

Version 2.0

Preterm labour and birth

Appendices I & J

NICE Guideline 25 Methods, evidence and recommendations November 2015, updated June 2022

Final

Commissioned by the National Institute for Health and care Excellence



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Update information

In June 2022 this document was updated to redact some content that was now out of date as a result of the 2022 evidence review on the use of repeat courses of maternal corticosteroids. See the NICE website for the current recommendations at https://www.nice.org.uk/guidance/ng25.

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Appendix A: Scope

The scope is presented in a separate document

Appendix B: Stakeholders

The scope is presented in a separate document

Appendix C: Declarations of interest

The scope is presented in a separate document

Appendix D: Review protocols

The scope is presented in a separate document

Appendix E: Search strategies

The scope is presented in a separate document

Appendix F: PRISMA flow diagrams

The scope is presented in a separate document

Appendix G: Excluded studies

The scope is presented in a separate document

Appendix H: Evidence tables

The scope is presented in a separate document

Appendix I: Forest plots

I.1 Forest plots for review question: Information and support

No forest plots were generated for this review question

I.2 Prophylactic vaginal progesterone and prophylactic cervical cerclage

I.2.1 Prophylactic progesterone

This section was updated and replaced in 2019. Please see the nice website for the updated guideline.

I.2.2 Prophylactic cervical cerclage

Figure 1: Prophylactic cervical cerclage versus no cerclage - perinatal death

	Experim	ental	Contr	lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
1.1.1 History-indicate	ed cerclag	e vs no	cerclage	3			
Ezechi 2004	0	39	2	42	1.9%	0.21 [0.01, 4.34]	
Rush 1984	9	96	9	98	6.9%	1.02 [0.42, 2.46]	+
MRC/RCOG 1993	53	635	66	629	51.3%	0.80 [0.56, 1.12]	
Subtotal (95% CI)		770		769	60.0%	0.80 [0.58, 1.10]	•
Total events	62		77				
Heterogeneity: Chi ² =	1.03, df=	2(P = 0.	60); I ^a = 1	0%			
Test for overall effect	Z = 1.35 (P = 0.18)					
1.1.2 One-off ultraso	und-indica	ated cere	clage in l	high ris	sk for PT	vs no cerclage	
To 2004	2	26	3	30	2.2%	0.77 [0.14, 4.25]	
Subtotal (95% CI)		26	-	30	2.2%	0.77 [0.14, 4.25]	-
Total events	2		3				
Heterogeneity: Not a	oplicable						
Test for overall effect		P = 0.76	10				
1.1.3 Serial ultrasou	nd-indicat	ed cercl	age in hi	gh risk	for PTL	vs no cerclage	
Althuisius 2001	0	19	3	16	2.9%	0.12 [0.01, 2.19]	
Berghella 2004	4	25	4	22	3.3%	0.88 [0.25, 3.11]	
Rust 2000	7	61	5	66	3.7%	1.51 [0.51, 4.52]	
Owen 2009	13	148	25	152	19.1%	0.53 [0.28, 1.00]	-
Subtotal (95% CI)		253		256	29.0%	0.66 [0.41, 1.06]	•
Total events	24		37				
Heterogeneity: Chi? =	4.17, df=	3 (P = 0.	24); I*= :	28%			
Test for overall effect	Z = 1.72 (P = 0.09))				
1.1.4 One-off ultraso	und-indica	ated cere	clage in l	low/un	specified	risk for PTL vs no cercla	age
Berghella 2004	0	3	0	7		Not estimable	
Rust 2000	5	43	2	37	1.7%	2.15 [0.44, 10.44]	+
To 2004	7	101	9	96	7.1%	0.74 [0.29, 1.91]	
Subtotal (95% CI)		147		140	8.8%	1.01 [0.46, 2.22]	*
Total events	12		11				
Heterogeneity: Chi# =	1.30, df=	1 (P = 0.	26); 1=	23%			
Test for overall effect							
Total (95% CI)		1196		1195	100.0%	0.78 [0.61, 1.00]	•
Total events	100		128			and the second	
Heterogeneity: Chi#=		9 (P = 0		0%			ton de la company
Test for overall effect							0.002 0.1 1 10 5
Test for subgroup dif							Favours experimental Favours control

	Experim	ental	Contr	lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
1.2.2 One-off ultraso	und-indica	ted cer	clage in	high ris	sk for PTI	vs no cerclage	
To 2004 Subtotal (95% CI)	2	26 26	3	30 30	6.8% 6.8%	0.77 [0.14, 4.25]	
Total events	2		3				
Heterogeneity: Not a	oplicable		1				
Test for overall effect		P = 0.76)				
1.2.3 Serial ultrasou	nd-indicate	ed cerc	lage in hi	gh risk	for PTL	vs no cerclage	
Berghella 2004	6	25	6	22	15.5%	0.88 [0.33, 2.33]	
Owen 2009	16	148	18	153	43.0%	0.92 [0.49, 1.73]	
Rust 2000	3	61	6	66	14.0%	0.54 [0.14, 2.07]	
Subtotal (95% CI)		234		241	72.5%	0.84 [0.51, 1.37]	•
Total events	25		30				
Heterogeneity: Chi ² =	0.50, df=	2 (P = 0	78); 12=	0%			
Test for overall effect	Z = 0.70 (P = 0.48)				
1.2.5 One-off ultraso	und-indica	ted cer	clage in	low/un	specified	risk for PTL vs no cercla	ge
Berghella 2004	1	3	2	7	2.9%	1.17 [0.16, 8.48]	
Rust 2000	4	43	3	37	7.8%	1.15 [0.27, 4.80]	
To 2004	7	101	4	96	10.0%	1.66 [0.50, 5.50]	
Subtotal (95% CI)		147		140	20.7%	1.40 [0.61, 3.23]	*
Total events	12		9				
Heterogeneity: Chi ² =	0.19, df=	2 (P = 0	.91); = 1	0%			
Test for overall effect	Z = 0.79 (P = 0.43)				
Total (95% CI)		407		411	100.0%	0.95 [0.63, 1.43]	+
Total events	39		42				
Heterogeneity: Chi ² =	1.72, df=	6 (P = 0	.94); 1=	0%			0.01 0.1 1 10 100
Test for overall effect	Z= 0.25 (P = 0.80)				Favours experimental Favours control
Test for subgroup dif	ferences: 0	chi ² = 1.	13, df = 2	(P = 0)	57), P= (196	ratouis experimental ratouis condoi

Figure 2: Prophylactic cervical cerclage versus no cerclage - Serious neonatal morbidity

Figure 3: Prophylactic cervical cerclage versus no cerclage- Preterm birth before 37+0 weeks

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.7.1 History-indicate	ed cerclag	e vs no	cerclage	2			100
Ezechi 2004	3	39	15	42	1.8%	0.22 [0.07, 0.69]	
Lazar 1984	18	268	13	238	4.5%	1.23 [0.62, 2.46]	
MRC/RCOG 1993	161	635	190	629	19.5%	0.84 [0.70, 1.00]	-
Rush 1984 Subtotal (95% CI)	33	96 1038	31	98 1007	9.9% 35.7%	1.09 [0.73, 1.62] 0.86 [0.59, 1.27]	•
Total events	215		249				23 C
Heterogeneity: Tau ² = Test for overall effect				= 0.05)); I² = 62%	6	
1.7.2 One-off ultraso	und-indica	ited cer	clage in	high ris	sk for PTI	L vs no cerclage	
To 2004	9	26	19	30	5.7%	0.55 [0.30, 0.99]	
Subtotal (95% CI)		26		30	5.7%	0.55 [0.30, 0.99]	•
Total events	9		19				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z=1.99 (P = 0.05)				
1.7.3 Serial ultrasou	nd-indicat	ed cerci	lage in hi	gh risk	for PTL	vs no cerclage	
Althuisius 2001	4	19	10	16	2.6%	0.34 [0.13, 0.87]	
Berghella 2004	13	25	14	22	7.6%	0.82 [0.50, 1.34]	
Owen 2009	66	148	91	153	17.3%	0.75 [0.60, 0.94]	-
Rust 2000	27	61	29	66	10.2%	1.01 [0.68, 1.49]	-
Subtotal (95% CI)		253	2021	257	37.6%	0.78 [0.60, 1.02]	•
Total events	110		144				
Heterogeneity: Tau ² :	= 0.03; Chi	= 4.80,	df = 3 (P	= 0.19)); I ² = 38%	6	
Test for overall effect	Z=1.82 (P = 0.07)				
1.7.5 One-off ultraso	und-indica	ited cer	clage in	low/un:	specified	risk for PTL vs no cerclage	5
Berghella 2004	1	3	6	7	0.9%	0.39 [0.08, 1.98]	
Rust 2000	22	43	18	37	8.8%	1.05 [0.68, 1.64]	+
To 2004	32	101	44	96	11.3%	0.69 [0.48, 0.99]	+
Subtotal (95% CI)		147		140	21.0%	0.80 [0.55, 1.16]	+
Total events	55		68				25
Heterogeneity: Tau ² :	= 0.03; Chi	= 2.90,	df= 2 (P	= 0.23); I ² = 31%	6	
Test for overall effect	Z=1.16 (P = 0.25)				
Total (95% CI)		1464		1434	100.0%	0.80 [0.69, 0.95]	•
Total events	389		480				30 23 24
Heterogeneity: Tau ² :	= 0.03; Chi	= 18.11	, df = 11	(P = 0.)	08); I ² = 3	9%	
Test for overall effect						2.67	0.01 0.1 i 10 10
Test for subgroup dif			- *	-			Favours experimental Favours control

Figure 4: Prophylactic cervical cerclage versus no cerclage- Preterm birth before 34+0 weeks

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.8.1 History-indicate	ed cerclag	e vs no	cerclage	2			3 Con
Ezechi 2004	0	39	11	42	0.3%	0.05 [0.00, 0.77]	· · · · · · · · · · · · · · · · · · ·
MRC/RCOG 1993	92	635	113	629	39.5%	0.81 [0.63, 1.04]	-
Rush 1984	14	96	14	98	5.4%	1.02 [0.51, 2.03]	
Subtotal (95% CI)		770		769	45.2%	0.76 [0.40, 1.46]	+
Total events	106		138				
Heterogeneity: Tau ² :	= 0.17; Chi ²	= 4.66,	df = 2 (P	= 0.10); I ² = 57%	6	
Test for overall effect	Z = 0.81 (P = 0.42)				
1.8.2 One-off ultraso	und-indica	ated cer	clage in l	high ris	sk for PTI	L vs no cerclage	
To 2004	6	26	11	30	3.5%	0.63 [0.27, 1.46]	
Subtotal (95% CI)	<u>_</u>	26		30	3.5%	0.63 [0.27, 1.46]	-
Total events	6		11				
Heterogeneity: Not a							
Test for overall effect		P = 0.28)				
1.8.3 Serial ultrasou	nd-indicate	ed cercl	age in hi	gh risk	for PTL	vs no cerclage	23
Althuisius 2001	0	19	7	16	0.3%	0.06 [0.00, 0.92]	·
Berghella 2004	10	25	11	22	6.2%	0.80 [0.42, 1.51]	
Owen 2009	42	148	57	153	23.3%	0.76 [0.55, 1.06]	
Rust 2000	13	61	15	66	5.8%	0.94 [0.49, 1.81]	
Subtotal (95% CI)		253		257	35.7%	0.77 [0.55, 1.10]	•
Total events	65		90				2.25
Heterogeneity: Tau ² =	= 0.03; Chi ²	² = 3.92,	df = 3 (P	= 0.27); I ² = 23%	6	
Test for overall effect	Z=1.42 (P = 0.15)				
1.8.5 One-off ultraso	und-indica	ated cer	clage in l	low/un:	specified	risk for PTL vs no cerclag	16
Berghella 2004	0	3	1	7	0.3%	0.67 [0.03, 12.96]	
Rust 2000	11	43	12	37	5.3%	0.79 [0.40, 1.57]	
To 2004	22	101	25	96	10.0%	0.84 [0.51, 1.38]	
Subtotal (95% CI)		147		140	15.6%	0.82 [0.55, 1.22]	+
Total events	33		38				
Heterogeneity: Tau ² =		= 0.04.	df = 2 (P	= 0.98); I ² = 0%		
Test for overall effect							
Total (95% CI)		1196		1196	100.0%	0.79 [0.68, 0.93]	•
Total events	210		277				
Heterogeneity: Tau ² :		= 8.88		P = 0.5	4): $P = 0.9$	6	
Test for overall effect				- 0.0		T0	0.01 0.1 i 10 10
Learner exercise enect					.96), I [#] = (Favours experimental Favours control

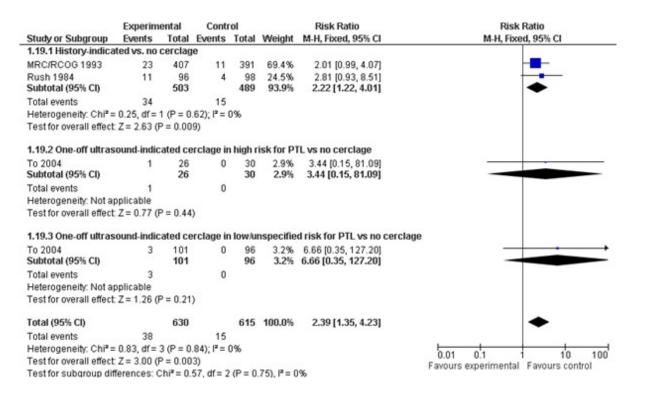
Figure 5: Prophylactic cervical cerclage versus no cerclage- Preterm birth before 38+0 weeks

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
1.9.1 History-indicate	ed cerclag	e vs no	cerclage	2			
Ezechi 2004	0	39	1	42	1.0%	0.36 [0.02, 8.54]	
MRC/RCOG 1993	53	635	65	629	43.8%	0.81 [0.57, 1.14]	-
Rush 1984	7	96	7	98	4.6%	1.02 [0.37, 2.80]	
Subtotal (95% CI)		770		769	49.4%	0.82 [0.59, 1.13]	•
Total events	60		73				
Heterogeneity: Chi ² =	0.45, df=	2(P = 0.	80); I ² = I	0%			
Test for overall effect	Z= 1.21 (P = 0.23)				
1.9.2 One-off ultraso	und-indica	ated cer	clage in l	hiah ris	sk for PT	vs no cerclage	
To 2004	3	26	5	30	3.1%	0.69 [0.18, 2.62]	
Subtotal (95% CI)	2	26	2	30	3.1%	0.69 [0.18, 2.62]	
Total events	3		5			see for showed	
Heterogeneity: Not a			~				
Test for overall effect		P - 0 50					
reactor overall enect	2-0.54(- 0.00	/				
1.9.3 Serial ultrasou	nd-indicat	ed cercl	age in hi	gh risk	for PTL	vs no cerclage	25
Althuisius 2001	0	19	3	16	2.5%	0.12 [0.01, 2.19]	· · · · · · · · · · · · · · · · · · ·
Berghella 2004	6	25	5	22	3.6%	1.06 [0.37, 2.99]	
Owen 2009	21	148	33	153	21.8%	0.66 [0.40, 1.08]	
Rust 2000	9	61	11	66	7.1%	0.89 [0.39, 1.99]	
Subtotal (95% CI)		253		257	35.0%	0.71 [0.48, 1.04]	•
Total events	36		52				7.6
Heterogeneity: Chi ² =	2.38, df =	3 (P = 0.	50); I ² = 1	0%			
Test for overall effect	Z=1.78 (P = 0.08)				
1.9.5 One-off ultraso	und-indica	ated cer	clage in l	low/un:	specified	risk for PTL vs no cercla	qe
Berghella 2004	0	3	1	7	0.7%	0.67 [0.03, 12.96]	
Rust 2000	7	43	5	37	3.6%	1.20 [0.42, 3.48]	
To 2004	12	101	12	96	8.3%	0.95 [0.45, 2.01]	
Subtotal (95% CI)		147		140		1.01 [0.55, 1.83]	+
Total events	19	2222	18	332			T
Heterogeneity: Chi ² =		2(P = 0)		0%			
Test for overall effect							
Total (95% CI)		1196		1196	100.0%	0.80 [0.64, 1.00]	•
Total events	118	849.52	148	1111-11			23 2
Heterogeneity: Chi ² =		10 (P = 1		0%			
Test for overall effect				0.0			0.01 0.1 1 10 1
	ferences: (Favours experimental Favours control

Figure 6: Prophylactic cervical cerclage versus no cerclage- maternal side effects

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.17.1 History-indica	ted cercla	ge vs no	cerclag	e			23. 66621
Lazar 1984	60	268	43	238	47.9%	1.24 [0.87, 1.76]	-
Rush 1984	11	96	4	98	29.7%	2.81 [0.93, 8.51]	
Subtotal (95% CI)		364		336	77.6%	1.57 [0.76, 3.24]	★
Total events	71		47				
Heterogeneity: Tau ² =	= 0.16; Chi	= 1.92,	df = 1 (P	= 0.17	; I ² = 48%		
Test for overall effect	Z=1.21 (P = 0.23)					
1.17.2 One-off ultras	ound-indic	ated ce	rclage in	high r	isk for Pi	L vs no cerclage	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	Not applie	able					
1.17.3 Serial ultraso	und-indica	ted cerd	lage in h	nigh ris	k for PTL	vs no cerclage	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a	oplicable						
Test for overall effect		able					
1.17.4 Physical exar	n-indicate	d cercla	ge in higl	h risk 1	or PTL vs	s no cerclage	
Subtotal (95% CI)		0	1000000	0		Not estimable	
Total events	0		0				
Heterogeneity: Not a	oplicable						
Test for overall effect	Not applie	able					
1.17.5 One-off ultras	ound-indic	ated ce	rclage in	low/u	nspecifie	d risk for PTL vs no cerclag	e
To 2004	12	127	2	126	22.4%	5.95 [1.36, 26.06]	
Subtotal (95% CI)		127		126	22.4%	5.95 [1.36, 26.06]	
Total events	12		2				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z = 2.37 (P = 0.02)	0				
Total (95% CI)		491		462	100.0%	2.25 [0.89, 5.69]	•
Total events	83		49				
Heterogeneity: Tau ^a :	= 0.44; Chi	= 5.83.	df = 2 (P	= 0.05	; I ² = 66%		
							0.01 0.1 1 10 10
Test for overall effect	Z=1./00	P = 0.09	L.)				Favours experimental Favours control

Figure 7: Prophylactic cervical cerclage versus no cerclage- pyrexia



I.3 Diagnosing preterm prelabour rupture of membranes (P-PROM

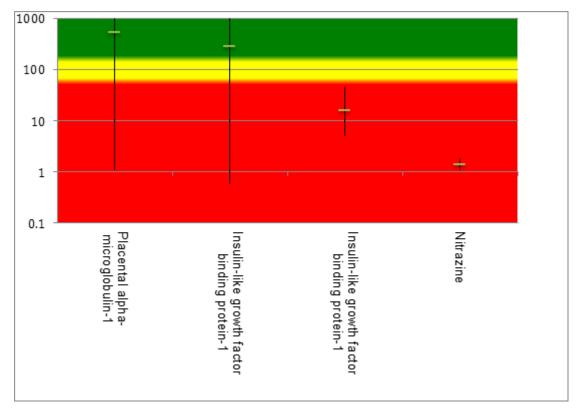
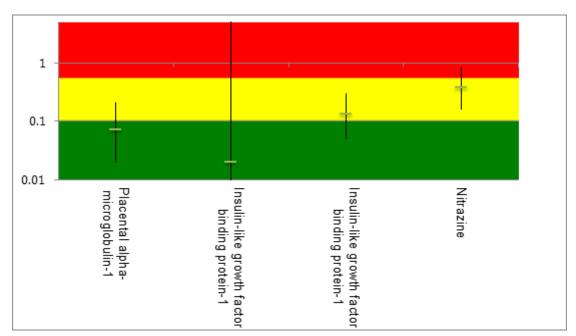
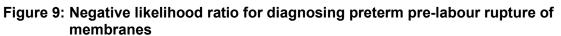


Figure 8: Positive likelihood ratio for diagnosing preterm pre-labour rupture of membranes

Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





I.4 Antenatal prophylactic antibiotics for women with P-PROM

I.4.1 Any antibiotic versus placebo

I.4.1.1 Neonatal outcomes

Carcia 1995 2 30 5 30 1.7% 0.40 [0.08, 1.90] Carbie 1996 0 31 2 29 0.5% 0.19 [0.01, 3.75] Johnston 1990 3 40 4 45 2.12% 0.84 [0.20, 3.54] Kerryon 2001 226 3584 82 1225 71.2% 0.94 [0.74, 212.52] Mercer 1992 1 57 1 58 0.6% 1.02 (0.07, 15.88] Mercer 1992 6 106 10 114 4.4% 0.65 [0.24, 1.71] Mercer 1997 19 299 18 312 10.9% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 43 4.2% 1.19 [0.44, 3.26] Subtal (95% Ch) 4315 1986 100.0% 0.93 [0.76, 1.14] Total events 276 138 Heterogeneity: Tau ² = 0.00; Ch ² = 8.73, df = 11 (P = 0.65); l ² = 0% Test for overall effect: Z = 0.69 (P = 0.49) 1.2.2 All penicillin (excluding co-amoxiclav) versus placebo Crable 1995 0 31 2 29 9.6% 0.19 [0.01, 3.75] Johnston 1990 3 40 4 45 42.0% 0.84 [0.20, 3.54] Kurki 1992 1 57 1 58 11.5% 1.02 (0.07, 15.88] Lockwood 1993a 3 37 3 35 36.9% 0.95 [0.20, 4.38] Subtotal (95% Ch) 165 167 100.0% 0.78 [0.31, 1.97] Total events 7 10 Heterogeneity: Tau ² = 0.05; Ch ² = 0.50; l ² = 0% Test for overall effect: Z = 0.53 (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Subtotal (95% Ch) 1236 644 100.0% 0.40 [0.08, 1.90] Keryon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% Ch) 1236 644 100.0% 0.40 [0.08, 1.90] Keryon 2001 79 1205 41 613 71.6% 0.98 [0.64, 1.28] Heterogeneity: Tau ² = 0.05; Ch ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.4 Macrolide (including erythromycin) versus placebo Carcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Keryon 2001 70 1390 41 61 3 54.11 0.059, 2.06] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Micree 1997 1 42 6 42 25.9% 1.17 [0.43, 3.18] Subta 1995 7 42 6 42 25.9% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Ch ² = 0.02; df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.56 (P = 0.57) 	igure 10:	Treatm	nent		rol	10140-04-	Risk Ratio	Risk Ratio
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Test for overall effect: $Z = 0.69$ ($P = 0.49$) 1.2.2 All penicillin (excluding co-amoxiclav) versus placebo Grable 1996 0 31 2 29 9.6% 0.19 [0.01, 3.75] Johnston 1990 3 40 4 45 42.0% 0.84 [0.20, 3.54] Kurki 1992 1 57 1 58 11.5% 1.02 [0.07, 15.88] Lockwood 1993a 3 37 3 35 36.9% 0.95 [0.20, 4.38] Subtotal (95% CI) 165 167 100.0% 0.78 [0.31, 1.97] Total events 7 10 Heterogeneity: Tau ² = 0.00; Chi ² = 1.00, df = 3 ($P = 0.80$); $I^2 = 0$ % Test for overall effect: $Z = 0.53$ ($P = 0.60$) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.65 ($P = 0.51$) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] MeGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212, 52] Mercer 1992 6 106 10 114 26.9% 0.63 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 ($P = 0.19$); $I^2 = 38\%$ Test for overall effect: $Z = 0.56 (P = 0.57)$ 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 ($P = 0.99$); $I^2 = 0\%$ Test for overall effect: $Z = 0.46 (P = 0.65)$							2 0.00	
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$ \begin{array}{cccc} binston 1990 & 3 & 40 & 4 & 45 & 42.0\% & 0.84 [0.20, 3.54] \\ Kurki 1992 & 1 & 57 & 1 & 58 & 11.5\% & 1.02 [0.07, 15.88] \\ boktood 1993a & 3 & 37 & 3 & 35 & 36.9\% & 0.95 [0.20, 4.38] \\ Subtotal (95% CI) & 165 & 167 & 100.0\% & 0.78 [0.31, 1.97] \\ Total events & 7 & 10 \\ Heterogeneity: Tau2 = 0.00; Chi2 = 1.00, df = 3 (P = 0.80); l2 = 0\% \\ Test for overall effect: Z = 0.53 (P = 0.60) \\ 1.2.3 Beta lactum (including co-amoxiclav) versus placebo \\ Cox 1995 & 1 & 31 & 5 & 31 & 28.4\% & 0.20 [0.02, 1.61] \\ Kenyon 2001 & 79 & 1205 & 41 & 613 & 71.6\% & 0.98 [0.68, 1.41] \\ Subtotal (95% CI) & 1236 & 644 & 100.0\% & 0.62 [0.15, 2.56] \\ Total events & 80 & 46 \\ Heterogeneity: Tau2 = 0.69; Chi2 = 2.17, df = 1 (P = 0.14); l2 = 54\% \\ Test for overall effect: Z = 0.65 (P = 0.51) \\ 1.2.4 Macrolide (including erythromycin) versus placebo \\ Garcia 1995 & 2 & 30 & 5 & 30 & 14.0\% & 0.40 [0.08, 1.90] \\ Kenyon 2001 & 70 & 1190 & 41 & 613 & 54.1\% & 0.88 [0.61, 1.28] \\ McGregor 1991 & 6 & 28 & 0 & 27 & 5.0\% & 12.55 [0.74, 212.52] \\ Subtotal (95% CI) & 1354 & 784 & 100.0\% & 0.63 [0.43, 1.60] \\ Total events & 84 & 56 \\ Heterogeneity: Tau2 = 0.17; Chi2 = 4.82, df = 3 (P = 0.19); l2 = 38\% \\ Test for overall effect: Z = 0.56 (P = 0.57) \\ 1.2.5 Other antibiotic versus placebo \\ Mercer 1997 & 19 & 299 & 18 & 312 & 66.8\% & 1.10 [0.59, 2.06] \\ Ovalle Salas 1997 & 7 & 42 & 6 & 42 & 25.9\% & 1.17 [0.43, 3.18] \\ Subtotal (95\% CI) & 371 & 391 & 100.0\% & 1.13 [0.68, 1.88] \\ Total events & 28 & 26 \\ Heterogeneity: Tau2 = 0.00; Chi2 = 0.02, df = 2 (P = 0.99); l2 = 0\% \\ Test for overall effect: Z = 0.46 (P = 0.65) \\ \end{array}$	1.2.2 All penicillin (e	excluding	co-am	oxiclav)	versus	placebo		
Kurki 1992 1 57 1 58 11.5% 1.02 [0.07, 15.88] Lockwood 1993a 3 37 3 35 36.9% 0.95 [0.20, 4.38] Subtotal (95% Cl) 165 167 100.0% 0.78 [0.31, 1.97] Total events 7 10 Heterogeneity: Tau ² = 0.00; Chi ² = 1.00, df = 3 (P = 0.80); l ² = 0% Test for overall effect: Z = 0.53 (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% Cl) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.65; Ch ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mecreer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% Cl) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Grable 1996	0	31	2	29	9.6%	0.19 [0.01, 3.75]	
Lockwood 1993a 3 37 3 35 36.9% 0.95 [0.20, 4.38] Subtotal (95% CI) 165 167 100.0% 0.78 [0.31, 1.97] Total events 7 10 Heterogeneity: Tau ² = 0.00; Chi ² = 1.00, df = 3 (P = 0.80); l ² = 0% Test for overall effect: $Z = 0.53$ (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGreagor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] McGreagor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: $Z = 0.56$ (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: $Z = 0.46$ (P = 0.65)	Johnston 1990	3	40	4	45	42.0%	0.84 [0.20, 3.54]	
Subtotal (95% CI) 165 167 100.0% 0.78 [0.31, 1.97] Total events 7 10 Heterogeneity: Tau ² = 0.00; Chi ² = 1.00, df = 3 (P = 0.80); l ² = 0% Test for overall effect: Z = 0.53 (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Sware 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997 19 29 18 312 66.8% 1.10 [0.59, 2.06] Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Kurki 1992	1	57	1	58	11.5%	1.02 [0.07, 15.88]	
Total events 7 10 Heterogeneity: Tau ² = 0.00; Chi ² = 1.00, df = 3 (P = 0.80); l ² = 0% Test for overall effect: Z = 0.53 (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: $Z = 0.56 (P = 0.57)$ 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Lockwood 1993a	3	37	3	35	36.9%	0.95 [0.20, 4.38]	
The theorements: Tau ² = 0.00; Chi ² = 1.00, df = 3 (P = 0.80); l ² = 0% Test for overall effect: $Z = 0.53$ (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: $Z = 0.65$ (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: $Z = 0.56$ (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Sware 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: $Z = 0.46$ (P = 0.65)	Subtotal (95% CI)		165		167	100.0%	0.78 [0.31, 1.97]	+
Test for overall effect: $Z = 0.53$ (P = 0.60) 1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.65; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: $Z = 0.65$ (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] McGregor 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: $Z = 0.56$ (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: $Z = 0.46$ (P = 0.65)	Total events	7		10				
1.2.3 Beta lactum (including co-amoxiclav) versus placebo Cox 1995 1 31 5 31 28.4% 0.20 [0.02, 1.61] Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo García 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Heterogeneity: Tau ² =	= 0.00; Ch	$hi^2 = 1.0$	00, df =	3 (P =	0.80); I2	= 0%	
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Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: $Z = 0.65$ (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mecregor 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: $Z = 0.56$ (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Sals 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: $Z = 0.46$ (P = 0.65)	1.2.3 Beta lactum (ir	cluding o	o-amo	xiclav) v	ersus	placebo		
Kenyon 2001 79 1205 41 613 71.6% 0.98 [0.68, 1.41] Subtotal (95% CI) 1236 644 100.0% 0.62 [0.15, 2.56] Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: $Z = 0.65$ (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] McGregor 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: $Z = 0.56$ (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: $Z = 0.46$ (P = 0.65)	Cox 1995	1	31	5	31	28.4%	0.20 [0.02, 1.61]	
Total events 80 46 Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Kenyon 2001	79	1205	41	613	71.6%		
Heterogeneity: Tau ² = 0.69; Chi ² = 2.17, df = 1 (P = 0.14); l ² = 54% Test for overall effect: Z = 0.65 (P = 0.51) 1.2.4 Macrolide (including erythromycin) versus placebo Garcia 1995 2 30 5 30 14.0% 0.40 [0.08, 1.90] Kenyon 2001 70 1190 41 613 54.1% 0.88 [0.61, 1.28] McGregor 1991 6 28 0 27 5.0% 12.555 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% CI) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Subtotal (95% CI)		1236		644	100.0%	0.62 [0.15, 2.56]	-
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McGregor 1991 6 28 0 27 5.0% 12.55 [0.74, 212.52] Mercer 1992 6 106 10 114 26.9% 0.65 [0.24, 1.71] Subtotal (95% Cl) 1354 784 100.0% 0.83 [0.43, 1.60] Total events 84 56 Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); l ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% Cl) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)								
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Heterogeneity: Tau ² = 0.17; Chi ² = 4.82, df = 3 (P = 0.19); I ² = 38% Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% Cl) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Total events	84		56				1
Test for overall effect: Z = 0.56 (P = 0.57) 1.2.5 Other antibiotic versus placebo Mercer 1997 19 299 18 312 66.8% 1.10 [0.59, 2.06] Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% Cl) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)			$1i^2 = 4.8$		3 (P =	0.19) 12	= 38%	
Mercer 1997 19 299 18 312 66.8% 1.10 $[0.59, 2.06]$ Ovalle Salas 1997 7 42 6 42 25.9% 1.17 $[0.43, 3.18]$ Svare 1997a 2 30 2 37 7.2% 1.23 $[0.18, 8.25]$ Subtotal (95% CI) 371 391 100.0% 1.13 $[0.68, 1.88]$ Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)					. (
Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% Cl) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); l ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	1.2.5 Other antibiot	ic versus	placebo					
Ovalle Salas 1997 7 42 6 42 25.9% 1.17 [0.43, 3.18] Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% Cl) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)					312	66.8%	1.10 (0.59, 2.06)	-
Svare 1997a 2 30 2 37 7.2% 1.23 [0.18, 8.25] Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)								_ _ _
Subtotal (95% CI) 371 391 100.0% 1.13 [0.68, 1.88] Total events 28 26 Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)								
Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 2 (P = 0.99); I ² = 0% Test for overall effect: Z = 0.46 (P = 0.65)	Subtotal (95% CI)	0.750						+
Test for overall effect: Z = 0.46 (P = 0.65)					1010	1022-02	1000	
					2 (P =	0.99); l ²	= 0%	
	Test for overall effect	Z = 0.46	5 (P = 0)	.65)				
								0.001 0.1 1 10 100

