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What is the test's accuracy in my practice population?

Tailored meta-analysis provides a plausible estimate

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Running title: *Tailored meta-analysis*

Abstract

Objective

Diagnostic test accuracy studies and meta-analyses may, in some cases, provide estimates which are highly improbable in practice; tailored meta-analysis provides a potential solution. To investigate the utility of tailored meta-analysis in synthesising estimates of a test's accuracy compared with conventional meta-analysis for three case examples.

Study design and setting

MEDLINE, EMBASE, AND CINAHL were searched for relevant studies and routine data were collected on the test positive rate and disease prevalence from the case settings to define an applicable region for each setting. Three cases were evaluated: Mammography in the NHS Breast Screening Program; PHQ-9 questionnaire to screen for depression in general practice; Centor's criteria used to diagnose group A beta-haemolytic streptococcus in general practice. For conventional meta-analysis, studies were selected using standard systematic review methods; for tailored meta-analysis this selection was refined to those with results compatible with the applicable region for the setting.

Results

In each example, studies were excluded as a result of incorporating an applicable region for the setting. Comparing tailored with conventional meta-analysis, the positive likelihood ratios (with 95% confidence intervals in brackets) were 36.5 (23.0-57.9) and 19.8 (12.8-30.9) respectively for mammography; and 4.89 (2.02-11.8) and 2.35 (1.51-3.67) respectively for Centor's criteria. This had the effect of increasing the positive predictive value from 17 to 27% for mammography and 23% to 38% for Centor's criteria.

Conclusion

Tailored meta-analysis has the potential to provide a plausible estimate for a test's accuracy which is specific to the practice setting. When compared with conventional meta-analysis, the difference may, in some cases, be sufficient to lead to different decisions on patient management.

What is new?

This paper illustrates a novel method that provides a basis for evidence-based diagnosis in practice.

Key findings

The study demonstrates that routine data from real-life general practice and screening programmes may be combined with test evaluation research to assist in making decisions on the applicability of test research

What was known?

Meta-analysis may be used to synthesise summary estimates for a test's sensitivity and specificity when there are multiple studies. However, these summary estimates may be unrepresentative of the test accuracy in practice, and may be virtually impossible to achieve in some cases.

What this study adds

Tailored meta-analysis may be used to synthesise estimates for a test's accuracy that are customised to practice. Compared with estimates derived from conventional meta-analysis these may lead to different decisions on patient management. This method generalises to different tests and different settings including routine tests used in general practice.

What is the implication

The increased use of electronic patient records provides an opportunity to collect routine data on tests used in practice. If these are combined with test evaluation research there is the potential to improve diagnostic decision-making at an individual practice level.

Introduction

One of the main concerns in diagnostic test research is the evaluation of a test's accuracy. In relevant studies the objective is to determine how 'accurate' the test is at discriminating those patients with a target disorder from those who do not.

Although, primary diagnostic test accuracy (DTA) studies do provide estimates of a test's accuracy, these in general may vary between studies; being governed by factors relating to the conduct of the study, test execution and patient spectrum [1]. Some of the variation may be mitigated by standardizing the study conduct, but this is more difficult to achieve for the other factors. Hence a single study reports on the average performance for the test for circumstances particular to the study's setting. This clearly has implications for meta-analysis and explains why heterogeneity is frequently observed [2].

In therapeutics, meta-analysis as a technique has been largely successful at 'ironing out' the effects of differences between individual studies to make assertions about the underlying effect [3]. In diagnostics such an approach may be taken to estimate the average performance of the test across all the studies [4,5]. However, for the specific question of 'what is the performance of the test in my practice population', it is not clear whether knowing the average accuracy across a number of studies is that useful, particularly when there is widespread heterogeneity. If a test's performance in a particular practice is better represented by one of the outlier studies, the estimate derived from meta-analysis is likely to be significantly different from that experienced – indeed, in some cases the estimate may be virtually impossible in the practice setting of interest [6].

It is this observation that motivated the development of a novel method which uses information from the target setting in order to select the studies most likely to be informative in practice [6]. Although the method has been developed and described in detail elsewhere its utility has yet to be fully investigated [6]. Here we will evaluate its utility in three case examples. In the first example, like the previous study [6], we will illustrate its use by applying it to a UK national screening programme. However, in the next two examples we will demonstrate for the first time how the method may help individual clinicians directly by applying it to a single general practice setting.

Method

The aim is to provide a plausible estimate for the accuracy of a test within a specific setting without conducting a further primary study. Broadly, the approach relies upon using routine data from the target setting in order to define an 'applicable region' where the test's performance is likely to lie [6]. This is used to 'tailor' the selection of included studies in a systematic review by excluding those that report test performances which are incompatible with this region [6].

The principal statistic for defining the applicable region is the test positive rate, *r*, which is obtained from counting the number of test positives in the setting at a particular threshold as a proportion of all those tested. Such data are collected routinely in the NHS screening programmes and it is increasingly possible to do the same in UK general practice through the electronics record systems. Having an estimate for *r* allows us to constrain the region in ROC space (after Receiver Operating Characteristic curve) where the sensitivity, *s*, and false positive rate, *f*, for the test must lie. The size of the applicable region is dependent on both the size of *r* and its standard error. Thus, large sample sizes provide more precise, narrower applicable regions.

The region may be refined further by including estimates of the prevalence, *p*, which if known without error will constrain the sensitivity and false positive rate to a straight line. When the error in the estimate is incorporated the applicable region is narrowed usually to a trapezium-shaped area [6]. Thus, the applicable region for the setting represents the set of feasible values for the sensitivity and false positive rate given the estimates for the test positive rate and prevalence for the setting. This should be contrasted with the prediction region of conventional meta-analysis which is the model prediction on where a new study's estimate would lie based only on data from the included studies [7]. The applicable region is in effect a prediction region, but more specific; it is for a particular setting based on data from the actual setting of interest. When there is no such data, the best prediction for the setting of interest would be provided by the prediction region otherwise it is provided by the applicable region. The corollary of this is where the prediction region lies outside of the applicable region this is an improbable estimate for the test in the setting.

Systematic review methods are used to provide an initial selection of studies for conventional meta-analysis. Each study's compatibility with the setting is then determined by the magnitude of the tail probability of the study's estimate for a potential study parameter lying in the applicable region. From all candidate parameters within the applicable region the maximum likelihood estimate is chosen when calculating probabilities - the level of significance is set to 0.025 for selecting studies. Consistent with previous analyses the sensitivity and false positive rate are assumed to have independent binomial distributions [5,6]. A summary of the process is given in appendix 1, and is detailed elsewhere [6].

Data collection

Three diagnostic/screening tests were analysed using data collected from practice. In the first case, data were obtained from the NHS Breast screening programme (available in the public domain) and the applicable region was defined using *r* only. For the next two cases both *r* and *p* were used to define the applicable region for the test after collecting data from a single general practice in the UK.

To obtain estimates on the accuracy of each of the tests analysed, the literature was searched for relevant meta-analyses. These provided the primary studies which were assessed for applicability in the target setting. Where appropriate, meta-analyses were either updated or synthesised *de novo*.

Statistical methods used to aggregate studies

The bivariate random effects model was used to derive summary estimates for the sensitivity and specificity (1 – false positive rate) [5] from which other relevant statistics were calculated. Confidence and predictions regions, as determined by methods previously described [8, 9] were also included in the figures. When the prediction region is much larger than the associated confidence region this suggests heterogeneity between studies [10]. The results of 'tailored' meta-analysis, where only applicable studies were aggregated were compared with 'conventional' meta-analysis where all the studies were aggregated. Unless otherwise stated, any estimate is followed by a 95% confidence interval (CI) in brackets.

Results

1. Breast Screening with mammography

In the UK, there has been a national breast screening programme since 1988 [11]. It originally screened women between the ages 50-64 years with single view mammography, but since 2005 it has screened women between 50-70 years old with two-view mammography (mediolateral oblique and craniocaudal) triennially [11].

Following screening, patients are recalled for further investigation if, for technical reasons, the mammogram is an inadequate view or has features indicative of a potential abnormality [11]. Investigation involves further views, clinical or ultrasound examination or biopsy.

Although several reviews have evaluated the efficacy of breast screening in terms of its effect on mortality [12-16] only one meta-analysis aimed to estimate the sensitivity and specificity of the mammogram as a screening test for breast cancer [17]. In that review they used the following definitions: a positive test result was when a patient was referred for further work-up on the basis of the mammogram result; a false positive as those patients referred for further investigation and diagnosed negative by biopsy; and a false negative as a cancer detected in the interval between screens.

The original meta-analysis published in 1998, included six studies in their analysis [17]. However, the studies reported on the first round (prevalent) screening performance and none reported on the programme screening performance which is mixture of prevalent and subsequent (or incident) screens. In addition, as there have been several large-scale studies since this review, the analysis was updated (see appendix 2). Ten studies were included.

