National Clinical Guideline Centre

Forest plots

Pneumonia

Diagnosis and management of community- and hospital-acquired pneumonia in adults

Clinical guideline 191

Appendix I

3 December 2014

Final version

Commissioned by the National Institute for Health and Care Excellence

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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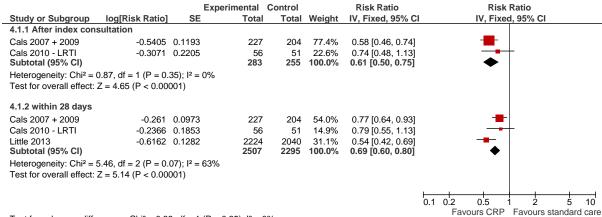
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1 Community-acquired pneumonia

1.1 Diagnostic tests

1.1.1.1 CRP compared with standard care

Figure 1: Antibiotic treatment



Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.35), $I^2 = 0\%$

Figure 2: Mortality

	CRF	•	Standard	care		Peto Odds Ratio			Pe	eto Od	lds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI			Pet	o, Fix	ed, 95% CI		
Cals 2007 + 2009	0	227	0	204		Not estimable							
Cals 2010 - LRTI	0	56	0	51		Not estimable							
Little 2013	0	2224	0	2040		Not estimable							
							0.1	0.2	0	5	1 2		10
							0		avours	-	Favours s	tandar	

Figure 3: Hospital admission

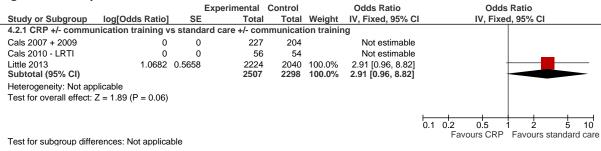


Figure 4: Resolution of symptoms

			CRP	Usual care		Adjusted Hazard Ratio	Adju	sted Ha	azard Rat	io	
Study or Subgroup	log[Adjusted Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV	, Fixed	l, 95% CI		
Little 2013	-0.0726	0.0508	2224	2040	100.0%	0.93 [0.84, 1.03]					
Total (95% CI)			2224	2040	100.0%	0.93 [0.84, 1.03]					
Heterogeneity: Not app Test for overall effect: 2						Fav	0.1 0.2 0 /ours standard	0.5 1 care	2 Favours	-	10

Figure 5: Resolution of symptoms (Feeling recovered as a surrogate at 7 days)

	CRF	•	Standard	l care		Risk Ratio		Risk R	atio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I	M-H, Fixed	, 95% C	l	
Cals 2010 - LRTI	12	51	9	49	100.0%	1.28 [0.59, 2.77]					
Total (95% CI)		51		49	100.0%	1.28 [0.59, 2.77]					
Total events	12		9								
Heterogeneity: Not approperties to rover all effect:	•	P – 0 5	3)				0.1 0.2	0.5	2	5	10
rest for overall effect.	2 - 0.00 (- 0.5	3)			Favo	ours standa	ard care F	avours	CRP	

Figure 6: Quality-of-life (patient enablement score)

		CRP		Stand	dard c	are		Mean Difference		Mea	n Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Ra	ndom, 9	5% CI	
Cals 2007 + 2009	2.97	2.59	227	3.4	2.48	204	54.7%	-0.43 [-0.91, 0.05]					
Cals 2010 - LRTI or URTI	2.5	2.6	129	2.3	2.4	129	45.3%	0.20 [-0.41, 0.81]			•		
Total (95% CI)			356			333	100.0%	-0.14 [-0.76, 0.47]			•		
Heterogeneity: $Tau^2 = 0.12$ Test for overall effect: $Z = 0$		-	f = 1 (P	= 0.11)	; I ² = 6	1%		Fa	-10	-5 tandard ca	0 0	5 ours CRP	10

Figure 7: Re-consultation (follow-up 28 days)

	CRF	•	Standard	d care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Cals 2007 + 2009	79	227	62	204	100.0%	1.15 [0.87, 1.51]	—
Total (95% CI)		227		204	100.0%	1.15 [0.87, 1.51]	•
Total events	79		62				
Heterogeneity: Not ap	plicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 0.97 (P = 0.3	3)				Favours CRP Favours standard care

1.1.1.2 PCT compared with standard care

Figure 8: Antibiotic treatment (initiation of antibiotics-overall)

