Meta-analysis using RevMan

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Contents

1	Introduction	1
2	Dataset	1
PAF	אד ו	2
3	Starting RevMan	2
4	Data and analyses in RevMan	2
5	RevMan calculator tool	2
Т	able 1. Data for derivation of 2x2 table for Cooke 1999	3
6	Add an analysis	4
7	Exporting data	6
PAF	RT II (if you have time)	6
8	Entering results from external analyses into RevMan	6
Т	able 2. Estimates of bivariate model parameters	7
Т	able 3. Estimates of parameters for confidence and prediction regions	7
9	Additional information	9
Ref	erences	10

1 Introduction

This practical is in two parts. The first part will introduce you to using RevMan for diagnostic test accuracy reviews and basic meta-analyses. You will explore options provided for presenting and analyzing data. The second part focuses on meta-analysis in Stata by fitting the bivariate model using the user written program metandi. The third and final part shows how to use the results obtained in Stata to generate graphical output in RevMan.

2 Dataset

The example dataset used in all the practical sessions on this course is a subset of data from the Cochrane diagnostic test accuracy (DTA) 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. Immunochromatographic rapid diagnostic tests (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 panspecific 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

Launch Review Manager by double clicking on the RevMan file titled "Pf malaria in endemic countries - example". The file already contains studies and two tests—Type 1 RDTs and Type 4 RDTs. The file also contains some analyses. We will attempt to recreate analysis 1 which is the meta-analysis of type 1 RDTs.

4 Data and analyses in RevMan

Double click on *Data and analyses* or click on its node in the outline pane on the left to expand the tree to show data tables, covariates and analyses nodes.



Double click on **Data tables by test** to view the list of tests. Double click on **Type 4 RDTs** to see the studies that have been added for this test.

5 RevMan calculator tool

With this tool, you can derive 2x2 data when only test accuracy measures such as sensitivity and specificity or LRs are reported in a primary study, as well as sample sizes for the 2 groups, or prevalence and total sample size.

Click on the study **Cooke 1999**. Let's delete the study 2x2 data by entering 0 into the four cells for Cooke 1999. The data should look like that below.

[] [Pf malaria in endemic countries.rm5] Rapid diagnostic tests for diag	nosing uncomplicated P. falcip	arum mala	aria in en	demic co	untries										r 🛛 🖂
🕒 🖻 🖪 🎯 🕬 🏦 🐨 🎯 🖬 🔒 📍 📑 🔚 🎽	Text of Review 🗶 2 Type	4 RDTs	🗙 1 Ty	pe 1 RDT	s										
Diagnostic test accuracy review	Test: 2 Type 4 RDTs											1	8 8 6	1 ? 🗖	+
	Study /	TP	FP	FN	TN	RDT brand	d	Country	Age gro	up	Continent	Sensitivity (95% CI)	Sp	acificity (95% C	0
🗢 🗒 Main text	Chayani 2004	93	0	136	3	OptiMAL	-	India	▼ INUL atotad	-	Asia 🔻		-		
🕶 🛄 Tables	Cooke 1999	0	0	0	0	OptiMAL	-	The Gambia	▼ atotad	-	Africa 💌				
• 🕼 Studies and references	Dev 2004	69	0	54	16	OptiMAL	-	India	 Mixed 	-	Asia 💌				
🕈 📲 Data and analyses	Gersti 2009	168	7	167	1	Carestart	-	Sierra Leone	 Children 	-	Africa 💌	-			
Data tables by test	Hopkins 2007	254	0	629	35	Parabank	-	Uganda	- contrarent	-	Africa 💌	-			_
Type TROIs	Hopkins 2008a	2385	358	3939	318	Parabank	-	Uganda	 Mixed 	-	Africa 💌				
- Chavani 2004	lgbal 2003	111	3	796	20	OptiMAL	-	Pakistan	▲ wixed	-	Asia 💌			_	
- 🚱 Cooke 1999	Kolaczinski 2004	24	1	468	6	OptiMAL	Ŧ	Pakistan	▼ Not	Ŧ	Asia 💌				
- 🕅 Dev 2004	Mens 2007a	3	0	151	0	OptiMAL	Ŧ	Tanzania	 Children 	-	Africa 💌				
Gersti 2009	Mens 2007b	58	3	121	2	OptiMAI	-	Kenva		-	Africa 💌			_	_
Hopkins 2007	Pattanasin 2003	50	19	190	7	OptiMAL JT	-	Thailand	 Mixed 	Ţ	Asia 🔻				
HOPKINS 2008a	Ratsimbasoa 2007	67	12	111		Carestart	-	Madanascar	 Mixed 	-	Africa 💌	-			
Kolaczinski 2004	Singh 2003a	22	0	56		OntiMAL	-	India	MIXEU	-	Acio V				
- Mens 2007a	Singh 2003b	42	2	20		OptiMAL	-	India	- Mixeu					_	
— 🕅 Mens 2007b	Siligit 20030	400	2	23	00	Optimize	-	inuia Iedie	_ mixeu	-	Asia -				
- 🕅 Pattanasin 2003	valecha 2003	190	5	4/8	20	OpumAL	-	india	• • • • •	-	Asia •	-			
- 🕅 Ratsimbasoa 2007	Van den Broek 2006	127	13	731	25	Optimal-II		Colombia	Not		South				.
Singh 2003a												0 0.2 0.4 0.6 0.8	3 1 0 0.2	0.4 0.6	0.8 1
Valacha 2003															
W Van den Broek 2006															
Data tables by study															
🗢 🗋 Covariates															
- 🗅 Analyses															