In 2012, the NHS Breast Screening programme screened 1,722,677 women between the ages 50-70 with a mammogram; 67,415 were referred for further assessment [18] – this equates to a test positive rate, r = 3.91% [99% CI: 3.88-3.95]. Imposing this on the results of the meta-analysis leads to six of the ten included studies being outside the range of performance possible in the UK Breast Screening programme (figure 1). Only one study was conducted in the UK and it reported test performances which were compatible with the applicable region and was included.

For the conventional meta-analysis the sensitivity and specificity were 87.2% [95% CI: 81.1-91.5] and 95.6% [95% CI: 93.0-97.3]. This compared to the tailored meta-analysis where the sensitivity and specificity were 78.0% [95% CI: 70.0-84.4] and 97.9% [95% CI: 96.4-98.7]. Although tailoring the study selection brings about a modest increase in specificity, the effect on the positive likelihood is more striking: 19.8 [95% CI: 12.8-30.9] compared with 36.5 [95% CI: 23.0-57.9].

The NHS Breast screening programme reports 8.1 cases of breast cancer per 1000 women screened. This is likely to be an underestimate of the prevalence due to the presence of false negatives [18]. If we assume the background prevalence of breast cancer to be 1%, the effect of nearly doubling the positive likelihood ratio is to increase estimates of the post-test probability from 17% to 27%. Thus, when either the sensitivity or specificity is estimated to be close to 1, modest differences between estimates may have significant effects on the predictive values.

2. Screening for depression using the PHQ-9 in general practice

In general practice in the UK, the patient health questionnaire (PHQ-9) is most commonly used to monitor depression [19,20]. However, it was originally developed as a screening tool [21] and it is its accuracy as a screening tool that is of interest here. It consists of 9 questions with each question scored between 0 and 3, giving a maximum of 27 points. The usual threshold for a positive test result is 10 and all subsequent analyses will be at this threshold [21].

The accuracy of the PHQ-9 as a screening tool for depression was evaluated in a meta-analysis published in 2012 [22]. Studies were included if the target disorder was a major depressive disorder as defined by a standardised diagnostic interview schedule based on the Diagnostic and Statistical manual of mental disorders (DSM) or the International Classification of Diseases (ICD).

However, to estimate its performance in general practice and to capture the latest studies, a more specific meta-analysis was synthesised, where, in addition to the inclusion criteria above, we considered only those studies that had evaluated the tool in a family or general practice setting (see appendix 3).

There were ten included studies which reported the performance characteristics for the PHQ-9 questionnaire at a test threshold of 10. Two studies evaluated an English version of the PHQ-9 questionnaire and only one study was located in the UK. There were also six different versions of the reference standard used between the studies which may have implications for the definition of the target disorder.

To gain an insight on the performance of the PHQ-9 as a screening tool for depression in a particular general practice, audit data were collected on adult patients attending a general practice surgery of one of the authors (BHW) which has a patient population of *circa* 6500. In particular, those attending were asked to complete a PHQ-9 questionnaire, irrespective of their presenting complaint. Over a 6 week period, a total of 124 patients completed the questionnaire. Twenty-eight patients scored 10 or more, giving a test positive rate r = 22.6% [99% CI: 14.4-33.5]. Thus for the applicable region, r was taken to vary between 14.4 and 33.5.

To estimate the background prevalence of depression, a UK household survey of mental health carried out in 2007 was consulted [23]. These surveys are used to monitor the mental health of 16-74 year olds in the community. The methods involve interviewing subjects on average for 90 minutes, using the clinical interview schedule (CIS-R) to ascertain any mental health symptoms. These are then combined using a computer algorithm to give an ICD-10 diagnosis. The survey reported a prevalence of depression of 2.8%, with 849 individuals taking part in the overall survey [23]. Based on this, a range of 1-10% was taken as the estimated prevalence range prior to testing.

To summarise, the intervals $0.144 \leq r \leq 0.335$ and $0.01 \leq p \leq 0.1$ were used to derive the applicable region for the PHQ-9 tool in this general practice. Studies were then selected for tailored meta-analysis based on the individual study estimate being compatible (not improbable) with this region (see figure 2).

Although the one UK-based study [24] was applicable to this general practice, the most striking feature is that three of the studies reported performances which were incompatible with this practice despite all being conducted in primary care settings. This adds weight to the argument that studies which are performed in settings that are *prima facie* similar to the practice setting may still be uninformative.

The effects on the performance characteristics were as follows: for conventional meta-analysis the sensitivity and specificity were 74.2% [95% CI: 63.1-82.9] and 91.5% [95% CI: 86.4.-94.8]; for tailored meta-analysis the sensitivity and specificity were 79.7 [95% CI: 71.5-86.1] and 87.9 [95% CI: 83.1-91.5].

In fact, the changes in all of the statistics were fairly modest and as a result would be unlikely to have any significant effect on clinical decision making.

3. Using Centor's criteria in the diagnosis of sore throats in general practice.

Centor's criteria is a clinical prediction rule used to diagnose group A beta haemolytic streptococcus (GABHS) infection in those patients presenting with a sore throat [25]. It consists of eliciting four clinical features from those patients presenting with a sore throat. The test result is usually considered positive when three or more features are found to be present [25].

Over the course of a 4-month period, 83 patients presented with a sore throat to the general practice of one of the authors (BHW) with a patient population of *circa* 6500. Each patient was tested using Centor's criteria and the responses recorded. There were 7 [8.4%; 99% CI: 3.4-19.6%] patients who scored 3 or more on Centor's criteria. Thus, when imposing the constraints, r was taken to have a range of 0.34-0.196.

To estimate the prevalence of GABHS in those attending with a sore throat, the first 45 patients had their throats swabbed. The prevalence was found to be 11.1% [99% CI: 3.7%-28.4%] and so p was considered to have the range of values 0.037-0.284 for the linear constraints.

To estimate the accuracy of Centor's criteria in general practice we reviewed the literature for studies which had evaluated the prediction rule in a primary care or general practice setting. The target disorder was GABHS and a throat swab was considered to be a suitable reference standard (see appendix 4 for details). In addition, the references from a previous meta-analysis were located [26].

Twelve studies were included for analysis; none was in a UK setting. Although a sore throat was the predominant presenting symptom amongst patients selected, there was variation in the patient selection criteria between studies. Furthermore the age ranges of patients selected varied and blinding between the reference standard and test was not always reported.

The results of applying constraints to the meta-analysis and defining an applicable region are given in figure 3. Five studies reported performances which were feasible in the practice setting analysed here. It is also worth reiterating that the seven excluded studies were all in primary care settings, supporting the hypothesis that superficial equivalence of setting does not necessarily lead to applicability.

The corresponding sensitivity and specificity for the tailored meta-analysis were 38.4% [95% CI: 30.3-47.2] and 92.1% [95% CI: 83.4-96.5] respectively. In contrast the sensitivity and specificity estimated from the conventional meta-analysis were 50.3% [95% CI: 42.7-58.4] and 78.5% [95% CI: 65.7-87.5].

The effects of using the different estimates of the likelihood ratios on the predictive values are considered in table 1. For a mean prevalence of GABHS of 11.1%, the more than doubling of the positive likelihood ratio may potentially lead to an increase in the PPV from 23% to 38%. This could influence clinical decisions, such as whether to investigate further with other tests or to institute treatment without further testing.

The performance statistics for all three tests are summarised in table 1.

Discussion

The central issue raised by the foregoing analysis is whether it is safe to apply the results of a DTA study or meta-analysis to clinical practice without more specific knowledge of the test in the intended setting than has hitherto been considered.

One of the blights of meta-analysis in general is heterogeneity and it affects around 70% of meta-analyses of diagnostic test accuracy studies [2]. Indeed in each of the three cases

analysed here, the prediction regions were larger than the confidence regions for both tailored and conventional meta-analysis suggesting heterogeneity (figures 1-3). However, it should be noted that the size of the prediction region is also influenced by the number of studies and where there are few studies, such as in tailored meta-analysis, this significantly increases the region's size irrespective of the tightness of clustering of the constituent studies.

When there is heterogeneity, methodologists usually advocate hunting for the sources of variation by extending the base model with the relevant covariates [27]. In principle such a deterministic approach allows for biases to be studied and for homogeneous sub-groups to be defined. However, in practice, reviewers are often faced with insufficient data of adequate quality to initiate or at least be comprehensive with such analyses, as illustrated by the three examples evaluated here. As discussed earlier there are likely to be multiple factors contributing to the estimates reported by studies and meta-regression models may allow for the effects of study design factors such as blinding to be investigated. However, it is more difficult to incorporate in these models other important factors such as differences in patient spectrum, test execution and position of threshold.