Figure 11: Neonatal necrotising enterocolitis

Study or Subgroup	Treatm		Cont		Walaba	Risk Ratio	Risk Ratio
			Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.5.1 Any antibiotic				1212			
Cox 1995	5	31	0	31	3.1%	11.00 [0.63, 190.79]	
Fuhr 2006	1	47	3	58	4.8%	0.41 [0.04, 3.83]	
Grable 1996	1	31	1	29	3.3%	0.94 [0.06, 14.27]	
Johnston 1990	2	40	3	45	7.2%	0.75 [0.13, 4.26]	
Kenyon 2001	55	3584	6	1225	19.2%	3.13 [1.35, 7.26]	
Lockwood 1993a	2	37	0	35	2.8%	4.74 [0.24, 95.33]	
McGregor 1991	2	26	4	27	8.2%	0.52 [0.10, 2.60]	
Mercer 1992	8	106	12	114	18.9%	0.72 [0.31, 1.69]	
Mercer 1997	24	299	27	312	27.6%	0.93 (0.55, 1.57)	+
Ovalle Salas 1997	0	42	1	43	2.5%	0.34 [0.01, 8.14]	
Svare 1997a	0	30	1	37	2.5%	0.41 [0.02, 9.68]	
Subtotal (95% CI)		4273		1956	100.0%	1.09 [0.65, 1.83]	•
Total events	100		58				
Heterogeneity: Tau ² +	= 0.18; Ch	$i^2 = 13$.98, df =	= 10 (P	= 0.17);	$l^2 = 2.8\%$	
Test for overall effect	Z = 0.32	(P = 0)	.75)				
1.5.2 All penicillin (excluding	co-am		versus	placebo		
Fuhr 2006	1	47	3	58	31.3%	0.41 [0.04, 3.83]	
Johnston 1990	2	40	3	45	51.5%	0.75 [0.13, 4.26]	
Lockwood 1993a	2	37	0	35	17.3%	4.74 [0.24, 95.33]	
Subtotal (95% CI)		124		138	100.0%	0.85 [0.25, 2.97]	+
Total events	5		6				
Heterogeneity: Tau2 =	= 0.00; Ch	$i^2 = 1.7$	71, df =	2 (P =	0.43); I2	= 0%	
Test for overall effect	Z = 0.25	(P = 0	.80)				
1.5.3 Beta lactum (in	cluding c	o-amo	xiclav) v	ersus	placebo		Contraction of the second s
Cox 1995	5	31	0	31	15.0%	11.00 [0.63, 190.79]	
Kenyon 2001	24	1205	3	613	85.0%	4.07 [1.23, 13.46]	
Subtotal (95% CI)		1236		644	100.0%	4.72 [1.57, 14.23]	•
Total events	29		3				
Heterogeneity: Tau ²	= 0.00; Ch	$i^2 = 0.4$	40, df =	1 (P =	0.53); I2	= 0%	
Test for overall effect	: Z = 2.76	(P = 0)	.006)				
1.5.4 Macrolide (incl	uding ery	thromy	cin) ver	sus pla	cebo		
Kenvon 2001	11	1190	3	613	26.3%	1.89 [0.53, 6.75]	
	11 2	1190 26	3	613 27	26.3% 16.5%	1.89 [0.53, 6.75] 0.52 [0.10, 2.60]	
McGregor 1991							-
McGregor 1991 Mercer 1992	2	26	4	27 114	16.5%	0.52 [0.10, 2.60]	
McGregor 1991 Mercer 1992 Subtotal (95% CI)	2	26 106	4	27 114	16.5% 57.2%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events	2 8 21	26 106 1322	4 12 19	27 114 754	16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	+
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² :	2 8 21 = 0.01; Ch	26 106 1322 $hi^2 = 2.0$	4 12 19 03, df =	27 114 754	16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	+
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² :	2 8 21 = 0.01; Ch	26 106 1322 $hi^2 = 2.0$	4 12 19 03, df =	27 114 754	16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	•
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	2 8 21 = 0.01; Ch : Z = 0.39	26 106 1322 $hi^2 = 2.0$ (P = 0)	4 12 19 03, df = .70)	27 114 754	16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	•
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibiot	2 8 = 0.01; Ch : Z = 0.39 ic versus	26 106 1322 $hi^2 = 2.0$ (P = 0) placebo	4 12 19 03, df = .70)	27 114 754 2 (P =	16.5% 57.2% 100.0% 0.36); l ²	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2%	*
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² - Test for overall effect 1.5.5 Other antibiot Grable 1996	2 8 = 0.01; Ch : Z = 0.39 ic versus 1	26 106 1322 $hi^2 = 2.0$ P = 0 placebo 31	4 12 19 03, df = .70)	27 114 754 2 (P = 29	16.5% 57.2% 100.0% 0.36); l ² 3.4%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2%	
McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997	2 8 = 0.01; Ch : Z = 0.39 ic versus 1 24	26 106 1322 $ni^2 = 2.0$ (P = 0) placebo 31 299	4 12 19 03, df = .70) 1 27	27 114 754 2 (P = 29 312	16.5% 57.2% 100.0% 0.36); l ² 3.4% 91.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57]	
McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997	2 8 = 0.01: Ch : Z = 0.39 ic versus 1 24 0	$26 \\ 106 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 0 \\ 1299 \\ 42 \\ 0 \\ 1299 \\ 42 \\ 0 \\ 120 \\ 100 \\ $	4 12 19 03, df = .70) 1 27 1	27 114 754 2 (P = 29 312 43	16.5% 57.2% 100.0% 0.36); l ² 3.4% 91.5% 2.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² - Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997	2 8 = 0.01; Ch : Z = 0.39 ic versus 1 24	$26 \\ 106 \\ 1322 \\ hi^2 = 2.1 \\ 0 (P = 0) \\ placebo \\ 31 \\ 299 \\ 42 \\ 30 \\ \end{bmatrix}$	4 12 19 03, df = .70) 1 27	27 114 754 2 (P = 29 312 43 37	16.5% 57.2% 100.0% 0.36); l ² 3.4% 91.5% 2.5% 2.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI)	2 8 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0	$26 \\ 106 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 0 \\ 1299 \\ 42 \\ 0 \\ 1299 \\ 42 \\ 0 \\ 120 \\ 100 \\ $	4 12 19 03, df = .70) 1 27 1 1	27 114 754 2 (P = 29 312 43 37	16.5% 57.2% 100.0% 0.36); l ² 3.4% 91.5% 2.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14]	
Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² - Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI) Total events	2 8 21 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 25	$26 \\ 106 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 \\ 0 \\ 1322 \\ 0 \\ 102 \\ 0 \\ 0 \\ 102 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\$	4 12 19 03, df = .70) 1 27 1 1 30	27 114 754 2 (P = 29 312 43 37 421	16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² : Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI) Total events Heterogeneity: Tau ²	2 8 211 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 0 25 = 0.00; Ch	$26 \\ 106 \\ 1322 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 \\ 0 \\ 0 \\ 132 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ $	4 12 19 03, df = .70) 1 27 1 1 30 51, df =	27 114 754 2 (P = 29 312 43 37 421	16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² - Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI) Total events	2 8 211 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 0 25 = 0.00; Ch	$26 \\ 106 \\ 1322 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 \\ 0 \\ 0 \\ 132 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ $	4 12 19 03, df = .70) 1 27 1 1 30 51, df =	27 114 754 2 (P = 29 312 43 37 421	16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² : Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI) Total events Heterogeneity: Tau ²	2 8 211 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 0 25 = 0.00; Ch	$26 \\ 106 \\ 1322 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 \\ 0 \\ 0 \\ 132 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ $	4 12 19 03, df = .70) 1 27 1 1 30 51, df =	27 114 754 2 (P = 29 312 43 37 421	16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² : Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI) Total events Heterogeneity: Tau ²	2 8 211 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 0 25 = 0.00; Ch	$26 \\ 106 \\ 1322 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 \\ 0 \\ 0 \\ 132 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ $	4 12 19 03, df = .70) 1 27 1 1 30 51, df =	27 114 754 2 (P = 29 312 43 37 421	16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47] = 0%	
McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² : Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% CI) Total events Heterogeneity: Tau ²	2 8 211 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 0 25 = 0.00; Ch	$26 \\ 106 \\ 1322 \\ 1322 \\ 0 (P = 0) \\ 0 (P = 0) \\ 0 \\ 1322 \\ 0 \\ 0 \\ 0 \\ 132 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ $	4 12 19 03, df = .70) 1 27 1 1 30 51, df =	27 114 754 2 (P = 29 312 43 37 421	16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47] = 0%	

Figure 12: Neonatal necrotising enterocolitis

Study or Subgroup	Treatm		Conti		10.000	Risk Ratio	Risk Ratio
			Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.5.1 Any antibiotic							
Cox 1995	5	31	0	31	3.1%		
Fuhr 2006	1	47	3	58	4.8%	0.41 [0.04, 3.83]	
Grable 1996	1	31	1	29	3.3%	0.94 [0.06, 14.27]	
Johnston 1990	2	40	3	45	7.2%	0.75 [0.13, 4.26]	
Kenyon 2001	55	3584	6	1225	19.2%	3.13 [1.35, 7.26]	
Lockwood 1993a	2	37	0	35	2.8%	4.74 [0.24, 95.33]	
McGregor 1991	2	26	4	27	8.2%	0.52 [0.10, 2.60]	
Mercer 1992	8	106	12	114	18.9%	0.72 [0.31, 1.69]	
Mercer 1997	24	299	27	312	27.6%	0.93 [0.55, 1.57]	+
Ovalle Salas 1997	0	42	1	43	2.5%	0.34 [0.01, 8.14]	
Svare 1997a	0	30	1	37	2.5%	0.41 [0.02, 9.68]	
Subtotal (95% CI)		4273		1956	100.0%	1.09 [0.65, 1.83]	+
Total events	100		58				
Heterogeneity: Tau ² =	= 0.18; Ch	$h^2 = 13$.98, df =	= 10 (P	= 0.17);	$l^2 = 2.8\%$	
Test for overall effect	Z = 0.32	(P = 0)	.75)				
1.5.2 All penicillin (e	-				-		
Fuhr 2006	1	47	3	58	31.3%	0.41 [0.04, 3.83]	
Johnston 1990	2	40	3	45	51.5%	0.75 [0.13, 4.26]	
Lockwood 1993a	2	37	0	35	17.3%	4.74 [0.24, 95.33]	
Subtotal (95% CI)		124		138	100.0%	0.85 [0.25, 2.97]	-
Total events	5		6				
Heterogeneity: Tau ² =				2 (P =	0.43); l ²	= 0%	
Test for overall effect	Z = 0.25	(P = 0)	.80)				
	de aller a						
1.5.3 Beta lactum (ir	-			1.			
Cox 1995	5	31	0	31	15.0%	11.00 [0.63, 190.79]	
Kenyon 2001	24	1205	3	613	85.0%	4.07 [1.23, 13.46]	
Subtotal (95% CI)		1236		044	100.0%	4.72 [1.57, 14.23]	-
Total events	29		3		0.000.02		
Heterogeneity: Tau ² =				1 (P =	0.53); l*	= 0%	
	Z = 2.76	(P = 0)	.006)				
restion overall effect							
100/12/09/ 1001 DI 1	udina erv	throm	vcin) ver	sus pla	cebo		
1.5.4 Macrolide (incl						1 89 (0 53 6 75)	
1.5.4 Macrolide (incl Kenyon 2001	11	1190	3	613	26.3%	1.89 [0.53, 6.75] 0.52 [0.10, 2.60]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991	11 2	1190 26	3 4	613 27	26.3% 16.5%	0.52 [0.10, 2.60]	-
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992	11	1190 26 106	3	613 27 114	26.3% 16.5% 57.2%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69]	-
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI)	11 2 8	1190 26	3 4 12	613 27 114	26.3% 16.5%	0.52 [0.10, 2.60]	
Test for overall effect 1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² a	11 2 8 21	1190 26 106 1322	3 4 12 19	613 27 114 754	26.3% 16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	*
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	11 2 8 21 = 0.01; Ch	1190 26 106 1322 $ni^2 = 2.1$	3 4 12 19 03, df =	613 27 114 754	26.3% 16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	+
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	11 2 8 21 = 0.01; Ch	1190 26 106 1322 $ni^2 = 2.1$	3 4 12 19 03, df =	613 27 114 754	26.3% 16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	*
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	11 2 8 21 = 0.01; Ch : Z = 0.39	1190 26 106 1322 mi2 = 2.0 (P = 0)	3 4 12 19 03, df =).70)	613 27 114 754	26.3% 16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	*
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events	11 2 8 21 = 0.01; Ch : Z = 0.39	1190 26 106 1322 mi2 = 2.0 (P = 0)	3 4 12 19 03, df =).70)	613 27 114 754	26.3% 16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibioti Grable 1996	11 2 8 21 = 0.01; Ch : Z = 0.39 ic versus	1190 26 106 1322 ni2 = 2.0 (P = 0) placebo 31	3 4 12 19 03, df =).70) 0	613 27 114 754 2 (P = 29	26.3% 16.5% 57.2% 100.0% 0.36); 1 ²	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2%	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997	11 2 8 21 = 0.01; Ch : Z = 0.39 ic versus 1	$ \begin{array}{r} 1190 \\ 26 \\ 106 \\ 1322 \\ 1322 \\ 0 (P = 0) \\ placebo \\ \end{array} $	3 4 12 19 03, df = 0.70) 0	613 27 114 754 2 (P =	26.3% 16.5% 57.2% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibioti	11 2 8 = 0.01; Ch : Z = 0.39 ic versus 1 24	1190 26 106 1322 hi2 = 2.0 (P = 0) placebo 31 299	3 4 12 19 03, df = 0.70) 0 1 27 1	613 27 114 754 2 (P = 29 312 43	26.3% 16.5% 57.2% 100.0% 0.36); 1 ² 3.4% 91.5% 2.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a	11 2 8 = 0.01; Ch : Z = 0.39 ic versus 1 24 0	1190 26 106 1322 ni2 = 2.0 (P = 0) placebox 31 299 42	3 4 12 19 03, df =).70) 0 1 27	613 27 114 754 2 (P = 29 312 43 37	26.3% 16.5% 57.2% 100.0% 0.36); l ² 3.4% 91.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibiot Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% Cl)	11 2 8 21 21 2 0.01; Ch 2 0.39 ic versus 1 24 0 0	1190 26 106 1322 ni2 = 2.0 (P = 0) placebox 31 299 42 30	3 4 12 19 03, df = 0.70) 0 1 27 1 1	613 27 114 754 2 (P = 29 312 43 37	26.3% 16.5% 57.2% 100.0% 0.36); l ² 3.4% 91.5% 2.5% 2.5%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibioti Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% Cl) Total events	11 2 8 21 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 0	1190 26 106 1322 ni2 = 2.0 (P = 0) placebo 31 299 42 30 402	3 4 12 19 03, df = 0.70) 0 1 27 1 1 30	613 27 114 754 2 (P = 29 312 43 37 421	26.3% 16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibioti Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% Cl) Total events Heterogeneity: Tau ² =	11 2 8 21 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 25 = 0.00; Ch	1190 26 106 1322 m2 = 2.0 (P = 0) placebo 31 299 42 30 40 40 40 40 40 40 40 4	3 4 12 19 03, df = 0.70) 0 1 27 1 1 30 61, df =	613 27 114 754 2 (P = 29 312 43 37 421	26.3% 16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibioti Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% Cl) Total events	11 2 8 21 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 25 = 0.00; Ch	1190 26 106 1322 m2 = 2.0 (P = 0) placebo 31 299 42 30 40 40 40 40 40 40 40 4	3 4 12 19 03, df = 0.70) 0 1 27 1 1 30 61, df =	613 27 114 754 2 (P = 29 312 43 37 421	26.3% 16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47]	
1.5.4 Macrolide (incl Kenyon 2001 McGregor 1991 Mercer 1992 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.5.5 Other antibioti Grable 1996 Mercer 1997 Ovalle Salas 1997 Svare 1997a Subtotal (95% Cl) Total events Heterogeneity: Tau ² =	11 2 8 21 = 0.01; Ch : Z = 0.39 ic versus 1 24 0 0 25 = 0.00; Ch	1190 26 106 1322 m2 = 2.0 (P = 0) placebo 31 299 42 30 40 40 40 40 40 40 40 4	3 4 12 19 03, df = 0.70) 0 1 27 1 1 30 61, df =	613 27 114 754 2 (P = 29 312 43 37 421	26.3% 16.5% 57.2% 100.0% 0.36); I ² 3.4% 91.5% 2.5% 2.5% 100.0%	0.52 [0.10, 2.60] 0.72 [0.31, 1.69] 0.88 [0.45, 1.69] = 2% 0.94 [0.06, 14.27] 0.93 [0.55, 1.57] 0.34 [0.01, 8.14] 0.41 [0.02, 9.68] 0.89 [0.54, 1.47] = 0%	

Figure 13: Birth before 37 weeks' gestation

	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Kenyon 2001	3049	3584	1041	1225	84.3%	1.00 [0.97, 1.03]	
McGregor 1991	28	28	27	27	13.0%	1.00 [0.93, 1.07]	+
Svare 1997a	27	30	34	37	2.7%	0.98 [0.84, 1.14]	+
Total (95% CI)		3642		1289	100.0%	1.00 [0.98, 1.03]	
Total events	3104		1102				
Heterogeneity: Tau2 =	= 0.00; Ci	$hi^2 = 0.$	08. df =	2 (P =	0.96); 12	= 0%	0.1 0.5 1 2 5 10
Test for overall effect	Z = 0.03	P = 0	.98)				0.1 0.5 1 2 5 10

	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events Tota		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fuhr 2006	17	47	32	58	5.4%	0.66 [0.42, 1.02]	
Grable 1996	17	31	21	29	6.6%	0.76 [0.51, 1.12]	
Johnston 1990	22	40	37	45	9.2%	0.67 [0.49, 0.91]	
Kenyon 2001	2067	3584	775	1225	27.4%	0.91 [0.87, 0.96]	
Lockwood 1993a	22	38	33	37	9.9%	0.65 [0.48, 0.87]	
Mercer 1992	77	106	94	114	19.8%	0.88 [0.76, 1.02]	
Mercer 1997	166	299	229	312	21.8%	0.76 [0.67, 0.85]	-
Total (95% CI)		4145		1820	100.0%	0.79 [0.71, 0.89]	•
Total events	2388		1221				66
Heterogeneity: Tau ² =	0.01; C	$ni^2 = 16$	5.94, df	= 6 (P =	= 0.010);	$l^2 = 65\%$	

Figure 14: Birth within 7 days of randomisation

0 (r = 0.010), r = 03% Test for overall effect: Z = 3.99 (P < 0.0001)

I.4.2 Maternal outcomes

Figure 15: Maternal death

	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Any antibiotic	versus pl	acebo					
Johnston 1990	0	40	0	45		Not estimable	
Mercer 1997	0	299	0	312		Not estimable	
Svare 1997a	0	30	0	37		Not estimable	
Subtotal (95% CI)		369		394		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	Not appl	icable					
1.1.2 All penicillin (excluding	co-am	oxiclav)	versus	placebo		
Johnston 1990	0	40	0	45		Not estimable	
Subtotal (95% CI)		40		45		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	Not appl	icable					
1.1.5 Other antibiot	ic versus	placeb	0				
Mercer 1997	0	299	0	312		Not estimable	
Svare 1997a	0	30	0	37		Not estimable	
Subtotal (95% CI)		329		349		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect		icable					
							0.10.2 0.5 1 2 5 10
							Favours treatment Favours control
							renous o content i arouis control

Figure 16: Maternal infection after delivery prior to discharge

	Treatm	ent	Control			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
Garcia 1995	8	30	7	30	1.9%	1.14 [0.47, 2.75]	+		
Kenyon 2001	686	3584	262	1225	90.5%	0.89 [0.79, 1.02]			
Mercer 1997	33	299	36	312	7.3%	0.96 [0.61, 1.49]	Ŧ		
Svare 1997a	2	30	1	37	0.3%	2.47 [0.23, 25.91]			
Total (95% CI)		3943		1604	100.0%	0.91 [0.80, 1.02]			
Total events	729		306						
Heterogeneity: Tau ² =	0.00; C	hi ² = 1.	06. df =	3 (P =	0.79); I ²	= 0%	1 000 01 1 10 1000		
Test for overall effect	Z = 1.61	(P = 0)).11)				0.001 0.1 1 10 1000		

Figure 17.	Treatm		Cont)	Risk Ratio	Risk Ratio
Study or Subgroup			Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ernest 1994	3	77	9	67	6.4%	0.29 [0.08, 1.03]	
Garcia 1995	3	30	1	30	2.5%	3.00 [0.33, 27.23]	
Grable 1996	4	31	8	29	7.9%	0.47 [0.16, 1.39]	
Johnston 1990	3	40	16	45	7.2%	0.21 [0.07, 0.67]	
Kurki 1992	1	50	7	51	2.9%	0.15 [0.02, 1.14]	
Lockwood 1993a	10	35	10	37	12.4%	1.06 [0.50, 2.23]	
McGregor 1991	7	28	6	27	9.4%	1.13 [0.43, 2.92]	
Mercer 1992	18	105	22	112	15.9%	0.87 [0.50, 1.53]	
Mercer 1997	69	299	101	312	22.3%	0.71 [0.55, 0.93]	-
Ovalle Salas 1997	2	42	11	45	5.2%	0.19 [0.05, 0.83]	
Svare 1997a	6	30	5	37	7.9%	1.48 [0.50, 4.38]	
Total (95% CI)		767		792	100.0%	0.66 [0.46, 0.96]	•
Total events	126		196				2000
Heterogeneity: Tau2 =	0.14; C	$hi^2 = 18$	3.29, df -	= 10 (P	= 0.05);	$I^2 = 45\%$	0.01 0.1 1 10
Test for overall effect:	Z = 2.18	8 (P = 0)	.03)				0.01 0.1 1 10

Figure 17: Chorioamnionitis

Figure 18: Major adverse drug reaction

	Treatm	nent	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	-H, Rand	om, 95%	CI
Kenyon 2001	0	3584	0	1225		Not estimable				
Mercer 1997	0	299	0	312		Not estimable				
Svare 1997a	0	30	0	37		Not estimable				
Total (95% CI)		3913		1574		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	plicable						h.+	0.0		\$ 10
Test for overall effect	Not appl	icable					0.1	0.5	1 2	5 10

	Treatm		Cont			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
4.1.1 New Subgroup							
Amon 1988a	2	43	6	39	1.5%	0.30 [0.06, 1.41]	
Camli 1997	3	15	4	16	2.1%	0.80 [0.21, 3.00]	
Christmas 1992	1	48	3	46	0.7%	0.32 [0.03, 2.96]	
Cox 1995	1	31	5	31	0.8%	0.20 [0.02, 1.61]	
Garcia 1995	2	30	5	30	1.5%	0.40 [0.08, 1.90]	
Grable 1996	0	31	2	29	0.4%	0.19 [0.01, 3.75]	
Johnston 1990	3	40	4	45	1.8%	0.84 [0.20, 3.54]	
Kenyon 2001	226	3584	82	1225	61.2%	0.94 [0.74, 1.20]	
Kurki 1992	1	57	1	58	0.5%	1.02 [0.07, 15.88]	
Lockwood 1993a	3	37	3	35	1.6%		
Magwali 1999	8	82	11	86	4.9%	0.76 [0.32, 1.80]	-
McGregor 1991	6	28	0	27	0.5%		
Mercer 1992	6	106	10	114	3.8%	0.65 [0.24, 1.71]	-+
Mercer 1997	19	299	18	312	9.4%	1.10 [0.59, 2.06]	+
Morales 1989	5	42	3	37	2.0%		
Ovalle Salas 1997	7	42	6	43	3.6%		+
Owen 1993a	4	59	7	58	2.7%		-+
Svare 1997a	2	30	2	37	1.0%		
Subtotal (95% CI)	20	4604	12	2268	100.0%		
Total events	299		172				1
Heterogeneity: Tau ² =	0.00; Cł	$hi^2 = 12$	2.87. df	= 17 (P	= 0.75):	$l^2 = 0\%$	
Test for overall effect:							
4.1.2 Antibiotics ver	sus no tr	eatme	nt (no pl	acebo)			
Amon 1988a	2	43	6	39	11.0%	0.30 [0.06, 1.41]	
Camli 1997	3	15	4	16	15.0%		
Christmas 1992	1	48	3	46	5.3%		
Magwali 1999	8	82	11	86	35.5%		
Morales 1989	5	42	3	37	14.1%		
Owen 1993a	4	59	7	58	19.0%		
Subtotal (95% CI)		289			100.0%		•
Total events	23		34				
Heterogeneity: Tau ² =		$hi^2 = 2$.	97. df =	5 (P =	0.70); I ²	= 0%	
Test for overall effect:							
						ŀ	
						č	0.001 0.1 1 10 1