			PCT	Standard care		Adjusted Odds Ratio		Adjusted (Odds Ratio		
Study or Subgroup	log[Adjusted Odds Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	d, 95% CI		
Schuetz 2012	-1.4271	0.093	2085	2126	100.0%	0.24 [0.20, 0.29]					
Total (95% CI)			2085	2126	100.0%	0.24 [0.20, 0.29]		•			
Heterogeneity: Not app Test for overall effect: 2	olicable Z = 15.35 (P < 0.00001)						0.05	0.2 Favours PCT	1 . Favours sta	i andard	20 d care

Figure 9: Antibiotic treatment (initiation of antibiotics- primary and ED settings)

			PCT	Standard care		Adjusted Odds Ratio		Adjusted	Odds Ratio	
Study or Subgroup	log[Adjusted Odds Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% C	I	IV, Fixe	d, 95% CI	
2.2.2 Primary care										
Schuetz 2012	-2.3026	0.182	507	501	100.0%		-	-		
Subtotal (95% CI)			507	501	100.0%	0.10 [0.07, 0.14]	•	-		
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 12.65 (P < 0.00001)									
2.2.3 ED										
Schuetz 2012	-1.0788	0.0991	1291	1314	100.0%	0.34 [0.28, 0.41]				
Subtotal (95% CI)			1291	1314	100.0%	0.34 [0.28, 0.41]		•		
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 10.89 (P < 0.00001)									
									<u></u>	
							0.05	0.2	5	20
Test for subgroup diffe	rences: Chi² = 34.87 df = 1 (F	- 0 000)()1) 2 -	- 97 1%				Favours PCT	Favours stand	ard care

lest for subgroup differences: $Chi^2 = 34.87$, df = 1 (P < 0.00001), $i^2 = 97.1$

Figure 10: Mortality (all settings)

•	, ,	.						
			Favours PCT	Standard care		Adjusted Odds Ratio	Adjusted Odds Ratio	
Study or Subgroup	log[Adjusted Odds Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Schuetz 2012	-0.0619	0.1432	2085	2126	100.0%	0.94 [0.71, 1.24]	-	
Total (95% CI)			2085	2126	100.0%	0.94 [0.71, 1.24]	•	
Heterogeneity: Not appl Test for overall effect: Z							0.1 0.2 0.5 1 2 5 Favours PCT Favours standa	10 ard care

Figure 11: Mortality (Primary and ED settings)

•	• •			• .				
			PCT	Standard care		Adjusted Odds Ratio	Adjusted C	dds Ratio
Study or Subgroup log	[Adjusted Odds Rati	o] SE	Total	Total	Weight	IV, Fixed, 95% C	I IV, Fixed	, 95% CI
2.9.2 Primary care								
Schuetz 2012	-1.112	5 1.6342	507	501	100.0%	0.33 [0.01, 8.09]	+	
Subtotal (95% CI)			507	501	100.0%	0.33 [0.01, 8.09]		
Heterogeneity: Not applicabl	e							
Test for overall effect: $Z = 0$.	68 (P = 0.50)							
2.9.3 ED								_
Schuetz 2012	0.029	6 0.1971	1291	1314			-	-
Subtotal (95% CI)			1291	1314	100.0%	1.03 [0.70, 1.52]	•	>
Heterogeneity: Not applicabl	е							
Test for overall effect: $Z = 0$.	15 (P = 0.88)							
							0.1 0.2 0.5 1	Ż 5 1
							Favours PCT	Favours standard ca

Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I^2 = 0%

Figure 12: Hospital admission (ED)

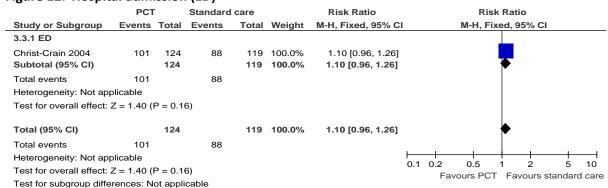


Figure 13: Resolution of symptoms (days with restricted activities for primary care setting)

			PCT	Standard care		Risk Difference		Risk Differe	ence	
Study or Subgroup	Risk Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95	5% CI	
2.6.2 Primary care										
Schuetz 2012 Subtotal (95% CI)	0.05	0.2602	507 507	501 501	100.0% 100.0 %	0.05 [-0.46, 0.56] 0.05 [-0.46, 0.56]		•		
Heterogeneity: Not ap Test for overall effect:	•								1	1
Test for subgroup diffe	erences: Not applica	able					-10 -5 Fav	0 ours PCT Fa	5 vours standa	10 ard care