This has meant that clinicians and policy-makers have been left with a largely subjective decision on whether the results of a meta-analysis on a test's accuracy are even plausible for their practice or not. Methods of appraisal of both primary studies individually and as part of a larger systematic review go some way to deciding when a study may be applicable. The limitations and problems arising from transferring results between different settings have also been described [1]. However, what seems to have been overlooked is the possibility of using more specific information on the clinical setting to help decide which studies are applicable particularly when the sources of heterogeneity between studies may be largely unknown.

Specifically, estimates of the prevalence and the use of unverified test positive data from the practice setting can help determine which studies should be excluded from providing information on the test accuracy. Thus, the included studies report performances which lie within the range of possible performances for the test in that setting which is not always the case with conventional meta-analysis. The corollary of this is that without a tailored approach to study selection, conventional meta-analysis may provide summary estimates which are virtually impossible for the test in some settings – this was demonstrated when applying the results of a meta-analysis of the Pap test to the NHS Cervical screening programme [6]. As a

result, tailored meta-analysis provides a summary estimate that is at least plausible for the test in the setting.

Of course plausibility does not necessarily equate to accuracy and without a separate primary study in the setting in question it is difficult to determine how close any estimate is to the 'true' accuracy. Undoubtedly meta-regression [27] and, better still, individual patient data (IPD) analyses [28] would provide a more accurate estimate if the relative contributions that each of the factors which drive a test's accuracy could be established. The use of IPD has been at the forefront of recent prediction research and one proposed framework suggested that different model intercepts may be appropriate depending on the data available [29]. However, as with all model approaches, their effectiveness is contingent upon the availability of high quality data which ultimately depends on the adequate reporting of research.

Thus, tailored meta-analysis represents a probabilistic and pragmatic approach to the question of applicability based on the information available. Consequently, any summary estimate should be interpreted as the most plausible estimate for the test in the setting in question given the available studies and the region of feasible performances for the test in the setting, (a comparison between conventional and tailored meta-analysis is given in table 2).

Also of interest is the importance the test positive rate, r has in determining the size of the applicable region and hence the feasible values for the sensitivity and specificity [6]. Studies have shown how presenting symptoms may influence a test's sensitivity and specificity [30] and a potential mechanism could be their effect on r. Once r is known, changing the prevalence also affects the shape of the applicable region. Thus, affirming empirical research that the sensitivity and specificity also depend on the prevalence [30,31].

Although defining an applicable region allows us to tailor the selection of studies for the test to the practice setting it is clear from the examples analysed that this does not always lead to a significant change in the aggregate estimates - such as in the case of applying the PHQ-9 questionnaire to screen for depression. Nonetheless, there were two examples here where it was important, and, in a previous study, it was demonstrated to have a significant effect on the results [6]. This suggests that if information on the test positive rate, r and background prevalence, p, is available then it may be useful in meta-analysis.

As systems of data collection improve, knowing total numbers of test results is becoming increasingly possible at all levels from primary to tertiary care, as well as on a national scale. As a result, greater information on diagnostic and screening performance may influence policies on patient management and follow up.

The example of applying Centor's criteria to patients with sore throats, in general practice, establishes what may be achieved with a relatively small sample of test positive data from practice. A larger sample size would have narrowed the applicable region further and potentially refined the selection of studies more as a result. It also demonstrated that the methods extend beyond screening tests, even when the test positive rates are higher. Not only did the summary estimates from aggregating all studies lie outside the applicable region for the practice setting, the effect of using a more targeted selection of studies was to potentially increase the predictive value by 15%.

It is clear, from the examples of the diagnostic/screening tests applied in general practice, that conducting studies in a similar setting (primary care) is not sufficient to guarantee that the findings will be applicable. This should be considered as a natural consequence of having more specific information on the target setting. It also suggests that external validity or generalizability of a study's findings may be unachievable in some cases.

Future research

Although the benefits of taking a tailored approach to meta-analysis have been demonstrated, several areas relating to the method are worthy of further research. In particular, the current model has been developed within a classical framework but could be explored within a Bayesian framework. This would allow both the incorporating of prior information and the assessment of heterogeneity using a recently developed bivariate I^2 statistic [32].

One of the shortcomings of tailored meta-analysis is a loss of statistical precision from excluding improbable studies. Whilst the potential for bias would not be eliminated, meta-regression models that include some of the characteristics analysed here have the potential to improve the precision of summary estimates and could be investigated in future studies.

In summary, the analysis given here demonstrates that performing meta-analyses without specific information regarding the intended clinical setting may result in misleading summary

statistics on a test's performance. Furthermore, if information is available on the test positive rate and prevalence for the target setting, this should be used when deciding which studies are likely to provide a plausible estimate of performance within that setting.

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Conflicts of interest

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Figure 1. Breast Screening using Mammography**.**

Studies lying within the range of performance for the NHS Breast screening program (green rectangle) are depicted as red boxes. The corresponding summary performance estimate (red cross) and associated 95% confidence ellipse (red continuous) and prediction ellipse (red dashed) are also given. Studies outside the applicable region are depicted as blue triangles. For conventional meta-analysis (where all studies are included), the summary performance estimate (black cross) with 95% confidence ellipse (black continuous) and prediction ellipse (black dashed) are also given

Figure 2. PHQ-9 as a screening tool for depression for a test threshold of 10.

The applicable region for the general practice is represented by the green trapezium. The red coloured studies have performance estimates which lie in the applicable region for the practice and their associated summary estimate, confidence ellipse (continuous) and prediction ellipse (dashed) are also in red. Studies whose performances are improbable for the practice setting are depicted by the blue triangles. The overall summary estimate with 95% confidence ellipse (continuous) and prediction ellipse (dashed) from conventional meta-analysis (where all studies were included) are in black.

Figure 3. Centor's criteria for diagnosing GABHS for a test threshold of 3.

The applicable region for the general practice is represented by the green enclosed region. The applicable region is represented by the green trapezium. The red coloured studies have performance estimates which lie in the applicable region for the practice and their associated summary estimate, confidence ellipse and prediction ellipse (dashed) are also in red. Studies whose performances are improbable for the practice setting are depicted by the blue triangles. The overall summary estimate with 95% confidence ellipse and prediction ellipse from conventional meta-analysis (where all studies were included) are in black

Test	Studies	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
Mammography	All (n=10)	87.2 (81.1-91.5)	95.6 (93.0-97.3)	19.8 (12.8-30.9)	0.13 (0.09-0.20)
	AR (n=4)	78.0 (70.0-84.4)	97.9 (96.4-98.7)	36.5 (23.0-57.9)	0.22 (0.16-0.31)
PHQ-9	All (n=10)	74.2 (63.1-82.9)	91.5 (86.4-94.8)	8.8 (5.7-13.5)	0.28 (0.20-0.41)
	AR (n=7)	79.7 (71.5-86.1)	87.9 (83.1-91.5)	6.6 (4.6-9.5)	0.23 (0.16-0.33)
Centor	All (n=12)	50.3 (42.7-58.4)	78.5 (65.7-87.5)	2.35 (1.51-3.67)	0.63 (0.54-0.73)
	AR (n=5)	38.4 (30.3-47.2)	92.1 (83.4-96.5)	4.89 (2.02-11.8)	0.67 (0.56-0.80)

Table 1. Performance characteristics for the different tests as estimated by conventional meta-analysis and tailored meta-analysis.

Note: LR = Likelihood ratio. All = all studies included in the analysis. AR = Applicable region – only those studies in the applicable region are in the analysis.
95% confidence intervals in brackets.

	Conventional meta-analysis	Tailored meta-analysis
Criteria for study selection	Qualitative	Qualitative and probabilistic
Data from setting of interest	Generally not used	Yes, incorporates *r* and *p* from the setting when selecting studies
Predicted location of test performance for setting of interest	Prediction region	Applicable region
Applicability of summary estimate in setting of interest	May be implausible for setting in some cases	Plausible for setting
Precision of summary estimate	More precise	Less precise. There may be too few studies to aggregate in some cases
When should summary results be applied to practice	When there is limited or no heterogeneity	When there is heterogeneity and *r* and *p* are available for the setting

Table 2. Comparison of conventional meta-analysis and tailored meta-analysis

Appendix
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Appendix 1 Tailored meta-analysis model

All studies that meet the inclusion criteria of the review are considered for selection for tailored meta-analysis by first deriving an applicable region for the test in the setting and comparing the observed estimate reported in each study with the applicable region. This is outlined below.

a) Defining an applicable region based on the test positive rate, r

Using data collected from the practice setting we may derive an interval estimate for the test positive rate r, such that we assume $r_{lcl} \leq \mu_r \leq r_{ucl}$ where μ_r is the parameter for r, r_{lcl} and r_{ucl} are the lower and upper confidence limits. This constrains the feasible values the sensitivity, s and false positive rate, f may take in the practice setting, since

$$\text{if } f \leq s \text{ then it follows that } f \leq r \text{ and } s \geq r \quad (1)$$

Combining this logical relation with the uncertainty of the interval estimate produces an applicable region (shaded) such as the one in illustration 1 below.