Figure 19: Antibiotics therapy versus either placebo or no antibiotics therapy

Figure 20: Intraventricular haemorrhage

	Treatm	ient	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Amon 1988a	4	42	6	36	6.2%	0.57 [0.17, 1.87]	· · · · · ·
Christmas 1992	2	48	3	45	3.0%	0.63 [0.11, 3.57]	I
Fuhr 2006	0	47	2	58	2.2%	0.25 [0.01, 5.00]	
Johnston 1990	5	40	14	45	12.7%	0.40 [0.16, 1.02]	
Lockwood 1993a	5	37	7	36	6.8%	0.69 [0.24, 1.99]	
Mercer 1992	57	299	68	312	64.2%	0.87 [0.64, 1.20]	i 📫
Owen 1993a	1	59	5	58	4.9%	0.20 [0.02, 1.63]	
Total (95% CI)		572		590	100.0%	0.73 [0.56, 0.95]	•
Total events	74		105				
Heterogeneity: Chi ² =	5.05, df	= 6 (P	= 0.54);	$ ^2 = 09$	5		bas also da sad
Test for overall effect							0.01 0.1 1 10 100 Favours experimental Favours control

Figure 21: Sepsis

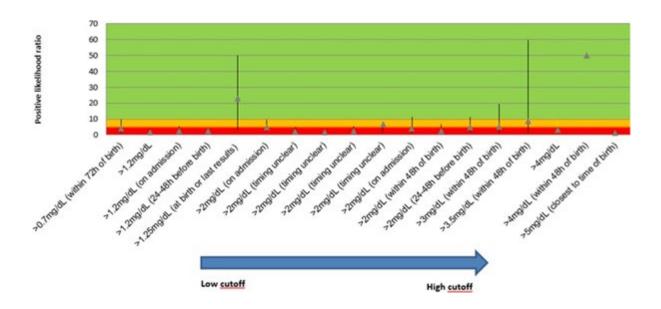
	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95	5% CI
Amon 1988a	1	42	6	38	7.7%	0.15 [0.02, 1.20	0]	
Christmas 1992	2	48	0	45	0.6%	4.69 [0.23, 95.19	9]	
Lockwood 1993a	2	37	3	36	3.7%	0.65 [0.12, 3.66	5]	-
Mercer 1997	46	299	67	312	80.5%	0.72 [0.51, 1.0]	1] 🔜	
Owen 1993a	2	59	6	58	7.4%	0.33 [0.07, 1.56	5]	
Total (95% CI)		485		489	100.0%	0.67 [0.49, 0.9]	1] 🔶	
Total events	53		82					
Heterogeneity: Chi ² =	4.57, df	= 4 (P)	= 0.33);	$l^2 = 12$	2%			10 100
Test for overall effect	Z = 2.52	2 (P = 0)	0.01)				0.01 0.1 1 Favours experimental Favo	10 100 urs control

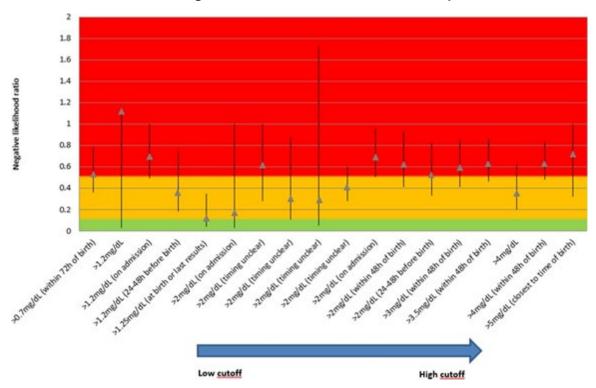
Figure 22: Delivery delayed ≥ 7 days

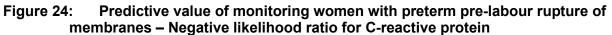
	Treatm	ient	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Amon 1988a	20	43	11	39	8.6%	1.65 [0.91, 2.99	1 +
Christmas 1992	20	48	7	46	5.3%	2.74 [1.28, 5.85	1
Fuhr 2006	30	47	26	58	17.3%	1.42 [1.00, 2.04	1
Johnston 1990	18	40	8	45	5.6%	2.53 [1.24, 5.18	i
Lockwood 1993a	16	38	4	37	3.0%	3.89 [1.44, 10.56	1
Mercer 1997	133	299	83	312	60.3%	1.67 [1.34, 2.09	1
Total (95% CI)		515		537	100.0%	1.80 [1.52, 2.13	1
Total events	237		139				
Heterogeneity: Chi ² =	6.49, df	= 5 (P)	= 0.26);	$ ^2 = 23$:%		
Test for overall effect	Z = 6.76	5 (P < 0	.00001)				0.01 0.1 1 10 10 Favours experimental Favours control

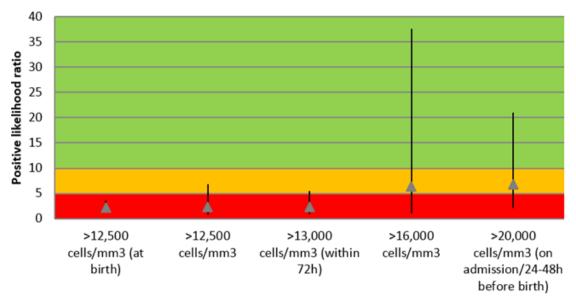
I.5 Identifying infection in women with P-PROM

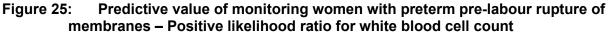
Figure 23: Predictive value of monitoring women with preterm pre-labour rupture of membranes – Positive likelihood ratio for C-reactive protein



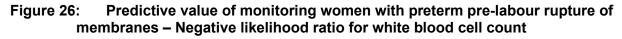


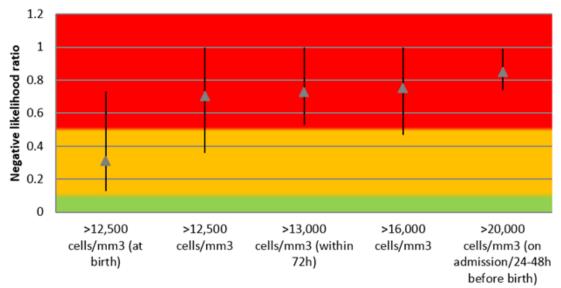




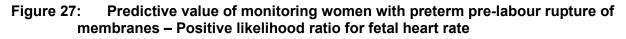


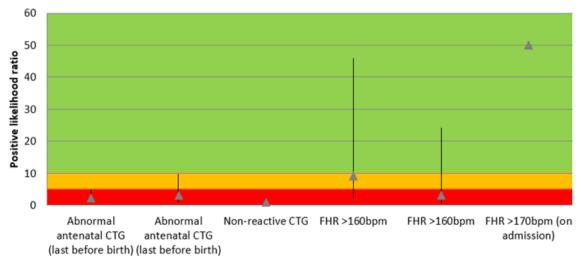
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful



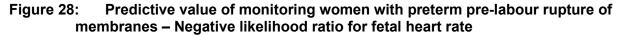


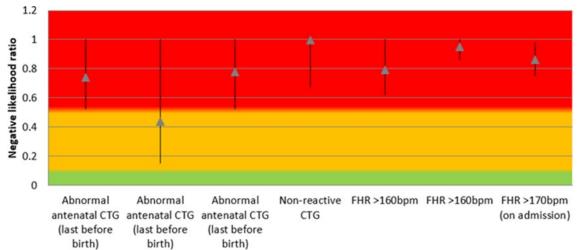
Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





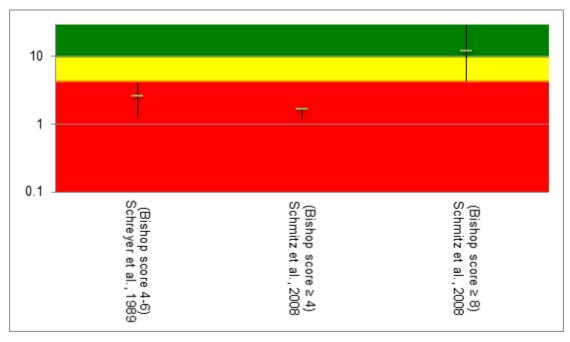
Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

I.6 'Rescue' cervical cerclage

No forest plots were generated for this review question

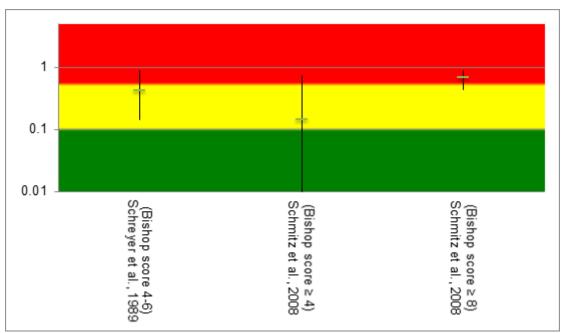
I.7 Diagnosing preterm labour for women with intact membranes

Figure 29: Positive likelihood ratio of Bishop score to diagnose pre-term birth within 48 hours

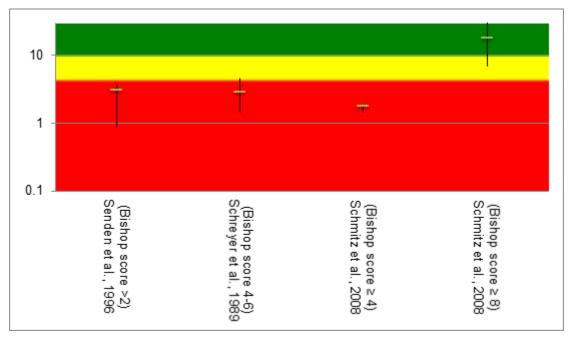


Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

Figure 30: Negative likelihood ratio of Bishop score to diagnose pre-term birth within 48 hours

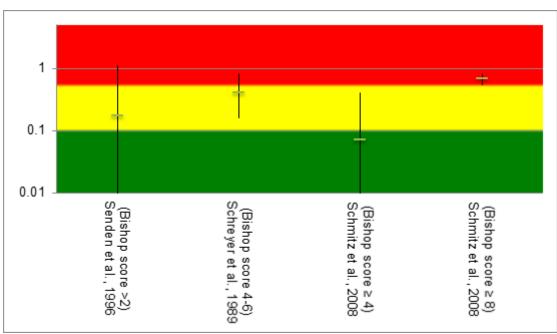






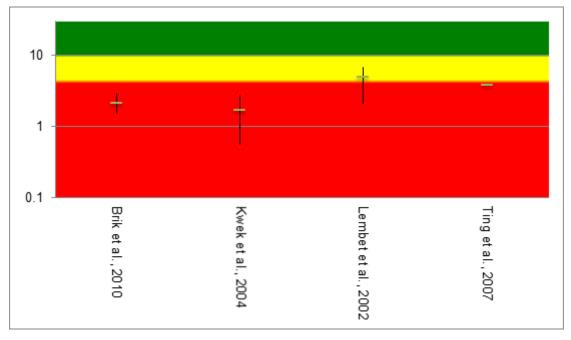
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





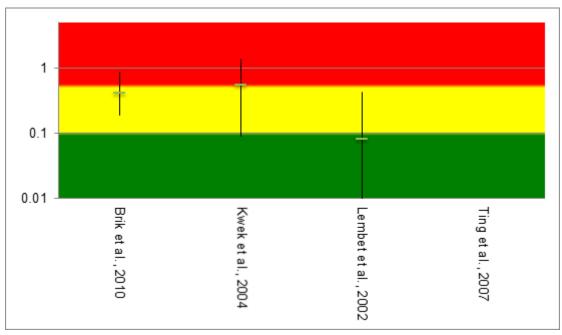
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

Figure 33: Positive likelihood ratio of pIGFBP-1 to diagnose pre-term birth within 48 hours



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





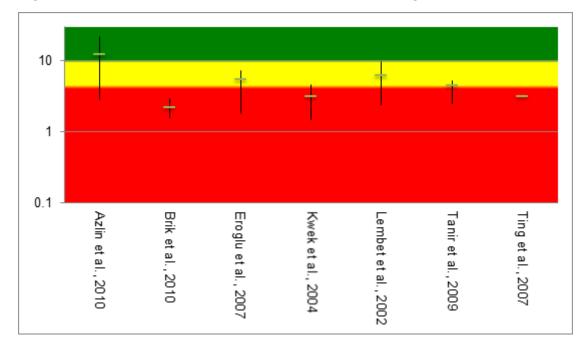


Figure 35: Positive likelihood ratio of pIGFBP-1 to diagnose pre-term birth within 7 days

Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful



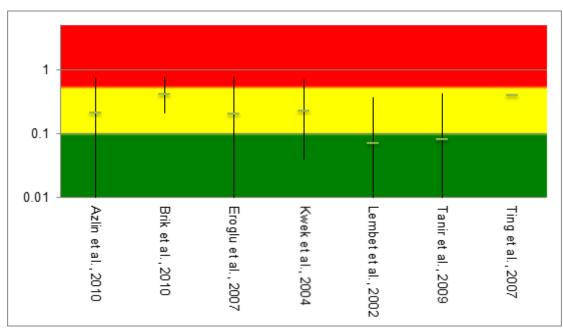
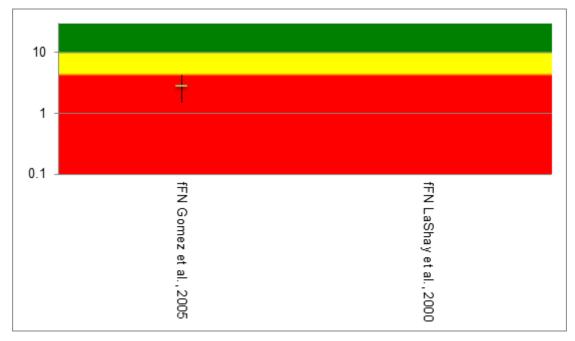
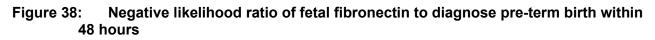
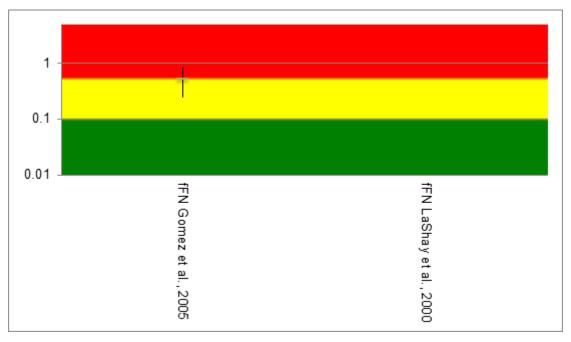


Figure 37: Positive likelihood ratio of fetal fibronectin to diagnose pre-term birth within 48 hours



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





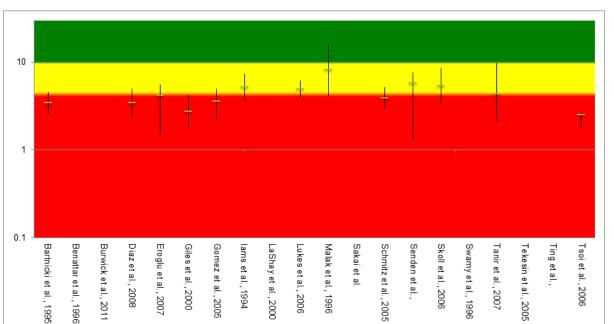
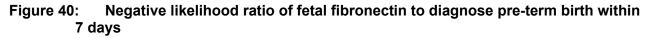


Figure 39: Positive likelihood ratio of fetal fibronectin to diagnose pre-term birth within 7 days

Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful



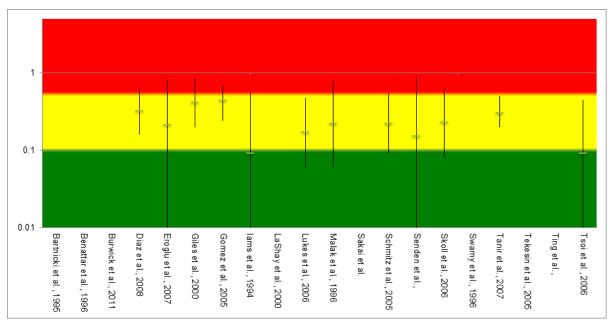
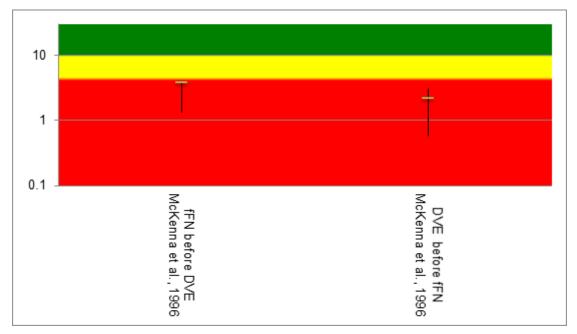
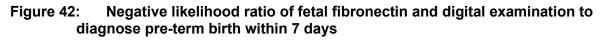
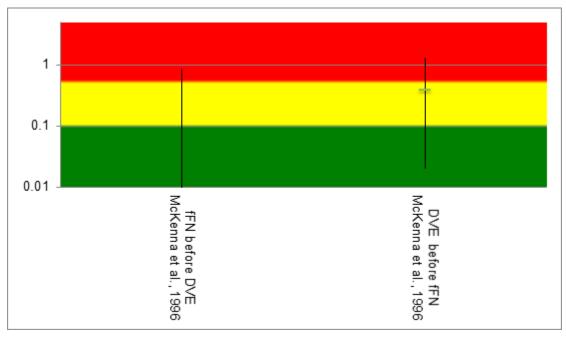


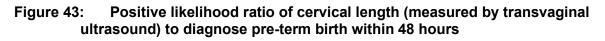
Figure 41: Positive likelihood ratio of fetal fibronectin and digital examination to diagnose pre-term birth within 7 days

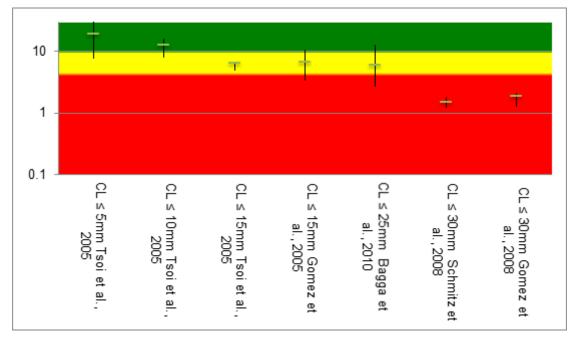


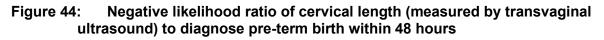
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

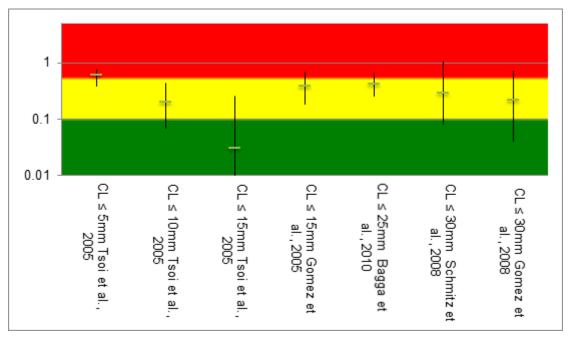












Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

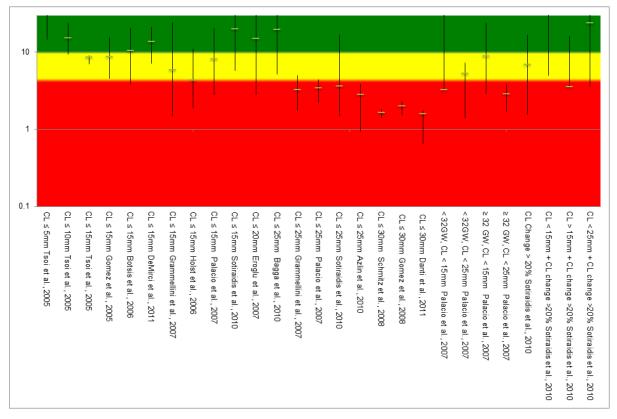


Figure 45: Positive likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 7 days

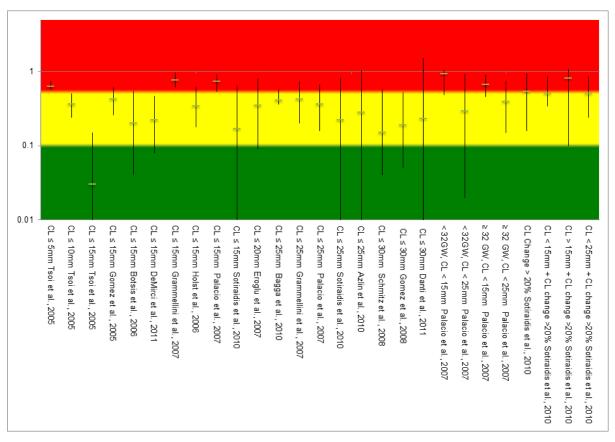
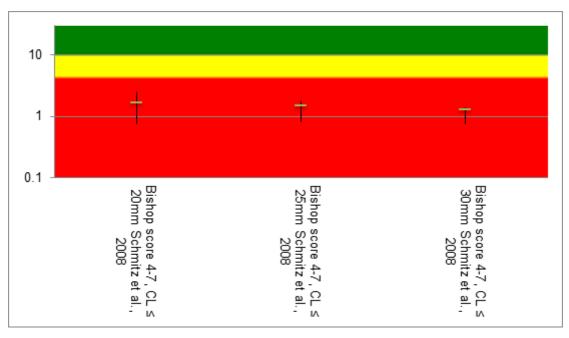


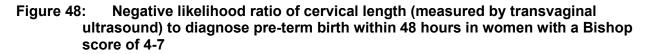
Figure 46: Negative likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 7 days

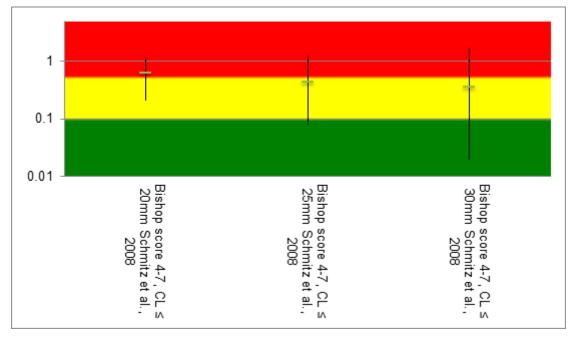
Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

Figure 47: Positive likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 48 hours in women with a Bishop score of 4-7



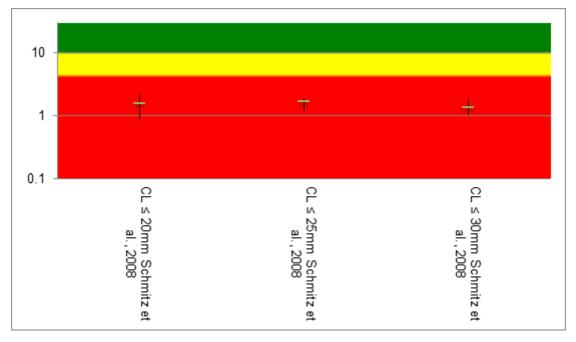
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

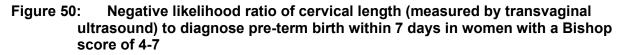


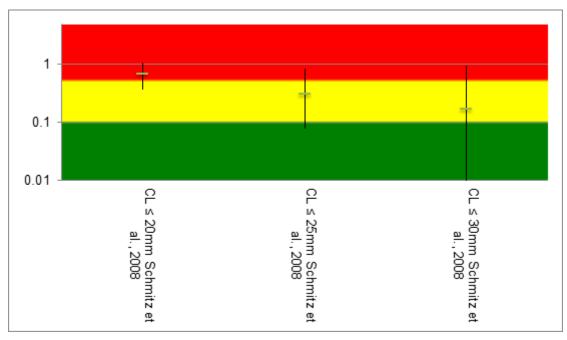


Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

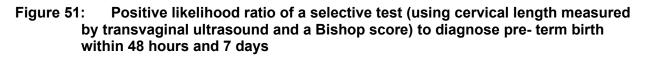
Figure 49: Positive likelihood ratio of cervical length (measured by transvaginal ultrasound) to diagnose pre-term birth within 7 days in women with a Bishop score of 4-7

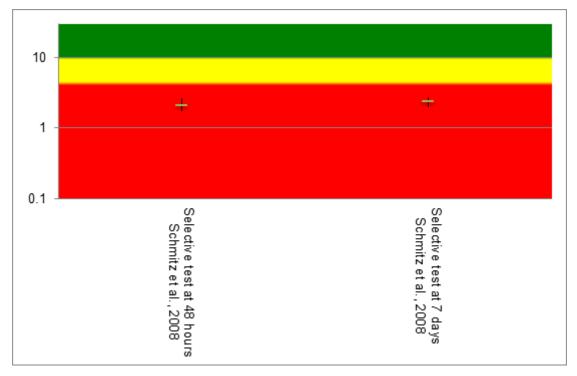




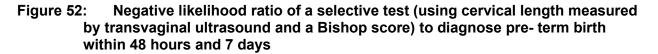


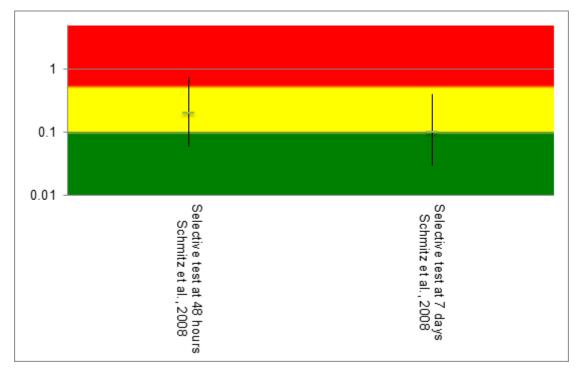
Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





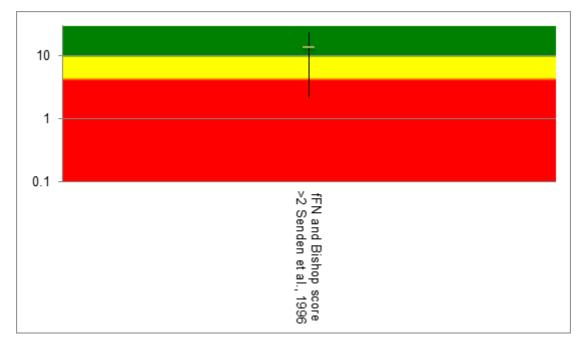
Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

Figure 53: Positive likelihood ratio for fetal fibronectin score and Bishop score to diagnose pre-term birth within 7 days



Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

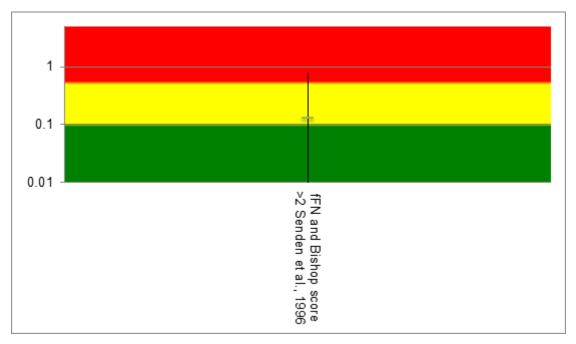
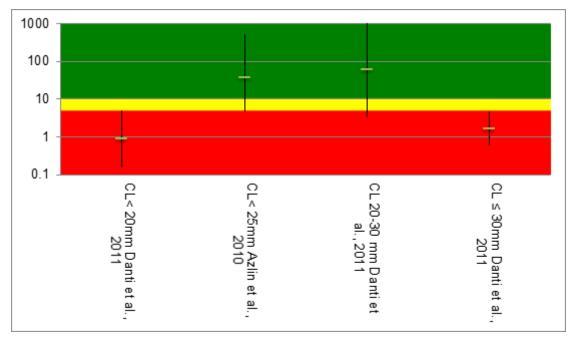