Figure 14: Resolution of symptoms (treatment failure - all settings)

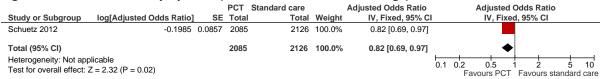
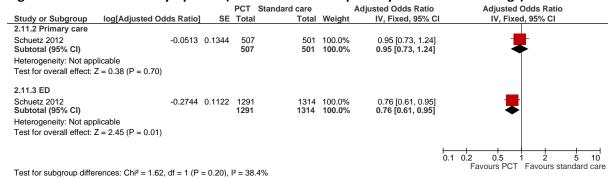
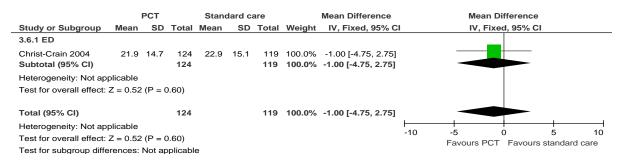


Figure 15: Resolution of symptoms (treatment failure - primary care and ED settings)



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Figure 16: Quality-of-life (final score, scale not known- ED setting)



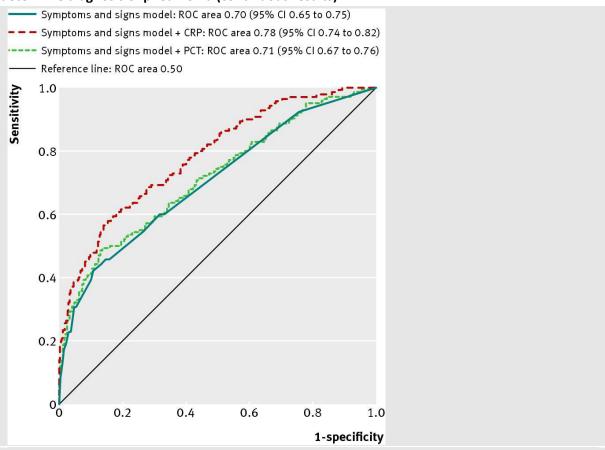
1.1.1.3 CRP compared with PCT (indirect comparison)

Figure 17: Antibiotic treatment (at index consultation)

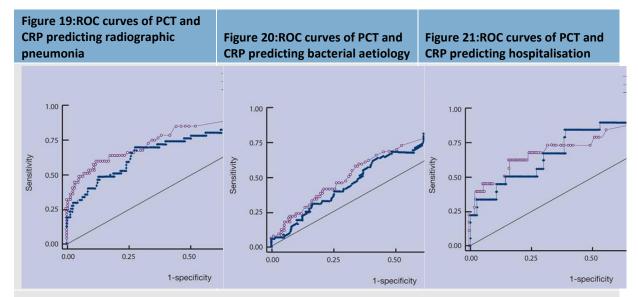
		CRP	PCT		Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio] SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Indirect comparison	0.4733 0.0525	283	114	100.0%	1.61 [1.45, 1.78]	
Total (95% CI)		283	114	100.0%	1.61 [1.45, 1.78]	•
Heterogeneity: Not app Test for overall effect:	plicable Z = 9.02 (P < 0.00001)		0.1 0.2 0.5 1 2 5 10 Favours CRP Favours PCT			

1.1.2 Receiver operating characteristic curves

Figure 18: ROC curves of symptoms and signs and added value of CRP and procalcitonin to determine diagnosis of pneumonia (continuous results)



Source/Note:van Vugt SF, Broekhuizen BD, Lammens C, Zuithoff NP, de Jong PA, Coenen S et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough



Source/Note:Holm A, Pedersen SS, Nexoe J, Obel N, Nielsen LP, Koldkjaer O et al. Procalcitonin versus C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care. British Journal of General Practice. 2007; 57(540):555-560. (Guideline Ref ID HOLM2007)