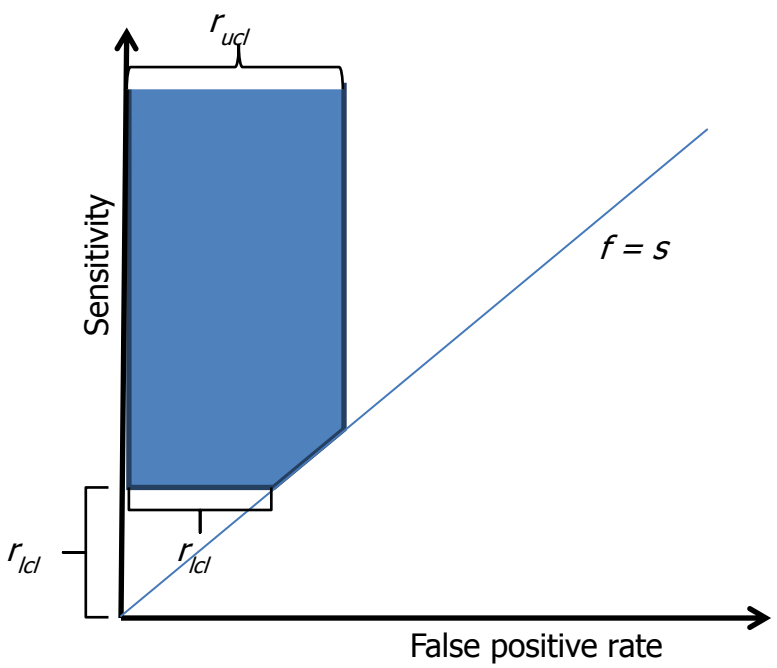

Illustration 1.

b) Defining an applicable region based on the test positive rate, r and prevalence, p

Including information on the prevalence, p in addition to the test positive rate, r allows us to refine the applicable region further by exploiting both (1) and the following relation

$$s = \frac{r}{p} - \frac{(1-p)f}{p} \qquad (2)$$

Using interval estimates we again assume that $r_{lcl} \leq \mu_r \leq r_{ucl}$ and $p_{lcl} \leq \mu_p \leq p_{ucl}$ where μ_p is the parameter for p, p_{lcl} and p_{ucl} are the lower and upper confidence limits respectively. Combining (1) and (2) with the uncertainty of the interval estimates produces illustration 2. The two inner constraints (defined by [$r = r_{ucl}$; $p = p_{ucl}$] and [$r = r_{lcl}$; $p = p_{lcl}$] respectively) are surplus since when the outer constraints are 'violated' so are the inner constraints, but the converse is not true.

The effect these have on the size and shape of the applicable region (shaded) is shown in illustration 3.

2b

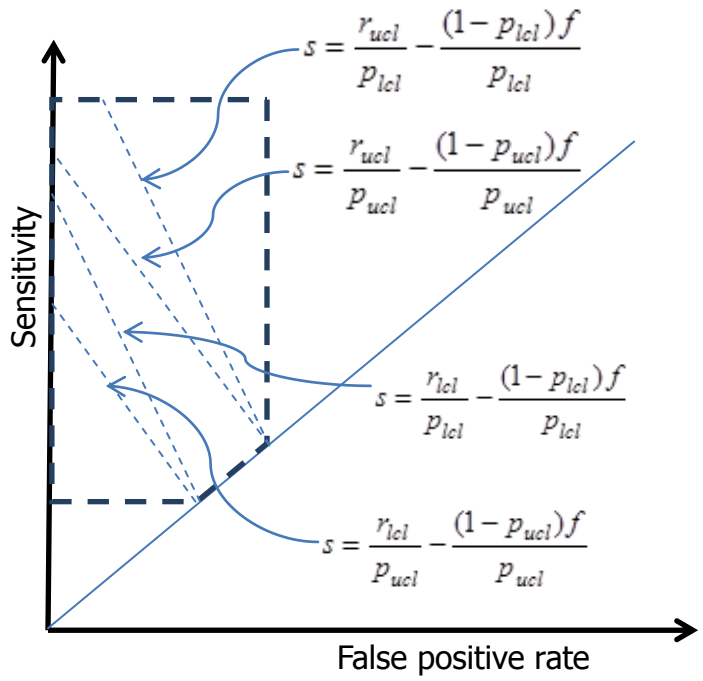

Illustration 2

c) Selecting studies based on their compatibility with the applicable region

After deriving an applicable region for the test in the setting, for each primary study, we consider what the estimate for the false positive rate and sensitivity parameter pair ($\mu_{f,i}$, $\mu_{s,i}$) would be if it was constrained to lie in the applicable region.

Consistent with the meta-analysis model of Chu and Cole [5] we assume the sensitivity and false positive rate for each study to have independent binomial distributions. We then derive the maximum likelihood estimate (MLE) for ($\mu_{f,i}$, $\mu_{s,i}$) subject to it being constrained to lie in the applicable region. This is made easier by noting that if the observed study estimate (f_i , s_i) lies outside of the applicable region the MLE for ($\mu_{f,i}$, $\mu_{s,i}$) must lie on the closest boundary (see illustration 3).

A tail probability for the observed study estimate (f_i, s_i) may be calculated given the MLE of the parameter pair lying on the boundary and noting f_i and s_i have independent binomial distributions as described above. A study i is excluded if the tail probability is less than the level of significance. The included studies are then aggregated using standard methods [5].

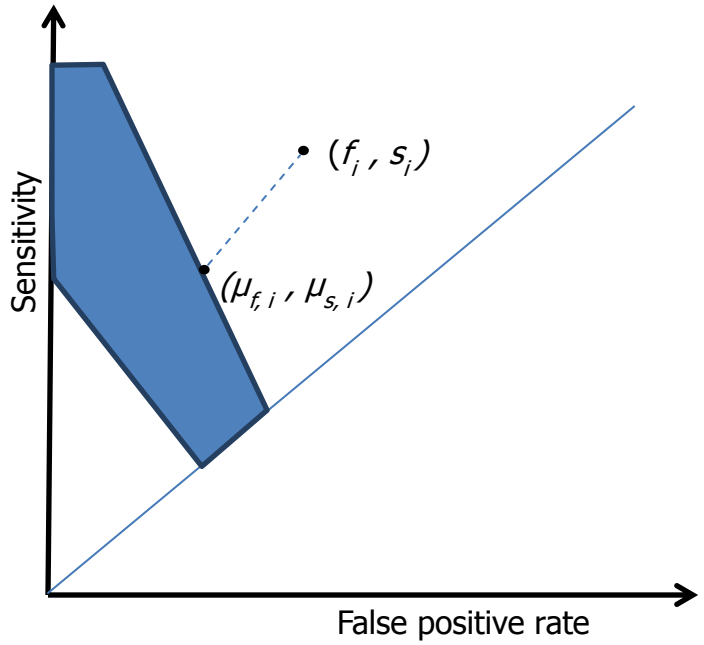

Illustration 3.

Appendix
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Appendix 2: Update of meta-analysis of Mammography.

The objective was to estimate the average sensitivity and specificity of mammography in the NHS breast screening programme in the UK by updating an earlier meta-analysis.

Method

Medline, EMBASE, and CINAHL were searched for studies published after 1996. Studies published prior to 1996 were retrieved from the results of a previous meta-analysis.[1] Studies were included if: the study was a primary study; it evaluated two-view x-ray mammography as a screening test in a normal population cohort; a suitable reference standard was applied; a suitable threshold was applied; sufficient data were reported to complete the 2 x 2 table on the programme performance of mammography.

The methodology relies upon the threshold between the data collected from practice and the primary studies being consistent. A suitable threshold for positive was a recommendation for further work-up' as in the UK or Breast Imaging Reporting and Data Systems (BIRADS) categories 0,3,4 and 5 as in the US.[2] An acceptable reference standard was considered to involve biopsy confirmation of positives or linkage of patients to cancer registries. Negatives were confirmed by extended follow up such as 12 months or more. From each included study the following data items were recorded: study identifier, the location of the study, details of the study population and when sampled, details of the technology and reference standard, number of readers, screening interval, definitions of positive and negative screens and 2 x 2 table data.

The sensitivity and false positive rate (FPR) were estimated using conventional and tailored meta-analysis. In the latter study selection is tailored to include only those that have estimates which are compatible with the NHS Breast screening programme (see main article). We intended to conduct meta-regression analyses but this was not possible due to insufficient studies in the sample.