Figure 54: Negative likelihood ratio for fetal fibronectin score and Bishop score to diagnose pre-term birth within 7 days

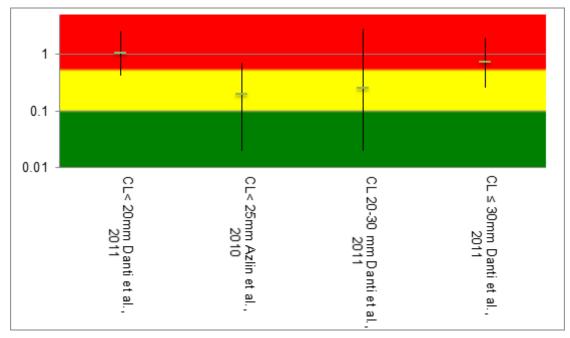
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful



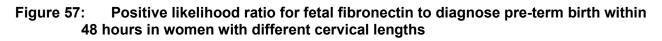


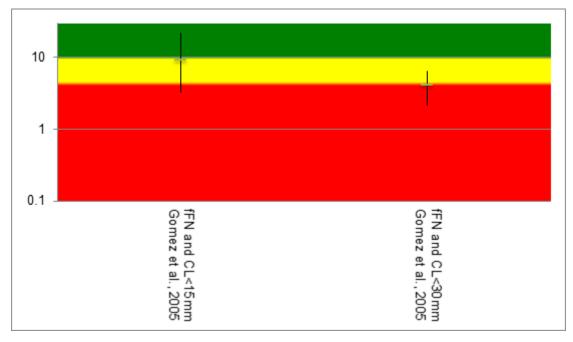
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful



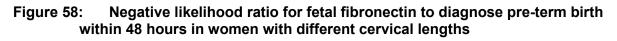


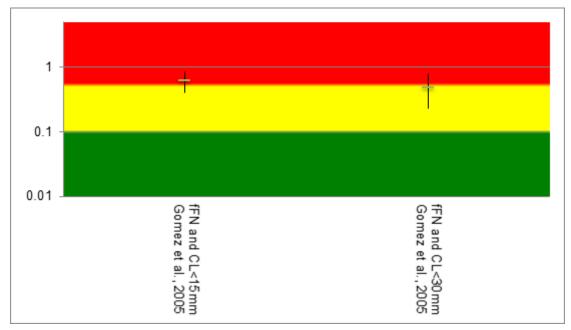
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





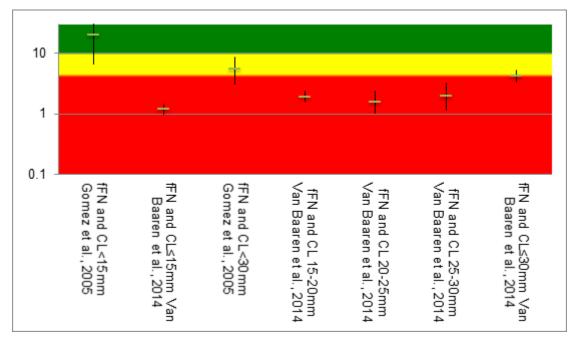
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





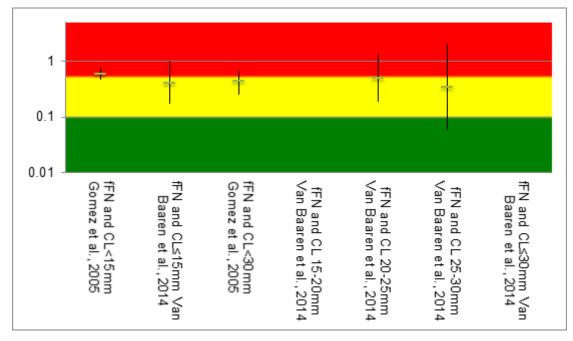
Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful

Figure 59: Positive likelihood ratio for fetal fibronectin to diagnose pre-term birth within 7 days in women with different cervical lengths



Colours indicate diagnostic thresholds – Green: very useful; Yellow: moderately useful; Red: not useful





Colours indicate diagnostic thresholds - Green: very useful; Yellow: moderately useful; Red: not useful

I.8 A. 8 Maternal corticosteroids

I.8.1 Different gestations

Single-course corticosteroids versus placebo or expectant management

Figure 61: Fetal and neonatal mortality

Amonim 1999 Rinck 1927		Total	Events	ol Total	Weight	Risk Ratio M.H. Fixed, 95% CI	Risk Ratio III-H, Foxed, 95% CI
	24	110	36	108	10.5%		
Collaborative 1991	47	.60 378	47	54 379	12.00	0.60 (0.42, 1.04) 0.60 (0.16, 2.01) 1.00 (0.08), 1.40 0.39 (0.13, 1.21) 0.20 (0.11, 0.73)	
Dexprom 1999	1	105				0 39 30 13 1 213	
Doran 1990	4		14 22 12 6 122	63	29% 46% 62% 33%	0.20 (0.11.0.73)	
Olampiu 1989 Olambe 1992	15 12	121	22	127	6.2%	0.71 (0.39, 1.31) 1.14 (0.59, 2.21)	
	12		52	- 41	17%	1.14(0.59, 2.21) 0.82(0.26, 2.61)	
Karl 1994 Liggins 1972a Parsons 1989		601 23	122	617	1.7%	0.82 (0.26, 2.61) 0.91 (0.72, 1.15)	
Parsons 1988	108 G	23	1.1	22		0.32 (0.01, 7.45)	
Porto 2011 Oublian 2001	21	144	41	131	0.9%	0 30 (0 03, 2 88) 0 49 (0 32, 0 72)	
Schutte 1980	6	72 65		- 58	12.5%	0450018 1111	
Taewach 1979	10	58 1957	12	.71	31%	1.06 (0.40, 2.27) 0.77 (0.66, 0.88)	
Schutte 1980 Taeusch 1979 Settotal (95% Cl) Total events Helerogeneity: Chi# = 1			344	1945	100.0%	0.37 (0.66, 0.88)	•
Testfor overall effect .					2011/13-0		
	om preg	105	10	103	31.2%	Isrn rsphure of membranes at 1st dose 0.39 (0.13, 1.21) 0.86 (0.56, 1.33) 0.22 (0.01, 7.45) 0.44 (0.32, 0.72) 0.41 (0.32, 0.72)	
Liggins 1972a Parsons 1989	30	105 168	36	173	39.5%	0 86 10 56, 1.33	
Parsons 1989	0	23 72	1	22	1.7%	0.2230.01,7.458	-
Gublan 2001 Sebtotal (95% CI)	25	368	41	565	\$10.0%	0.48 (0.32, 0.72) 0.62 (0.46, 0.82)	-
	0 21 55		88			and land and	
Hoterogeneity Chi# = Testfor overall effect ;			(25);/*= (09)	34%			
1.1.3 In babies born 4	28 week	8					22 2
1.1.3 In babies born < Dorav 1980 Liggins 1972a Sebtosal (95% CI)	3	11 43 60	10	18	15.3%	0.49 (0.17, 1.40) 0.87 (0.71, 1.07) 0.81 (0.65, 1.01)	
Subtotal (95% Cit	1	60	•3	69	100.05	0.81 [0.65, 1.01]	-
Yotal comete						2704-000-00-000-00-00-00-00-00-00-00-00-00	0.245
Heterogeneity Chill = Test for overall effect -	1.32, df = Z = 1.85 (25);#= 0	24%			
1.1.4 in babies born 4	30 uvees	15		227		1111111111111	
Lippins 1972a Sabtotal (95% CI)	59	99	71	102	100.0%	0.86 (0.70, 1.05) 0.86 (0.70, 1.05)	
		99	71	trank.	_ cessifit	and by a swall	
Heterogeneits: Not ap-							
Test for overall effect.	2=1,47.0	P=0.14	0				
1.1.5 In babies born 4	32 10009	6					
Block 1977 Dorien 1980	2	. 14	5	19	2.0%	0.54 (0.12, 2.40)	
Doran 1980	4	37	54	.05	12.6%	0 28 (0 10, 0 76)	
Liggins 1972a Sebtotal (95% CI)		230	30	168 223	100.0%	0.54 (0.52, 2.40) 0.20 (0.10, 0.76) 0.79 (0.53, 0.96) 0.71 (0.57, 0.86)	-
Total mainte	92		110				
Heterogeneity Chi# = Test for overall effect :	4.19, 8F= Z= 3.12 (2 (P = 0 P = 0.00	(12); (** (2)	52%			
1.1.6 to holizes hore a	14						1000
Lippins 1972s Sebtotel (95% CI) Total events	90	312	113	296	100.0%	0.73 (0.58, 0.91)	
Seblotal (95% CI)		312		255	100.0%	0.73 [0.58, 0.91]	•
Total events	90		113				
Hoterogeneity: Not ap Testfor overall effect ;	2=2734	P = 0.00	(D)				
		÷			****	0.74 0 02 0 475	
Dovan 1990	1 0100						· · · · · · · · · · · · · · · · · · ·
Doran 1980 Liggins 1972a	4 103	58	14	423	29.0%	0 82 80 65, 1 038	· · ·
Doran 1980 Lippins 1972a Sebtotal (95% CI)	4 103	58 440 496	14 121	42 423 471	29.0% 100.0%	0.82 (0.65, 1.03) 0.75 (0.61, 0.94)	••••
				42 423 471 81%	89.0% 100.0%	0.24 (0.08, 0.67) 0.62 (0.65, 1.03) 0.75 (0.61, 0.94)	
Heterogeneity. Chi# = Test for overall effect .	5.25, df = Z = 2.52 (1 (P = 0 P = 0.01	1,15 (02); (**)	81%	09.0% 100.0%	0.62 (0.65, 1.03) 0.75 (0.61, 0.94)	
Heterogenetic Chille : Test for overall effect :	5.25, df = Z = 2.52 (1 (P = 0 P = 0.01	1.15 (02); P=)	81%			
Heterogenetic Chiller Testfor overall effect : 1.1.8 in babies < 26 w Liggins 1972a Sebtofal (II-5% CI)	5 25, df = Z = 2.52 (weks' ge 15	1 (P = 0 P = 0.07 station 23 23	1,15 (02); P =) at 1st de \$7	81% 26 26			
Heterogeneith: Chill = Heterogeneith: Chill = Test for overall effect ; 1.1.8 in babies < 26 w Liggins 1972a Sobotal (95% C0 Total events Heteropeneith: Not an	5 25, df = 2 = 2 52 (weks' ge 15 15 15	1 (P = 0 P = 0.07 station 23 23	1,15 (02); P =) at 1st de 17 17	81% 26 26			*
Heterogenetic Chi*=: Test for overall effect : 1.1.8 in babies < 26 w Liggins 1972a Sabtotal (JISN CD Total wants	5 25, df = 2 = 2 52 (weks' ge 15 15 15	1 (P = 0 P = 0.07 station 23 23	1,15 (02); P =) at 1st de 17 17	81% 26 26			:
India Peers India Peers Test for overall effect / 1.1.8 In bables < 26 w Upgins 1972a Seboolar (MS CD Total events Indiaropeenity: Not ap Test for overall effect / 1.1.9 In bables betwee	5 25, df = Z = 2 52 (meks' pe 15 15 15 2 = 0.01 (en 26 an	1 (P = 6 P = 0.01 etation 23 P = 0.92	1,55 1,020; P = 2 att 1st de 17 17 17	61% 26 26 28	100.0% 100.0%	1.50 (0.06, 1.50) 1.50 (0.66, 1.58)	+
India Peers India Peers Test for overall effect / 1.1.8 In bables < 26 w Upgins 1972a Seboolar (MS CD Total events Indiaropeenity: Not ap Test for overall effect / 1.1.9 In bables betwee	5 25, df = Z = 2 52 (meks' pe 15 15 15 2 = 0.01 (en 26 an	1 (P = 6 P = 0.01 etation 23 P = 0.92	1,55 1,020; P = 2 att 1st de 17 17 17	61% 26 26 28	100.0% 100.0%	1.50 (0.06, 1.50) 1.50 (0.66, 1.58)	-
Incluipenents Incluipenents: Chill = : Test for overall effect : 1.1.8 in babies < 26 w Liggins 1972a Subtotal (Info. Cl) Total events Hotorogeneity: Not ag Test for overall effect : 1.1.9 in babies betwee Liggins 1972a Subtotal (Info. Cl)	107 5.25, df = 2 = 2.52 (works' go 15 15 15 15 215 215 215 215 215 215 215	1 (P = 0 P = 0.07 23 23 P = 0.92 E < 30 m 140	1,55 (32); P =) at 1st de 17 17 0 eeks*9 54	e1% 26 26 28 estatic 121 121	100.0% 100.0%	1.00 (5.66, 1.56) 1.00 (5.66, 1.58)	
India points India points Test for overall effect 1.1.8 in bables < 20 w Uppins 1972s Sabidate (IdA CD) Total winds India points India points India points Test for overall effect 1.1.9 in bables betwee Uppins 1972s Sabidate (IdA CD) Total events Interconnects: Not as	107 5.25, df = 2 = 2.52 (welks' ge 15 15 plicable 2 = 0.01 (en 26 an 50 50 corrable	1 (P = 6 P = 0.01 23 23 P = 0.50 £ < 30 w 140 140	1,55 (02); P=) at 1st de 17 17 17 0 eeeks*g 54 54	e1% 26 26 28 estatic 121 121	100.0% 100.0%	1 50 (0 66, 1 50) 1.00 (0.66, 1.58)	
India points India points Test for overall effect. 1.1.8 in bables < 20 w Uppins 1972s Sabidate (IdA CD) Total winds India points Test for overall effect. 1.1.9 in bables betwee Uppins 1972a Sabidate (IdA CD) Total events Interconnects: Not as	107 5.25, df = 2 = 2.52 (welks' ge 15 15 plicable 2 = 0.01 (en 26 an 50 50 corrable	1 (P = 6 P = 0.01 23 23 P = 0.50 £ < 30 w 140 140	1,55 (02); P=) at 1st de 17 17 17 0 eeeks*g 54 54	e1% 26 26 28 estatic 121 121	100.0% 100.0%	1 50 (0 66, 1 50) 1.00 (0.66, 1.58)	+
total events Test for overall effect 1.1.8 in bables < 24 Sector 22 Sector 22 Sector 25 Sector 26 Test for overall effect 1.1.9 in bables between Sector 26 Sector 26	5 25, df = 2 = 2 52 (welks' ge 15 15 15 plicable 2 = 0.01 (en 26 an 50 60 plicable 2 = 1.47 (ean 30 a	1 (P = 0 P = 0.01 23 23 P = 0.50 £ < 30 w 140 140 P = 0.14 m < 33	1,55 (02); P =) at 1st de 17 17 0 54 54 0 0	61% 26 26 28 rstatic 121 121	100.0% 100.0% at 1st o 100.0% 500.0%	1.50 () 66, 1.50 1.60 () 66, 1.50 0.00 () 59, 1.50 0.40 () 59, 1.60 0.40 () 59, 1.60	
total events Test for overall effect 1.1.8 in bables < 24 Sector 22 Sector 22 Sector 25 Sector 26 Test for overall effect 1.1.9 in bables between Sector 26 Sector 26	5 25, df = 2 = 2 52 (welks' ge 15 15 15 plicable 2 = 0.01 (en 26 an 50 60 plicable 2 = 1.47 (ean 30 a	1 (P = 0 P = 0.01 23 23 P = 0.50 £ < 30 w 140 140 P = 0.14 m < 33	1,55 (02); P =) at 1st de 17 17 0 54 54 0 0	61% 26 26 28 rstatic 121 121	100.0% 100.0% at 1st o 100.0% 500.0%	1.50 () 66, 1.50 1.60 () 66, 1.50 0.00 () 59, 1.50 0.40 () 59, 1.60 0.40 () 59, 1.60	
Ioau events Ioau events Text for overail effect Text for overail effect (Lagens 1972s Stability (Lagens 1972s Stabi	5 25, df = 2 = 2 52 (weeks' ge 15 15 15 15 15 2 = 0.01 (en 26 an 50 50 50 50 50 50 50 15 15 15 15 15 15 15 15 15 15	1 (P = 0 P = 0.01 23 23 P = 0.50 £ < 30 to 140 140 P = 0.14 to 140 c < 33 165	1,55 (02); P =) at 1st de 17 17 17 0 0 0 54 54 0 0 0 9 0 9 0 9 0 9 0 9 0 9 0 9 0 9 0	estatic 26 26 28 121 121 121 121 121	100.0% 100.0% at 1st o 100.0% 500.0%	1.50 () 66, 1.50 1.60 () 66, 1.50 0.00 () 59, 1.50 0.40 () 59, 1.60 0.40 () 59, 1.60	
toa events toa events Test for overail effect 1.1.8 is babies < 30 Subport 1972 Sabobal (95% CD Todal watch instructional effect 1.1.9 is babies between Lagois 1972 Sabobal (95% CD Todal events Heatergoareek, Not ag- Test for overail effect 1.1.9 is babies between Lagois 1972 Sabobal (95% CD Todal events Heatergoareek, Not ag- Test for overail effect 1.1.9 is babies between Lagois 1972 Sabobal (95% CD Todal events Heatergoareek, Not ag-	525, df = 2 2 = 2 52 c weeks' ge 15 15 15 15 15 15 15 2 = 0.01 c en 26 an 50 60 00 cable 2 = 1.47 c een 30 a 19 19 19	1 (P = 0 P = 0.01 23 23 P = 0.50 £ < 30 to 140 140 P = 0.14 to 140 c < 33 165	1,55 (02); P =) at 1st de 17 17 0 54 54 0 0	estatic 26 26 28 121 121 121 121 121	100.0% 100.0% at 1st o 100.0% 500.0%	1.50 () 66, 1.50 1.60 () 66, 1.50 0.00 () 59, 1.50 0.40 () 59, 1.60 0.40 () 59, 1.60	1
Ioau events Ioau events Helersgenetic, Curl = 1 Text for overail effect (Lagren 1972a Section 2015) Section 2015 Section 2	107 525 df = 2 2 = 2 52 (weeks' ge 15 15 plicable 2 = 0.01 (en 26 an 50 60 plicable 2 = 1.47 (een 30 a 19 19 chiratie	1 (P = 0 P = 0.07 station 23 23 P = 0.50 a < 30 m 140 P = 0.14 md < 33 165 165	1,00 (022); P = 3 at 1st de 17 17 17 0 merks" 9 54 54 0 weeks", 30 30	estatic 26 26 28 121 121 121 121 121	100.0% 100.0% at 1st o 100.0% 500.0%	1.50 () 66, 1.50 1.60 () 66, 1.50 0.00 () 59, 1.50 0.40 () 59, 1.60 0.40 () 59, 1.60	
I road entrals I road entrals Test Erv overall effect: Test Erv overall effect: I as B bables e 28 w Upgins 19725 Sabolada (1976 CO Total events Sabolada (1975 CO Total events Sabolada (1975 CO Total events Sabolada (1975 CO Total events Test Erv overail effect. Not applicable total Sabolada (1976 CO Total events Test Erv overail effect. Sabolada (1976 CO Total events Test Erv overail effect.	107 525, df = 2 2 = 2 52 (weeks' go 15 15 plicable 2 = 0.01 (ees 26 an 50 plicable 2 = 1.47 (ees 30 a 19 19 plicable 2 = 1.52 (15 50 50 50 50 15 15 50 50 50 15 15 15 15 15 15 15 15 15 15	1 (P = 0 P = 0.01 23 22 P = 0.30 140 140 140 P = 0.14 140 140 145 165	125 127 127 137 17 17 17 17 17 17 17 17 17 1	81% 28 28 121 121 121 154	100.0% 100.0% 100.0% 100.0% 100.0%	102 (2016), 152 1020 (2016), 153 2010 (2016), 100 2010 (2016), 100 2010 (2016), 100 0 (2010), 100 0	1
I road entrals I road entrals Test Erv overall effect: Test Erv overall effect: I as B bables e 28 w Upgins 19725 Sabolada (1976 CO Total events Sabolada (1975 CO Total events Sabolada (1975 CO Total events Sabolada (1975 CO Total events Test Erv overail effect. Not applicable total Sabolada (1976 CO Total events Test Erv overail effect. Sabolada (1976 CO Total events Test Erv overail effect.	107 525, df = 2 2 = 2 52 (weeks' go 15 15 plicable 2 = 0.01 (ees 26 an 50 plicable 2 = 1.47 (ees 30 a 19 19 plicable 2 = 1.52 (15 50 50 50 50 15 15 50 50 50 15 15 15 15 15 15 15 15 15 15	1 (P = 0 P = 0.01 23 22 P = 0.30 140 140 140 P = 0.14 140 140 145 165	1,29 (2), P** at 1st do 17 17 17 17 17 17 17 17 54 54 54 54 0 0 0 0 0 0 0 0 0 0 0 0 0 0	81% 28 28 28 121 121 121 154 154	100.0% 100.0% en al 1at d 100.0% 100.0%	1.50 () 56, 1.60 1.60 () 566, 1.60 0.00 () 500, 1.00 0.00 () 5, 1.00 659 0.50 () 5, 1.01 0.59 () 5, 5, 5, 1.01 0.59 () 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5,	*
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Indexergents Index properties Test for overall effect Test for overall effect Index provide the second Department Statistics of the second Test for overall effect Department Statistics of the second Statistics of the	505, df = 2 = 252; 15 15 15 50 50 50 50 50 50 50 50 50 50 50 50 50	1 (P = 0 P = 0.01 31athon 23 23 P = 0.92 4<30 w 140 140 P = 0.14 145 145 145 145 145 145 145 1	1,29 (2), P** at 1st do 17 17 17 17 17 17 17 17 54 54 54 54 0 0 0 0 0 0 0 0 0 0 0 0 0 0	81% 28 28 28 121 121 121 154 154	100.0% 100.0% en al 1at d 100.0% 100.0%	102 (2016), 152 1020 (2016), 153 2010 (2016), 100 2010 (2016), 100 2010 (2016), 100 0 (2010), 100 0	* * *
Index optimized on the second	1007 22 = 252 (15 15 15 15 15 15 15 15 15 15 15 15 15	1 (P = 0 P = 0.07 23 23 P = 0.92 24 140 140 140 140 140 140 140 14	1,29 1,29 1,27 1,27 1,27 1,7 1,7 1,7 1,7 1,7 1,7 1,7 1,	81% 28 28 28 121 121 121 154 154	100.0% 100.0% en al 1at d 100.0% 100.0%	1 55 () 56 () 1 56 () 56 () 0 05 5 50 () 0 05 5	*
Total elevity Testific overall effects (1) and the second effects (1) and (1) and	1007 22 = 252 (15 15 15 15 15 15 15 15 15 15 15 15 15	$\begin{array}{c} 1 \ (P=0) \\ P=0.01 \\ 23 \\ 23 \\ P=0.91 \\ 140 \\ 140 \\ 140 \\ 140 \\ 140 \\ 140 \\ 160 \\ 150 \\ 160 \\ 100 \\ 1$	1,29 1,29 1,20 1,27	81% 26 28 99 121 121 121 154 154 185 185	100.0% 100.0% 100.0% 100.0% 100.0% 100.0%	1 30 () 36, 1 50 1 30 () 34, 1 50 3 0 () 35, 1 (0) 3 0 () 35, 1 (0) 3 0 () 5, 1 (0) 6 0 () 5 () 3, 1 (0) 6 0 () 5 () 3, 1 (0) 6 0 () 1 () 1 () 1 () 1 () 1 () 1 () 1 ()	* * *
That even a set of the second	100,000	1 (P = 0 P = 0.01 23 23 P = 0.30 4 < 30 165 P = 0.10 165 P = 0.0 168 168 168 168 168 168 168 168	2,1,9 2,1,9 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	81% 26 26 28 estatic 121 121 121 121 154 154 185 185	100.0% 100.0% 100.0% 100.0% 100.0%	1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 2.02 (2.55, 1.02) 2.02 (2.55, 1.02) 3.559 (2.5, 1.02) 4.59 (2.5, 1.02) 4000 4000 410 (2.55, 2.65) 4.59 (2.55, 2.65)	*
Testfor overall effect : 1.1.1 is to block < 2 % is general to the second of the sec	5 25, df = 2 = 2 52 (15 15 15 15 15 26 20 01 (15 26 00 1) 50 00 10 20 20 20 20 20 20 20 20 20 20 20 20 20	$10^{9} = 0.01$ 213 2233 2233 2233 2233 2233 2233 2233	12,0°= 12,0°= 12,0°= 12,0°= 13,0°= 13,0°= 14,0°=	estatic 26 26 26 26 26 26 26 26 26 26 26 26 26	100.0% 100.0% 100.0% 100.0% 100.0%	1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 2.02 (2.55, 1.02) 2.02 (2.55, 1.02) 3.559 (2.5, 1.02) 4.59 (2.5, 1.02) 4000 4000 410 (2.55, 2.65) 4.59 (2.55, 2.65)	*
Little version devices. Conv Conv Conv Little based of the Little based of the Little based of the Little based of Little b	525, dF = 52 = 252 (15 = 252 (15 = 15 = 15 = 16 = 17 = 18 = 19 = 10	1 (P = 0 01 9 = 0.01 23 23 P = 0.91 4 < 30 w 140 140 140 145 165 9 = 0.91 168 168 9 = 0.71 168 168 9 = 0.71 168 168 168 168 168 168 168 16	21,0% 21,0% 21,0% 21,0% 21,0% 20,0%	estatic 26 26 26 26 26 26 26 26 26 26 26 26 26	100.0% 100.0% 100.0% 100.0% 100.0%	1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 2.02 (2.55, 1.02) 2.02 (2.55, 1.02) 3.559 (2.5, 1.02) 4.59 (2.5, 1.02) 4000 4000 410 (2.55, 2.65) 4.59 (2.55, 2.65)	
Total elevity Testific overall effects (1) and the second effects (1) and (1) and	525, 07 = 52 = 252; 07 = 15 = 15 = 15 = 15 = 15 = 50 = 5	1 (P = 6 P = 0.01 23 23 23 P = 0.50 140 140 140 140 140 140 140 14	122,0°= 122,0°= 121	estatic 26 26 26 26 26 26 26 26 26 26 26 26 26	100.0% 100.0% 100.0% 100.0% 100.0%	1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 1.02 (2.06, 1.52) 2.02 (2.55, 1.02) 2.02 (2.55, 1.02) 3.559 (2.5, 1.02) 4.59 (2.5, 1.02) 4000 4000 410 (2.55, 2.65) 4.59 (2.55, 2.65)	* * *
The test of weak which is the test of	5 25, 07 = 5 25 27 252 (27 = 27 252 (27 = 15 12 52 (27 = 1	1 (P = 0 0) P = 0.01 23 23 P = 0.92 140 140 140 140 140 140 140 140 140 165 165 165 165 165 168	122,0°= 123,0°= 127 17 17 17 17 17 17 17 17 17 1	81% 000 26 26 28 estatic 121 121 121 154 154 154 pestat 107 107	100.0% 100.0% in at 1std 100.0% 100.0% 100.0% 100.0%	1 50 (2) 56, 1 52 1 50 (2) 56, 1 50 50 (2) 50, 1 50 50 (2) 50, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 1 10 (2) 5, 5 60 1 2 (2) (2), 5 50 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) (2) (
The test of weak which is the test of	5 25, 07 = 5 25 27 252 (27 = 27 252 (27 = 15 12 5 15 15 15 15 15 15 15 15 15 15 15 15 1	1 (P = 0 0) P = 0.01 23 23 P = 0.92 140 140 140 140 140 140 140 140 140 165 165 165 165 165 168	122,0°= 123,0°= 127 17 17 17 17 17 17 17 17 17 1	81% 000 26 26 28 estatic 121 121 121 154 154 154 pestat 107 107	100.0% 100.0% in at 1std 100.0% 100.0% 100.0% 100.0%	1 50 (2) 56, 1 52 1 50 (2) 56, 1 50 50 (2) 50, 1 50 50 (2) 50, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 1 10 (2) 5, 5 60 1 2 (2) (2), 5 50 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) (2) (
The test of the second	5 (5, 07 = 5 (5, 07 = 5 (5, 07 = 5 = 252; (5 = 15 = 15 = 15 = 15 = 15 = 16 = 27 = 0.01; (5 = 16 = 17 = 19 = 10 =	1 (P = 0.5) P = 0.01 21 22 P = 0.50 140 140 142 165 165 168 195 198 P = 0.71 168 198 P = 0.71 168 198 P = 0.71 108 198 P = 0.71 108 198 108 198	122,0°= 123,0°= 127 17 17 17 17 17 17 17 17 17 1	81% 000 26 26 28 estatic 121 121 121 154 154 154 pestat 107 107	100.0% 100.0% in at 1std 100.0% 100.0% 100.0% 100.0%	1 50 (2) 56, 1 52 1 50 (2) 56, 1 50 50 (2) 50, 1 50 50 (2) 50, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 1 10 (2) 5, 5 60 1 2 (2) (2), 5 50 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) (2) (
Lindowski, C. Ore - Construction of the con	5 25, 07 = 5 25, 07 = 5 25, 07 = 7 25 25 25 25 25 25 25 25 25 25 25 25 25	1 (P = 6 P = 0.01 23 23 P = 0.52 23 23 P = 0.52 24 20 25 27 27 27 27 27 27 27 27 27 27	122, (** 123, (** 127, (** 127, (** 127, (**), (**	81% 000 26 26 28 estatic 121 121 121 154 154 154 pestat 107 107	100.0% 100.0% in at 1std 100.0% 100.0% 100.0% 100.0%	1 50 (2) 56, 1 52 1 50 (2) 56, 1 50 50 (2) 50, 1 50 50 (2) 50, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 1 10 (2) 5, 5 60 1 2 (2) (2), 5 50 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) (2) (
The test of the second	5 25, 07 = 5 25, 07 = 5 25, 07 = 7 25 25 25 25 25 25 25 25 25 25 25 25 25	1 (P = 6 P = 0.01 23 23 P = 0.52 23 23 P = 0.52 24 20 25 27 27 27 27 27 27 27 27 27 27	122, (** 123, (** 127, (** 127, (** 127, (**), (**	81% 000 26 26 28 estatic 121 121 121 154 154 155 107 107	100.0% 100.0% in at 1std 100.0% 100.0% 100.0% 100.0%	1 50 (2) 56, 1 52 1 50 (2) 56, 1 50 50 (2) 50, 1 50 50 (2) 50, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 1 10 (2) 5, 5 60 1 2 (2) (2), 5 50 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) (2) (
Lindowski, C. Ore - Construction of the con	5 25, 07 = 5 25, 07 = 5 25, 07 = 7 25 25 25 25 25 25 25 25 25 25 25 25 25	1 (P = 6 P = 0.01 23 23 P = 0.52 23 23 P = 0.52 24 20 25 27 27 27 27 27 27 27 27 27 27	122, (** 123, (** 127, (** 127, (** 127, (**), (**	81% 000 26 26 28 estatic 121 121 121 154 154 155 107 107	100.0% 100.0% in at 1std 100.0% 100.0% 100.0% 100.0%	1 50 (2) 56, 1 52 1 50 (2) 56, 1 50 50 (2) 50, 1 50 50 (2) 50, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 0 98 (2) 5, 1 60 1 10 (2) 5, 5 60 1 2 (2) (2), 5 50 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) 1 2 (2) (2) (2) (2) (2) (2) (2) (2) (2) (