Click the calculator button in the top right hand corner (first icon) above the forest plots. Click reset. The calculator cells are now empty. Enter the information below in Table 1 into the calculator.

Table 1. Data for derivation of 2x2 table for Cooke 1999

Study	Positive likelihood ratio	Negative likelihood ratio	Number of malaria cases	Number without malaria	
Cooke 1999	17.98	0.095	144	257	



Click OK. The relevant fields in the 2x2 table for Cooke 1999 should be auto-populated with data. If using sensitivity and specificity or predictive values, note that they must be entered into the calculator in decimal form.

6 Add an analysis

To add an analysis right click on *Analyses* and click *Add Analysis*. In the *New Analysis Wizard*, enter "Meta-analysis of Type 1 RDTs - example" as the name of the analysis.

	New Ana	lysis Wizard	X							
0 00	New An What	New Analysis Wizard What name should the analysis have?								
	<u>N</u> ame:									
F										
p										
p	Cano	el < <u>B</u> ack <u>N</u> ext >	<u>F</u> inish							

Next select the type of analysis. We want to analyse a single index test. Select Type 1 RDTs as the test.

New Analysis Wizard
New Analysis Wizard
Which type of analysis to you want to create?
Туре:
<u>S</u> ingle test analysis
○ <u>M</u> ultiple tests analysis
Analyse paired data only
Investigate sources of heterogeneity
Tests
I Type 1 RDTs
2 Type 4 RDTs
Cancel <back next=""></back>

Multiple tests analysis enables test comparisons. Once selected the Analyse paired data only option will become enabled so that a direct comparison can be performed if required. The SROC plots for such analyses can show pairs of points from each study connected. If you select Investigate sources of heterogeneity then you can produce separate SROC curves for different categories of a chosen covariate or responses to a quality item.

Complete the wizard to create the analysis shown below.

· ·												
Forest plot								-		Default color O Select colo	r	
Study	тр	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Spec		Default symbol O Study symbol	loc	O Ellipse 🔻
A-Elgayoum 2009 Abeku 2008a	28	220	U 55	382	1.00 [0.88, 1.00]	1.00 [0.99, 1.00]				Default range O Specificity	range	Low: 0.7 High: 0.99
Abeku 2008b	9	1	1	989	0.90 [0.55, 1.00]	1.00 [0.99, 1.00]				-Externally Calculated Parameters		
Banchongaksom 1996a	226	12	16	659	0.93 [0.89, 0.96]	0.98 [0.97, 0.99]				Externally calculated Parameters		
Banchongaksom 1997	598	20	21	2722	0.97 [0.95, 0.98]	0.99 [0.99, 1.00]				Issues In the second		
Bechem 1999	98	17	2	82	0.98 [0.93, 1.00]	0.83 [0.74, 0.90]				Parameter		Estimate
Coraballo 1999	28	5	3	49	0.96 [0.90, 0.99]	0.91 [0.80, 0.97]				Lambda		A
Chitkara 2004	135	5	2	531	0.97 [0.92, 0.90]	0.99 (0.98, 1.00)				Theta		
De Oliveira 2009	163	65	25	1574	0.87 [0.81, 0.91]	0.96 (0.95, 0.97)	-	_		beta		
Dov 2004	21	n	0	0	1 00 0 94 1 001	1001 3301001		-		Var(accuracy)		
A. 											_	
SROC plot								-		 <u>B</u>ivariate model parameters 		
			~						1000	Parameter		Estimate
	- (50	-6)			1	1		E(logitSe)		^
	~ 0	9					and the second se		100	E(logitSp)		=
)0	C	2						Var(logitSe)		
			0				and the second se	_		Var(logitSp)		
0									10000	Confidence and prediction regions		
0.8-/ 0							en e			Parameter		Estimate
L L										SE(E(logitSe))		
L L L	D								100	SE(E(logitSp))		
0.7-	0									Cov(Es)		
						1000				Studies		
0.6-						er e				Display summary curve		,
tivity										Display summary point		
10.5-					and a start of the					Display 95% confidence region		
					and the second sec			-	10000	Display 95% prediction region		

