \{0.1, 0.1902, 0.2, 0.3\}$, the Wald CI for θ contains the value 1, and therefore in these cases we do not reject the equality of the weighted kappa coefficients of the Expert Microscopy Test and of the HRP2-Based Rapid Diagnostic Test. Therefore, when the clinician

considers that a false positive is 9, 4 or 2.33 times more important than a false negative, we do not reject the equality between the weighted kappa coefficients of the Expert Microscopy Test and of the HRP2-Based Rapid Diagnostic Test in the population studied. The rest of the intervals for θ also contain the value 1.

For $c = \{0.4, 0.5, ..., 0.8, 0.9\}$, the Wald CI θ does not contain the value 1, and therefore in all of these cases we reject the equality of the weighted kappa coefficients of the Expert Microscopy Test and of the HRP2-Based Rapid Diagnostic Test in the population studied. Therefore, the clinician considers that $0.5 < c \leq 0.9$, i.e. a false negative is more important than a false positive (as happens in the situation in which the diagnostic tests are applied as screening tests), the weighted kappa coefficient of the HRP2-Based Rapid Diagnostic Test is significantly greater than the weighted kappa coefficient of the Expert Microscopy Test in the population studied. The same conclusion is obtained when the clinician considers that a false positive and a false negative have the same importance ($c = 0.5$). If the clinician considers that a false positive is 1.5 times greater than a false negative (i.e. $c = 0.4$), then the same conclusion is obtained. The rest of the CIs for θ do not contain the value 1. For example, considering $c = 0.9$, it is concluded that in the population being studied the beyond-chance agreement between the HRP2-Based Rapid Diagnostic Test and the PCR is, with a confidence of 95%, a value between 1.72 ($1/0.582 \approx 1.72$) and 2.94 ($1/0.341 \approx 2.94$) times greater than the beyond-chance agreement between the Expert Microscopy Test and the PCR.

In order to illustrate the method to calculate the sample size presented in Section 5 we will consider that $c = 0.9$, and therefore that the two BDTs are applied as a screening test. In this situation, the 95% Wald CI for θ is (0.341 , 0.582), and the precision is 0.1205. As an example, we will consider that the clinician wishes to estimate the ratio between the two weighted kappa coefficients with a precision $\phi = 0.10$. As with the sample of 300 individuals the desired precision ($\phi = 0.10 < 0.1205$) was not achieved, then using this sample as a pilot sample and running the programme "citwkc" with the command "citwkc $(41, 0, 40, 8, 5, 1, 24, 181, 0.9, 0.1)$" it holds that $n = 435$. Therefore, to the sample pilot of 300 individuals we must add 135 more. Once the new sample has been taken, it is necessary to check that the precision $\phi = 0.10$ is verified.

8. DISCUSSION

The weighted kappa coefficient of a BDT is a measure of the beyond-chance agreement between the BDT and the GS, and depends on the sensitivity and specificity of the BDT, on the disease prevalence and on the weighting index. The weighted kappa coefficient is a parameter that is used to assess and compare the performance of BDTs. In this article, we have studied the comparison of the weighted kappa coefficients of two BDTs through confidence intervals when the sample design is paired. Three intervals have been studied for the difference of the two weighted kappa coefficients and five more intervals for the ratio of the two parameters. All the intervals studied are asymptotic and simulation experiments have been carried out to study their coverage probabilities and average lengths subject to different scenarios and for different sample sizes. Based on the results of the simulation experiments, some general rules of application have been given. When the sample size is moderate ($n = 100$) or large ($n = 200 - 400$) it is preferable to compare the two weighted

