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

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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. <u>https://revman.cochrane.org/#/createPracticeReview/034323081408561635?key=drcgwop655I1HLXI</u>. 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.

Cochrane RevMan				脊 My reviews 🕑 Help –
Default view Full text		E [Practice] DTA practice template: p.f. malaria in endemic countries		
🚯 Dashboard		Dashboard		Add Review note
Review information	<	Status	~	Actions
🖹 Text	< 9	Review type: Diagnostic test accuracy review		
📽 Review criteria		Advanced features: None enabled		Sag current version
<u> </u>	< ~	Expires: September 13, 2023 Practice review - so most of the dashboard has been disabled.		O Make global edits
Other references	<	14 14 14 14 14 14 14 14 14		are are are are are are a
Analyses		Validation		
I Tables	< <	Errors: 39		
Figures		Warnings: 89		
Appendices		View the list of validation rules here.	-	15 15 15 15 15 15

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. <u>Delete this new test</u>.

Introduction to meta-analysis of diagnostic accuracy studies

Review	criteria			
Tests	Covariates Characteristics Methodological quality			
				+ Add Test
	Name	Full name	Description	Action
	Type 1 RDTs			Action -
	Type 4 RDTs			Action -
	New Test 3			Action -
			sice " sice " sice " sice	
			8. 8 9. 9. 9. 9. 9.	🛍 Delete 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.

Review	riteria					
Tests	Covariates	Characteristics Methodo	ological quality			
						+Add Covariate
		Name	Level	Data Type	Default value	Action
	RDT br	rand	Test level	Categorical		Action -
	Count	ry	Study level	Categorical	ſ₫ E	dit Covariate
	Age gr	oup	Study level	Categorical	Ŭ D	elete Covariate Action -
	Contin	ient	Study level	Categorical		Action -

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.

Edit Covar	iate	Edit Cova	riate
Name	New Covariate 5	Name Full name	New Covariate 5
Full name		Level	● Study level ○ Test level
Level	 Study level Test level 	Data Type	○ Continuous ● Categorical
Data Type	● Continuous ○ Categorical	Categories	Name Action
Default value		Default value	
	OK Cancel		OK Cancel

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 'Ir	ncluded ' to	view the	included	studies
-----------------------------	---------------------	----------	----------	---------

Default view Full text	E [Practice] DTA practice template: p.f. malaria in endemic countries	Context
🕸 Dashboard	Included studies 74 TFiler	I Action - Add Note
Review information <	Abeku 2008a	C t v
🖺 Text <	Abeku 2008b	ぼうく
✿ Review criteria	4-Eleavour 2009	i 2 m ∨
∆ Studies ~	Banchangaleorg 1006a	
Included Excluded		
Awaiting classification	Delicificitigezoni	
Other references <	Brier 1959	
Analyses	Polyuč Taaa	
III Tables <	Caraballo 1996	
🖬 Figures	Chayani 2004	C I V
Appendices	Chitkara 2004	C û v

🍘 Dashboard		Included studies 74		T Filter		a sala rata sata sata sata sata sata	Add Study I Ac	ion - Add	Note
Review information	<	Abeku 2008a						6 0	~
E Text	< <					(2 sale	Study I Action	- Add Not	10
O ₀ ⁰ Review criteria		Year: 2002		Data source: Published data only (u	npublished not sought)	CRS ID: Not available	Judy		*
A Studies	~	Study references							
Included		Abeku TA, Kristan M, Jones C, Beard J, Mueller DH, Oku	a M. Determinants of the accuracy of rapid dia	ignostic tests in malaria case manager	ment: evidence from low and moderar	te transmission settings in the East African highlands. Malaria Journal 2002;7:202.			
Excluded		Patient Sampling				Patient Selection			
Awaiting classification		Patient characteristics and setting				Could the selection of patients have introduced bias?			
Ongoing		Target condition and reference standard(s)				Not applicable			
Other references		Flow and timing				Patient Selection	a 14 cm		
		Comparative				Are there concerns that the included patients and setting do not match the r	eview question?		
Analyses		Notes				The applicable			
m Tables						Index Test			
illi Tables						Could the conduct or interpretation of the index test have introduced bias?: Not applicable	All tests		
🔚 Figures						The oppression			
						Index Test			
Appendices						Are there concerns that the index test, its conduct, or interpretation differ fr	om the review questi	onr: All tests	
						•			
						Reference Standard	and block		
						Not applicable	ed blast		
						Reference Standard	dard door not match	the question?	,
						(Not applicable	and a see not matth	and question.	
						Flow and Timing			

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.

eku 2008a	a												© Previous O N	ext Add
Seneral Rei	eferences	Characteristics	Covariates	Test data	Methodological	quality								
													+ Add Test data row	py to clipboar
Test 🔺							WE	ТР	FP	FN	TN	Sensitivity (95% CI)	+ Add Test data row 🖉 Co Specificity (95% CI)	py to clipboar

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.