Results

There were 862 citations (23 retrieved from previous meta-analysis for screening) and 10 studies were included for analysis. The set of included studies is given in Table A2a. Also shown in tables A2a and A2b are the study characteristics and the reported accuracies with inclusions decisions after each study has been compared with the applicable region for the NHS. The main risk of bias was in the reference standard due to the possibility of reviewer bias. None of the studies reported applying the reference standard blind to the index test, although, it was unclear due to inadequate reporting whether blinding featured in the study design. Six studies used a follow up period of 12 months for negative screens with the remaining studies following up over 24 months or more. There was also variation in

the length of follow up of negative screens with half. Although each study evaluated a screening population cohort the age range and the screening interval varied which could potentially introduce patient spectrum differences. The results of the conventional and tailored meta-analysis are given in the main article.

Table A2a. Included studies

A2.1.	Muir TM, Tresham J, Fritschi L, Wylie E. Screening for breast cancer post reduction mammoplasty. Clin Radiol. 2010;65(3):198-205
A2.2.	Vernet Mdel M, Checa MA, Macià F, Casamitjana M, Carreras R. Influence of hormone replacement therapy on the accuracy of screening mammography. Breast J. 2006; 12(2):154-8.
A2.3a	Hofvind S, Wang H, Thoresen S, Do the results of the process indicators in the Norwegian Breast Cancer Screening Program predict future mortality reduction from breast cancer? Acta Oncol. 2004;43(5):467-73.
A2.3b	Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. Radiology. 2007;244(3):708-17
A2.4	Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, et al. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 2004;329(7464):477
A2.5	Elmore JG, Carney PA, Abraham LA, Barlow WE, Egger JR, Fosse JS, Cutter GR, Hendrick RE, D'Orsi CJ, Paliwal P, Taplin SH. The association between obesity and screening mammography accuracy. Arch Intern Med. 2004;164(10):1140-7.
A2.6	Bulliard JL, De Landtsheer JP, Levi F. Results from the Swiss mammography screening pilot programme. Eur J Cancer. 2003;39(12):1761-9
A2.7	Van Landeghem P, Bleyen L, De Backer G. Age-specific accuracy of initial versus subsequent mammography screening: results from the Ghent breast cancer-screening programme. European Journal of Cancer Prevention 2002;11:147–151
A2.8a	Rosenberg RD, Yankaskas BC, Hunt WC, Ballard-Barbash R, Urban N, Ernster VL et al. Effect of variations in operational definitions on performance estimates for screening mammography. Acad Radiol. 2000;7(12):1058-68
A2.8b.	Rosenberg RD, Lando JF, Hunt WC, Darling RR, Williamson MR, Linver MN et al. Screening mammography performance in Albuquerque, New Mexico, 1991 to 1993. Cancer 1996; 78:1731-9.
A2.9a	Duijm LEM, Louwman MWJ, Groenewoud JH, van de Poll-Franse LV, Fracheboud J, Coebergh JW. Inter-observer variability in mammography screening and effect of type and number of readers on screening outcome. British Journal of Cancer. 2009; 100: 901 – 907
A2.9b	Duijm LEM , Groenewoud JH, Fracheboud J, de Koning HJ. Additional Double Reading of Screening Mammograms by Radiologic Technologists: Impact on Screening Performance Parameters. J Natl Cancer Inst 2007;99: 1162 – 70
A2.10	Seigneurin A, Exbrayat C, Labare` J, Colonna M. Comparison of interval breast cancer rates for two- versus single-view screening mammography: A population-based study. Breast 2009;18: 284–288.

Study id	Population	Study Design	Readers	Screening interval	Follow up (months)
A2.1	Women aged 49-69, Western Australia	Retrospective cohort Jan 1998-Dec 2007	2	2 years	12
A2.2	Screening population 50-69, Barcelona, Spain	Prospective cohort Jan 2000 - Dec 2002	2	2 years	24
A2.3a & A2.3b	Women eligible for screening 45-49 and 50-69. Oslo, Norway	RCT on prospective cohort - Nov 2000-Dec 2001	2	1 year for 45-49, 2 years for 50-69.	12
A2.4	Women invited for screening, between 50 -64, over 21 months. UK.	Prospective cohort 1996-1998	Unclear	3 years	12
A2.5	Women 40-79 eligible for screening. Group Health Cooperative NW US	1996-2004	Unclear	Unclear, probably 2 years	12
A2.6	Screening cohort 50-69, Lausanne, Switzerland	Prospective cohort 1993-1999	2	2 years	27
A2.7	All female residents 40-69 in city, screened over 8 years, Ghent, Belgium	Prospective cohort 1992-1999	2	2 years	24
A2.8a & A2.8b	Female residents 35-84. Elected screening not invited. Albuquerque, New Mexico	Prospective cohort 1991-1993	1	1 year	12
A2.9a & A2.9 b	Women eligible for screening 50-75. Netherlands	Retrospective cohort 2003-2006	1 and 2	2 years	24
A2.10	Women eligible for screening 50-69. Isere, France	Retrospective cohort 1994-2004	2	2.5 years til 2002, then 2 years.	12

Table A2b. Characteristics of the included studies. Readers = number of readers reading mammogram; follow up = time given before confirming a negative.

Study id	TP	FN	TN	FP	Sensitivity	FPR	p value	Decision
A2.1	3961	381	686719	32736	0.91	0.046	0	Exclude
A2.2	92	12	22825	1331	0.88	0.055	0	Exclude
A2.3a & b	2295	110	375150	15905	0.95	0.041	10^{-4}	Exclude
A2.4	629	97	117841	3885	0.87	0.032	1	Include
A2.5	617	85	86272	13648	0.86	0.137	0	Exclude
A2.6	68	28	9947	328	0.71	0.032	1	Include
A2.7	195	52	28026	671	0.79	0.023	1	Include
A2.8a & b	951	158	204870	25629	0.86	0.111	0	Exclude
A2.9a & b	528	242	104403	920	0.69	0.009	1	Include
A2.10	221	10	28881	2265	0.96	0.073	0	Exclude

Table A2c. Reported data and accuracy of included studies. 'P value' shows the probability that the study estimate for the FPR and sensitivity could have arisen from the parameters ('true values') lying in the applicable region for the NHS. The applicable region was defined based on $0.0388 \leq r \leq 0.0395$ (see main article); 'Decision' is the decision to include/exclude for tailored meta-analysis for a level of significance of 0.025.

Appendix 2 References

1. Mushlin AI, Kouides RW, Shapiro DE, Estimating the Accuracy of Screening Mammography: A Meta-analysis, *Am J Prev Med* 1998;14:143-153.

2. Smith-Bindman R, Chu PW, Miglioretti DI, Sickles EA, Blanks R, Ballard-Barbash R, Bobo JK, Lee NC, Wallis MG, Patnick J, Kerlikowske K. Comparison of screening mammography in the United States and the United Kingdom. *JAMA* 2003; 290:2129–2137

Appendix 3: Meta-analysis of the PHQ-9 questionnaire in General practice.

The objective was to estimate the average sensitivity and specificity of the PHQ-9 questionnaire in diagnosing depression at a threshold of 10 in a general practice in the UK.

Method

Medline, EMBASE, and PsychInfo were searched for studies published after 1966 using a combination of search terms which included “phq” , “patient health questionnaire”, “depression”, “primary care”, “family practice”, “general practice”, “sensitivity”, “specificity”, “ROC curve” We also used citations from 3 existing meta-analyses. Studies were included if: the study was a primary study; it evaluated the PHQ-9 questionnaire in a general practice or family practice setting; the target diagnosis was a major depressive disorder; the reference standard was a standardised interview schedule based on the Diagnostic and Statistical manual of mental disorders (DSM IV) or the International Classification of Diseases (ICD-10); sufficient data were reported to complete the 2 x 2 table at a test threshold of 10.

The methodology relies upon the threshold between the data collected and the primary studies being consistent. In general when implementing the PHQ-9 tool the optimum threshold has been found to be 10, so this was used when calculating the test positive rate from the routine data collected from the general practice setting. From each included study the following data items were recorded: study identifier; the location of the study; details of the study population; sampling; language of PHQ-9 tool; reference standard; blinding between the test and reference standard; and 2 x 2 table data.

The sensitivity and false positive rate (FPR) were estimated using conventional and tailored meta-analysis using a bivariate random effects model (BRM) and the intention was to extend this model for meta-regression analyses to test for significant covariates if the sample of studies was adequate.

Results

The searches identified 139 unduplicated studies. After applying the inclusion criteria there were ten studies which evaluated the PHQ-9 on what may be considered an unselected adult primary care population (see table A3a). In seven studies the population was completely drawn from general or family practice and included all adults and both sexes. For the remaining three studies: one study selected 90% of the patients from general practice with the remainder drawn from hospital outpatients [A3.9]; the second study was conducted in hospital but this was the primary care entry point for the local population [A3.8]; the third selected only women from family practice but the selection was neither based on age nor co-morbidity [A3.10]. The characteristics of individual studies are shown in Table A3b. Meta-regression was not attempted owing to the small sample of studies (n = 10).