Figure 62:	Cerebroventricular	haemorrhage
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Study or Subgroup 1.2.1 In all babies	Treatm Events	Total	Coetr Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
1.2.1 In all babies Amorim 1999		100	17	100	10.7%	0.35 (0.15, 0.86)	
Dexiprom 1999	ő	105	0	101		Not extinuable	
Doran 1980	1	80		60	2.9%	0.19 (0.02, 1.63)	• • • • • • • • • • • • • • • • • • • •
Fekih 2002 Gamsy 1989	5 2	63 130	14	68	8.5%	0.19 [0.02, 1.63] 0.39 [0.15, 1.01] 0.51 [0.09, 2.72]	
Garte 1992	2 10	130 33 77	14 19 18 3 27 20 8 17	40	10.9%	0.64 (0.35, 1.16)	
Kari 1994	8	77	18	66	12.3%	0.38 (0.18, 0.82) 0.15 (0.01, 2.74)	
Lewis 1996	8 0 16	38 554	3	39	2.2%	0.15 [0.01, 2.74]	••
Liggins 1972a Morales 1989	10	954 87	27	507	16.9%	0.61 (0.33, 1.11) 0.58 (0.31, 1.09)	Contraction of the second
Oublan 2001	2	70	8	65	5.2%	0 23 10 05 1 05	• • • • •
Silver 1996	25	54	17	42	12.1%	1 14 (0.72, 1.02) 0.14 (0.01, 2.57)	
Taeusch 1979 Subtotal (95% CI)	0	54	4	69	2.5%	0.14 [0.01, 2.57] 0.54 [0.43, 0.69]	
Total events Heterogeneity: Chi ^a = 1	08 6.25, df	= 11 (P	155			and form and	
Test for overall effect 2							
1.2.2 In babies born fr Davierom 1999	om preg	105	s compê	tot	by prema	ture rupture of membrane Not estimable	s at 1st dose
Dexiprom 1999 Lewis 1995	0	.38	3	39	8.7%	0 15 10 01 2 741	•••
Liggins 1972a			7	158	17.4%	0.59 (0.18, 1.96) 0.58 (0.31, 1.09) 0.23 (0.05, 1.05) 0.47 (0.28, 0.79)	
Lippins 1995 Lippins 1972a Morales 1999 Gublan 2001	13	87 70	20	158 78 65	53.1%	0.58 (0.31, 1.09)	
Subtotal (95% CI)	2	454		441	100.0%	0.47 [0.28, 0.79]	+
Heterogeneity Chi ^a = 2 Test for overall effect 2	= 2.88 (P = 0.0	0.57); P+ 04)	0%			
1.2.3 In babies born <	28 week 5	34	12	20	100.0%	0.7410.14.0.961	
Liggins 1972a Subtotal (95% CI)		- 34		28	100.0%	0.34 (0.14, 0.86) 0.34 (0.14, 0.86)	
Total events	5		12				
Heterogeneity: Not app Test for overall effect 3	licable (= 2.29 (P=0.0	25				
1.2.4 In babies born 4	10 meek						
Lipgins 1972a Sebtotal (95% CI)	11	76	19	74	100.0%	0.56 [0.29, 1.10] 0.56 [0.29, 1.10]	
Subtotal (95% CI) Total events	н			74	100.0%	0.56 [0.29, 1.10]	
Total events Heterogeneity: Not app	11 icable		19				
Test for overall effect 2	= 1.68 (P = 0.0	9)				
1.2.5 In babies born <	32 week	15					
Lipgins 1972a Sebtotal (95% CI)	13	144	23	133	100.0%	0.52 (0.28, 0.99)	
Subtotal (95% CI)		144		133	100.0%	0.52 [0.28, 0.99]	-
Total events. Heterogeneity: Not app			23				
Test for overall effect 1	= 2.00 (P = 0.0	5)				
1.2.6 in babies born <							
1.2.6 In babies born <	34 week	373		-		0.6240.20.0.00	
Liggins 1972a Subtotal (95% CI)	10	273		242	100.0%	0.53 (0.29, 0.95) 0.53 (0.29, 0.95)	-
Total events	16		27				1212
Heterogeneity: Not app	incable :						
Test for overall effect 3			39				
1.2.7 In babies born <	36 meek	15					
Liggins 1972a Subtotal (95% CI)	16	394	27	373	100.0%	0.56 (0.31, 1.02) 0.56 (0.31, 1.02)	
Total events	16		27			and from the staff	
Heterogeneity: Not app	licable						
Test for overall effect 2							
1.2.8 in babies < 26 w	eeks' ge	station	at 1st di	ose	100.00		
Liggins 1972a Subtotal (95% CI)	- +	15	*	12	100.0%	1.20 [0.24, 6.06] 1.20 [0.24, 6.06]	
Total events	2						
Heteropeneity: Not app Test for overall effect 2	inclable						
1.2.9 In babies betwee Amorim 1999 Liggins 1972a	0	1	0	1	100.0%	Not estimable	_
Liggins 1972a	9	120	18	107	100.0%	0.45 (0.21, 0.95)	
Subtotal (95% CI) Total events		121	10	108	100.0%	0.45 [0.21, 0.95]	
Heterogeneity: Not app	licable						
Test for overall effect 3	t+ 2.09 (P = 0.0	4)				
1.2.10 In babies betw	ee 30 a	nd < 33	weeks'	pestat	ion at 1st	dose	
Liggins 1972a Subtotal (95% CI)	1	155	4	140	100.0%	0.23 [0.03, 2.00]	-
Total events		100		140	100.0%	ersa linear yool	
Heterogeneity: Not app	licable		-				
Test for overall effect 2	= 1.34 (P = 0.1	69				
1.2.11 In babies betw	ien 33 a	nd < 35	weeks'	pestat	ion at 1st	dose	
Liggins 1972a Subtotal (95% CI) Total events	3	161	3	178	100.0%	1.51 (0.23, 5.40)	
Subtotal (95% CI) Total events		101		178	100.0%	1.11 [0.23, 5.40]	
Heteropenetik: Not app	licable						
Test for overall effect 2							
1.2.12 In babies betw	ien 35 a	nd < 37	weeks'	pestat	ion at 1st	dose	
Lipgins 1972a Subtotal (95% CI)	0	85	0	108		Not estimable Not estimable	
Total events	0		Ó	10-0		THE REPORT OF	
Heterogeneity: Not app Test for overall effect. P	licable		đ.				
1.2.13 In babies > 36 v	veeks' g	estatio	e at 1st	dose		hist askessing	
Lipgins 1972a Subtotal (95% CI)	0	18	0	24		Not estimable Not estimable	
Total events	0		0				
	drable.						
Heteropeneith: Not app	int next	and the second					
Heterogeneity: Not app Test for overall effect ?	ict appli	cable					
Heteropeneith: Not app	iot appli	cable					01 02 05 1 2 5 1 Favours treatment Favours control

Figure 63: Intraventricular haemorrhage – grades 3 or 4

weather to an end of the second	Treatm	nent	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	al Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Doran 1980	1	80	4	60	0.0%	0.19 [0.02, 1.63]	an and an a star of the star of the star
Gamsu 1989	2	130	4	132	0.0%	0.51 [0.09, 2.72]	
Garite 1992	1	33	9	40	27.1%	0.13 [0.02, 1.01]	
Lewis 1996	0	38	3	39	11.5%	0.15 [0.01, 2.74]	• • •
Morales 1989	3	87	12	78	42.1%	0.22 [0.07, 0.77]	
Silver 1996	2	28	6	30	19.3%	0.36 [0.08, 1.63]	• • • • •
Total (95% CI)		186		187	100.0%	0.22 [0.10, 0.49]	•
Total events	6		30				27 22 N 22 A
Heterogeneity: Chi ² =	0.70, df=	3 (P =	0.87); I ² =	= 0%			0.01 0.1 1 10 100
Test for overall effect							0.01 0.1 1 10 100 Favours experimental Favours control

Figure 64: Chronic lung disease

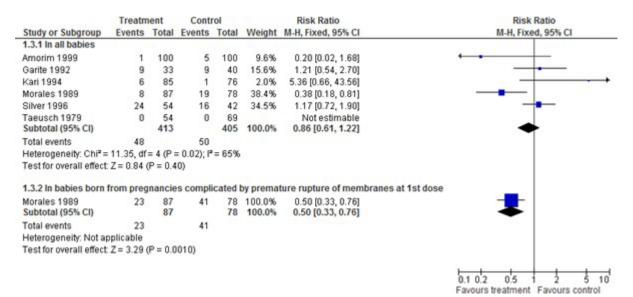


Figure 65: Need for mechanical intervention

	Treatm	ent	Contr	lor		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.4.1 In all babies							
Amorim 1999	28	100	45	100	72.3%	0.62 [0.42, 0.91]	
Block 1977	5	57	12	53	0.0%	0.39 [0.15, 1.03]	
Dexiprom 1999	15	105	16	101	0.0%	0.90 [0.47, 1.73]	
Garite 1992	14	24	19	29	27.7%	0.89 [0.58, 1.37]	
Porto 2011	2	144	1	131	0.0%	1.82 [0.17, 19.83]	
Subtotal (95% CI)		124		129	100.0%	0.70 [0.52, 0.93]	•
Total events	42		64				
Heterogeneity: Chi# =	= 1.59, df =	1 (P =	0.21); F=	37%			
Test for overall effect	: Z = 2.42 ((P = 0.0	(2)				
1.4.2 In babies born	from preg	nancie	s compli	icated	by prema	ture rupture of membranes at	1st dose
Dexiprom 1999	15	105	16	101	100.0%	0.90 [0.47, 1.73]	
Subtotal (95% CI)		105		101	100.0%	0.90 [0.47, 1.73]	-
Total events	15		16				
Heterogeneity: Not a	pplicable						
Test for overall effect		P = 0.7	5)				
							01 02 05 1 2 5 10
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	Treatm	ent	Contr	lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.5.1 In all babies							1000
Amorim 1999	13	100	28	100	42.6%	0.46 [0.26, 0.84]	
Collaborative 1981	4	307	10	299	15.4%	0.39 [0.12, 1.23]	
Dexiprom 1999	11	105	11	101	17.1%	0.96 [0.44, 2.12]	
Gamsu 1989	4	130	7	132	10.6%	0.58 [0.17, 1.93]	
Parsons 1988	0	23	0	22		Not estimable	
Porto 2011 Subtotal (95% CI)	6	144 809	9	131 785	14.3% 100.0%	0.61 [0.22, 1.66] 0.57 [0.39, 0.83]	•
Total events	38		65				
Heterogeneity: Chi ² =	2.58, df =	4 (P =	0.63); P=	0%			
Test for overall effect	Z = 2.91 ((P = 0.0	104)				
1.5.2 In babies born	from preg	nancie	s compli	icated I	by prema	ture rupture of membranes at	1st dose
Dexiprom 1999	11	105	11	101	100.0%	0.96 [0.44, 2.12]	
Parsons 1988 Subtotal (95% CI)	0	23 128	0	22 123	100.0%	Not estimable 0.96 [0.44, 2.12]	-
Total events Heterogeneity: Not a	11 nalicable		11				
Test for overall effect		(P = 0.9	(2)				
							0.1 0.2 0.5 1 2 5 1 Favours treatment Favours control

Figure 66: Neonatal sepsis (systemic infection in first 48 hours of life)

Figure 67: Cerebral palsy in childhood

	Treatm	ent	Conti	rol		Risk Ratio		Risk F	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	1, 95% CI
1.6.1 In all babies					1002			-	
Amorim 1999	1	60	2	34	8.4%	0.28 [0.03, 3.01]		•	
Collaborative 1981	9	200	15	206	48.6%	0.62 [0.28, 1.38]			_
Kari 1994	5	50	7	32	28.1%	0.46 [0.16, 1.32]	_	-	
Liggins 1972a	3	129	2	107	7.2%	1.24 [0.21, 7.31]	-		•
Schutte 1980 Subtotal (95% CI)	2	51 490	2	35 414	7.8%	0.69 [0.10, 4.64] 0.60 [0.34, 1.03]		-	
Total events	20		28						
Heterogeneity: Chi ² =	1.31, df=	4 (P =	0.86); I ² =	= 0%					
Test for overall effect	Z=1.85	(P = 0.0)	(7)						
							0.1 0.2	0.5 1	2 5

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Figure 68: Visual impairment in childhood

	Treatm	nent	Contr	lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.7.1 In all babies							
Kari 1994	2	50	3	32	27.8%	0.43 [0.08, 2.41]	
Schutte 1980	7	50	8	34	72.2%	0.59 [0.24, 1.49]	
Subtotal (95% CI)		100		66	100.0%	0.55 [0.24, 1.23]	
Total events	9		11				
Heterogeneity: Chi ² =	0.11, df=	1 (P=	0.74); I ² =	= 0%			
Test for overall effect	Z=1.45	(P = 0.1)	5)				

0.1 0.2 0.5 1 2 5 10 Favours treatment Favours control

Figure 69: Hearing impairment in childhood

	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
1.8.1 In all babies								
Kari 1994	1	50	1	32	100.0%	0.64 [0.04, 9.87]	←	_
Schutte 1980	0	50	0	34		Not estimable		
Subtotal (95% CI)		100		66	100.0%	0.64 [0.04, 9.87]		_
Total events	1		1					
Heterogeneity: Not ap	oplicable							
Test for overall effect	Z=0.32 ((P = 0.7)	'5)					
							0.1 0.2 0.5 1 2 5	10
							Favours treatment Favours cont	

Figure 70: Neurodevelopment delay in childhood

	Treatm	nent	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.9.1 In all babies							
Kari 1994 Subtotal (95% CI)	3	50 50	3	32	100.0%	0.64 [0.14, 2.98]	
Total events	3		3	02	1001011	olo i [oli i Lioo]	
Heterogeneity: Not ap	oplicable						
Test for overall effect	Z=0.57	(P = 0.5)	7)				
							0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Figure 71: Developmental delay in childhood

	Treatm	nent	Cont	rol		Risk Ratio		Risk R	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	95% CI	
1.10.1 In all babies					1.00					
Amorim 1999	4	60	7	34	43.4%	0.32 [0.10, 1.03]				
Collaborative 1981	7	206	12	218	56.6%	0.62 [0.25, 1.54]	-			
Subtotal (95% CI)		266		252	100.0%	0.49 [0.24, 1.00]	-			
Total events	11		19							
Heterogeneity: Chi ² =	0.74, df=	1 (P =	0.39); I ² =	= 0%						
Test for overall effect	Z=1.97 ((P = 0.0)	15)							
							0102	0.5 1	+	5 10





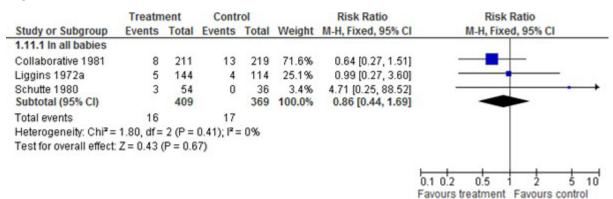


Figure 73: Behavioural/learning difficulties in childhood

	Treatm	ent	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.12.1 In all babies									
Schutte 1980	9	54	7	36	100.0%	0.86 [0.35, 2.09]			
Subtotal (95% CI)		54		36	100.0%	0.86 [0.35, 2.09]			
Total events	9		7						
Heterogeneity: Not ap	plicable								
Test for overall effect	Z=0.34 (P = 0.7	4)						
							0102	05 1 2 5	10

0.1 0.2 0.5 1 2 5 10 Favours treatment Favours control

Figure 74: Maternal mortality

	Treatm	nent	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.13.1 In all women			100000					and the second sec	
Amorim 1999	1	110	1	108	100.0%	0.98 [0.06, 15.50]	+	_	
Dexiprom 1999	0	28	0	18		Not estimable			
Schutte 1980	0	50	0	51		Not estimable			
Subtotal (95% CI)		188		177	100.0%	0.98 [0.06, 15.50]	_		
Total events	1		1						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=0.01	(P = 0.9	19)						
							0.1 0.2	0.5 1 2	5 10
							0.1 0.2	0.5 1 2	5 IU

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Figure 75: Side-effects of therapy in women

	Treatm	ent	Cont	rol		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
1.14.1 In all women								Sector State	
Schutte 1980 Subtotal (95% CI)	0	50 50	0	51 51		Not estimable Not estimable			
Total events Heterogeneity: Not ap Test for overall effect:		cable	0						
								\vdash	

0.1 0.2 0.5 1 2 5 10 Favours treatment Favours control

Figure 76: Puerperal sepsis

	Treatm	nent	Contr	lo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
.3.1 In all women							and the second sec
morim 1999	9	110	13	108	30.4%	0.68 [0.30, 1.52]	
Dexiprom 1999	4	102	7	102	16.2%	0.57 [0.17, 1.89]	
Barite 1992	10	33	5	38	10.8%	2.30 [0.88, 6.06]	
ewis 1996	2	38	4	39	9.2%	0.51 [0.10, 2.64]	· · · · · · · · · · · · · · · · · · ·
ublan 2001	9	72	2	67	4.8%	4.19 [0.94, 18.68]	
Schutte 1980	1	50	1	51	2.3%	1.02 [0.07, 15.86]	· · · · · ·
Silver 1996	11	39	5	36	12.1%	2.03 [0.78, 5.28]	
aeusch 1979 Subtotal (95% CI)	11	52 496	7	66 507	14.3%	1.99 [0.83, 4.79] 1.35 [0.93, 1.95]	•
otal events	57		44				100
leterogeneity: Chi ² =		= 7 (P =		= 36%			
est for overall effect.							
.3.4 In women with p	pregnanc	ies co	mplicate	d by pr	emature	rupture of membranes at 1st	dose
Dexiprom 1999	4	102	7	102	49.7%	0.57 [0.17, 1.89]	
ewis 1996	2	38	4	39	28.1%	0.51 [0.10, 2.64]	• • • • • • • • • • • • • • • • • • •
oublan 2001	9	72	2	67	14.7%	4.19 [0.94, 18.68]	
Schutte 1980	1	30	1	27	7.5%	0.90 [0.06, 13.70]	• •
Subtotal (95% CI)		242		235	100.0%	1.11 [0.55, 2.25]	-
otal events	16		14				
	5 00 df-	3 (P =	0.17); I ² =	41%			
leterogeneity: Chi ² = :	J.05, ui -						

I.8.2 Repeat courses

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline

I.9 Magnesium sulphate for neuroprotection

Figure 77: Stillbirth

	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	9	629	11	626	50.5%	0.81 [0.34, 1.95]	
Marret et al., 2007	2	352	3	336	14.0%	0.64 [0.11, 3.78]	
Rouse et al., 2008	5	1179	8	1252	35.5%	0.66 [0.22, 2.02]	
Total (95% CI)		2160		2214	100.0%	0.74 [0.39, 1.40]	•
Total events	16		22				
Heterogeneity: Chi ² = 0	0.11, df = 2 (P = 0.	95); I ² = 0	1%				0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.94 (P = 0.35))					Favours MgSO4 Favours control

Figure 78: Neonatal mortality: before discharge

	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	76	629	92	626	47.6%	0.82 [0.62, 1.09]	
Marret et al., 2007	31	352	32	336	16.9%	0.92 [0.58, 1.48]	-
Rouse et al., 2008	80	1179	71	1252	35.5%	1.20 [0.88, 1.63]	· •
Total (95% CI)		2160		2214	100.0%	0.97 [0.80, 1.18]	•
Total events	187		195				
Heterogeneity: Chi ² = 3	3.12, df = 2 (P = 0.	21); I ² = 3	86%				0.01 0.1 1 10 100
Test for overall effect: Z	Z = 0.29 (P = 0.77)					Favours MgSO4 Favours control

Figure 79: Neonatal/paediatric mortality: between discharge and follow-up

	Magnesium	Sulphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Crowther et al., 2003	2	629	4	626	19.6%	0.50 [0.09, 2.71]	
Rouse et al., 2008	18	1179	17	1252	80.4%	1.12 [0.58, 2.17]	
Total (95% CI)		1808		1878	100.0%	1.00 [0.55, 1.84]	+
Total events	20		21				
Heterogeneity: Chi ² = ().77, df = 1 (P =	0.38); I ² = 0	1%				0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.01 (P = 1.	00)					Favours MgSO4 Favours control

Figure 80: Total perinatal, neonatal and paediatric mortality

	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	87	629	107	626	44.6%	0.81 [0.62, 1.05]	a contraction of the second
Marret et al., 2008	34	352	38	336	16.2%	0.85 [0.55, 1.32]	
Mittendorf et al., 2002	2	30	1	29	0.4%	1.93 [0.19, 20.18]	
Rouse et al., 2008	103	1179	96	1252	38.8%	1.14 [0.87, 1.49]	+
Total (95% CI)		2190		2243	100.0%	0.95 [0.80, 1.13]	•
Total events	226		242				
Heterogeneity: Chi ² = 3	.82, df = 3 (P = 0.)	28); I ² = 2	2%				
Test for overall effect Z	(= 0.60 (P = 0.55)						0.01 0.1 1 10 100 Favours MgSO4 Favours control

Figure 81: Findings on cranial ultrasound: grades III or IV intracranial haemorrhage

	Magnesium	Sulphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	49	596	50	586	56.2%	0.96 [0.66, 1.40]	· · · · · · · · · · · · · · · · · · ·
Mittendorf et al., 2002	0	30	2	29	2.8%	0.19 [0.01, 3.87]	+ · · · · · · · · · · · · · · · · · · ·
Rouse et al., 2008	23	1112	38	1184	41.0%	0.64 [0.39, 1.07]	
Total (95% CI)		1738		1799	100.0%	0.81 [0.60, 1.09]	•
Total events	72		90				
Heterogeneity: Chi ² = 2	46, df = 2 (P =	0.29); I ² = 1	9%				
Test for overall effect Z	= 1.37 (P = 0.1	7)					0.01 0.1 1 10 100 Favours MgSO4 Favours control

Figure 82: Findings on cranial ultrasound: periventricular leukomalacia

	Magnesium	Sulphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	22	596	21	586	44.3%	1.03 [0.57, 1.85]	
Mittendorf et al., 2002	1	30	0	29	1.1%	2.90 [0.12, 68.50]	
Rouse et al., 2008	21	1112	27	1184	54.7%	0.83 [0.47, 1.46]	
Total (95% CI)		1738		1799	100.0%	0.94 [0.63, 1.40]	•
Total events	44		48				
Heterogeneity: Chi ² = 0	.78, df = 2 (P =	0.68); I [#] = 0	%				has also to the sect
Test for overall effect Z	= 0.30 (P = 0.3	76)					0.01 0.1 1 10 100 Favours MgSO4 Favours control

Figure 83: Cerebral palsy: any

	Magnesium	Sulphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	36	620	42	621	28.9%	0.86 [0.56, 1.32]	-
Marret et al., 2008	22	347	30	331	21.2%	0.70 [0.41, 1.19]	
Mittendorf et al., 2002	3	30	0	29	0.4%	6.77 [0.37, 125.65]	
Rouse et al., 2008	41	1133	74	1203	49.5%	0.59 [0.41, 0.85]	-
Total (95% CI)		2130		2184	100.0%	0.71 [0.56, 0.91]	•
Total events	102		146				
Heterogeneity: Chi ² = 4	.02, df = 3 (P =	0.26); I ² = 2	5%				0.01 0.1 1 10 100
Test for overall effect Z	= 2.71 (P = 0.0	007)					0.01 0.1 1 10 100 Favours MgSO4 Favours control

Figure 84: Cerebral palsy: moderate or severe (at 2 years)

	Magnesium :	Sulphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Crowther et al., 2003	15	620	21	620	36.2%	0.71 [0.37, 1.37]	
Rouse et al., 2008	20	1041	38	1095	63.8%	0.55 [0.32, 0.95]	
Total (95% CI)		1661		1715	100.0%	0.61 [0.40, 0.92]	•
Total events	35		59				-
Heterogeneity: Chi ² = 0).35, df = 1 (P =	0.55 ; $l^2 = 0$	1%				0.01 0.1 1 10 100
Test for overall effect: 2	z = 2.33 (P = 0.0)2)					0.01 0.1 1 10 100 Favours MgSO4 Favours control

Figure 85: Maternal death

	Magnesium Sul	phate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther et al., 2003	0	535	0	527		Not estimable	
Marret et al., 2007	0	286	1	278	100.0%	0.32 [0.01, 7.92]	
Rouse et al., 2008	0	1096	0	1145		Not estimable	
Total (95% CI)		1917		1950	100.0%	0.32 [0.01, 7.92]	
Total events	0		1				
Heterogeneity: Not app	licable						0.01 0.1 1 10 100
Test for overall effect: Z	= 0.69 (P = 0.49)						Favours MgSO4 Favours control