1.2 Severity assessment

1.2.1 PSI compared with CURB65, CRB65 or CURB

1.2.1.1 Prediction of mortality - range of point estimates of AUCs for PSI, CURB65 and CRB65

Figure 22: AUCs for PSI

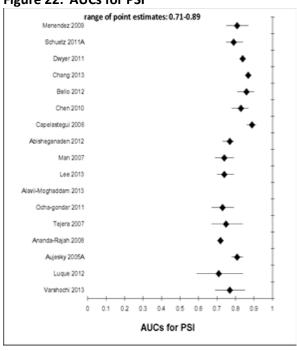


Figure 23: AUCs for CURB65

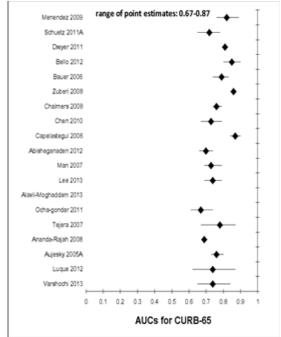


Figure 24: AUCs for CURB

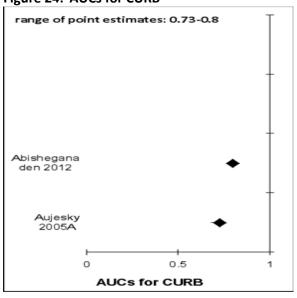


Figure 25: AUCs for CRB 65

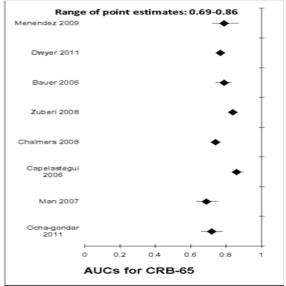


Figure 26: High-risk PSI (≥ IV) compared with low-risk PSI (< IV) to predict mortality

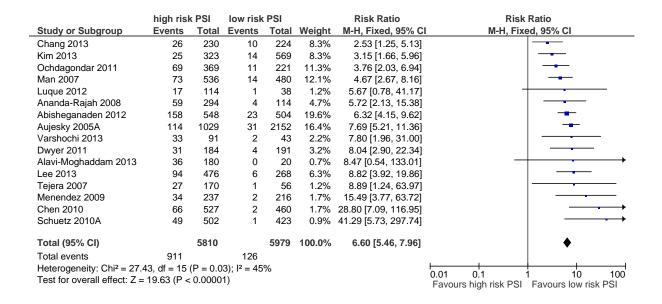


Figure 27: Intermediate-risk PSI (=III) compared with low-risk PSI (< III) to predict mortality

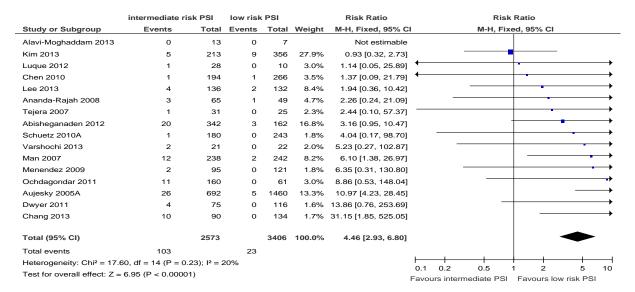


Figure 28: High-risk PSI (≥ IV) compared with intermediate-risk PSI (= III) to predict mortality

	high risl	(PSI	intermediate ris	sk PSI		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Chang 2013	26	230	10	90	10.4%	1.02 [0.51, 2.02]	
Man 2007	73	536	12	238	12.0%	2.70 [1.50, 4.88]	_ -
Ochdagondar 2011	69	369	11	160	11.1%	2.72 [1.48, 5.00]	_ -
Aujesky 2005A	114	1029	26	692	22.5%	2.95 [1.95, 4.46]	
Dwyer 2011	31	184	4	75	4.1%	3.16 [1.16, 8.64]	
Kim 2013	25	314	5	213	4.3%	3.39 [1.32, 8.72]	
Varshochi 2013	33	91	2	21	2.4%	3.81 [0.99, 14.63]	-
Luque 2012	17	114	1	28	1.2%	4.18 [0.58, 30.06]	-
Ananda-Rajah 2008	59	294	3	65	3.6%	4.35 [1.41, 13.44]	-
Tejera 2007	27	170	1	31	1.2%	4.92 [0.69, 34.91]	
Abisheganaden 2012	158	548	20	342	17.8%	4.93 [3.16, 7.69]	
Alavi-Moghaddam 2013	36	180	0	13	0.7%	5.65 [0.37, 87.21]	-
Lee 2013	94	476	4	136	4.5%	6.71 [2.51, 17.93]	
Menendez 2009	34	237	2	95	2.1%	6.81 [1.67, 27.80]	
Schuetz 2010A	49	502	1	180	1.1%	17.57 [2.44, 126.31]	
Chen 2010	66	527	1	194	1.1%	24.30 [3.40, 173.85]	
Total (95% CI)		5801		2573	100.0%	3.83 [3.14, 4.68]	•
Total events	911		103				
Heterogeneity: Chi ² = 27.5	59, df = 15	(P = 0.0))2); I ² = 46%				0.01 0.1 1 10 100
Test for overall effect: Z =	13.13 (P <	0.0000	01)				Favours high PSI Favours intermediate PSI

