# Systematic reviews of diagnostic test accuracy studies: Introduction to meta-analysis

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# Contents

# 1 Introduction

This document is in two parts. The first part will introduce you to using RevMan Web for diagnostic accuracy reviews and basic meta-analyses. You will explore options provided for presenting and analysing data. The second part shows how to use the results obtained in R to generate graphical output in RevMan Web.

# 2 Dataset

The example dataset is a subset of data from the Cochrane diagnostic accuracy review of rapid diagnostic tests (RDTs) for diagnosis of uncomplicated *Plasmodium falciparum* malaria in endemic countries (Abba et al 2011). Malaria is a life-threatening infectious disease caused by the parasitic protozoan *Plasmodium*. *Plasmodium falciparum* and *Plasmodium vivax* are the two most common species infecting humans. The 'gold standard' for diagnosing malaria is microscopic examination of thick and thin blood films. Parasitological confirmation of malaria enables selection of appropriate treatment. However, timely, high-quality microscopy may be unavailable in resource-poor settings. RDTs are alternatives to microscopic diagnosis.

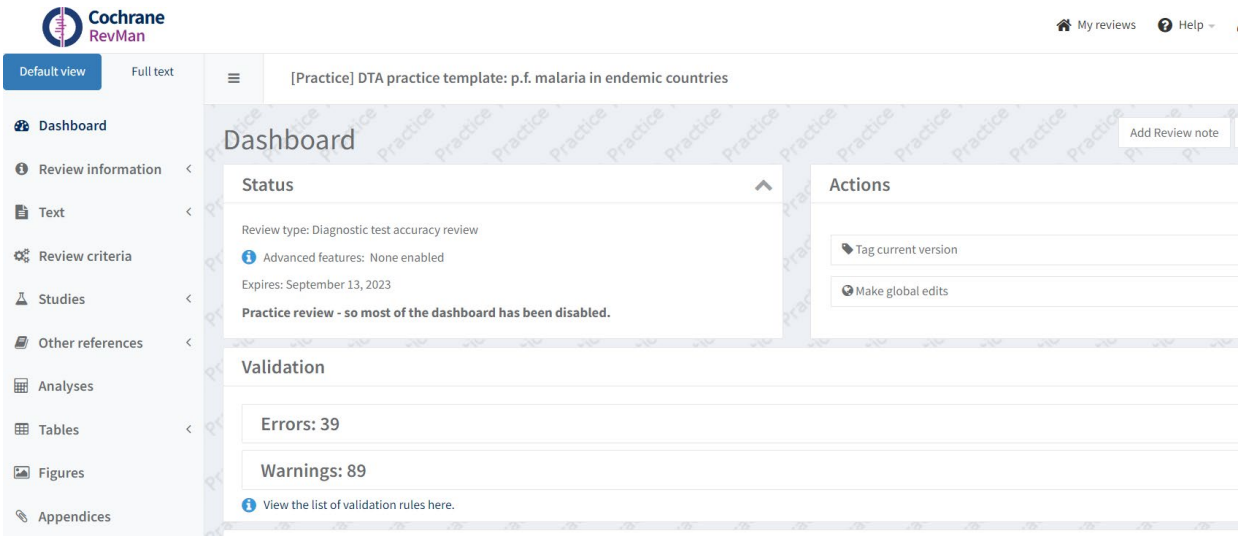
RDTs use different types of antibody or antibody combinations to detect *Plasmodium* antigens. Some antibodies aim to detect a particular species while others are panmalarial aiming to detect all *Plasmodium* species. Type 1 RDTs use antibodies which detect histidine-rich protein-2 (HRP-2) antigen expressed only by *P. falciparum*. Type 4 RDTs use antibodies which detect HRP-2 and also include pan-specific antibodies that detect plasmodium lactate dehydrogenase (pLDH) from all *Plasmodium* species.

The aim of the review was to assess the diagnostic accuracy of RDTs for detecting clinical *P. falciparum* malaria in people living in malaria endemic areas who present to ambulatory healthcare facilities with symptoms of malaria, and to identify which types and commercial brands best detect clinical *P. falciparum* malaria.

# PART I

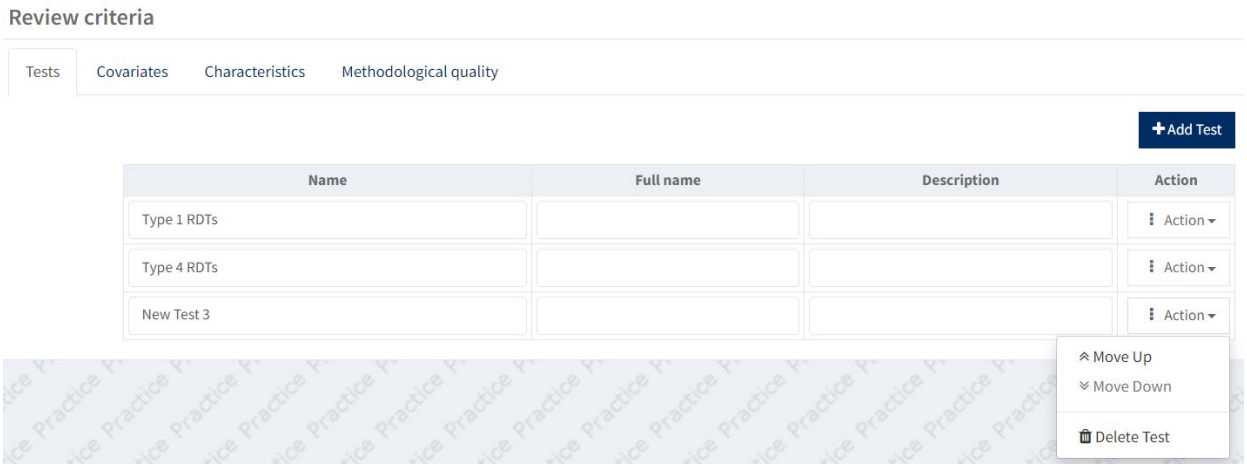
## 3 Starting RevMan Web

You should have already created a Cochrane account. Use the link below to create a practice review. https://revman.cochrane.org/#/createPracticeReview/0343230814085616 35?key=drcgwop655l1HLXI. You will be asked to log in with your Cochrane account. Once successfully logged in you will see something like the screenshot below which has been cropped to fit the page.