A3.1.	Arroll B, Goodyear-Smith F, Crengle S, Gunn J, Kerse N, Fishman T, Falloon K, Hatcher S. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Ann Fam Med. 2010;8:348-53
A3.2.	Ayalon L, Goldfracht M, Bech P. 'Do you think you suffer from depression?' Reevaluating the use of a single item question for the screening of depression in older primary care patients. Int J Geriatr Psychiatry. 2010;25(5):497-502.
A3.3	Azah N. Shah M, Juwita S, Bahri I, Rushidi W, Jamil Y. Validation of the Malay version brief Patient Health Questionnaire (PHQ-9) among adult attending family medicine clinics. *Int Med J* 2005;12:259-64.
A3.4	Cheng C, Cheng M. To validate the Chinese version of the 2Q and PHQ-9 questionnaires in Hong Kong Chinese patients. *HK Pract* 2007;29:381-390
A3.5	Zuithoff NP, Vergouwe Y, King M, Nazareth I, van Wezep MJ, Moons KG, Geerlings MI. The Patient Health Questionnaire-9 for detection of major depressive disorder in primary care: consequences of current thresholds in a crosssectional study. BMC Fam Pract. 2010 ;11:98.
A3.6	Gilbody S, Richards D, Barkham M. Diagnosing depression in primary care using self-completed instruments: UK validation of PHQ–9 and CORE–OM BJGP 2007; 57: 650–652.
A3.7	Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. BMC Psychiatry. 2008; 8:46.
A3.8	Inagaki M, Ohtsuki T, Yonemoto N, Kawashima Y, Saitoh A, Oikawa Y, Kurosawa M, Muramatsu K, Furukawa TA, Yamada M. Validity of the Patient Health Questionnaire (PHQ)-9 and PHQ-2 in general internal medicine primary care at a Japanese rural hospital: a cross-sectional study. Gen Hosp Psychiatry. 2013;35(6):592-7
A3.9	Liu SI, Yeh ZT, Huang HC, Sun FJ, Tjung JJ, Hwang LC, Shih YH, Yeh AW. Validation of Patient Health Questionnaire for depression screening among primary care patients in Taiwan. Compr Psychiatry. 2011 Jan-Feb;52(1):96-101
A3.10.	Sherina MS, Arroll B, Goodyear-Smith F. Criterion Validity of the PHQ-9 (Malay Version) in a Primary Care Clinic in Malaysia. Med J Malaysia. 2012;67(3):309-15

Table A3a – The included studies

Study id	Population	Location	Sampling	Language	Reference standard	Blinding
A3.1	Age > =16 in family practice in Auckland, New Zealand	Auckland, New Zealand	Consecutive	English	CIDI	Yes
A3.2	Family practice	Israel	Unclear	?Hebrew	SCID-I	Unclear
A3.3	Adults in Family practice	Kelantan, Malayasia	Unclear	Malay	CIDI	Yes
A3.4	Adults in Family practice	Hong Kong	Consecutive	Chinese	HADS	Yes
A3.5	Age > =18 in family practice	Utrecht, Netherlands	Consecutive recruits	Dutch	CIDI	Yes
A3.6	General practice	UK.	Randomised	English	SCID-I	Yes
A3.7	GP clinic in Hospital	Bangkok, Thailand	Systematic sampling	Thai	MINI, HAM-D	Yes
A3.8	Age > =19, outpatients in Hospital	Tohoku, Japan	Random sampling of consecutive patients	Japanese	MINI	Yes
A3.9	Age > =18 in family practice & 10% in hospital outpatients	Taipai, Taiwan	Consecutive recruits	Chinese	SCAN	Yes
A3.10	Adult women in primary care	Urban, Malaysia	Consecutive	Malayan	CIDI	Yes

Table A3b – Characteristics of studies.

Note: CIDI – Composite International Diagnostic Interview; SCID – Structured Clinical Interview for DSM IV; HADS – Hospital Anxiety and Depression Scale; MINI – Mini-International Psychiatry Interview; HAM-D – Hamilton rating scale for Depression; SCAN – Schedule for Clinical Assessment in Neuropsychiatry.

Although in each of the studies the reference standard took the form of a standardised interview, there were 6 different types used which could have implications for the definition of the target condition (Major depressive disorder). Blinding between the reference standard and the test was consistently reported across all but one of the studies.

The PHQ-9 instrument was applied in English in only two studies and seven of the studies were conducted in the far-east. The sample size was too small to evaluate whether either of these factors could potentially affect the way the test is executed or have patient spectrum effects particularly when compared to a UK general practice setting.

Imposing an applicable region for the practice as defined for $0.144 \leq r \leq 0.335$, $0.01 \leq p \leq 0.1$, (see main article) table A3c shows the 2 x 2 tables with the corresponding inclusions decisions after each study has been compared with the applicable region for the general practice setting. The results of the conventional and tailored meta-analysis are given in the main article

Study id	TP	FN	FP	TN	Sensitivity	FPR	p value	Decision
A3.1	121	42	220	2259	0.74	0.089	1	Include
A3.2	4	2	2	145	0.67	0.014	0.000711	Exclude
A3.3	18	12	29	121	0.60	0.193	1	Include
A3.4	24	6	26	301	0.80	0.080	1	Include
A3.5	86	89	59	1117	0.49	0.050	6.54×10^{-11}	Exclude
A3.6	33	3	13	47	0.92	0.217	1	Include
A3.7	14	5	38	222	0.74	0.146	1	Include
A3.8	4	3	2	95	0.57	0.021	0.00432	Exclude
A3.9	43	7	90	1392	0.86	0.061	0.174508	Include
A3.10	27	4	21	94	0.87	0.183	1	Include

Table A3c. Reported data and accuracy of included studies. ‘P value’ shows the probability that the study estimate for the FPR and sensitivity could have arisen from the parameters (‘true values’) lying in the applicable region for the general practice setting; ‘Decision’ is the decision to include/exclude for tailored meta-analysis for a level of significance of 0.025.

Appendix 4: Meta-analysis of Centor's criteria for diagnosing Group A β haemolytic streptococcus (GABHS) infection in general practice.

The objective was to estimate the accuracy of Centors' criteria at a threshold of 3 in diagnosing GABHS infection in patients presenting with a sore throat in a general practice in the UK.

Method

Medline, EMBASE, and PsychInfo were searched for studies published after 1980 using a combination of search terms which included "streptococcal Infections", "streptococc$", "pharyngitis", "sensitivity", "specificity", "ROC curve", "predictive value of tests". We also used citations from one published meta-analysis.[1] Studies were included if: the study was a primary study; it evaluated Centor's criteria in an unselected general practice or family practice population; eligible subjects included those presenting with a sore throat; the target diagnosis was GABHS; the reference standard was by throat swab; sufficient data were reported to complete the 2 x 2 table at a test threshold of 3.

The usual threshold when applying Centor's criteria to patients with a sore throat is 3 and this was used when calculating the test positive rate from data collected from the practice setting. For each included study the following data items were recorded: study identifier; the location of the study; details of the study population; sampling; reference standard; blinding between the test and reference standard; and 2 x 2 table data. The sensitivity and false positive rate (FPR) were using conventional and tailored meta-analysis and meta-regression analyses were planned if the sample of studies was adequate.

Results

We identified 506 unduplicated studies and eleven of these met the inclusion criteria (see table A4a). None of the studies was conducted in a UK setting. Although all studies selected subjects from a general practice population or equivalent, the age groups analysed in the individual studies varied. In four studies the study sample consisted of children only, in two studies the sampling was from an adult population and in the remaining studies the age range included both children and adults.

There was also variation in the eligibility criteria for study subjects. In general patients were selected if they had symptoms of a sore throat, acute pharyngitis or an upper respiratory tract infection depending on the study. Such differences in entry criteria have the potential to affect the spectrum of patients tested. Studies which used one or more of Centor's criteria as part of the eligibility criteria were excluded. In six of the studies the mode of sampling was not clear and blinding between the test and the reference standard was in general inadequately reported. The study characteristics are shown in Table A4b and meta-regression was not performed owing to the small sample of studies (n = 11).