Back to Included studies								
Abeku 2008a						O Previous	O Next	Add Note
General References Characteristics Covariates Test data Methodological quality								
						+ Add Test data row	ළු Copy to	o clipboard
Test A	тр	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	1	Action
1 Type 1 RDTs	554	220	55	5 408	0.91 [0.88, 0.93]	0.65 [0.61	, 0.69]	Action -
2 Type 4 RDTs	0	0	9	0 0	Not estimable	Not esti	mable	Action -
						t D	lete Test o	data row
						Real Inc	alculator	2 ¹
								_
						AC AC	ld Note	5

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

		,	Reference standard			
		+	-	Total		
		TP	FP	Test+	Sensitivity	Specificity
	+	131	13	144	0.9098	0.9494
dex test		FN	TN	Test-	PPV	NPV
	-	13	244	257	0.9097	0.9495
	_	D+	D-	N	LR+	LR-
	Total	144	257	401	17.98	0.095
						Prevalence
						0.3591

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 <u>delete this new test data row</u> as shown below.

Abeku 20	008a														O Pre	vious O Ne	ext /	\dd Not
General	References	Characteristics	Covariates	Test data	Methodological qual	ity												
														+	Add Test data r	row Cop	y to clipbo	bard
Test 🔺								TP		FP	FN	TN		Sensitivity (95% CI)	Specificity (95% CI)	Action	
1 Type 1 F	1 Type 1 RDTs							554	220		55	408	0.91 [0.88, 0.93]	0.	65 [0.61, 0.69]	E Actio	vn •	
2 Type 4 F	RDTs						~		131	13		13	244	0.91 [0.85, 0.95]	0.	95 [0.92, 0.97]	Actio	m •
																🛱 Delete Te	st data ro	w
															e 95° , e 5	E Calculat	or	R
															e Statut	📕 Add Note	0	

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).

Introduction to meta-analysis of diagnostic accuracy studies

Analyses Add Analysis	Add Note
1 Meta-analysis of Type 1 RDTs	C 🛈 🗸
2 Type 1 RDTs - effect of continent	2 1 v
3 Type 1 RDTs - children only	2 🕯 🗸
4 Type 1 RDTs versus Type 4 RDTs - indirect comparison	C û v
5 Type 1 RDTs versus Type 4 RDTs - direct comparison	C û v

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

lew Analysis		Add No
ptions Data Forest plot SROC	plot	
Name	New Analysis	
Tests	1 Type 1 RDTs	
	2 Type 4 RDTs	
Sources of heterogeneity		
Subgroup by	No subgroups	
Statistical settings		
Paired data only		
CI level for study estimates	95%	
Confidence region for summary points(s)	95%	

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.

6 Type 4 RDTs: effect of continent		Add Note				
Options Data Forest plot SROC	ptions Data Forest plot SROC plot					
Name	Type 4 RDTs: effect of continent					
Tests	□ 1 Type 1 RDTs					
	☑ 2 Type 4 RDTs					
Sources of heterogeneity						
Subgroup by	Covariate	~				
Covariate	Continent	~				
Categories						
	Africa					
	✓ Asia					
	✓ South America					

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.

6 Type 4 RDTs: effect of continent Add									Add Note
Options Data	Forest p	olot	SROC	plot					
Covariates dis									
					intry				
				□ Age	group				
				Con	tinent				
		So	ort by	Cova	ariate 🗸	Continent		~	Ascending ~
				Sens	sitivity			~	Ascending 🗸
				Spee	cificity			~	Ascending ~
Study	TP	FP	FN	TN	Continent	Sensitivity (95% CI)	Specificity (95% CI)	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]		
						. ,	. ,	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

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

Subgroup

Colour

Specificity range Symbol type South America

Default

🗹 Default



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 <u>Cochrane Handbook of Systematic</u> <u>Reviews of Diagnostic Test Accuracy</u> 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.

04 -

0.3-

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
                               ЗQ
                                       Max
-0.90667 -0.14566 -0.01918 0.27616 1.22543
Random effects:
         Name Variance Std.Dev. Corr
Groups
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|)
      2.9071
                 0.1650
                          17.61 <2e-16 ***
sens
      2.9668
                          16.27 <2e-16 ***
spec
                 0.1824
```

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	2 Matrix of c	lass "dpoMatrix"
	sens	s 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.

1 Meta-a	nalysis	of Type 1 RDTs			
Options	Data	Forest plot SROC plot			
			Test	1 Type 1 RDTs	
	Externa	ally calculated parameters			
			Model	Bivariate	
			E(logitSe)	2.9071	$\mu_{A_{\nu}}$ mean logit sensitivity
			E(logitSp)	2.9668	$\mu_{B},$ mean logit specificity
			Var(logitSe)	1.270	$\sigma^2_{A_{\rm P}}$ variance of logit sensitivity
			Var(logitSp)	1.869	σ^2_{B} , variance of logit-specificity
			Cov(logits)		$\sigma_{AB},$ covariance of logitSe and logitSp
			Corr(logits)	-0.14	ρ_{AB*} correlation of logitSe and logitSp
	Confide	ence and prediction regions			
			SE(E(logitSe))	0.1650	$SE(\mu_A),$ standard error of mean logit-sensitivity
			SE(E(logitSp))	0.1824	$SE(\mu_B),$ standard error of mean logit specificity
			Cov(Es)	-0.003333053	$\text{Cov}(\mu_{A},\mu_{B}),$ covariance of estimated mean logit sensitivity and mean logit specificity
			Studies	65	Number of studies

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.

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

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

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