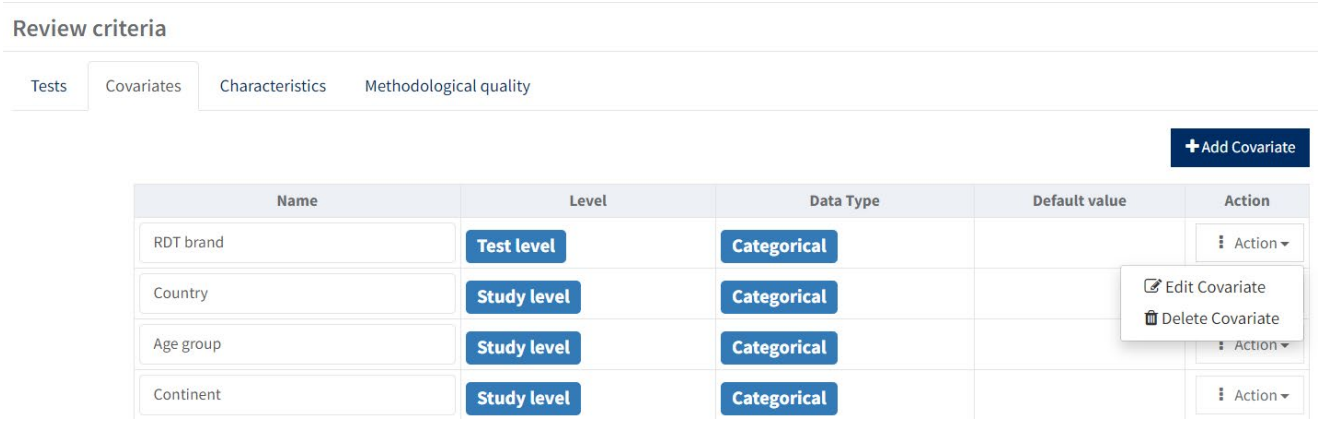



## 4 Review criteria in RevMan Web

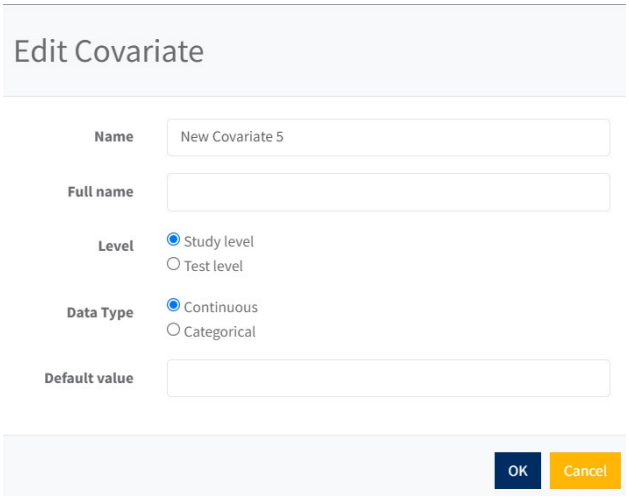
Click on '**Review criteria**' in the menu to the left of the screen. The screen shows the following tabs: **Tests**, **Covariates**, **Characteristics** and **Methodological quality**. The '**Tests**' tab shows that the review currently includes two tests namely Type 1 and Type 4 RDTs. To add more tests, click on '**Add Test**'. RevMan Web creates a new test 'New Test 3' which you can rename. To edit or delete a test, click on '**Action**' next to the test you want to delete. **Delete this new test.**

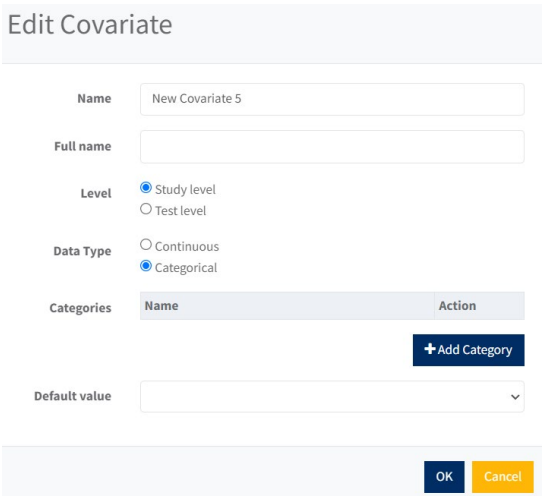



Click on the '**Covariates**' tab to view the covariates included in the review. These covariates are potential sources of heterogeneity that were investigated in the review. Covariates can be created at test level, e.g. RDT brand, or study level, e.g. country or continent where a study was conducted. To edit or delete a covariate, click on '**Action**' and select accordingly.




To add a covariate, click on '**Add Covariate**'. The first dialogue box shown below pops up. There you see options for level (study or test) and data type (continuous or categorical). If you select categorical data type, you can then add the categories for the covariate as shown in the other dialogue box.