Figure 86: Maternal adverse effects: any

	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% Cl
Crowther et al., 2003	476	535	199	527	50.1%	2.36 [2.10, 2.64]		
Rouse et al., 2008	833	1078	140	1125	49.9%	6.21 [5.30, 7.27]		
Total (95% CI)		1613		1652	100.0%	3.82 [1.38, 10.59]		•
Total events	1309		339					
Heterogeneity: Tau ² = I	0.54; Chi ² = 109.5	57, df = 1	(P < 0.00	001); P	= 99%		0.01 0.1	1 10 100
Test for overall effect 2	Z = 2.58 (P = 0.01)					****	Favours control

Figure 87: Maternal adverse effects: leading to stopping of infusion

	Magnesium	Sulphate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Crowther et al., 2003	78	535	28	527	64.3%	2.74 [1.81, 4.15]	
Rouse et al., 2008	45	1078	16	1125	35.7%	2.94 [1.67, 5.16]	
Total (95% CI)		1613		1652	100.0%	2.81 [2.01, 3.93]	•
Total events	123		44				
Heterogeneity: Chi ² = (0.04, df = 1 (P =	: 0.85); l ² = 0	1%				0.01 0.1 1 10 100
Test for overall effect: 2	Z = 6.06 (P < 0.)	00001)					Favours MgSO4 Favours control

Figure 88: Maternal adverse effects: cardiac or respiratory arrest

	Magnesium Su	Iphate	Place	bo		Risk Ratio	Risk Ra	tio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed,	95% CI
Crowther et al., 2003	0	535	0	527		Not estimable	5	
Marret et al., 2007	0	286	0	278		Not estimable		
Total (95% CI)		821		805		Not estimable		
Total events	0		0					
Heterogeneity: Not app	licable							10 100
Test for overall effect: N	lot applicable						0.01 0.1 1 Favours MgSO4 Fi	10 100 avours control

I.10 Tocolysis

Figure 89: Neonatal mortality

•	•
Comparison	Odds Ratio (95% Crl)
Placebo/control v.	
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments	1.1 (0.39, 3.4) 1.5 (0.56, 4.1) 1.0 (0.49, 2.1) 0.62 (0.21, 1.8) 0.98 (0.016, 62.) 0.73 (0.23, 2.2) 2.3 (0.41, 14.) 0.56 (0.11, 2.6)
Prostaglandin inhibitors v.	
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments Other t	1.3 (0.45, 3.8) 0.90 (0.32, 2.4) 0.55 (0.16, 1.7) - 0.86 (0.013, 56.) 0.64 (0.16, 2.4) 2.1 (0.29, 14.) 0.49 (0.078, 2.7)
Magnesium sulfate v.	
Betamimetics	0.68 (0.26, 1.8) 0.42 (0.13, 1.2) 0.65 (0.010, 42.) 0.49 (0.13, 1.7) 1.6 (0.24, 10.) 0.37 (0.065, 1.8)
Betamimetics v.	0.01 (0.000, 1.0)
Calcium channel blockers	0.61 (0.25, 1.4) 0.96 (0.016, 57.) 0.71 (0.26, 1.8) 2.3 (0.44, 12.) 0.54 (0.10, 2.6)
Calcium channel blockers v.	
Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments	1.6 (0.024, 1.1e+02) 1.2 (0.36, 3.8) 3.7 (0.60, 25.) 0.89 (0.15, 5.1)
Nitrates v.	
Oxytocin receptor blockers Alcohol/ethanol Other treatments O	- 0.74 (0.011, 50.) - 2.4 (0.030, 1.9e+02) - 0.57 (0.0071, 44.)
Oxytocin receptor blockers v.	
Alcohol/ethanol Other treatments Alcohol/ethanol v.	3.2 (0.49, 22.) 0.76 (0.12, 4.7)
Other treatments	0.24 (0.021 1.6)
	0.24 (0.031, 1.6)
0.007 1 fav	200 ours treatment in bold

favours treatment in bold

Figure 90: Perinatal mortality

-	•
Comparison	Odds Ratio (95% Crl)
Placebo/control v.	
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments	0.72 (0.22, 2.3) 1.2 (0.35, 3.7) 1.0 (0.48, 2.) 0.76 (0.25, 2.2) 0.10 (0.0030, 1.1) 0.86 (0.25, 2.6) 2.6 (0.50, 14.) 2.0 (0.41, 9.7)
Prostaglandin inhibitors v.	
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments	$\begin{array}{c} 1.6 \ (0.44, \ 6.3) \\ 1.4 \ (0.43, \ 4.5) \\ 1.1 \ (0.25, \ 4.3) \\ 0.14 \ (0.0036, \ 1.9) \\ 1.2 \ (0.24, \ 5.4) \\ 3.6 \ (0.54, \ 25.) \\ 2.8 \ (0.41, \ 19.) \end{array}$
Magnesium sulfate v.	
Betamimetics	0.85 (0.28, 2.7) 0.64 (0.18, 2.5) 0.085 (0.0022, 1.1) 0.72 (0.15, 3.3) 2.2 (0.34, 16.) 1.7 (0.26, 12.)
Betamimetics v.	
Calcium channel blockers	0.75 (0.31, 1.8) 0.10 (0.0031, 1.1) 0.85 (0.28, 2.4) 2.6 (0.57, 13.) 2. (0.42, 9.7)
Calcium channel blockers v.	
Nitrates Oxytocin receptor blockers Alcohol/ethanol Other treatments Nitrates v.	0.13 (0.0037, 1.6) 1.1 (0.27, 4.4) 3.4 (0.60, 21.) 2.6 (0.43, 16.)
	0.4 (0.65, 0.45, 00)
Oxytocin receptor blockers Alcohol/ethanol Other treatments	8.4 (0.65, 3.1e+02) → 26. (1.6, 1.2e+03) 20. (1.2, 8.7e+02)
Oxytocin receptor blockers v.	
Alcohol/ethanol o Other treatments o	3.0 (0.50, 22.) 2.3 (0.37, 16.)
Alcohol/ethanol v.	
Other treatments	0.77 (0.13, 4.5)
0.002 1	2000
fa	avours treatment in bold

Figure 91: Respiratory distress syndrome

•		
Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.1 (0.68, 1.9) 1.2 (0.76, 1.9) 0.88 (0.65, 1.2) 0.81 (0.50, 1.3) 0.96 (0.66, 1.4) 2.5 (0.78, 9.1) 0.75 (0.26, 2.2)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		1.1 (0.69, 1.7) 0.78 (0.49, 1.3) 0.71 (0.41, 1.3) 0.85 (0.52, 1.4) 2.2 (0.65, 8.4) 0.66 (0.20, 2.2)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments		0.73 (0.47, 1.2) 0.67 (0.41, 1.1) 0.80 (0.51, 1.3) 2.1 (0.62, 7.9) 0.63 (0.19, 2.0)
Betamimetics v.		
Calcium channel blockers Oxytocin receptor blockers Alcohol/ethanol Other treatments	+ + 	0.92 (0.61, 1.4) 1.1 (0.77, 1.5) 2.9 (0.92, 9.8) 0.85 (0.28, 2.6)
Calcium channel blockers v.		
Oxytocin receptor blockers Alcohol/ethanol Other treatments	 	1.2 (0.73, 1.9) 3.1 (0.93, 11.) 0.93 (0.28, 3.0)
Oxytocin receptor blockers v.		
Alcohol/ethanol Other treatments	 	2.6 (0.80, 9.5) 0.79 (0.25, 2.4)
Alcohol/ethanol v.		
Other treatments0.05	-0	0.29 (0.057, 1.5)
0.05	' favou	rs treatment in bold

Figure 92: Intraventricular haemorrhage

U		0
Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments –		0.76 (0.35, 1.6) 0.69 (0.33, 1.4) 0.79 (0.51, 1.2) 0.40 (0.21, 0.74) 0.34 (0.081, 1.1) 0.82 (0.48, 1.4) 0.14 (0.016, 0.77)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments		0.91 (0.54, 1.5) 1.0 (0.53, 2.1) 0.53 (0.27, 1.0) 0.45 (0.096, 1.7) 1.1 (0.48, 2.4) 0.19 (0.023, 0.94)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments		1.2 (0.58, 2.3) 0.58 (0.30, 1.1) 0.49 (0.11, 1.9) 1.2 (0.53, 2.7) 0.21 (0.026, 0.95)
Betamimetics v.		
Calcium channel blockers Nitrates Oxytocin receptor blockers Other treatments	- 0 	0.50 (0.30, 0.83) 0.43 (0.11, 1.4) 1.0 (0.63, 1.7) 0.18 (0.021, 0.96)
Calcium channel blockers v.		
Nitrates Oxytocin receptor blockers Other treatments	 	0.85 (0.20, 3.0) 2.1 (1.0, 4.1) 0.36 (0.042, 1.9)
Nitrates v.		
Oxytocin receptor blockers Other treatments		— 2.4 (0.68, 10.) 0.42 (0.037, 3.7)
Oxytocin receptor blockers v.		
Other treatments -0.01	 1 fi	0.17 (0.019, 0.98) 20 avours treatment in bold

56

Figure 93: Mothers with adverse events requiring cessation of treatment

Comparison	Odds Ratio (95% Crl)
Placebo/control v.	
Magnesium sulfateBetamimeticsCalcium channel blockersNitratesOxytocin receptor blockers	→ → 16. (1.9, 1.8e+02) → → 1.3e+02 (19., 1.3e+03) → → 5.2 (0.35, 57.) → → 5.6 (0.26, 1.6e+02) → → 3.1 (0.31, 23.)
Magnesium sulfate v.	
BetamimeticsCalcium channel blockersNitratesOxytocin receptor blockers	→→ 8.0 (2.2, 34.) 0.32 (0.045, 1.4) 0.34 (0.013, 9.2) 0.19 (0.019, 1.1)
Betamimetics v.	
Calcium channel blockers ——— Nitrates ——— Oxytocin receptor blockers ————	0.039 (0.0059, 0.14) 0.042 (0.0015, 1.2) 0.023 (0.0033, 0.091)
Calcium channel blockers v.	
Nitrates	• 1.1 (0.039, 49.) • 0.59 (0.071, 5.3)
Nitrates v.	
Oxytocin receptor blockers	0.54 (0.013, 15.) 1 2000
	favours treatment in bold

Figure 94: Delay of birth by at least 48 hours

0		
Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors		3.1 (1.5, 7.1)
Magnesium sulfate	-0	2.1 (1.1, 4.1)
Betamimetics		2.0 (1.2, 3.6)
Calcium channel blockers	-0	2.0 (1.1, 3.8)
Nitrates		0.89 (0.40, 2.0)
Oxytocin receptor blockers		1.9 (1.0, 3.7)
Alcohol/ethanol		0.83 (0.12, 5.6)
Other treatments	<u>P</u>	1.1 (0.38, 3.2)
Prostaglandin inhibitors v.		
Magnesium sulfate	-0+	0.67 (0.33, 1.3)
Betamimetics	-0-	0.65 (0.32, 1.3)
Calcium channel blockers	-0-	0.64 (0.31, 1.3)
Nitrates	<u> </u>	0.28 (0.100, 0.78)
Oxytocin receptor blockers		0.61 (0.26, 1.4)
Alcohol/ethanol —		0.26 (0.035, 1.9)
Other treatments		0.35 (0.099, 1.2)
Magnesium sulfate v.		
Betamimetics		0.97 (0.57, 1.7)
Calcium channel blockers		0.96 (0.56, 1.6)
Nitrates		0.43 (0.17, 1.1)
Oxytocin receptor blockers Alcohol/ethanol		0.92 (0.45, 1.9)
Other treatments		0.40 (0.057, 2.7) 0.53 (0.17, 1.7)
		0.55 (0.17, 1.7)
Betamimetics v.		
Calcium channel blockers	-	0.99 (0.65, 1.5)
Nitrates		0.44 (0.19, 1.0)
Oxytocin receptor blockers Alcohol/ethanol		0.95 (0.54, 1.6)
Other treatments		0.41 (0.062, 2.6) 0.54 (0.18, 1.6)
		0.54 (0.10, 1.0)
Calcium channel blockers v.		
Nitrates		0.44 (0.19, 1.0)
Oxytocin receptor blockers		0.96 (0.52, 1.7)
Alcohol/ethanol Other treatments		0.41 (0.060, 2.7)
		0.54 (0.18, 1.6)
Nitrates v.		
Oxytocin receptor blockers	+ •	2.2 (0.85, 5.5)
Alcohol/ethanol		0.93 (0.12, 7.0)
Other treatments		1.2 (0.34, 4.5)
Oxytocin receptor blockers v.		
Alcohol/ethanol		0.43 (0.062, 3.)
Other treatments		0.57 (0.19, 1.8)
Alcohol/ethanol v.		
Other treatments		- 1.3 (0.21, 8.6)
0 03		9
	1	ษ
favours treatmen	l III dola	

Figure 95: Neonatal sepsis

Comparison		Odds Ratio (95% Crl)
Placebo/control v.		
Prostaglandin inhibitors Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Other treatments		1.6 (0.33, 9.3) 1.9 (0.43, 11.) 1.1 (0.25, 6.6) 0.83 (0.18, 4.7) 1.2 (0.22, 7.1) 1.3 (0.21, 8.0)
Prostaglandin inhibitors v.		
Magnesium sulfate Betamimetics Calcium channel blockers Oxytocin receptor blockers Other treatments		1.2 (0.63, 2.4) 0.72 (0.29, 1.8) 0.52 (0.23, 1.1) 0.73 (0.25, 2.1) 0.81 (0.065, 9.)
Magnesium sulfate v.		
Betamimetics Calcium channel blockers Oxytocin receptor blockers Other treatments –		0.59 (0.26, 1.3) 0.43 (0.21, 0.86) 0.60 (0.22, 1.6) 0.67 (0.056, 7.0)
Betamimetics v.		
Calcium channel blockers Oxytocin receptor blockers Other treatments	 	0.72 (0.42, 1.2) 1.0 (0.55, 1.9) - 1.1 (0.093, 12.)
Calcium channel blockers v.		
Oxytocin receptor blockers Other treatments		1.4 (0.65, 3.0) — 1.6 (0.13, 17.)
Oxytocin receptor blockers v	·.	
Other treatments	P	1.1 (0.086, 13.)
0.05	5 1	20
	favou	irs treatment in bold

59

Figure 96: Gestational age at birth

Comparison	Mean difference (95% Crl)
Placebo/control v.	
Prostaglandin inhibitorsOMagnesium sulfate-OBetamimetics-OCalcium channel blockers-ONitrates-OOxytocin receptor blockersO	- 2.3 (1.3, 3.3) 1.3 (0.29, 2.3) 1.2 (0.40, 2.1) 1.7 (0.69, 2.7) 1.7 (0.52, 2.8) 0.68 (-1.3, 2.7)
Prostaglandin inhibitors v.	
Magnesium sulfate -O Betamimetics -O Calcium channel blockers -O Nitrates -O Oxytocin receptor blockers -O	-1.0 (-2.0, -0.039) -1.1 (-2.1, -0.054) -0.64 (-1.7, 0.42) -0.67 (-2., 0.67) -1.6 (-3.8, 0.52)
Magnesium sulfate v.	
Betamimetics	-0.040 (-0.99, 0.91) 0.40 (-0.51, 1.3) 0.36 (-0.88, 1.6) -0.61 (-2.7, 1.5)
Betamimetics v.	
Calcium channel blockers	0.44 (-0.32, 1.2) 0.40 (-0.54, 1.4) -0.57 (-2.6, 1.5)
Calcium channel blockers v.	0.000 (4.0. 4.4)
Nitrates	-0.033 (-1.2, 1.1) -1.0 (-3., 0.99)
Nitrates v.	
Oxytocin receptor blockers	-0.98 (-3.1, 1.2) 4
favours treatment in bold	

I.11 Fetal monitoring

I.11.1 EFM versus IA

No forest plots were generated for this review question

I.11.2 Use of FSE

No forest plots were generated for this review question

I.11.3 CTG interpretation

No forest plots were generated for this review question

I.11.4 Blood sampling

No forest plots were generated for this review question

I.12 Mode of birth

I.12.1 Planned immediate caesarean section versus planned vaginal delivery in singletons

I.12.1.1 Neonatal outcome

Figure 97: Perinatal death

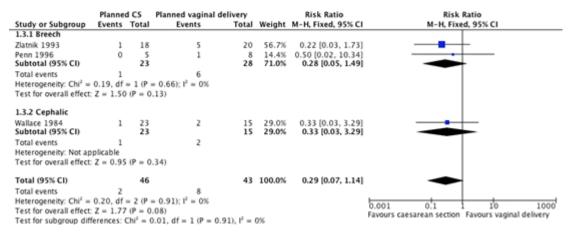


Figure 98: Intracranial pathology (outcome not pre-specified)

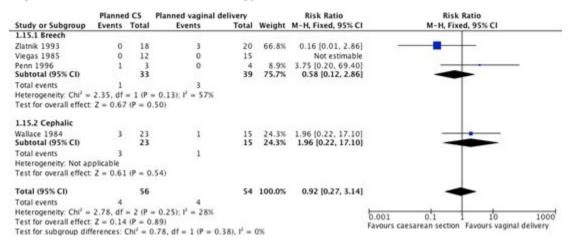


Figure 99: Hypoxic ischemic encephalopathy

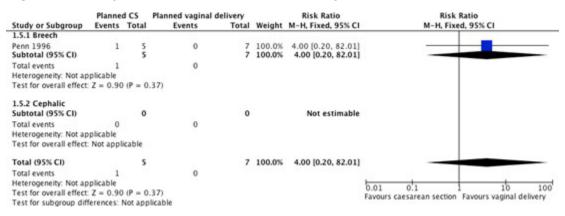
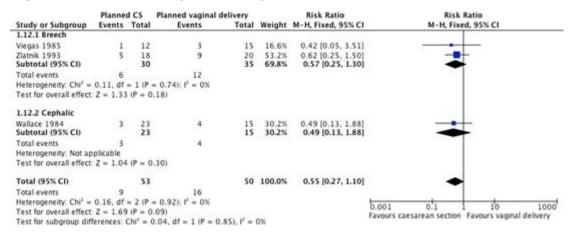


Figure 100: Respiratory distress syndrome



I.12.2 Immediate caesarean section versus planned vaginal delivery in singletons

I.12.2.1 Maternal outcomes

Figure 101: Postpartum haemorrhage

	Planne	d CS	Planned vaginal de	livery		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.4.1 Breech		- 1.5.4		1000			
Viegas 1985	1	12	0	15	100.0%	3.69 [0.16, 83.27]	
Zlatnik 1993	0	18	0	20		Not estimable	
Lumley 1985	0	1	0	1		Not estimable	
Subtotal (95% CI)		31		36	100.0%	3.69 [0.16, 83.27]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect		(P = 0)	.41)				
2.4.2 Cephalic							
Wallace 1984 Subtotal (95% CI)	0	23	0	15		Not estimable Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect		icable					
Total (95% CI)		54		51	100.0%	3.69 [0.16, 83.27]	
Total events	1		0				
Heterogeneity: Not ap	plicable						have the de read
Test for overall effect		(P = 0)	.41)				0.001 0.1 1 10 1000
Test for subgroup diff							Favours caesarean section Favours vaginal delivery

Figure 102: Maternal wound infection

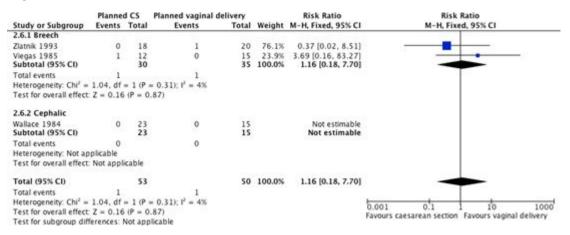


Figure 103: Other maternal infection

	Planne	d CS	Planned vaginal d	elivery		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.7.1 Breech							
Zlatnik 1993	9	18	4	20	89.4%	2.50 [0.93, 6.73]	
Viegas 1985 Subtotal (95% CI)	1	12 30	0	15 35	10.6%		
Total events	10		4				
Heterogeneity: Chi2 =	0.06, df	= 1 (P	$= 0.81$; $l^2 = 0\%$				
Test for overall effect	Z = 1.99	(P = 0)	.05)				
2.7.2 Cephalic							
Wallace 1984	0	23	0	15		Not estimable	
Subtotal (95% CI)		23		15		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	Not appl	icable					
Total (95% CI)		53		50	100.0%	2.63 [1.02, 6.78]	
Total events	10		4				
Heterogeneity: Chi2 =	0.06, df	= 1 (P	$= 0.81$; $l^2 = 0\%$				0.5 0.7 1.5 2
Test for overall effect	Z = 1.99	(P = 0)	.05)				Favours caesarean section Favours vaginal delivery
Test for subgroup diff	erences: I	Not app	licable				ravours caesarean section. Pavours vaginal delivery

I.13 Timing of cord clamping

I.13.1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Figure 104: Infant death

	More placenta	I trans	Less placenta	al trans		Risk Ratio		Risk Rat	0	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 9	5% CI	
1.1.1 Infant death ove	erall									
Ultee 2008	0	18	0	19		Not estimable				
Mercer 2003	0	16	0	16		Not estimable				
Kinmond 1993	0	17	0	19		Not estimable				
Strauss 2008	0	45	0	60		Not estimable				
Hofmeyr 1988	5	24	0	14	2.4%	6.60 [0.39, 111.10]				
Hofmeyr 1993	1	40	1	46	3.6%	1.15 [0.07, 17.80]				
Kugelman 2007	0	30	1	35	5.3%	0.39 [0.02, 9.16]				
Rabe 2000	0	19	1	20	5.6%	0.35 [0.02, 8.10]				
McDonnell 1997	0	23	2	23	9.6%	0.20 [0.01, 3.95]				
Baezinger 2007	0	15	3	24	10.5%	0.22 [0.01, 4.04]		•		
Oh 2002	2	16	3	17	11.2%	0.71 [0.14, 3.70]				
Hosono 2008	2	20	3	20	11.5%	0.67 [0.12, 3.57]				
Mercer 2006	0	36	3	36	13.4%	0.14 [0.01, 2.67]	-		_	
Ranjit 2014	0	44	5	50	19.8%	0.10 [0.01, 1.81]	+	•		
Subtotal (95% CI)		363		399	92.8%	0.51 [0.26, 1.01]		•		
Total events	10		22							
Heterogeneity: Chi ² =	6.44, df = 9 (P =	0.70); P=	0%							
Test for overall effect:	Z = 1.92 (P = 0.0	05)								
1.1.2 Uterotonic used	1									
Hofmeyr 1988	5	24	0	14		Not estimable				
McDonnell 1997	0	19	1	20		Not estimable				
Rabe 2000	0	19	1	20		Not estimable				
Baezinger 2007	1	44	2	50	7.2%	0.57 [0.05, 6.05]				
Subtotal (95% CI)		44		50	7.2%	0.57 [0.05, 6.05]				
Total events	1		2							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.47 (P = 0.6	64)								
Total (95% CI)		407		449	100.0%	0.52 [0.27, 0.99]		•		
Total events	11		24							
Heterogeneity: Chi ² =	6.45, df = 10 (P	= 0.78); P	= 0%				-	-	1	
Test for overall effect:			0.0000000				0.01	0.1 i	10	10
Test for subgroup diff			1 m - 0 0 0 R.					More PT better Les	ss PT better	

Figure 105: Intraventricular haemorrhage

	More placenta	I trans	Less placenta	I trans		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.2.1 New Subgroup									
Strauss 2008	1	45	1	60	1.1%	1.33 [0.09, 20.75]		-	
Ranjit 2014	0	44	1	50	1.8%	0.38 [0.02, 9.04]			
McDonnell 1997	0	15	1	16	1.9%	0.35 [0.02, 8.08]			
Oh 2002	4	16	3	17	3.8%	1.42 [0.37, 5.37]			
Rabe 2000	1	19	3	20	3.8%	0.35 [0.04, 3.09]			
Kugelman 2007	2	30	4	35	4.8%	0.58 [0.11, 2.96]			
Mercer 2003	3	16	5	16	6.5%	0.60 [0.17, 2.10]			
Hosono 2008	3	20	5	20	6.5%	0.60 [0.17, 2.18]			
Hofmeyr 1993	8	40	11	46	13.4%	0.84 [0.37, 1.87]			
Hofmeyr 1988	8	23	10	13	16.7%	0.45 [0.24, 0.85]			
Mercer 2006	5	36	13	36	17.0%	0.38 [0.15, 0.97]			
Subtotal (95% CI)		304		329	77.6%	0.59 [0.41, 0.84]		•	
Total events	35		57						
Heterogeneity: Chi# =	4.62, df = 10 (P =	= 0.92); I ^a	= 0%						
Test for overall effect.	Z = 2.88 (P = 0.0	04)							
1.2.2 Uterotonic used	1								
McDonnell 1997	0	15	1	16	1.9%	0.35 [0.02, 8.08]			
Rabe 2000	4	16	3	17	3.8%	1.42 [0.37, 5.37]			
Hofmeyr 1988	8	23	10	13	16.7%	0.45 [0.24, 0.85]			
Subtotal (95% CI)		54		46	22.4%	0.61 [0.34, 1.08]		•	
Total events	12		14						
Heterogeneity: Chi ² =	2.50, df = 2 (P =	0.29); I2 =	20%						
Test for overall effect.	Z = 1.71 (P = 0.0	9)							
Total (95% CI)		358		375	100.0%	0.59 [0.44, 0.81]		•	
Total events	47		71						
Heterogeneity: Chi ² =	7.08, df = 13 (P =	= 0.90); P	= 0%				h		
Test for overall effect.							0.01 0.1	i 10 e PT better Less PT bette	100
Test for subgroup diff			1 (P = 0.92) P=	: 0%			MORE	eribeder Lessribede	

Figure 106: Severe intraventricular haemorrhage

	More placenta	I trans	Less placenta	I trans	Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.3.1 New Subgroup									
Mercer 2003	0	16	0	16		Not estimable			
Rabe 2000	0	19	0	20		Not estimable		2.55	
Hofmeyr 1988	2	23	0	13	7.3%	2.92 [0.15, 56.51]			
Mercer 2006	0	36	1	36	17.4%	0.33 [0.01, 7.92]			
Hofmeyr 1993	1	40	2	46	21.6%	0.57 [0.05, 6.11]			
Hosono 2008	2	20	4	20	46.4%	0.50 [0.10, 2.43]			
Subtotal (95% CI)		154		151	92.7%	0.68 [0.23, 1.96]		-	
Total events	5		7						
Heterogeneity: Chi ² = 1	1.28, df = 3 (P =	0.73); P=	0%						
Test for overall effect 2									
1.3.2 Uterotonic used									
Rabe 2000	0	19	0	20		Not estimable			
Hofmeyr 1988	2	23	0	13	7.3%	2.92 [0.15, 56.51]			
Subtotal (95% CI)		42		33	7.3%	2.92 [0.15, 56.51]			
Total events	2		0						
Heterogeneity: Not app	plicable								
Test for overall effect 2	Z = 0.71 (P = 0.4	18)							
Total (95% CI)		196		184	100.0%	0.84 [0.32, 2.22]		•	
Total events	7		7			100000000000000000000000000000000000000			
Heterogeneity: Chi ² = 3	2.20, df = 4 (P =	0.70); P=	0%				+		
Test for overall effect			0.000				0.002	0.1 1 10	500
Test for subgroup diffe			1 /D - 0 203 IZ-	0.00				More PT better Less PT better	

Figure 107: Ventilated for respiratory distress syndrome

	More placenta	I trans	Less placenta	I trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.4.1 New Subgroup							
Strauss 2008	3	45	7	60	7.9%	0.57 [0.16, 2.09]	
Ranjit 2014	5	44	8	50	9.9%	0.71 [0.25, 2.01]	
Rabe 2000	9	19	8	20	10.3%	1.18 [0.58, 2.42]	
McDonnell 1997	9	23	9	23	11.8%	1.00 [0.49, 2.06]	
Baezinger 2007	6	15	12	24	12.1%	0.80 [0.38, 1.67]	
Kinmond 1993	13	17	13	19	16.1%	1.12 [0.75, 1.67]	-
Subtotal (95% CI)		163		196	68.1%	0.93 [0.69, 1.25]	+
Total events	45		57				
Heterogeneity: Chi# =	2.25, df = 5 (P =	0.81); P=	0%				
Test for overall effect:	Z = 0.49 (P = 0.6	53)					
1.4.2 Uterotonic used							12
Rabe 2000	3	45	7	60	7.9%	0.57 [0.16, 2.09]	
McDonnell 1997	9	23	9	23	11.8%	1.00 [0.49, 2.06]	
Baezinger 2007	6	15	12	24	12.1%	0.80 [0.38, 1.67]	
Subtotal (95% CI)		83		107	31.9%	0.82 [0.50, 1.33]	-
Total events	18		28				
Heterogeneity: Chi ² =	0.60, df = 2 (P =	0.74); P=	0%				
Test for overall effect:	Z = 0.81 (P = 0.4	12)					
Total (95% CI)		246		303	100.0%	0.89 [0.69, 1.15]	+
Total events	63		85				· · · · · · · · · · · ·
Heterogeneity: Chi ² =	3.24, df = 8 (P =	0.92); P=					
Test for overall effect.							0.1 0.2 0.5 1 2 5 10
Test for subgroup diff.			1 /D - 0 CO R-	0.00			More PT better Less PT better