Adjust the *Specificity range* (on the analysis pane) so that the SROC curve is drawn within the range of the data. Do you know which method produced this curve?

To edit the analysis, click on the properties button (third icon in the right hand corner). If you are doing ok for time, have a go at changing the properties of the SROC plot using the options on the **SROC plot** tab, and properties of the forest plot using options on the **Forest plot** tab. If you are running out of time, do this later when you have time.

🗋 Analysis Properties (1 I	Meta-analysis of Type 1 RDTs)	X	Analysis Properties (1 Meta-analy	sis of Type 1 RDTs)		X				
General SROC plot	Forest plot Sources of Heterogeneity		General SROC plot Forest plot Sources of Heterogeneity							
Display SROC curve(s	Display study points		Risk of bias and applicability items displayed on forest plot							
			Item							
AXIS OII	Display CI on study points		Was a consecutive or random sample of patients enrolled?							
Prediction region for su	mmary point(s):		Did the study avoid inappropri	ate exclusions?						
○ 50%	90%		Could the selection of patient	s have introduced bias?						
Confidence region for s	ummary point(s):		Are there concerns that the inc	cluded patients and setting do no	ot match the revie	w question?				
O 90%	95%		Covariates Displayed on Forest plot							
Symmetry	Scale for size of points			Covariate						
Symmetrie	Equal		RDT brand							
• <u>symmetric</u>	Cyuai									
Asymmetric	Sample size		Continent							
Weights for analysis	○ I <u>n</u> verse standard error									
● <u>E</u> qual	○ Covariate	-	Sort By							
Sample size			1 Study ID	•	Ascending	O Descending				
O Inverse variance	Percentage scaling for all points 0 20 40	60 80 100	2 None	•	Ascending	O Descending				
Paired data specificatio	n		3 None		Ascending	O Descending				
Display paired data li	ines Line type: Dotted Line color:									
?	Apply	OK Cancel	?		Apply OK	Cancel				

7 Exporting data

On the menu bar, click File>Export>Data and analyses to launch the *Export Analysis Data Wizard*. Expand the various sections and deselect any test or covariate you do not wish to export. Select everything except *Assessment of Domains*.

💐 Export Analysis Data Wizard	X
Export Analysis Data Wizard	9 🔳
Which analyses would you like to export?	
Analyses:	
Diagnostic test accuracy review	
ዮ 🗹 🛄 Data tables by test	
— 🗹 🏮 1 Type 1 RDTs	
🗆 🗹 🔋 2 Type 4 RDTs	
👇 🗹 🗋 Covariates	
- 🗹 🗋 RDT brand	
- 🗹 🗋 Country	
— 🗹 🗋 Age group	
- 🗹 🗋 Continent	
🚽 🚽 🚽 Data and analyses	
🗢 🔲 🖽 Assessment of Domains	
Cancel	<u>F</u> inish

On the subsequent pages accept the default fields selected and also the .csv (comma separated values) file format. Finish and save the file as "pf malaria.csv". Ensure the .csv extension is included in the name of the file as RevMan will not automatically add it on if you delete it. Open the file and examine the data you exported.

PART II (if you have time)

8 Entering results from external analyses into RevMan

For those authoring a diagnostic test accuracy review in RevMan or using it to simply generate forest plots and SROC plots, the parameter estimates for the bivariate model or HSROC model can be copied from the output of the analyses done in a statistical package and pasted into the relevant boxes in the *Externally Calculated Parameters* window of the corresponding analysis in RevMan as shown below using a Stata output for the bivariate model. To save time, rather than copying each parameter estimate for the bivariate model that I fitted in Stata and pasting into RevMan one at a time, you can highlight the column of estimates in Table 2 and Table 3, copy and paste into RevMan. For Table 2 only highlight and copy the first 4 parameter estimates to avoid pasting the correlation parameter estimate in the Cov(logits) box. See further explanation in the box below.