Figure 29: High-risk PSI (≥ IV) compared with low-risk PSI (< IV) to predict ITU admission

	high risl	k PSI	low risk	PSI		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Man 2007	28	536	13	480	35.4%	1.93 [1.01, 3.68]	-
Ananda-Rajah 2008	37	294	6	114	22.3%	2.39 [1.04, 5.51]	-
Kim 2013	57	314	23	569	42.2%	4.49 [2.82, 7.14]	-
Total (95% CI)		1144		1163	100.0%	3.11 [2.22, 4.37]	•
Total events	122		42				
Heterogeneity: Chi ² = 4	4.89, df = 2		0.01 0.1 1 10 100				
Test for overall effect:	Z = 6.58 (P)	Favourshigh risk PSI Favours low risk PSI					

Figure 30: High-risk CURB65 (≥ 3) compared with low-risk CURB65 (< 3) to predict mortality

	high risk CU	RB-65	low risk Cl	JRB-65		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Kim 2013	9	107	31	776	3.7%	2.11 [1.03, 4.30]	-
Schuetz 2010A	21	202	29	723	6.2%	2.59 [1.51, 4.45]	
Ananda-Rajah 2008	39	155	24	253	9.0%	2.65 [1.66, 4.23]	_
Abisheganaden 2012	46	108	135	944	13.7%	2.98 [2.28, 3.90]	
Alavi-Moghaddam 2013	36	193	0	7	0.5%	3.01 [0.20, 44.78]	· · · · · · · · · · · · · · · · · · ·
Ochdagondar 2011	26	77	54	513	7.0%	3.21 [2.15, 4.79]	
Lee 2013	51	181	49	563	11.8%	3.24 [2.27, 4.61]	-
Chen 2010	33	199	35	788	7.0%	3.73 [2.38, 5.85]	
Man 2007	51	261	36	755	9.1%	4.10 [2.74, 6.13]	
Luque 2012	13	59	5	93	1.9%	4.10 [1.54, 10.90]	
Chang 2013	14	98	10	315	2.3%	4.50 [2.06, 9.81]	
Aujesky 2005A	65	454	80	2727	11.3%	4.88 [3.57, 6.67]	
Varshochi 2013	29	60	6	74	2.7%	5.96 [2.65, 13.41]	
Tejera 2007	24	104	4	122	1.8%	7.04 [2.52, 19.63]	
Dwyer 2011	23	77	12	298	2.4%	7.42 [3.87, 14.23]	
Menendez 2009	27	118	9	335	2.3%	8.52 [4.13, 17.58]	
Zuberi 2008	14	36	4	101	1.0%	9.82 [3.46, 27.89]	
Capelastegui 2006	79	296	40	1550	6.3%	10.34 [7.22, 14.82]	
Total (95% CI)		2785		10937	100.0%	4.29 [3.83, 4.81]	♦
Total events	600		563				
Heterogeneity: Chi ² = 57.0	2, df = 17 (P <	0.00001)	; I ² = 70%				0.01 0.1 1 10 100
Test for overall effect: Z =	25.02 (P < 0.0	0001)					0.01 0.1 1 10 100 Favours high risk CURB-65 Favours low risk CURB-65

Figure 31: Intermediate-risk CURB65 (= 2) compared with low-risk CURB65 (< 2) to predict mortality