Test for subgroup differences: Chi# = 0.19, df = 1 (P = 0.66), I# = 0%

Figure 108: Hyperbilirubinemia

	More placenta	I trans	Less placenta	I trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.5.1 New Subgroup							
Ultee 2008	6	18	8	19	13.4%	0.79 [0.34, 1.83]	
Rabe 2000	12	19	12	20	20.2%	1.05 [0.64, 1.73]	
Strauss 2008 Subtotal (95% CI)	33	45 82	31	59 98	46.3% 79.8%	1.40 [1.03, 1.88] 1.21 [0.94, 1.55]	•
Total events	51		51				
Heterogeneity: Chi? =	2.16, df = 2 (P =	0.34); P=	8%				
Test for overall effect							
1.5.2 Uterotonic used	d						
Rabe 2000 Subtotal (95% CI)	12	19 19	12	20 20	20.2%	1.05 [0.64, 1.73] 1.05 [0.64, 1.73]	-
Total events	12		12				
Heterogeneity: Not ap	oplicable						
Test for overall effect	Z = 0.20 (P = 0.8	34)					
Total (95% CI)		101		118	100.0%	1.18 [0.94, 1.47]	+
Total events	63		63				
Heterogeneity: Chi ² =	2.49, df = 3 (P =	0.48); P=	= 0%				
Test for overall effect.							0.1 0.2 0.5 1 2 5 10 More PT better Less PT better
Test for subgroup diff			1 (P = 0.63) P =	0%			More Proeder Less Proeder

Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%

Figure 109: Transfused for anaemia

	More placenta	trans	Less placenta	I trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.6.1 New Subgroup							
Strauss 2008	2	45	5	59	4.5%	0.52 [0.11, 2.58]	
Kugelman 2007	3	30	5	35	4.9%	0.70 [0.18, 2.69]	
McDonnell 1997	4	23	6	23	6.3%	0.67 [0.22, 2.05]	
Kinmond 1993	1	13	7	13	7.4%	0.14 [0.02, 1.00]	
Hosono 2008	7	20	14	20	14.7%	0.50 [0.26, 0.97]	
Rabe 2000	9	19	16	20	16.4%	0.59 [0.35, 1.00]	
Mercer 2006 Subtotal (95% CI)	18	36 186	22	36 206	23.1%	0.82 [0.54, 1.24] 0.61 [0.46, 0.81]	•
Total events	44		75				2014
Heterogeneity: Chi ² = 4	4.50, df = 6 (P =	0.61); P=	0%				
Test for overall effect 2	Z = 3.46 (P = 0.0	005)					
1.6.2 Uterotonic used							
McDonnell 1997	4	23	6	23	6.3%	0.67 [0.22, 2.05]	
Rabe 2000 Subtotal (95% CI)	9	19 42	16	20 43	16.4%	0.59 [0.35, 1.00] 0.61 [0.37, 1.00]	•
Total events	13		22				
Heterogeneity: Chi ² = I	0.04, df = 1 (P =	0.85); P=					
Test for overall effect.							
Total (95% CI)		228		249	100.0%	0.61 [0.48, 0.78]	•
Total events	57		97				
Heterogeneity: Chi ² = 4	4.53, df = 8 (P =	0.81); P=	0%				
Test for overall effect 2							0.01 0.1 1 10 100 More PT better Less PT better
Test for subgroup diffe			1 (P = 0.98), I ² =	0%			More Pri beder Less Pi beder

Figure 110: Apgar score at 5th minute < 8

	More placenta	I trans	Less placenta	Less placental trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.8.1 New Subgroup							
Hofmeyr 1988	0	14	4	24	14.4%	0.19 [0.01, 3.20]	
Hofmeyr 1993	8	39	7	45	27.6%	1.32 [0.53, 3.31]	
Rabe 2000	5	19	7	20	29.0%	0.75 [0.29, 1.96]	
Subtotal (95% CI)		72		89	71.0%	0.86 [0.45, 1.62]	+
Total events	13		18				
Heterogeneity: Chi ² = 1	2.02, df = 2 (P =	0.36); P=	1%				
Test for overall effect.	Z = 0.47 (P = 0.6	(4)					
1.8.2 Uterotonic used	i i i						
Hofmeyr 1988	14	0	4	24		Not estimable	
Rabe 2000	5	19	7	20	29.0%	0.75 [0.29, 1.96]	
Subtotal (95% CI)		19		44	29.0%	0.75 [0.29, 1.96]	-
Total events	19		11				
Heterogeneity: Not ap	plicable						
Test for overall effect.	Z = 0.58 (P = 0.5	6)					
Total (95% CI)		91		133	100.0%	0.83 [0.49, 1.41]	+
Total events	32		29				
Heterogeneity: Chi ² = 1	2.12, df = 3 (P =	0.55); I ² =	0%				to a de la col
Test for overall effect 2	· · · · · · · · · · · · · · · · · · ·						0.01 0.1 1 10 100 More PT better Less PT better
Test for subgroup diffe	erences: Chi#= (0.05, df=	1 (P = 0.82), I ² =	0%			More Pri better Less Pri better

Figure 111: Haematocrit at 4 hours of life (%)

	More pla	More placental trans			Less placental trans			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.9.1 New Subgroup										
Baezinger 2007	55.56	8.42	15	50.2	7.73	24	8.7%	5.36 [0.09, 10.63]		
Oh 2002	44.4	7	16	40	5.6	17	12.8%	4.40 [0.06, 8.74]		
Nelle 1998	55	5	11	46	4	8	14.7%	9.00 [4.95, 13.05]		
McDonnell 1997	55	7	23	52.5	7	23	14.7%	2.50 [-1.55, 6.55]		
Kinmond 1993 Subtotal (95% CI)	56.4	4.8	17 82	50.9	4.5	19	25.9% 76.6%	5.50 [2.45, 8.55] 5.40 [3.62, 7.17]		
1.9.2 Uterotonic used										
1.9.2 Uterotonic used										
Baezinger 2007	55.58	8.42	15	50.2	7.73	24	8.7%	5.36 [0.09, 10.63]		
McDonnell 1997 Subtotal (95% CI)	55	7	23 38	52.5	7	23	14.7%	2.50 [-1.55, 6.55] 3.56 [0.35, 6.77]	-	
Heterogeneity: Chi# = I	0.71, df = 1	(P = 0.4	0); I [#] = 09	36					100	
Test for overall effect :	Z = 2.18 (P	= 0.03)								
Total (95% CI)			120			138	100.0%	4.97 [3.42, 6.52]	•	
Heterogeneity: Chi#=	6.89, df = 6	6 (P = 0.3	3); I ² = 13	3%					-10 -5 0 5 10	
Test for overall effect .	Z = 6.28 (P	< 0.0000	01)						More PT lower Less PT lower	
Test for subgroup diffe					17 0.04				more Fillower Less Fillower	

Figure 112: Haematocrit at 24 hours after birth (%)

	More pla	cental t	rans	Less pla	acental t	rans		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.10.1 New Subgroup	1								
Baezinger 2007	55.93	7.19	15	49.74	8.34	23	7.5%	6.19 [1.20, 11.18]	
Strauss 2008	56	8.32	41	53	8.16	55	16.8%	3.00 [-0.34, 6.34]	
Kugelman 2007	52.8	5.2	30	50.2	6	35	25.2%	2.60 [-0.12, 5.32]	
Ranjit 2014 Subtotal (95% CI)	58.5	5.1	44 130	50.8	5.2	50 163	43.0% 92.5%	7.70 [5.61, 9.79] 5.33 [3.91, 6.76]	•
Heterogeneity: Chi#= 1	10.81. df=	3(P = 0)	01): P=	72%					
Test for overall effect 2				17.000					
1.10.2 Uterotonic use	d								
Baezinger 2007 Subtotal (95% CI)	55.93	7.19	15 15	49.74	8.34	23 23	7.5%	6.19 [1.20, 11.18] 6.19 [1.20, 11.18]	-
Heterogeneity: Not app	olicable								1996-062
Test for overall effect 2		= 0.01)							
Total (95% CI)			145			186	100.0%	5.40 [4.03, 6.77]	•
Heterogeneity: Chi# = 1	10.92, df=	4(P = 0.	03); I ² = 1	63%					
									-10 -5 0 5 10
Test for overall effect 2	Z = 7.74 (P	< 0.000	01)						More PT lower Less PT lower

I.13.2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion

Figure 113: Infant death

	More placenta	I trans	Less placenta	I trans		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95%	CI	
2.1.1 Delayed clampin	g									
Ultee 2008	0	18	0	19		Not estimable				
Kinmond 1993	0	17	0	19		Not estimable				
Strauss 2008	0	45	0	60		Not estimable				
Mercer 2003	0	16	0	16		Not estimable				
Hofmeyr 1988	5	24	0	14	3.3%	6.60 [0.39, 111.10]			•	
Hofmeyr 1993	1	40	1	46	4.9%	1.15 [0.07, 17.80]				
Kugelman 2007	0	30	1	35	7.3%	0.39 [0.02, 9.16]	_			
Rabe 2000	0	19	1	20	7.7%	0.35 [0.02, 8.10]	_			
McDonnell 1997	0	23	2	23	13.1%	0.20 [0.01, 3.95]		• •	-	
Baezinger 2007	0	15	3	24	14.3%	0.22 [0.01, 4.04]		•	-	
Oh 2002	2	16	3	17	15.3%	0.71 [0.14, 3.70]			-	
Mercer 2006	0	36	3	36	18.4%	0.14 [0.01, 2.67]	+			
Subtotal (95% CI)		299		329	84.2%	0.62 [0.28, 1.36]		-		
Total events	8		14							
Heterogeneity: Chi ² = 5	5.12, df = 7 (P =	0.65); 12=	0%							
Test for overall effect 2	z = 1.19 (P = 0.2	23)								
2.1.2 Cord milking										
Hosono 2008	2	20	3	20	15.8%	0.67 [0.12, 3.57]			-	
Subtotal (95% CI)		20		20	15.8%	0.67 [0.12, 3.57]				
Total events	2		3							
Heterogeneity: Not app	licable									
Test for overall effect 2	z = 0.47 (P = 0.6	i4)								
Total (95% CI)		319		349	100.0%	0.63 [0.31, 1.28]		•		
Total events	10		17							
Heterogeneity: Chi ² = 5	5.14, df = 8 (P =	0.74); I ² =	0%				-		10	100
Test for overall effect 2							0.01	0.1 1	10	100
Test for subgroup diffe			1 /P = 0.04) /P-	0%				More PT better Less	PT better	

Figure 114: Severe intraventricular haemorrhage

	More placenta	I trans	Less placenta	I trans		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.2.1 Delayed clamping	ng						
Mercer 2003	0	16	0	16		Not estimable	
Rabe 2000	0	19	0	20		Not estimable	1.0
Hofmeyr 1988	2	23	0	13	7.9%	2.92 [0.15, 56.51]	
Mercer 2006	0	36	1	36	18.8%	0.33 [0.01, 7.92]	
Hofmeyr 1993	1	40	2	46	23.3%	0.57 [0.05, 6.11]	
Subtotal (95% CI)		134		131	50.0%	0.85 [0.20, 3.66]	-
Total events	3		3				
Heterogeneity: Chi2 = '	1.11, df = 2 (P =	0.58); P=	: 0%				
Test for overall effect.	Z = 0.21 (P = 0.8	3)					
2.2.2 Cord milking							
Hosono 2008	2	20	4	20	50.0%	0.50 [0.10, 2.43]	
Subtotal (95% CI)		20		20	50.0%	0.50 [0.10, 2.43]	-
Total events	2		4				
Heterogeneity: Not app	plicable						
Test for overall effect.	Z = 0.86 (P = 0.3	9)					
Total (95% CI)		154		151	100.0%	0.68 [0.23, 1.96]	-
Total events	5		7				
Heterogeneity: Chi2 =	1.28, df = 3 (P =	0.73); P=	: 0%				0.002 0.1 1 10 500
Test for overall effect 2	Z = 0.72 (P = 0.4	7)					0.002 0.1 1 10 500 More PT better Less PT better
Test for subgroup diffe	erences: Chi#= (0.24, df=	1 (P = 0.62), I ² =	: 0%			more riverer Less riverer

Figure 115: Transfused for anaemia

	More placental trans		Less placental trans			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.12.1 Delayed Clamp	ing						
Strauss 2008	2	45	5	59	4.7%	0.52 [0.11, 2.58]	· · · · · · · · · · · · · · · · · · ·
Kugelman 2007	3	30	5	35	5.1%	0.70 [0.18, 2.69]	
McDonnell 1997	4	23	6	23	6.6%	0.67 [0.22, 2.05]	
Kinmond 1993	1	13	7	13	7.7%	0.14 [0.02, 1.00]	· · · · · · · · · · · · · · · · · · ·
Rabe 2000	9	19	16	20	17.1%	0.59 [0.35, 1.00]	
Mercer 2006 Subtotal (95% CI)	18	36 166	22	36 186	24.1% 65.3%	0.82 [0.54, 1.24] 0.63 [0.46, 0.87]	
Total events	37		61				
Heterogeneity: Chi² = 3 Test for overall effect: 2			0%				
2.12.2 Cord milking							
Hosono 2008	7	20	14	20	15.3%	0.50 [0.26, 0.97]	· · · · ·
March 2011 Subtotal (95% CI)	17	21	16	17	19.4%	0.86 [0.68, 1.09] 0.70 [0.53, 0.94]	
Total events	24		30			en e ferest erest	
Heterogeneity: Chi ² = 3 Test for overall effect. 2	3.81, df = 1 (P =						
Total (95% CI)		207		223	100.0%	0.66 [0.52, 0.82]	•
Total events	61		91				
Heterogeneity: Chi ² = 9	8.17, df = 7 (P = Z = 3.66 (P = 0.0		24%				0.01 0.1 1 10 10

Appendix J: Network meta-analysis of tocolytics

J.1 Summary

Tocolytics are given to women in preterm labour to delay birth and therefore improve outcomes for the newborn. Whilst the treatment is given to the mother, the aim is to improve outcomes for the infant.

Network meta-analyses (NMA) of outcomes considered important to assess efficacy and safety were conducted. Eight outcomes were suitable for NMA:

- 1. IVH (infant)
- 2. RDS (infant)
- 3. Neonatal mortality (infant)
- 4. Neonatal sepsis (infant)
- 5. Perinatal mortality (infant)
- 6. Delay of birth by at least 48 hours (mother)
- 7. Termination of treatment due to adverse events (mother)
- 8. Estimated gestational age (EGA) at delivery (mother)

The first 7 outcomes are reported as the number of observed events out of the total number of infants or mothers, whilst EGA is reported as a continuous outcome (mean EGA) with a standard deviation. Because some studies included multiple births, allowing more than one infant per mother, it was not always clear which was the most appropriate number of individuals to consider for outcomes on the infant. Where available we used the number of infants as the denominator. Although this does not account for the expected correlation in outcomes of infants from the same mother, it prevents double counting of infants from the same mother who may both have had an event.

A total of 35 treatments (including Placebo and combinations of treatments) were evaluated in relevant trials. These treatments were classified into 9 classes (Table 1).

A NMA class model (Kew 2014) was used to estimate the relative effects of each treatment class compared to Placebo/control. Since there was no evidence of within-class variability for any of the outcomes considered, all the results presented assume that all treatments in a class have the same relative effect.

A binomial / logit model was used to model outcomes 1 to 7 and a normal model with identity link was used to model EGA (Dias 2011).

The final dataset consisted of data from 93 trials comparing 35 treatments, although not all trials report all the outcomes of interest. Studies reporting zero events on all arms were removed from the NMA as they do not contribute information on the relative treatment effects. Treatments were assigned to classes according to Table 2.

J.2 Methods

In order to take all trial information into consideration, without ignoring part of the evidence and without introducing bias by breaking the rules of randomisation (for example, by "naively" combining data across treatment arms from all RCTs), Mixed Treatment Comparison metaanalytic techniques, also termed Network meta-analysis (NMA), were employed. NMA is a generalization of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (Dias 2001; Lu 2004; Caldwell 2005). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from a A versus B trial, is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments, and, at the same time, allow simultaneous inference on all treatments while respecting randomisation (Lu 2004; Caldwell 2005). Simultaneous inference on the relative effects of all treatments is possible whenever treatments are part of a single "network of evidence", that is, every treatment is linked to at least one of the other treatments under assessment. The correlation between the random effects of multi-arm trials (i.e. those with more than 2 arms) in the network is taken into account in the analysis (Dias 2011).

A Bayesian framework is used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4.3 (Lunn 2000; Lunn 2013). In order to test whether starting values have an impact on the results, three chains with different initial values were run simultaneously. Convergence was assessed by inspection of the Gelman–Rubin diagnostic plots and by examining the history plots. Pre-convergence iterations were discarded, and further iterations on all chains were run on which results are based.

Sample WinBUGS code is provided in Section J.6.

J.2.1 Baseline probability (IVH, RDS and neonatal mortality)

Please see Health Economic Appendix K for details on calculating baseline probabilities for IVH, RDS and neonatal mortality.

J.2.2 Relative effects model

Models allowing for within-class differences in treatment effects were considered with both fixed and random treatment effects. These were compared with models assuming no withinclass variability (i.e. all treatments in a class have the same relative effect), allowing for fixed or random treatment effects. Goodness of fit was tested using the posterior mean of the residual deviance, which was compared to the number of data points in the model and by inspecting the fit of each data point. Models were compared using the deviance information criteria (DIC) (Spiegelhalter 2002). The model with the lowest DIC was chosen, with differences of 5 considered meaningful. When models had very similar DIC (differences less than 5), simpler models were preferred, provided the posterior mean of the residual deviance was still close to the number of data points.

J.2.3 NMA model for binary data (outcomes 1 to 7)

A logit model was used to obtain the log-odds ratios of each treatment relative to Placebo. For each arm k of a trial *i*, the number of events, r_{ik} , have a binomial likelihood

$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})$$

where p_{ik} is the probability of an event and n_{ik} the total number of patients in arm k of trial i.

The parameters of interest are the probabilities of an event and these are modelled using a NMA model on the log-odds scale using a logit link such that

$$\operatorname{logit}(p_{ik}) = \mu_i + \delta_{ik}$$

with μ_i being given non-informative normal priors, Normal(0,1000), and $\delta_{ii} = 0$ since there is no relative treatment effect estimated for arm 1 of each trial.

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In a random effects (RE) model the trial-specific treatment effects of the treatment in arm k, relative to the treatment in arm 1, are drawn from a common random effects distribution, under the assumption of consistency:

$$\delta_{ik} \sim N(d_{tik} - d_{til}, \tau^2)$$

where d_{ik} represents the mean effect of the treatment in arm k in trial i, t_{ik} , relative to Placebo, and τ^2 represents the between-trial variability in treatment effects (heterogeneity). The between-trials standard deviation, τ , was given a Uniform(0,5) prior.

In the FE model we replace equation (2) with

 $logit(p_{ik}) = \mu_i + d_t - d_t$

J.2.4 NMA model for continuous data (EGA)

For each arm k of a trial i, the observed mean EGA,

 y_{ik} , has a normal likelihood

 $y_{ik} \sim \text{Normal}(\theta_{ik}, s_{ik}^2)$

where θ_{ik} is the underlying (true) mean EGA and s_{ik} is the standard error of the mean EGA in

arm k of trial i.

The mean EGA is modelled using a NMA model such that

 $\theta_{ik} = \mu_i + \delta_{ik}$

with μ_i being given non-informative normal priors, Normal(0,1000), and $\delta_{i1} = 0$, since there is no relative treatment effect estimated for arm 1 of each trial.

In a random effects (RE) model the trial-specific treatment effects of the treatment in arm k, relative to the treatment in arm 1, are drawn from a common random effects distribution, under the assumption of consistency (equation (3)). The between-trials standard deviation was given a Uniform(0,20) prior.

In the FE model we replace equation (5) with

$$\theta_{ik} = \mu_i + d_t - d_t$$

For studies not reporting the standard error, this was calculated using imputed standard deviations (SD). For each treatment for which a SD was not reported, it was imputed based on the median SD for that treatment reported in other studies. When there were fewer than 2 other studies reporting SD for a given treatment, the SD was imputed based on the median of reported SDs for that class. A sensitivity analysis imputing the upper quartile instead of the median was carried out.

J.2.5 Class model

Due to the sparseness of the network, with most comparisons being informed by only a few trials, a class model was used to borrow strength within treatment classes.

Two models for class were explored: an **exchangeable class effects** model, where the pooled relative treatment effects were assumed exchangeable within class

$$d_{I,k} \sim N(m_{Dk} , \tau^2_{D})$$

with D_k indicating the class to which treatment k belongs to; and a **fixed class effects** model,

where the pooled relative treatment effects are assumed equal for all treatments in a class $d_{1,k} = m_{D_k}$. Magnesium sulphate belongs to a class formed only of itself (Class 3), so its

relative treatment effect was assumed to be equal to its class effect in both models.

Both class models were considered with fixed or random treatment effects. The within-class mean treatment effects were given vague priors $m_{j} \sim N(0,100^2)$ and the within-class standard deviations were assumed equal for all classes (due to insufficient data) and given Uniform(0,2) priors.

J.2.6 Consistency

Consistency was assessed by checking the agreement of direct and indirect evidence using a node-split model (Dias 2009) fitted in R (Anonymous 2010) through the GeMTC package (van Valkenhoef 2012). Bayesian p-values for agreement between direct and indirect evidence were calculated. When these were lower than 0.05, included trials were inspected to help determine reasons for the potential inconsistency, bearing in mind that multiple probabilities of disagreement are being calculated and there is the potential to find spurious results.

J.3 Results

J.3.1 Baseline models (IVH, RDS, neonatal mortality)

Convergence was satisfactory by at least 20,000 iterations in all cases. Models were then run for a further 50,000 iterations on three separate chains, and all results are based on this further sample.

Results from these models are used in the relative effects model to generate a baseline $A \sim Normal(m, sd^2)$ on the log-odds scale on which relative effects were added at each iteration, to deliver the posterior summaries on the absolute probability scale for each treatment (Dias 2011a; Dias 2011b).

The estimated probabilities of events were very imprecise and there was large betweenstudy heterogeneity in the log-odds of an event. This suggests that the included studies are very different in their baseline event rates and that they are perhaps not all representative of the UK population.

J.3.2 Imputing standard deviations (EGA)

51 studies were used in the NMA for EGA. 5 studies (Merkatz 1980, Leveno 1986, Larsen 1986, Rasanen 1995, Holleboom 1996) did not report the standard deviation (SD).

19 treatments were included in the network. No treatments in Class 8 (Alcohol/ethanol) were compared in trials reporting this outcome.

Five studies did not report SD for EGA (Merkatz 1980, Leveno 1986, Larsen 1986, Rasanen 1995, Holleboom 1996). This meant that the SD had to be imputed for 4 treatments: Placebo, Indomethacin, Sulindac and Ritodrine.

Placebo: 11 studies comparing this treatment to other treatments reported the SD, whilst 3 did not. The range of reported SD was 0.5 to 6.6 (Figure 133).

Indomethacin: 10 studies comparing this treatment to other treatments reported the SD, whilst 1 did not. The range of reported SD was 0.7 to 5.6 (Figure 133).

Sulindac: only 1 study comparing this treatment to other treatments reported the SD, whilst one other did not. The reported SD for other treatments of the same class (Class 2) were used as the basis for imputation. The range of reported SD for this class was 0.5 to 5.6 (Figure 133).

Ritodrine: 13 studies comparing this treatment to other treatments reported the SD, whilst 4 did not. The range of reported SD was 1.7 to 4.7 (Figure 133).

Imputed values for the main analysis were based on the median SD (Table 4, Figure 133). A sensitivity analysis using the upper quartile of the reported SD was also carried out (Table 4).

Model comparison using the DIC showed the fixed class with random treatment effects model as the preferred model (**Error! Reference source not found.**). The model with fixed lass and treatment effects was not fitted as it was expected to have a very poor fit, given the results of the exchangeable class, fixed effects model. Node-split models compared direct and indirect evidence on 11 comparisons. Some evidence of inconsistency was found for comparisons of placebo and magnesium sulphate (p=0.01).

J.3.3 Sensitivity to imputed SD

When imputing the upper quartile of the reported SD, the fixed class with fixed treatment effects model was preferred, although there were some poorly fitting data points and there was evidence of inconsistency for comparisons of placebo and prostaglandin inhibitors (p=0.02) and placebo and betamimetics (p=0.49). Apart from increased uncertainty the main results were not affected.

Table 1: Class descriptions

	Classes
1	Placebo/control
2	Prostaglandin inhibitors
3	Magnesium sulfate
4	Betamimetics
5	Calcium channel blockers
6	Nitrates
7	Oxytocin receptor blockers
8	Alcohol/ethanol
9	Other treatments

Table 2: Treatments with class assignments

	Treatment	class
1	Placebo	1
2	No treatment	1
3	Bed rest	1
4	Celecoxib	2
5	Indomethacin	2
6	Ketorolac	2
7	Mefenic Acid	2
8	Nimeluside	2
9	Rofecoxib	2
10	Sulindac	2
11	Magnesium Sulfate	3
12	Beta-Mimetics	4

	Treatment	class
13	Fenoterol	4
14	Hexoprenaline	4
15	Isoxsuprine	4
16	Ritodrine	4
17	Salbutamol	4
18	Terbutaline	4
19	Nylidrin	4
20	Calcium-Channel Blocker	5
21	Nicardipine	5
22	Nifedipine	5
23	Nitric Oxide	6
24	Nitroglycerin	6
25	Atosiban	7
26	Barisiban 1.0	7
27	Barusiban 0.3	7
28	Barusiban 10	7
29	Barusiban 3.0	7
30	Alcohol	8
31	Ethanol	8
32	Beta-Mimetics + Mag	9
33	Alcohol + Indomethacin	9
34	Other Tocolytic(s)	9
35	Tocolysis	9

Treatment classes are defined in Table 1

Outcome (number of		Exchangeable class eff	ects	Fixed class effects	
data points)	Measures of model fit	RE	FE	RE	FE
IVH (61)	\overline{D}_{res}	65.7	68.6	66.1	69.2
	DIC	285.1	284.2	284.0	282.9
	between-study standard deviation	0.27 (0.01, 0.83)	-	0.27 (0.01, 0.81)	-
	within-class standard deviation	0.44 (0.02, 1.78)	0.43 (0.02, 1.77)	-	-
RDS (102)	\overline{D}_{res}	110.0	114.3	<mark>-112.3</mark>	121.3
	DIC	506.5	505.8	506.9	507.6
	between-study standard deviation	0.20 (0.01, 0.50)	-	0.25 (0.02, 0.54)	-
	within-class standard deviation	0.30 (0.02, 0.87)	0.36 (0.04, 0.92)	-	-
Neonatal mortality	\overline{D}_{res}	111.6	132.5	<mark>112.2</mark>	144.0
(102)	DIC	429.1	437.4	429.2	443.3
	between-study standard deviation	0.79 (0.24, 1.42)	-	0.86 (0.39, 1.47)	-
	within-class standard deviation	0.79 (0.04, 1.90)	1.16 (0.14, 7.95)	-	-
Neonatal sepsis (39)	\overline{D}_{res}	42.8	45.4	44.0	47.0
	DIC	181.2	180.1	181.0	179.8
	between-study standard deviation	0.44 (0.02, 1.49)	-	0.41 (0.02, 1.41)	-
	within-class standard deviation	0.65 (0.03, 1.87)	0.60 (0.03, 1.84)	-	-
Perinatal mortality (88)	\overline{D}_{res}	*	*	95.6	115.1
	DIC	*	*	365.1	371.8
	between-study	*	*	0.79 (0.19, 1.47)	-

Table 3: Posterior mean of the residual deviance ($\overline{D_{res}}$) DIC for all models

Outcome (number of		Exchangeable class effe	ects	Fixed class effects	
data points)	Measures of model fit	RE	FE	RE	FE
	standard deviation				
	within-class standard deviation	*	*	-	-
Delay by 48hrs (132)	\bar{D}_{res}	130.7	301.0	130.7	NA
	DIC	727.9	862.6	727.2	NA
	between-study standard deviation	0.89 (0.68, 1.16)	-	0.89 (0.68, 1.14)	-
	within-class standard deviation	0.14 (0.01, 0.55)	0.29 (0.05, 0.61)	-	-
Termination due to AE	\overline{D}_{res}	80.1	103.2	82.0	102.5
(75)	DIC	297.7	308.7	298.5	306.7
	between-study standard deviation	1.34 (0.26, 2.68)	-	1.17 (0.18, 2.74)	-
	within-class standard deviation	0.36 (0.02, 1.60)	0.18 (0.01, 0.97)	-	-
EGA (101)	\overline{D}_{res}	100.3	352.7	100.0	NA
	DIC	191.0	418.4	190.4	NA
	between-study standard deviation	1.25 (0.96, 1.64)	-	1.25 (0.98, 1.62)	-
	within-class standard deviation	0.25 (0.01, 0.98)	1.53 (0.96, 2.67)	-	-

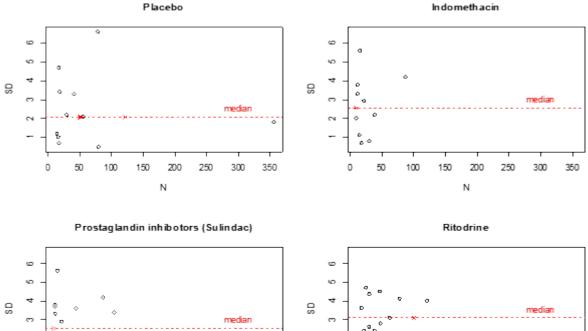
'NA' indicates the model was not fitted as it was expected to be a poor fit, and '*' indicated that the model was not fitted because there was not enough evidence to estimate all the parameters. Shaded cells indicate the preferred model. The median and 95% Credible Intervals of the between-study deviation (heterogeneity) and within-class standard deviation are also presented, A '--' indicates that this value was fixed at zero in the model.