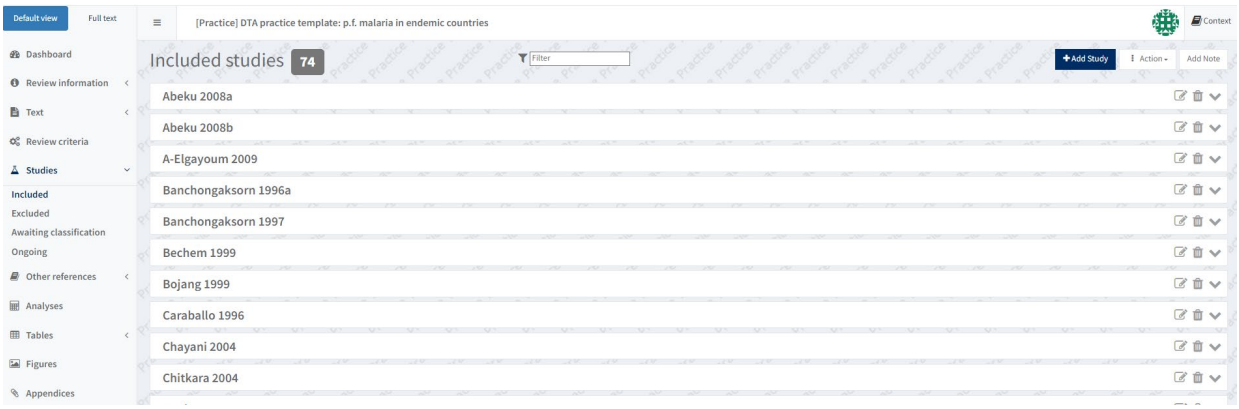


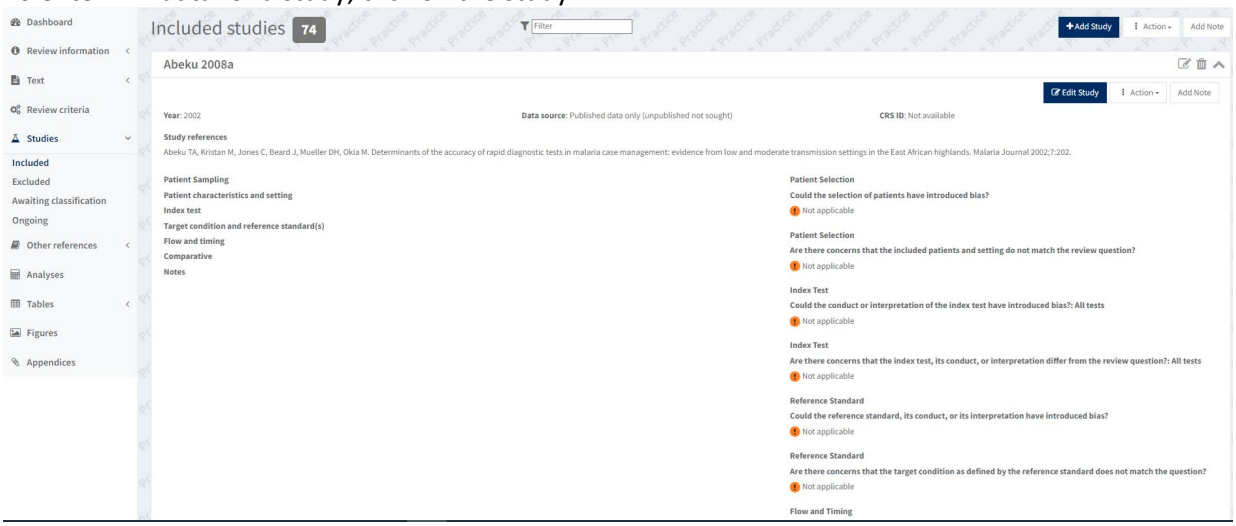

# 5 Entering study data and using the RevMan calculator

Using the calculator, you can derive 2x2 data when only test accuracy measures such as sensitivity and specificity or likelihood ratios (LRs) are reported in a primary study, as well as sample sizes for the 2 groups, or prevalence and total sample size.

Click on '**Studies**' then '**Included**' to view the included studies.



To enter 2x2 data for a study, click on the study …



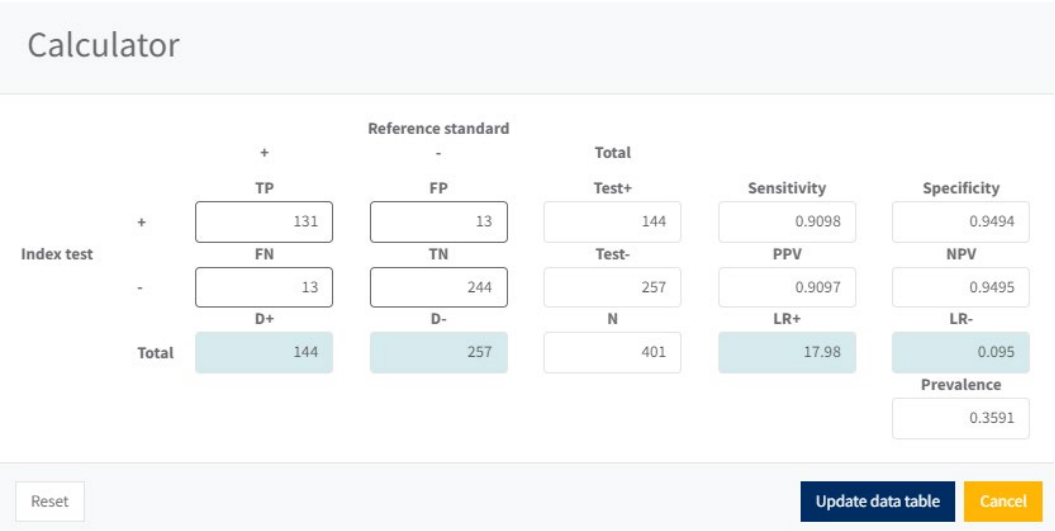

… and then click on '**Edit study**' and then click on the '**Test data**' tab.