A4.1.	Fine AM, Nizet V, Mandl KD. Large-Scale Validation of the Centor and McIsaac Scores to Predict Group A Streptococcal Pharyngitis. Arch Intern Med. 2012;172(11):847-852.
A4.2.	Regueras De Lorenzo G, Santos Rodríguez PM, Villa Bajo L, Pérez Guirado A, Arbesú Fernández E, Barreiro Hurlé L, Nicieza García M. Utilidad de una técnica antigénica rápida en el diagnostic de faringoamigdalitis por Streptococcus pyogenes. An Pediatr (Barc). 2012;77:193-199.
A4.3	Canada JM, Serna AC, Cruz NG-E, de la Iglesia JG, Ortiz LB, Fernandez MNF. Is streptococcal pharyngitis diagnosis possible? Aten Primaria 2007, 39:361-365.
A4.4	Treebupachatsakul P, Tiengrim S, Thamlikitkul V. Upper respiratory tract infection in Thai adults: prevalence and prediction of bacterial causes, and effectiveness of using clinical practice guidelines**.** J Med Assoc Thai 2006; 89: 1178-1186.
A4.5	Atlas SJ, McDermott SM, Mannone C, Barry MJ. The role of point of care testing for patients with acute pharyngitis. J Gen Intern Med 2005;20:759-61.
A4.6	Dagnelie CF, Bartelink ML, van der Graaf Y, Goessens W, de Melker RA. Towards a better diagnosis of throat infections (with group A beta-haemolytic streptococcus) in general practice. Br J Gen Pract. 1998;48:959-62.
A4.7	Hall MC, Kieke B, Gonzales R, Belongia EA. Spectrum bias of a rapid antigen detection test for group A beta-hemolytic streptococcal pharyngitis in a pediatric population. Pediatrics. 2004;114:182-6.
A4.8	Seppälä H, Lahtonen R, Ziegler T, Meurman O, Hakkarainen K, Miettinen A, Arstila P, Eskola J, Saikku P, Huovinen P. Clinical Scoring System in the Evaluation of Adult Pharyngitis. Arch Otolaryngol Head Neck Surg. 1993;119:288-91.
A4.9	McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ 1998;158:75-83.
A4.10	Alper Z, Uncu Y, Akalin H, Ercan I, Sinirtas M, Bilgel NG. Diagnosis of acute tonsillopharyngitis in primary care: a new approach for low-resource settings. J Chemother. 2013;25:148-55.
A4.11	Abu-Sabaah A H, Ghazi H O. Better diagnosis and treatment of throat infections caused by group A [beta]-haemolytic streptococci. Br J Biomed Sci; 2006; 63:155-58
A4.12	Schwartz K, Monsur J, Northrup J, West P, Neale AV. Pharyngitis clinical prediction rules: effect of interobserver agreement: a MetroNet study. J Clin Epidemiol. 2004; 57(2):142-6

Table A4a – The included studies

Table A4c shows the 2 x 2 tables with the corresponding inclusions decisions after each study has been compared with the applicable region for the general practice setting. Four of the eleven studies were included in the tailored meta-analysis. The results of the conventional and tailored meta-analysis are given in the main article

Study id	Population	Location	Selection criteria for study subjects	Sampling	Blinding
A4.1	General population, age 3+	500 clinics across US	Painful throat & received GABHS testing	Retrospective; unclear	Unclear
A4.2	Primary care, ages 2-14	Asturias, Spain	Acute pharyngitis, not defined	Prospective; consecutive	Yes
A4.3	Primary care centre, age 14+	Madrid, Spain	Sore throat	Unclear; unclear	Unclear
A4.4	Ambulatory care service of the social security program in OPD Hospital, age 15-65	Bangkok, Thailand	Symptoms of URTI: sore throat, rhinorrhoea	Unclear; unclear	Unclear
A4.5	Primary care patients, age 18+	Boston, USA	Symptoms of acute pharyngitis	Prospective; consecutive	Unclear
A4.6	Primary care patients, ages 4-60	Rotterdam, Netherlands	Sore throat for < 15 days	Prospective; unclear	Unclear
A4.7	Primary care setting, age 2-17	Wisconsin, USA	All undergoing RADT for suspected GABHS	Retrospective; consecutive	Unclear
A4.8	Primary care patients in private health, ages 15-62	Turku, Finland	Sore throat	Prospective; consecutive	Unclear
A4.9	Family medicine patients, age 3-14*	Toronto, Canada	Physician's opinion that they had an URTI	Prospective; unclear	Unclear
A4.10	Family practice, age >7	Emek, Turkey	Sore throat and no antibiotics in previous 3 days	Prospective; unclear	Unclear
A4.11	General practice in public hospitals and private clinics	Makkah, Saudi Arabia	Symptoms of pharyngo-tonsillitis	Prospective; unclear	Unclear
A4.12	Primary care, adults	Michigan, USA	Sore throat	Prospective; consecutive	Unclear

Table A4b – Characteristics of studies.

Note: The responses for sampling were related to design (prospective/retrospective/ unclear) and patient recruitment (consecutive/random/ systematic/unclear) respectively.
* Although the study sample included patients with age range of 3-76, there was only sufficient data to complete 2 x 2 table for Centor's criteria in the age group 3-14.

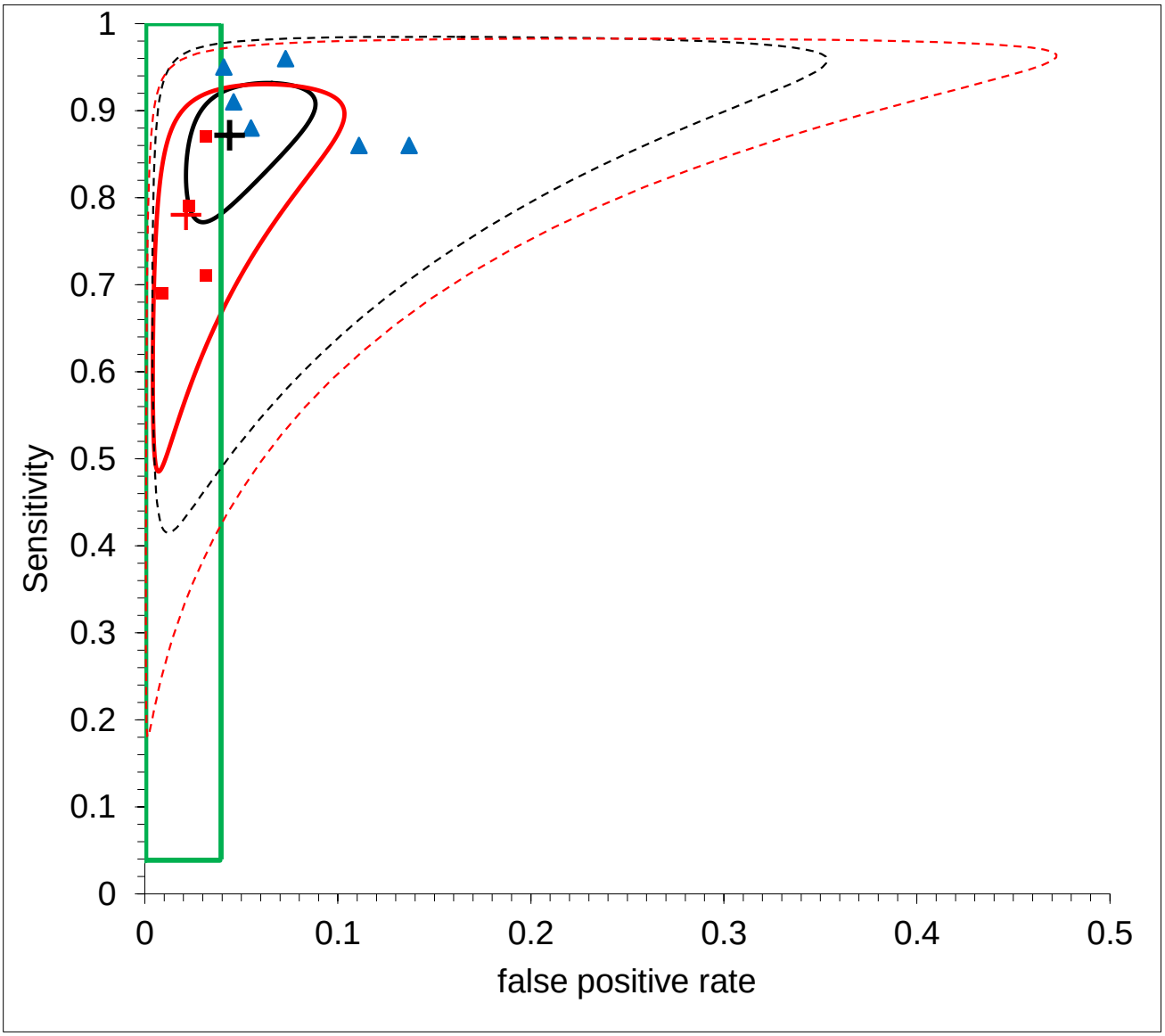
Study id	TP	FN	FP	TN	Sensitivity	FPR	p value	Decision
A4.1	27299	28714	30218	120639	0.49	0.20	0	Exclude
A4.2	40	34	73	45	0.54	0.62	0	Exclude
A4.3	26	8	40	66	0.76	0.38	6.1×10^{-8}	Exclude
A4.4	7	16	9	260	0.30	0.03	1	Include
A4.5	16	22	32	78	0.42	0.29	1.2×10^{-3}	Exclude
A4.6	116	67	131	244	0.63	0.35	4.5×10^{-16}	Exclude
A4.7	52	100	51	358	0.34	0.12	1	Include
A4.8	4	1	17	84	0.80	0.17	1	Include
A4.9	20	12	19	39	0.63	0.33	7.3×10^{-4}	Exclude
A4.10	13	19	38	212	0.41	0.15	1	Include
A4.11	37	30	140	148	0.55	0.49	0	Exclude
A4.12	6	2	1	71	0.75	0.01	1	Include

Table A4c. Reported data and accuracy of included studies. 'P value' shows the probability that the study estimate for the FPR and sensitivity could have arisen from the parameters ('true values') lying in the applicable region for the general practice setting; 'Decision' is the decision to include/exclude for tailored meta-analysis for a level of significance of 0.025.