Treatment	Median	Upper quartile
Placebo	2.1	3.35
Indomethacin	2.555	3.675
Sulindac	2.555	3.625
Ritodrine	3.1	4.1

Table 4: Vales used for the imputation of SD with these were not reported

J.4 Figures

Figure 133: Reported standard deviations (SD) in trials comparing the difference treatments, or treatments of the same class (open circles); SD in the only sulindac trial to report it (filled circle); imputed values (red crosses) and median SD, plotted against sample size



ഹ്ര 150 200 250 300 350 50 100 150 200 250 350 0 50 100 0 300 Ν N

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van Valkenhoef 2012

van Valkenhoef G, Lu G, De Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Research Synthesis Methods. 2012;3:285-299.

J.6 Sample WINGBUGS code for binary outcome analyses

FIXED CLASS, FIXED TREATMENT EFFECTS

Cla wit	iss m hin-c	ics: outcome is IVH nodel - treatments exchangeable within class, class variance is zero (fixed class effects)
	ay 2014	
Treat	tments	(code, Class, Treat)
1	1	Placebo
2	2	Indomethacin
3	2	Ketorolac
4	2	Rofecoxib
5	3	Magnesium Sulfate
6	4	Beta-Mimetics
7	4	Ritodrine
8	4	Salbutamol
9	4	Terbutaline
10	4	Terbutaline Nylidrin (NOT TO BE USED FOR RANKING)
11	5 6 7	Nifedipine
12	6	Nitric Oxide
13	7	Atosiban
14	8	Other Tocolytic(s) (NOT TO BE USED FOR RANKING)
# Fi	xed ef	l likelihood, logit link ffects model
-		ffects - zero within-class variance
mode		# *** PROGRAM STARTS
	i in l	
		<pre>~ dnorm(0,.0001)</pre>
		k in l:na[i]) {
+ ===		<pre>print content con</pre>
+ 100		p(i,k) <- mu[i] + d[t[i,k]] - d[t[i,1]]
± ex		d value of the numerators
	-	hat[i,k] <- p[i,k] * n[i,k]
#Dev		contribution
	de	<pre>ev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))</pre>
		+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat	[i,k]) }	
‡ su	mmed r	residual deviance contribution for this trial
	}	<pre>v[i] <- sum(dev[i,l:na[i]])</pre>
		<- sum(resdev[])
	-	<pre>‡ treatment effect is zero for reference treatment</pre>
		nt effects from Class - fixed class effects
IOL	(k in	$2:nt) \{ d[k] \le m[D[k]] \}$

PTLB Appendices I & J Network meta-analysis of tocolytics

2

2

2

2

1

2

2

2

13

5

5

NA

NA

NA

NA

4 4

1

```
m[1] < - 0
for (k in 2:nc) { m[k] ~ dnorm(0, .0001) } # priors for mean class effect
# all pairwise ORs
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)
        lor[c,k] \leq d[k] - d[c]
        OR[c,k] <- exp(lor[c,k])
      }
  3
# select treatments to be used for ranking and economic analysis
for(k in 1:9) { dR[k] <- d[k] }</pre>
# not treatment 10
for(k in 11:13) { dR[k-1] <- d[k] }
# not treatment 14
# ranking on relative scale
for (k in 1:ntR) {
     rk[k]<- (ntR+1)-rank(dR[],k)
                                        # events are "good"
                                        # events are "bad"
    rk[k] \leq - rank(dR[],k)
    best[k] <- equals(rk[k],1)</pre>
                                       # rank=1 is best
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in l:ntR) { logit(T[k]) <- A + dR[k] }
# all pairwise ORs for classes
for (c in 1: (nc-1)) {
    for (k in (c+1):nc) {
        lorClass[c,k] <- m[k] - m[c]</pre>
        ORClass[c,k] <- exp(m[k] - m[c])
    }
 -1
# rank all classes except last
for (k in 1:nc-1) {
     rkClass[k] <- (nc+1) -rank(m[],k)</pre>
                                               # events are "good"
    rkClass[k] <- rank(m[1:(nc-1)],k)
                                                       # events are "bad"
    bestClass[k] <- equals(rkClass[k],1)  # rank=1 is best</pre>
# prob class k is h-th best, prob[l,k]=best[k]
for (h in l:nc-1) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
    3
                                     # *** PROGRAM ENDS
}
Data
```

ns= number of studies; nt=number of treatments; nc=number of classes; D=index of classes # ntR = number of treat for ranking list(ns=29, nt=14, nc=8, meanA=-2.814, precA=0.9861, ntR=12, D=c(1, 2, 2, 2, 3, 4, 4, 4, 4, 4, 5, 6, 7, 8)) na[] t[,1] n[,1] n[,2] n[,3] #Study Year t[,2] t[,3] r[,1] r[,2] r[,3] #Cotton 1984 3 16 19 119 103 2 2 5 11 14 11 10 95 #Klauser 2012 3 13 13 5 7 4 56 61 58 #Goodwin ŏ ŇA 20 #Panter 1999 2 NA 19 NA 2 1 1 2 57 89 NA #Cox 1 NA 4 4 NA 78 1990 2 NA 4 2 NA 55 56 NA #Leveno 1986 2 7 NA 31 21 NA 391 380 NA #CPLIG 1992 1 2 16 2 12 NA NA 79 74 NA #Smith 2007 1 1 NA 19 246 243

4

6

4

NA

NA

NA

NA

49

14

47

52

18

50

NA

NA

NA

1996

#Romero 2000 #Morales 1993 #Parilla 1997

#Morales 1989

2 2 2	2 2 3	7 10 5	NA NA NA	3 2	2 0 0	NA NA NA	25 30 45	20 30 43	NA NA	#Besinger 1991 #Kurki 1991 #Schorr 1998
2 2	4 5	5 11	NA NA	6 3	7	NA	92 106	102 110	NA NA	#McWhorter 2004 #Lyell 2007
22	5	14 12	NA	8	22	NA	55 116	51 120	NA NA	#Mittendorf MAGnet2002 #Bisits 2004
2	7	7	NA	15 1	4	NA	111 35	111 35	NA NA	#Holleboom 1996 #Maitra 2007
2 2	7	11 11	NA NA	7 28	4 17	NA NA	43 90	48 95	NA NA	#Van de Water 2008 #Papatsonis (1997/2000)
2	7	13 13	NA NA	1	3	NA	63 107	63 107	NA NA	#Shim 2006 #Moutquin 2000
2	8	13	NA	2	4	NA	99 16	109 20	NA	#French/Australian 2001 #Laohapojanart 2007
2 2 END	9 11	13 11	NA NA	4 0	3 4	NA NA	105 48	101 52	NA NA	#European 2001 #Nassar 2009

FIXED CLASS, RANDOM TREATMENT EFFECTS

Tocolytics: outcome is RDS Class model - treatments exchangeable within class, within-class variance is zero (fixed class effects) _____ 6 August 2014 Treatments (code, Class, Treat) Placebo 1 1 2 Celecoxib 3 2 Indomethacin 4 2 Ketorolac 5 2 Rofecoxib 6 2 Sulindac 7 3 (TREATMENT IS ITS OWN CLASS) Magnesium Sulfate 8 4 Fenoterol 9 4 Hexoprenaline 10 4 Ritodrine 11 4 Salbutamol 12 4 Terbutaline 13 4 (NOT TO BE USED FOR RANKING) Nylidrin 5 14 Nicardipine 15 5 Nifedipine 6 16 Atosiban 17 6 Barisiban 1.0 (NOT TO BE USED FOR RANKING) Barusiban 0.3 18 6 (NOT TO BE USED FOR RANKING) 19 6 Barusiban 10 (NOT TO BE USED FOR RANKING) Barusiban 3.0 20 6 (NOT TO BE USED FOR RANKING) 21 7 Ethanol (NOT TO BE USED FOR RANKING) 22 8 Tocolysis (NOT TO BE USED FOR RANKING) Class "Nitrates" not compared Classes 7 and 8 not to be used for ranking _____ # Binomial likelihood, logit link # Random effects model for multi-arm trials # class effects - zero within-class variance # *** PROGRAM STARTS model{ for(i in 1:ns) { # LOOP THROUGH STUDIES w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm delta[i,1] <- 0 ‡ treatment effect is zero for control arm # vague priors for all trial baselines mu[i] ~ dnorm(0,.0001) # LOOP THROUGH ARMS for (k in l:na[i]) { r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor</pre> rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators</pre> #Deviance contribution dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))</pre> (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]rhat[i,k]))) # summed residual deviance contribution for this trial resdev[i] <- sum(dev[i,l:na[i]])</pre> # LOOP THROUGH ARMS for (k in 2:na[i]) { # trial-specific LOR distributions delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # mean of LOR distributions (with multi-arm trial correction)

```
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  3
totresdev <- sum(resdev[])</pre>
                                        # Total Residual Deviance
              # treatment effect is zero for reference treatment
d[11<-0
# treatment effects from Class - fixed class effects
for (k in 2:nt) \{ d[k] \le m[D[k]] \}
sd ~ dunif(0,5)
                    # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)</pre>
m[1] <- 0
for (k in 2:nc) { m[k] ~ dnorm(0, .0001) } # priors for mean class effect
# all pairwise ORs
for (c in 1: (nt-1)) {
    for (k in (c+1):nt) {
       lor[c,k]<- d[k]-d[c]
        OR[c,k] <- exp(lor[c,k])
      }
  }
# select treatments to be used for ranking and economic analysis
for(k in 1:12) { dR[k] <- d[k] }</pre>
# not treatment 13
for(k in 14:16) { dR[k-1] <- d[k] }
# not treatments 17-22
# ranking on relative scale
for (k in 1:ntR) {
±.
    rk[k] \leq (ntR+1) - rank(dR[], k)
                                        # events are "good"
    rk[k] \leq - rank(dR[],k)
                                        # events are "bad"
    best[k] <- equals(rk[k],1)</pre>
                                      # rank=1 is best
#calculate probability that treat k is h-th best
    for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }</pre>
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:ntR) { logit(T[k]) <- A + dR[k] }</pre>
# all pairwise ORs for classes
for (c in 1: (nc-1)) {
    for (k in (c+1):nc) {
        lorClass[c,k] <- m[k] - m[c]</pre>
        ORClass[c,k] <- exp(m[k] - m[c])
    }
# rank all classes except last two
for (k in 1:nc-2) {
    rkClass[k] <- rank(m[1:(nc-2)],k)
                                              # events are "bad"
    bestClass[k] <= rank(m[1:(nc-2)],k)  # events are "back
bestClass[k] <= equals(rkClass[k],1)  # rank=1 is best</pre>
# prob class k is h-th best, prob[1,k]=best[k]
    for (h in 1:nc-2) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
    3
                                        # *** PROGRAM ENDS
}
```

ns= number of studies; nt=number of treatments; nc=number of classes; D=index of classes # ntR = number of treat for ranking list(ns=47, nt=22, nc=8, meanA=-1.75, precA=0.555, ntR=15, D=c(1, 2, 2, 2, 2, 2, 3, 4, 4, 4, 4, 4, 5, 5, 6, 6, 6, 6, 6, 7, 8))

	47.41	# 21	# 21	+1.41	47.51 -F.11	-1.21	-021	-1.41	-1.51	of 11	n[,2]
na[]	t[,1] n[,3]	t[.2] n[.4]	ť[,3] n[,5]	t[,4] #	t[,5] r[,1] Study	r[,2]	r[,3]	r[.4]	r[,5]	n[,1]	
5	1 32	17 36	18 32	19 #	20 1 Thornton 2009	2	0	7	2	32	31
4	1 41	10 46	10 NA	10 #	NA 1 Larsen 1980	4	5	2	NA	45	44
3	1	7 NA	12 NA	ŇA #	NA 6 Cotton 1984	6	4	NA	NA	19	16
3	3	7	18	NA	NA 41	39	34	NA	NA	103	95
3	119 10	NA 16	NA 16	# NA	Klauser 2012 NA 5	8	7	3	2	56	61
2	58 1	62 3	57 NA	# NA	Goodwin 1996 NA 2	3	NA	NA	NA	15	16
2	NA 1	NA 3	NA NA	# NA	Niebyl 1980 NA 2	4	NA	NA	NA	20	19
2	NA 1	NA 3	NA NA	# NA	Panter 1999 NA 4	1	NA	NA	NA	18	18
2	NA 1	NA 7	NA NA	# NA	Zuckerman NA 15	1984 15	NA	NA	NA	89	78
	NA	ŇA	NA	#	Cox 1990		100	00	00	08	
2	1 NA	10 NA	NA NA	NA #	NA 3 Spellacy 1979	0	NA	NA	NA	15	14
2	1 NA	10 NA	NA	NA #	NA 6	3	NA	NA	NA	50	49
2	1	10	NA	NA	NA 24	20	NA	NA	NA	122	187
2	NA 1	NA 10	NA NA	# NA	Merkatz 1980 NA 24	25	NA	NA	NA	55	56
2	NA 1	NA 10	NA NA	# NA	Leveno 1986 NA 90	69	NA	NA	NA	391	380
2	NA 1	NA 16	NA NA	# NA	CPLIG 1992 NA 0	3	NA	NA	NA	57	57
2	NA 1	NA 16	NA NA	# NA	Goodwin 1994 NA 54	64	NA	NA	NA	292	283
	NA	NA	NA	#	Romero 2000						
2	1 NA	22 NA	NA NA	NA #	NA 22 Weiner 1988	15	NA	NA	NA	42	33
2	2 NA	3 NA	NA NA	NA #	NA 1 Stika 2002	1	NA	NA	NA	12	12
2	3 NA	6 NA	NA	NA #	NA 1	0	NA	NA	NA	10	10
2	3	7	NA NA	NA	Rasanen 1995 NA 5	5	NA	NA	NA	49	52
2	NA 3	NA 7	NA NA	# NA	Morales 1993 NA 5	5	NA	NA	NA	14	18
2	NA 3	NA 10	NA NA	# NA	Parilla 1997 NA 8	12	NA	NA	NA	47	50
	NA	NA	NA	#	Morales 1989						
2	3 NA	13 NA	NA NA	NA #	NA 3 Kurki 1991	2	NA	NA	NA	30	30
2	4 NA	7 NA	NA NA	NA #	NA 2 Schorr 1998	4	NA	NA	NA	45	43
2	5	7	NA	NA	NA 18	19	NA	NA	NA	92	102
2	NA 7	NA 12	NA NA	# NA	McWhorter NA 3	2004 2	NA	NA	NA	15	16
2	NA 7	NA 15	NA NA	# NA	Miller 1982 NA 4	5	NA	NA	NA	40	50
	NA	NA	NA	#	Floyd 1995						
2	7 NA	15 NA	NA NA	NA #	NA 24 Lyell 2007	21	NA	NA	NA	106	110
2	8 NA	10 NA	NA NA	NA #	NA 4 Essed 1978	2	NA	NA	NA	48	48
2	9	11	NA	NA	NA 7	4	NA	NA	NA	70	70
2	NA 10	NA 10	NA NA	# NA	Gummerus NA 17	1983 12	NA	NA	NA	111	111
2	NA 10	NA 12	NA NA	# NA	Holleboom NA 2	1996 5	NA	NA	NA	31	26
	NA	NA	NA	#	Caritis 1984						
2	10 NA	15 NA	NA NA	NA #	NA 1 Maitra 2007	0	NA	NA	NA	35	35
2	10 NA	15 NA	NA NA	NA #	NA 3 Cararach 2006	2	NA	NA	NA	39	39

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2	10	15	NA	NA	NA	3	3	NA	NA	NA	43	48
	NA	NA	NA	#	Van de W	/ater	2008					
2	10	15	NA	NA	NA	4	4	NA	NA	NA	28	30
	NA	NA	NA	#	Al-Qattan	2000						
2	10	15	NA	NA	NA	31	23	NA	NA	NA	90	95
	NA	NA	NA	#	Papatson	is (1997	(2000)	1997				
2	10	16	NA	NA	NA	0`	3 ΄	NA	NA	NA	63	63
	NA	NA	NA	#	Shim	2006						
2	10	16	NA	NA	NA	1	0	NA	NA	NA	22	23
	NA	NA	NA	#	Lin	2009						
2	10	16	NA	NA	NA	14	15	NA	NA	NA	107	107
-	NA	NA	NA	#	Moutquin	2000						
2	10	21	NA	NA	NA	6	15	NA	NA	NA	73	76
	NA	NA	NA	#	Lauersen	1977						
2	11	14	NA	NA	NA	3	5	NA	NA	NA	21	24
	NA	NA	NA	#	Trabelsi	2008						
2	11	16	NA	ŇA	NA	10	14	NA	NA	NA	99	109
	NA	NA	NA	#	French/A	ustralian	2001					
2	12	15	NA	ŇA	NA	2	2	NA	NA	NA	16	20
	NA	NA	NA	#	Laohapoj	anart	2007					
2	12	16	NA	ŇA	NA	28	17	NA	NA	NA	105	101
	NA	NA	NA	#	European		2001					
2	15	15	NA	NA	NA	6	10	NA	NA	NA	48	52
_	NA	NA	NA	#	Nassar	2009						
2	15	16	NA	NA	NA	10	5	NA	NA	NA	23	25
-	NA	NA	NA	#	Al-Omari		-					
END												

SAMPLE WINBUGS CODE FOR EGA

FIXED CLASS, RANDOM TREATMENT EFFECTS

Tocolytics: outcome is EGA at delivery Class model - treatments exchangeable within class, within-class variance is zero (fixed class effects)

1 August 2014

Treatments (code, Class, Treat)

1	1	Placebo
2	2	Celecoxib
3	2	Indomethacin
4	2	Ketorolac
5	2	Nimeluside
6	2	Rofecoxib
7	2	Sulindac
3	3	Magnesium Sulfate (TREATMENT IS ITS OWN CLASS)
9	4	Fenoterol
10	4	Isoxsuprine
11	4	Ritodrine
12	4	Salbutamol
13	4	Terbutaline
14	4	Nylidrin (NOT TO BE USED FOR RANKING)
15	5	Nicardipine
16	5	Nifedipine
17	6	Nitric Oxide
18	7	Atosiban
19	8	Tocolysis (NOT TO BE USED FOR RANKING)

Class "Alcohol/ethanol" not compared Class 8 not to be used for ranking

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
# class effects - zero within-class variance
model{
                                     # *** PROGRAM STARTS
for(i in l:ns){
                                         LOOP THROUGH STUDIES
                                     #
                  # adjustment for multi-arm trials is zero for control
   w[i,1] <- 0
arm
    delta[i,1] <- 0
                               ‡ treatment effect is zero for control arm
                            # vague priors for all trial baselines
# Joop Type
    mu[i] ~ dnorm(0,.0001)
                                     # LOOP THROUGH ARMS
    for (k in 1:na[i]) {
        var[i,k] <- pow(se[i,k],2) # calculate variances</pre>
       prec[i,k] <- l/var[i,k]</pre>
                                    # set precisions
       y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor</pre>
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]</pre>
      1
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,l:na[i]])</pre>
                                      # LOOP THROUGH ARMS
    for (k in 2:na[i]) {
# trial-specific LOR distributions
       delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
```

```
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
       taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
       w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
       sw[i,k] <- sum(w[i,1:k-1])/(k-1)</pre>
      }
 - 1
totresdev <- sum(resdev[])</pre>
                                        #Total Residual Deviance
d[1]<-0
             # treatment effect is zero for control arm
# treatment effects from Class - fixed class effects
for (k \text{ in } 2:nt) \{ d[k] \leq m[D[k]] \}
sd ~ dunif(0,20)
                   # vague prior for between-trial SD
tau <- pow(sd,-2)  # between-trial precision = (1/between-trial variance)
m[1] <- 0
for (k in 2:nc) { m[k] ~ dnorm(0, .0001) } # priors for mean class effect
# all pairwise differencess
for (c in 1: (nt-1)) {
   for (k in (c+1):nt) { diff[c,k]<- d[k]-d[c] }
  -}
# select treatments to be used for ranking
for(k in 1:13) { dR[k] <- d[k] }
# not treatment 14
for(k in 15:18) { dR[k-1] <- d[k] }
# not treatment 19
# ranking on relative scale
for (k in 1:ntR) {
    rk[k]<- (ntR+1)-rank(dR[],k)
                                      # larger values are "good"
    rk[k] < - rank(dR[],k)
                                       # larger values are "bad"
                                  # rank=1 is best
   best[k] <- equals(rk[k],1)</pre>
#calculate probability that treat k is h-th best
   for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
 - 1
# all pairwise differences for classes
for (c in 1: (nc-1)) {
    for (k in (c+1):nc) { diffClass[c,k] <- m[k] - m[c] }
 -1
# rank all classes except 8
for (k in 1:nc-1) {
    rkClass[k] <- nc-rank(m[1:(nc-1)],k) # larger values are "good"</pre>
   bestClass[k] <- equals(rkClass[k],1)  # rank=1 is best</pre>
# prob class k is h-th best, prob[1,k]=best[k]
    for (h in 1:nc-1) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
                                        # *** PROGRAM ENDS
}
```

Data

ns= number of studies; nt=number of treatments; nc=number of classes; D=index of classes
ntR = number of treat for ranking
list(ns=49, nt=19, nc=8, ntR=17,
D=c(1, 2, 2, 2, 2, 2, 2, 3, 4, 4, 4, 4, 4, 5, 5, 6, 7, 8))

na[] 3	t[.1] 1	t[,2] 8	t[,3] 13	y[.1] 32	y[.2] 31	y[.3] 33.1	se[,1] se[,2] 0.780013495	se[,3] 0.475	# 0.75707	Study 1922	Year #
3	Cotton 3	1984 5	7	37.2	38.4	38.1	0.632455532	0.158113	3883	0.31622	7766
3	# 3 #	Sawdy 8 Klauser		31.8	31.2	31.8	0.450287265	0.423014	4393	0.44126	1304

2	1 Zuckerma	3	NA 1984	31.2	36.4	NA	0.164991	582	0.164991	582	NA	#
2	1 Niebyl	3 1980	NA	33	35.2	NA	0.309838	668	0.284018	779	NA	#
2	1	3	NA	29.1	29.1	NA	1.107800	624	1.4	NA	#	
2	Panter 1	1999 8	NA	33	33.8	NA	0.055901	699	0.057353	933	NA	#
2	Cox 1	1990 8	NA	36.5	35.7	NA	0.401663	209	0.367423	461	NA	#
2	How 1	2006 10	NA	32.9	38.7	NA	0.242535	625	0.114707	867	NA	#
2	Casapo 1	1977 11	NA	33.4	34	NA	0.095399	809	0.090610	304	NA	#
2	CPLIG 1	1992 11	NA	32.5	34.6	NA	0.190125	067	0.226694	451	NA	#
2	Merkatz 1	1980 11	NA	32.6	32.8	NA	0.291217	603	0.421856	567	NA	#
2	Leveno 1	1986 11	NA	36.3	37.2	NA	0.296984	848	0.442857	143	NA	#
2	Larsen 1	1986 17	NA	34.1	35.2	NA	0.742558	015	0.569613	43	NA	#
2	Smith 1	2007 18	NA	38.3	37.8	NA	0.280624	304	0.467707	173	NA	#
2	Goodwin 1	1994 19	NA	30.1	31	NA	0.509201		0.504825		NA	#
2	Weiner 2	1988 3	NA	35.7	35.7	NA	1.068097		0.952627		NA	#
2	Stika 2	2002 8	NA	35.5	35.7	NA	0.291217		0.402157		NA	#
	Borna	2007										#
2	3 Rasanen		NA	39	39	NA	0.807961		0.807961		NA	-
2	3 Parilla	8 1997	NA	30.8	31.1	NA	1.096965		1.241303		NA	#
2	3 Besinger	11 1991	NA	35.5	33.8	NA	0.620414	085	0.853242	183	NA	#
2	3 Kurki	14 1991	NA	36.7	35.2	NA	0.146059	349	0.146059	349	NA	#
2	3 Kashania	16 n	NA 2011	35.2	34.1	NA	0.352281	938	0.432049	38	NA	#
2	4 Schorr	8 1998	NA	34.9	34.8	NA	0.536656	315	0.655743	852	NA	#
2	6 McWhorte	8	NA 2004	35.3	34.7	NA	0.331806	025	0.402287	04	NA	#
2	8 Suricham	13	NA 2001	36.21	36.01	NA	0.46	0.474976	691	NA	#	
2	8	15 1999	NA	35.5	35.6	NA	0.396911	151	0.490076	972	NA	#
2	8	16	NA	34.1	34.3	NA	0.191502	0.176162	803	NA	#	
2	Taherian 8	16	NA	35.2	34.5	NA	0.484138	662	0.448358	831	NA	#
2	Glock 8	1993 16	NA	35.8	36	NA	0.354474	504	0.31	NA	#	Lyell
2	2007	11	NA	37.4	36.9	NA	0.346410	162	0.404145	188	NA	#
2	Essed 10	1978 11	NA	35	35.6	NA	0.547722	558	0.481995	851	NA	#
2	Sirohiwal	16	NA	33.46	34.98	NA	0.394360	241	0.411889	7	NA	#
2	Rayamaji 11	11	2003 NA	35.7	35.4	NA	0.308461	529	0.31	NA	#	
2	Holleboor 11	m 16	1996 NA	29.5	30.2	NA	0.434659	144	0.474692	883	NA	#
2	Al-Qattan 11	2000 16	NA	36.1	36.2	NA	0.384307	569	0.384307	569	NA	#
2	Cararach 11	2006 16	NA	32.1	33.4	NA	0.464233	584	0.461690	258	NA	#
2	Papatson 11	is (1997/2) 16	000) NA	1997 34.07	34.71	NA	0.794197		0.495710		NA	#
2	Fan 11	2003	NA	31.8	33.3	NA	0.656392		0.593295		NA	#
2	Koks 11	1998 18	NA	37.4	37.1	NA	0.511681		0.521286		NA	#
2	Lin	2009	194	31.4	37.1	144	0.011081	18	0.021280	030	NPA .	*