Click on '**Add test data row**' if you wish to add additional 2x2 data for Abeku 2008a. If you need to use the calculate tool to reproduce a 2x2 table, click on '**Action**' to access the calculator as shown below.


Try out the calculator by entering the data in Table 1 into the calculator.

## Table 1. Data for derivation of a 2x2 table for a study

| Study | Positive likelihood ratio | Negative likelihood ratio | Number of malaria cases | Number without malaria |
|---|---|---|---|---|
| Abeku 2008a | 17.98 | 0.095 | 144 | 257 |




If you click on '**Update data table'**, the 2x2 table for the study will be auto-populated with the 2x2 data. If using prevalence, sensitivity and specificity or predictive values, note that they must be entered into the calculator in decimal form.

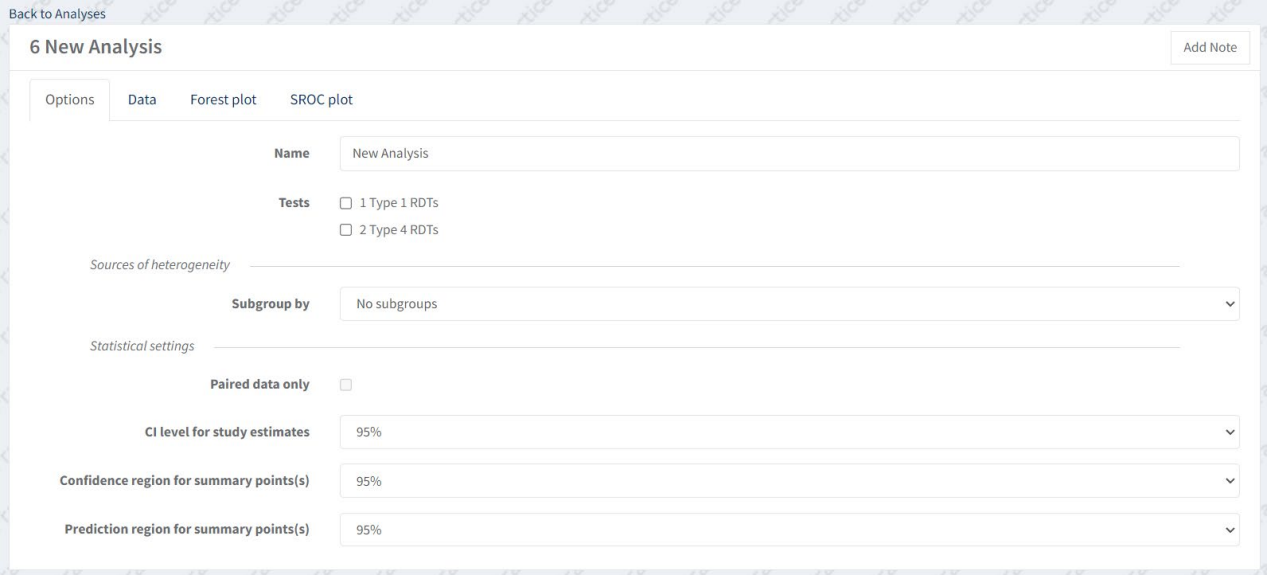
We do not want to keep the new 2x2 data for Abeku 2008a in the review so **delete this new test data row** as shown below.


# 6 Analyses

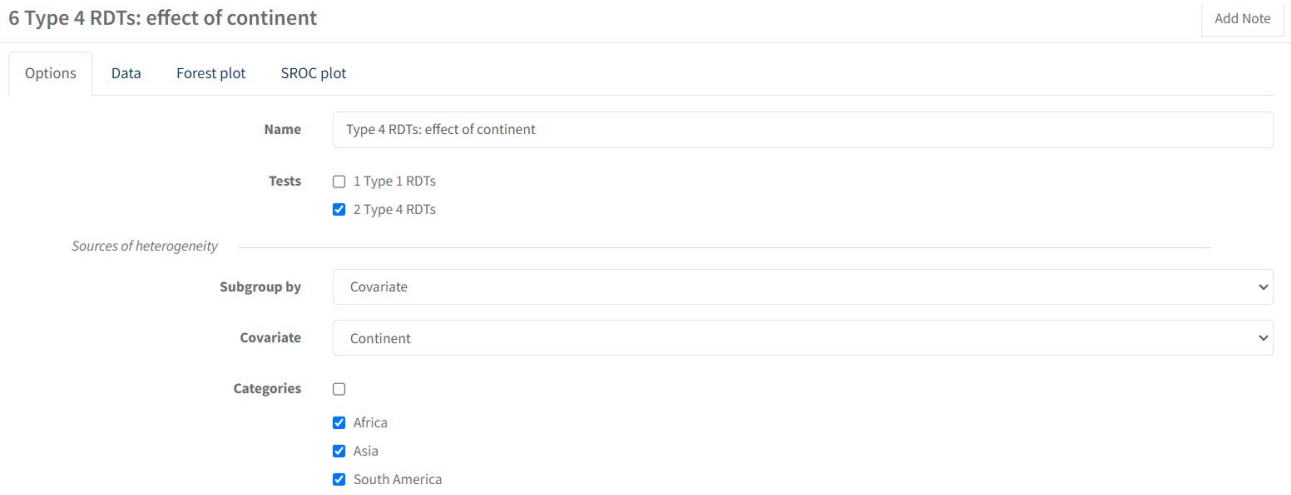
To add a new analysis or view/edit an existing analysis, click on '**Analyses'.** The screenshot below shows there are currently 5 analyses in the review:

1. Analysis of a single test;
2. Investigation of the effect of continent;
3. A subgroup analysis of studies of children;
4. A comparison of the accuracy of Type 1 and Type 4 RDTs using all data (indirect comparison);
5. A comparison of the 2 tests restricted to only head-to-head studies (direct comparison).


To add a new analysis, click '**Add Analysis**'. RevMan Web creates a new analysis.

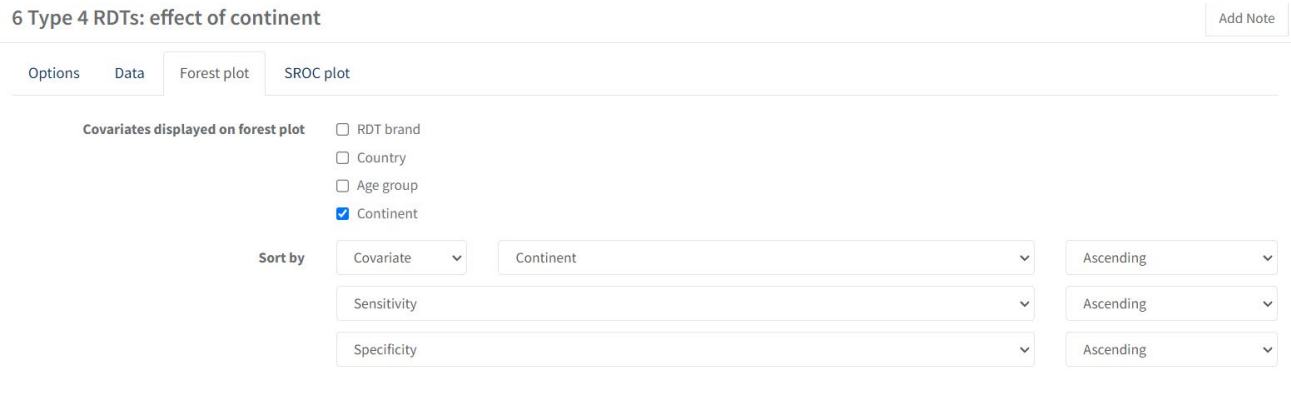



Rename the new analysis to "Type 4 RDTs: effect of continent" on the '**Options**' tab. Next select the type of analysis. We want to analyse a single index test. Select Type 4 RDTs as the test. Also, to explore heterogeneity by continent, first select 'Covariate' in the '**Subgroup by**' droplist and then select 'Continent' in the '**Covariate'** droplist. Select all three continent categories.



To view the forest plot for this analysis, click on the '**Forest plot**' tab. Covariates can be displayed on a forest plot and can also be used to sort studies on the forest plot to observe patterns in the scatter of sensitivity and specificity.

Select the continent covariate to show it on the forest plot. Sort by covariate and select continent, then sort by sensitivity and specificity (all in ascending order) to produce the forest plot shown below.