Appendix 4 References

1. Aalbers J, O'Brien KK, Chan WS, Falk G, Teljeur C, Dimitrov BD, Fahey T. Predicting streptococcal pharyngitis in adults in primary Care: a systematic review of the diagnostic accuracy of symptoms and signs and validation of the Centor Score. *BMC Med.* 2011 Jun 1;9:67.

Figure 1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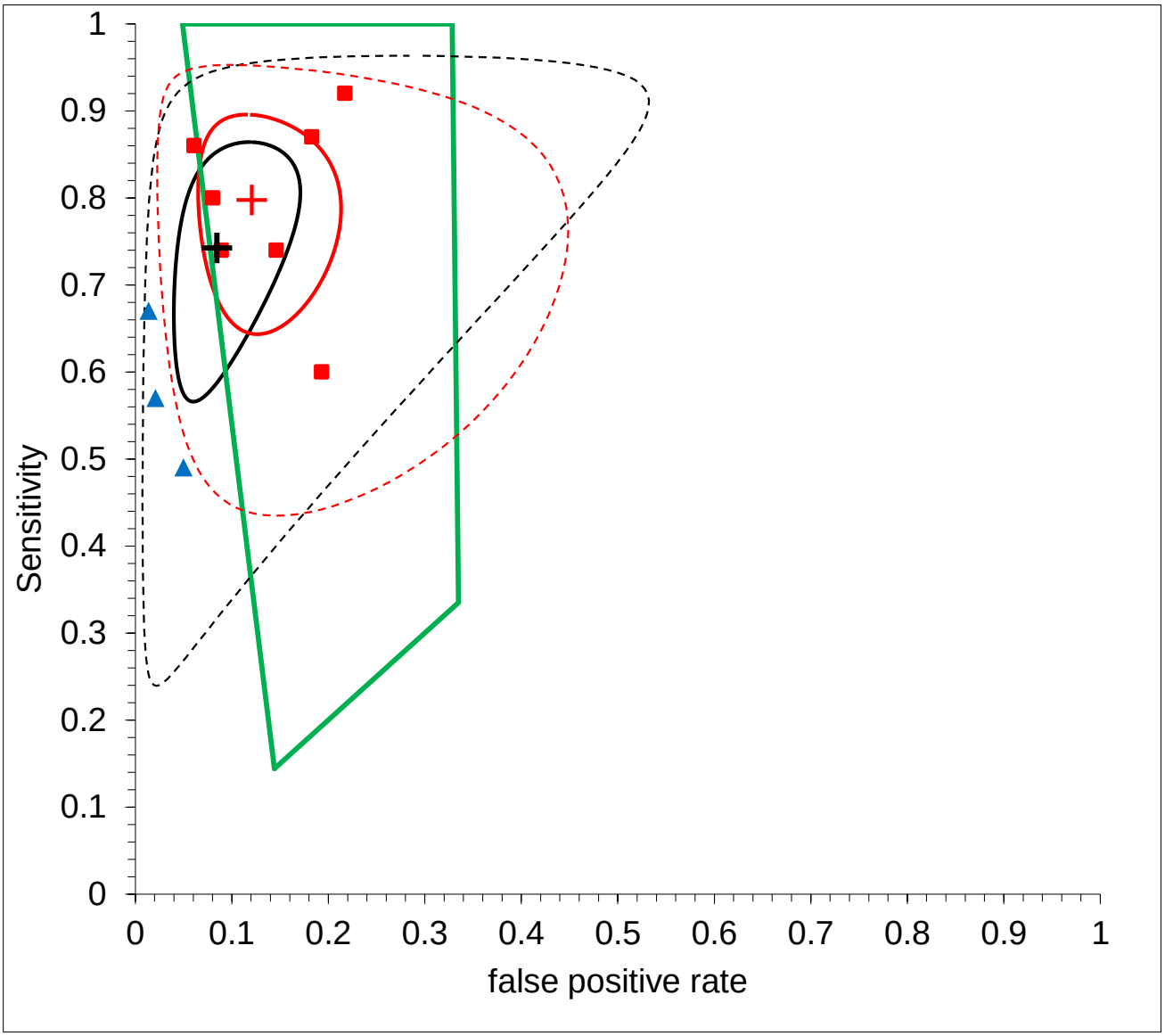
false positive rate

Figure 2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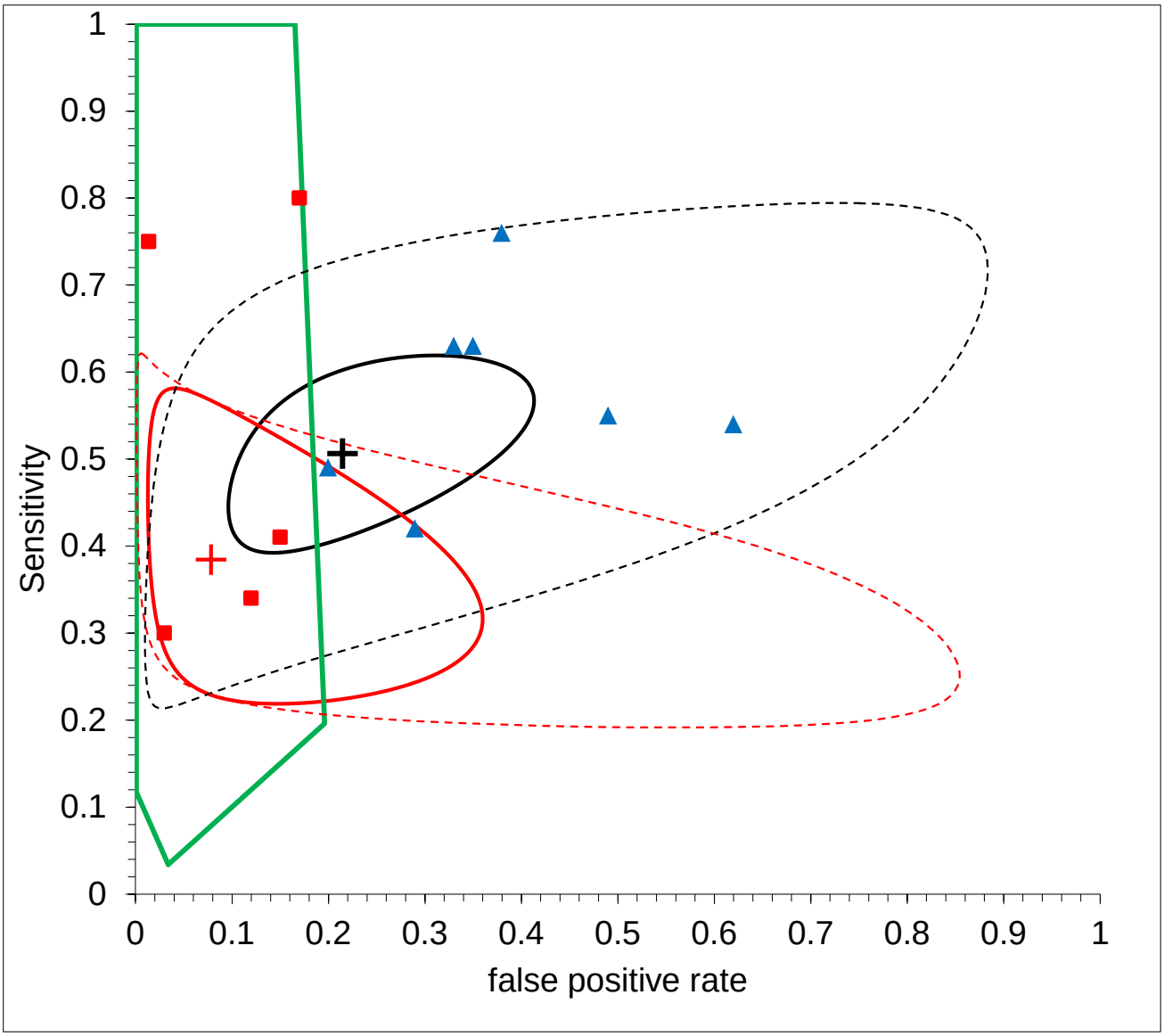
false positive rate

Figure 3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***Conflict of Interest/Financial Disclosure**

Conflicts of interest: None