kappa coefficients through an interval for the ratio, and when the sample size is very large ($n \geq 500$) the two weighted kappa coefficients can be compared through the difference or the ratio. When the sample size is small ($n \leq 50$), the interval with the best behaviour is the Wald CI for the ratio θ adding 0.5 to all of the observed frequencies. Adding 0.5 to all of the frequencies does not improve the behaviour of the intervals for the difference δ, since these continue to fail when they failed without adding the value 0.5. This question may be due to the fact that the ratio $\hat{\theta}$ converges more quickly to the normal distribution than the difference $\hat{\delta}$. In the simulation experiments, the asymptotic behaviour of the Bayesian CIs has been studied using the Beta$(1,1)$ distribution as prior distribution for all of the parameters. The choice of the values of the hyperparameters of the Beta distribution will depend on the previous information that the researcher has. If the researcher has some information and wants this information to have some weight in the data, then it is possible to use higher values of α and β, i.e. considering a Beta(α,β) distribution with $\alpha,\beta > 1$. The increase in α and β adds information and decreases the variance and, therefore, there is less uncertainty about the parameter. If the researcher does not want this information to have a great weight in the posteriori distribution, then the researcher chooses moderate values of α and β which are consistent with the information available, i.e. the average should be compatible with that information. To assess the effect that the Beta distribution has on the asymptotic behaviour of the Bayesian interval, we have carried out simulations (in a similar way to those carried out in Section 4) using as prior the distributions Beta$(5,5)$ and Beta$(25,25)$ for the Bayesian interval for $\theta = \frac{\kappa_1(c)}{\kappa_2(c)}$. These two distributions have the same average as the Beta$(1,1)$ distribution but different variances. The first distribution has a moderate weight in the subsequent distribution and the second has an important weight. In general terms, the results obtained with the distribution Beta$(5,5)$ are very similar to those obtained with the Beta$(1,1)$ distribution. Regarding the Beta$(25,25)$ distribution, there is no important difference in relation to the CPs obtained with the Beta$(1,1)$, although for $\theta = \{0.25, 0.50\}$ the AL is slightly lower with the Beta$(25,25)$, and when $\theta = \{0.75, 1\}$ the AL is slightly higher with the Beta$(25,25)$. In general terms, when the Bayesian interval fails using the Beta$(1,1)$ distribution then it also fails using the Beta$(5,5)$ and the Beta$(25,25)$. Furthermore, the Bayesian CI for $\theta = \kappa_1(c)/\kappa_2(c)$ with the Beta$(5,5)$ and Beta$(25,25)$, respectively, does not display a better CP than the Wald CI (when it does not fail), and therefore the Bayesian CI does not improve the asymptotic behaviour of the Wald CI. The application of the CIs requires the marginal frequencies s and r to be higher than zero. If the marginal frequency s (or r) is equal to zero, then it is not possible to estimate the weighted kappa coefficient of each BDT. Moreover, if a marginal frequency $s_{ij} + r_{ij}$ is equal to zero, then it is possible to calculate all of the CIs proposed; but not if two of these marginal frequencies are equal to zero. In this last situation, one of the weighted kappa coefficients (or both) is equal to zero, and the variance and the covariance are also equal to zero. If $s_{10} + r_{10} = s_{01} + r_{01} = 0$ then $\hat{\kappa}_1(c) = \hat{\kappa}_2(c)$ and $\widehat{\text{Var}}[\hat{\kappa}_1(c)] = \widehat{\text{Var}}[\hat{\kappa}_2(c)] = \text{Cov}[\hat{\kappa}_1(c), \hat{\kappa}_2(c)]$, and the frequentist intervals cannot be calculated. A solution to this problem is to add 0.5 to each observed frequency.

In this article, we have also proposed a method to calculate the sample size to estimate the ratio between the two weighted kappa coefficients with a determined precision and confidence. This method, based on the Wald CI for the ratio, is an iterative method, which starting from a pilot sample adds individuals to the sample until the CI has the set precision. From the initial sample we estimate a vector of parameters and in the second stage we calculate the sample size. Furthermore, the simulation experiments carried out to study

the robustness of the method to calculate the sample size have shown that the method has practical validity and the choice of the pilot sample has very little effect on this method.

When the two diagnostic tests are continuous, for each cut off point of each estimated ROC curve there will be a value of $\hat{Se}_h$ and of $\widehat{FPF}_h$ (and therefore of $\hat{Sp}_h = 1 - \widehat{FPF}_h$), with $h = 1, 2$. Once the clinician has set the value of the weighting index, $\hat{\kappa}_1(c)$ and $\hat{\kappa}_2(c)$ are calculated and therefore the CIs studied in Section 3 can be applied.

9. SUPPLEMENTARY MATERIAL

Appendices A, B and C are available as supplementary material of the manuscript in the URL:

`https://www.ugr.es/local/bioest/software/cmd.php?seccion=mdb`

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