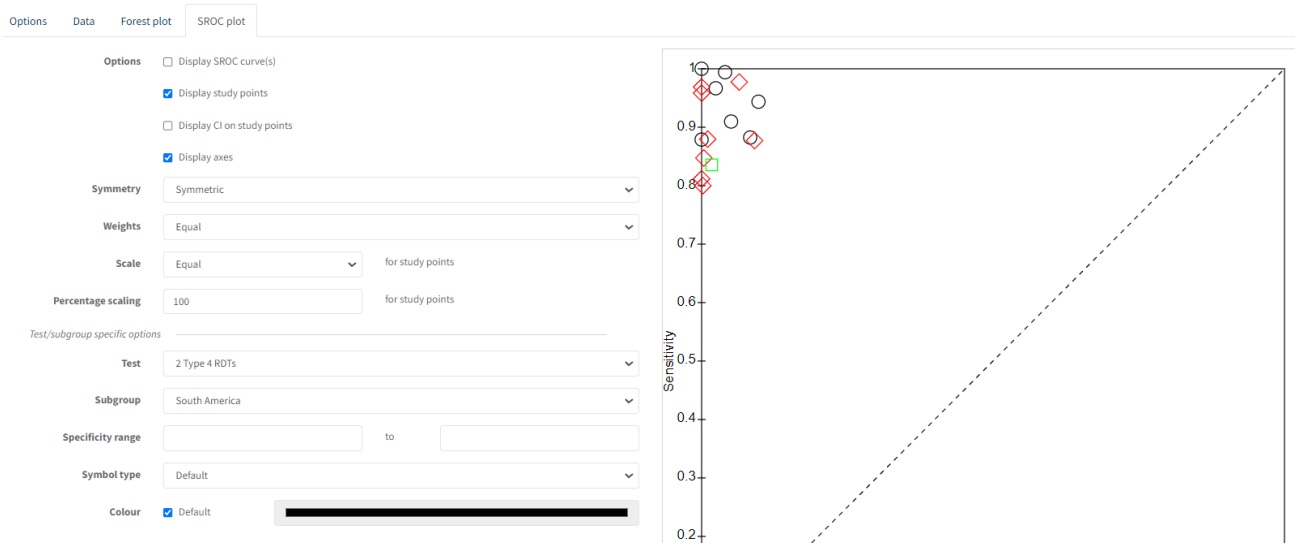

| Study | TP | FP | FN | TN | Continent | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|
| Hopkins 2007 | 254 | 0 | 35 | 629 | Africa | 0.88 [0.84, 0.91] | 1.00 [0.99, 1.00] |
| Hopkins 2008a | 2385 | 358 | 318 | 3939 | Africa | 0.88 [0.87, 0.89] | 0.92 [0.91, 0.92] |
| Cooke 1999 | 131 | 13 | 13 | 244 | Africa | 0.91 [0.85, 0.95] | 0.95 [0.92, 0.97] |
| Ratsimbasoa 2007 | 67 | 12 | 4 | 111 | Africa | 0.94 [0.86, 0.98] | 0.90 [0.84, 0.95] |
| Mens 2007b | 58 | 3 | 2 | 121 | Africa | 0.97 [0.88, 1.00] | 0.98 [0.93, 0.99] |
| Gerstl 2009 | 168 | 7 | 1 | 167 | Africa | 0.99 [0.97, 1.00] | 0.96 [0.92, 0.98] |
| Mens 2007a | 3 | 0 | 0 | 151 | Africa | 1.00 [0.29, 1.00] | 1.00 [0.98, 1.00] |
| Kolaczinski 2004 | 24 | 1 | 6 | 468 | Asia | 0.80 [0.61, 0.92] | 1.00 [0.99, 1.00] |
| Dev 2004 | 69 | 0 | 16 | 54 | Asia | 0.81 [0.71, 0.89] | 1.00 [0.93, 1.00] |
| Iqbal 2003 | 111 | 3 | 20 | 796 | Asia | 0.85 [0.77, 0.90] | 1.00 [0.99, 1.00] |
| Pattanasin 2003 | 50 | 19 | 7 | 190 | Asia | 0.88 [0.76, 0.95] | 0.91 [0.86, 0.94] |
| Valecha 2003 | 190 | 5 | 26 | 478 | Asia | 0.88 [0.83, 0.92] | 0.99 [0.98, 1.00] |
| Singh 2003a | 23 | 0 | 1 | 56 | Asia | 0.96 [0.79, 1.00] | 1.00 [0.94, 1.00] |
| Chayani 2004 | 93 | 0 | 3 | 136 | Asia | 0.97 [0.91, 0.99] | 1.00 [0.97, 1.00] |
| Singh 2003b | 43 | 2 | 1 | 29 | Asia | 0.98 [0.88, 1.00] | 0.94 [0.79, 0.99] |
| Van den Broek 2006 | 127 | 13 | 25 | 731 | South America | 0.84 [0.77, 0.89] | 0.98 [0.97, 0.99] |



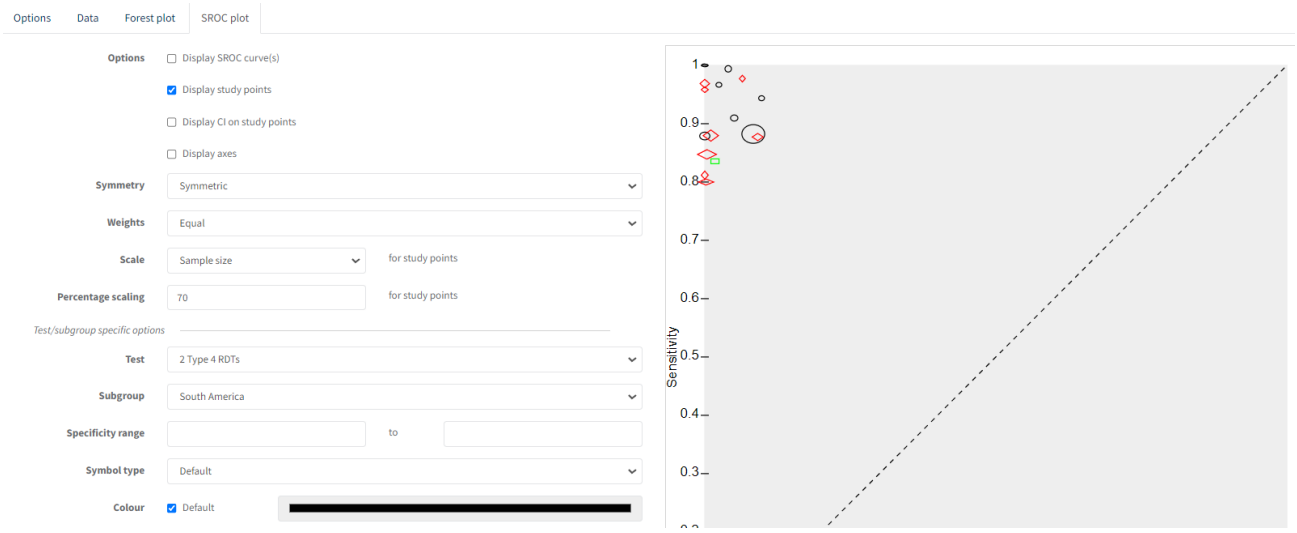
To view the SROC plot and edit it, click on the '**SROC plot**' tab. A SROC plot is shown with the default options as shown in screenshot (A) below. Most of the study points lie along the sensitivity axis and the points all have the same size (indicated by the option '**Scale'** which shows the selection '**Equal**').