Parameter	Estimate
E(logitSe)	2.907366
E(logitSp)	2.96643
Var(logitSe)	1.288736
Var(logitSp)	1.886708
Cov(logits)	-0.1300819

Table 2. Estimates of bivariate model parameters

Table 3. Estimates of parameters for confidence and prediction regions

Parameter	Estimate
SE(E(logitSe))	0.1659276
SE(E(logitSp))	0.183056
Cov(ES)	-0.0031803
Studies	65

W							
Meta-analysis	of diagnostic	c accuracy					
Log likelihood	= -445.639	948		Numbe	r of studies	= 65	
	Coef.	Std. Err.	z	P> z	[95% Conf	. Interval]	
Bivariate							
E(logitSe)	2.907366	.1659276			2.582154	3.232578	
E(logitSp)	2.96643	.183056			2.607647	3.325214	
Var(logitSe)	1.288736	.3130033			.8006215	2.074438	
Var(logitSp)	1.886708	.3931091			1.254154	2.838302	
Corr(logits)	1300819	.1559903			4151528	.1782501	
HSROC							
Lambda	5.894849	.2344721			5.435292	6.354405	
Theta	.2506229	.2479344			2353195	.7365654	
beta	.1905859	.1591698	1.20	0.231	1213811	.5025529	
s2alpha	2.712956	.6489215			1.697621	4.335554	
s2theta	.8810777	.1880231			.5799181	1.338634	
Summary pt.							
Se	.9482094	.0081484			.9297041	.962042	
Sp	.9510343	.0085246			.9313521	.9652837	
DOR	355.5963	83.15242			224.8603	562.3435	
LR+	19.36477	3.35792			13.78514	27.20281	
LR-	.0544572	.0085307			.0400604	.0740279	
1/LR-	18.36305	2.876562			13.50842	24.96233	
Covariance bet	ween estimate	es of E(logit	tSe) & E	(logitSp)	0031803		
					1		1
Externally Calcula	ted Parameters-				/		
O HSROC model	parameters				1		
Param	eter	Estim	ate		/		
Lambda				<i>i</i>	You n	eed either th	е
Theta				<i>i</i>	correl	lation or the	ovarianca
beta				= /	LUITEI		ovununce
Var(accuracy)					betwe	een the varia	nces of the
Var(threshold)				v '	rando	om effects for	logit
Bivariate mode	el parameters			//	sensit	ivity and logi	t
Param	eter	Estim	ate	/	specij	ricity. RevMai	n will
E(logitSe)			2.90	7366 🔺	disab	le one of the	textboxes
E(logitSp)			2.9	6643	when	one of them	has heen
Var(logitSe)			1.28	8736	WIEII	one of them	nus been
Var(logitSp)			1.88	6708	filled	in. metandi c	outputs the
Cov(logits)				•	correl	lation of the l	ogits (-
Confidence and pr	ediction regions		/	*****	0.130	0819 above)	so scroll
Param	neter	Est	imate /		. down	to use Corr/l	oaits)
SE(E(logitSe))		•	/ 0.1	659276	in at -		- <u>g</u> ,
SE(E(logitSp))			/ 0 .	183056	instea	ia oj using Co	w(logits).
Cov(Es)			-0.0	031803	See so	creen shot be	low.
Studies				65	١		

8



Display summary point, confidence region and prediction region to obtain the SROC plot shown below.

Remember to remove the SROC curve (based on the Moses-Littenberg method) generated by RevMan (see the *SROC plot* tab on the *Properties* dialogue box).

9 Additional information

metandi does not have an option for including a covariate in the bivariate model and so cannot be used for investigations of heterogeneity or test comparisons. You are also limited in what you can do to facilitate model convergence if there are model fitting problems (e.g. due to sparse data). Therefore it is useful to know how to fit the bivariate model using the command xtmelogit directly (for Stata 13 users, you can use meqrlogit instead of xtmelogit if you wish)—essentially doing what metandi does. A tutorial is available at <u>http://dta.cochrane.org/software-meta-analysis-dta-studies</u>. The aim of the tutorial is to guide both novice and experienced Stata users on how to perform meta-analysis of test accuracy studies by fitting the bivariate model using either the user written program metandi or the built in command xtmelogit.

References

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