To illustrate the precision of each study, scale the study points by changing 'Equal' to 'Sample size'. Some of the study points also overlap. To improve the visual appearance of the SROC plot, use the '**Percentage scaling**' option to reduce the overall size of the study points from 100% to 70% and so reduce the amount of overlap. Uncheck the '**Display axes**' box to improve the visibility of the study points that lie along the axes. This results in the second SROC plot shown in screenshot (B) below.

## A. Default options




## B. Using different options




Meta-regression can be performed to formally explore the effect of continent on sensitivity and specificity. Note that only one study was conducted in South America and so if proceeding with meta-regression exclude this study and compare Africa and Asia. Meta-analysis using a bivariate or HSROC model is not possible within RevMan. Rather data can be exported from RevMan and analyses performed externally using statistical packages like SAS, Stata, R, etc (see Chapter 10 of the Cochrane Handbook of Systematic Reviews of Diagnostic Test Accuracy for more information on undertaking meta-analysis). Following the external analyses, parameters from the model fitted can be copied and pasted into the appropriate fields on the '**Data**' tab.

## 7 Exporting data

Click on '**Dashboard**' in the left hand menu. Select the review version that you wish to export and click on '**Export**' near the bottom of the screen. Note: this feature is not enabled for practice reviews so cannot be explored in this session.

# PART II

## 8 Entering results from analyses in R into RevMan Web

The output in Box 1 was obtained from fitting a bivariate model in R to the data for 65 studies of Type 1 RDTs. The five parameters (mean logits, variances and correlation) of the bivariate model are shown in the red boxes: the estimate for **mean logit(sensitivity) is 2.9071**, the estimate for **mean logit(specificity) is 2.9668**; and the **variances of the random effects for logit(sensitivity) and logit(specificity) are 1.270 and 1.869**, respectively. The estimate of the **correlation of the logits across studies is −0.14**.

### Box 1. R output of bivariate model parameters using glmer

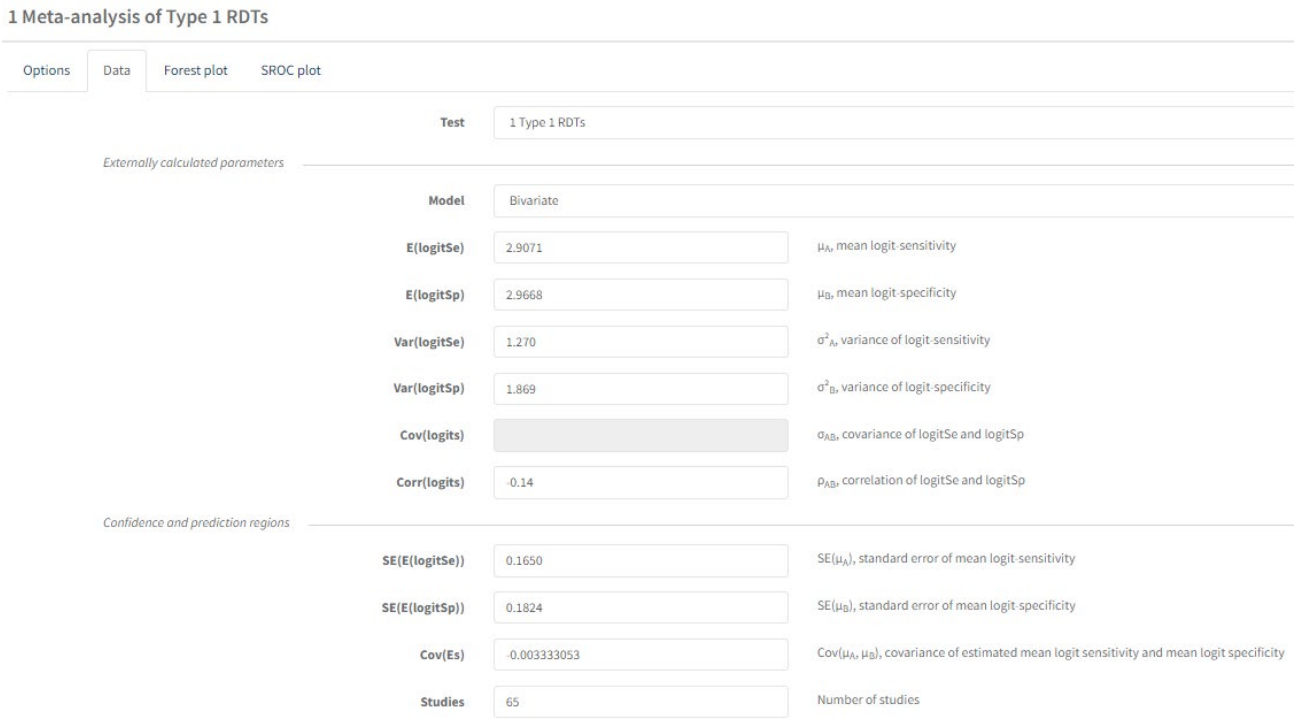
```
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial  ( logit )
Formula: cbind(true, n - true) ~ 0 + sens + spec + (0 + sens + spec |
    Study.ID)
   Data: Y

     AIC      BIC   logLik deviance df.resid
   899.9    914.2   -444.9    889.9      125

Scaled residuals:
     Min       1Q   Median       3Q      Max
-0.90667 -0.14566 -0.01918  0.27616  1.22543

Random effects:
 Groups   Name Variance Std.Dev. Corr
 Study.ID sens 1.270    1.127
          spec 1.869    1.367    -0.14
Number of obs: 130, groups:  Study.ID, 65

Fixed effects:
     Estimate Std. Error z value Pr(>|z|)
sens   2.9071     0.1650   17.61   <2e-16 ***
spec   2.9668     0.1824   16.27   <2e-16 ***
```

To draw confidence and prediction regions around the summary point on the SROC plot, you also need the **standard error of the estimates for mean logit(sensitivity), mean logit(specificity) and their covariance which are 0.1650, 0.1824 and −0.003333053** respectively (see the blue boxes in Box 1 and Box 2).

## Box 2. R output of variance-covariance matrix

```
2 x 2 Matrix of class "dpoMatrix"
              sens          spec
sens   0.027236423 -0.003333053
spec  -0.003333053  0.033252486
```

Click on '**Analyses**' in the menu on the left of the screen. Click on the first analysis titled 'Meta-analysis of Type 1 RDTs' and then click on '**Edit analysis**' to view the **Options**, **Data**, **Forest plot** and **SROC plot** tabs. You can see that the estimates have been copied and pasted into the corresponding cells on the '**Data**' tab of the analysis. The estimates in the practice file you have are from the analysis in Stata and differ slightly to what is shown in the R output. It is not unusual to find tiny differences between statistical packages because of the iterative nature of the analysis of hierarchical models like the bivariate and HSROC models. You can edit and update the estimates to the ones in the R output as shown below if you wish.



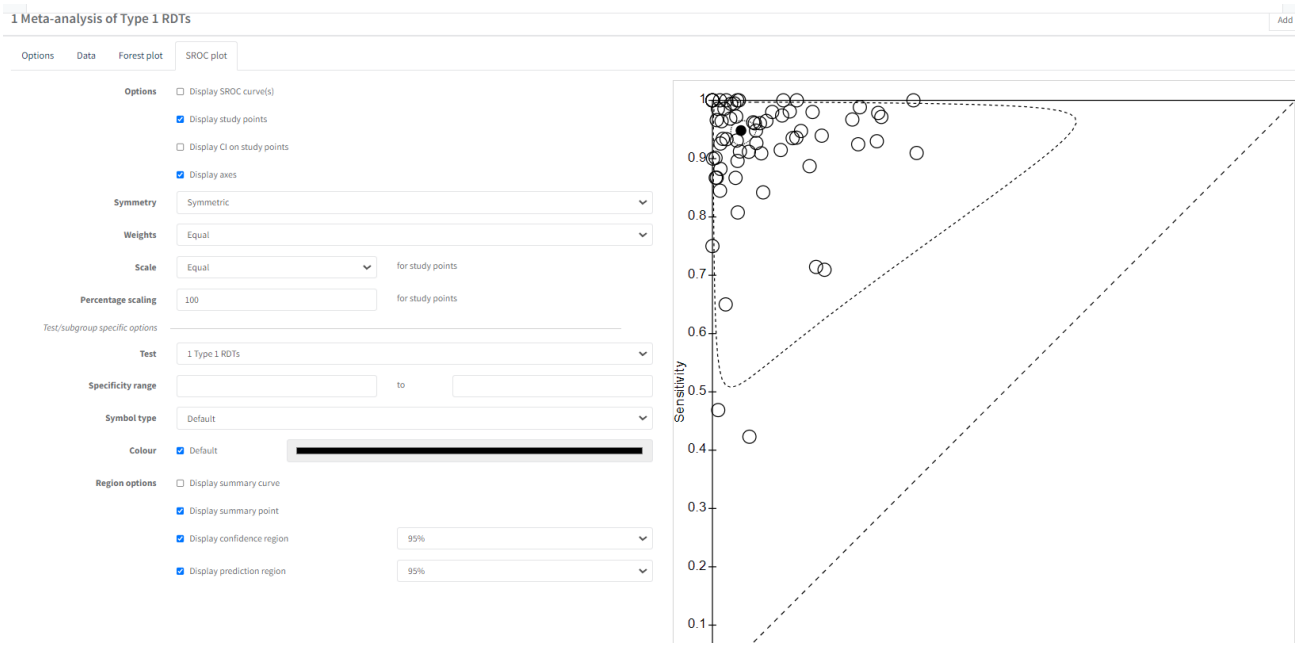

The summary sensitivity and specificity can be obtained by inverse transformation of the estimates for mean logit sensitivity and mean logit specificity to give a summary sensitivity and summary specificity of 0.95 and 0.95 respectively. This calculation can be done using the equations below.

$$Sensitivity = \frac{\exp\left(logit\ sensitivity\right)}{1 + \exp\left(logit\ sensitivity\right)} = \frac{\exp\left(2.9071\right)}{1 + \exp\left(2.9071\right)} = 0.95$$

$$Specificity = \frac{\exp\left(logit\ specificity\right)}{1 + \exp\left(logit\ specificity\right)} = \frac{\exp\left(2.9668\right)}{1 + \exp\left(2.9668\right)} = 0.95$$

The 95% confidence intervals (CI) for the summary estimates can be obtained in the same way by inverse transformation of the 95% CI of the mean logit estimates shown in the output.

View the SROC plot for Type 1 RDTs by clicking on the '**SROC plot**' tab.




## References

Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, Donegan S, Garner P. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane Database Syst Rev 2011;7:CD008122.

Takwoingi Y, Dendukuri N, Schiller I, Rücker G, Jones HE, Partlett C, Macaskill P. Chapter 10: Undertaking meta-analysis. In: Deeks JJ, Bossuyt PM, Leeflang MM, Takwoingi Y (editors). Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Version 2.0 (updated July 2023). Cochrane, 2023. Available from https://training.cochrane.org/handbook-diagnostic-test-accuracy/current