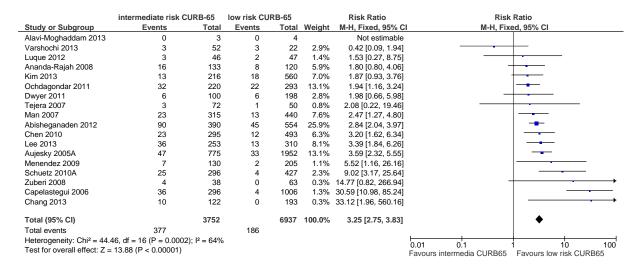


Figure 32: High-risk CURB65 (≥ 3) compared with intermediate-risk CURB65 (= 2) to predict mortality

	high risk CU	IRB-65	intermediate risk C			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Schuetz 2010A	21	202	25	296	7.5%	1.23 [0.71, 2.14]	 -
Kim 2013	9	107	13	216	3.2%	1.40 [0.62, 3.17]	
Alavi-Moghaddam 2013	36	193	0	3	0.4%	1.51 [0.11, 20.45]	
Chang 2013	14	98	10	122	3.3%	1.74 [0.81, 3.75]	+
Abisheganaden 2012	46	108	90	390	14.5%	1.85 [1.39, 2.45]	
Lee 2013	51	181	36	253	11.1%	1.98 [1.35, 2.90]	
Ananda-Rajah 2008	39	155	16	133	6.4%	2.09 [1.23, 3.57]	
Chen 2010	33	199	23	295	6.9%	2.13 [1.29, 3.51]	
Ochdagondar 2011	26	77	32	220	6.2%	2.32 [1.48, 3.63]	
Aujesky 2005A	65	454	47	775	12.9%	2.36 [1.65, 3.37]	- -
Man 2007	51	261	23	315	7.7%	2.68 [1.68, 4.26]	
Luque 2012	13	59	3	46	1.3%	3.38 [1.02, 11.16]	
Capelastegui 2006	79	296	36	474	10.3%	3.51 [2.44, 5.07]	
Zuberi 2008	14	36	4	38	1.4%	3.69 [1.34, 10.18]	
Menendez 2009	27	118	7	130	2.5%	4.25 [1.92, 9.39]	
Dwyer 2011	23	77	6	100	1.9%	4.98 [2.13, 11.62]	
Tejera 2007	24	104	3	72	1.3%	5.54 [1.73, 17.70]	
Varshochi 2013	29	60	3	52	1.2%	8.38 [2.71, 25.91]	
Total (95% CI)		2785		3930	100.0%	2.45 [2.17, 2.78]	•
Total events	600		377				
Heterogeneity: Chi ² = 30.2	23, df = 17 (P =	0.02); I ²	= 44%				0.01 0.1 1 10 100
Test for overall effect: Z =	14.04 (P < 0.0	0001)				,	0.01 0.1 1 10 100 Favours high risk CURB65 Favours intermediate

Figure 33: High-risk CURB65 (≥ 3) compared with low-risk CURB65 (< 3) to predict ITU admission

Study or Subgroup	high risk Cl Events	JRB65 Total	low risk Cl Events	JRB65 Total	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% CI
Kim 2013	9	107	51	776	32.9%	1.28 [0.65, 2.52]	- -
Man 2007	17	261	24	755	32.8%	2.05 [1.12, 3.75]	
Ananda-Rajah 2008	26	155	17	253	34.3%	2.50 [1.40, 4.45]	-
Total (95% CI)		523		1784	100.0%	1.95 [1.37, 2.77]	•
Total events	52		92				
Heterogeneity: Chi2 =	2.20, df = 2 (P	= 0.33); I	$^{2} = 9\%$				0.01 0.1 1 10 100
Test for overall effect:	Z = 3.71 (P = 0)	0.0002)					0.01 0.1 1 10 100 Favours high risk CURB-65 Favours low risk CURB-65

Figure 34: High-risk CURB (≥ 2) compared with low-risk CURB (< 2) to predict mortality

	high risk (CURB	low risk C	URB		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Aujesky 2005A	68	511	77	2670	70.0%	4.61 [3.38, 6.30]	-
Bauer 2006	43	297	24	1046	30.0%	6.31 [3.89, 10.22]	-
Total (95% CI)		808		3716	100.0%	5.12 [3.94, 6.66]	•
Total events	111		101				
Heterogeneity: Chi2 = 1	1.15, df = 1 (F	P = 0.28); I ² = 13%				0.01 0.1 1 10 100
Test for overall effect:	Z = 12.21 (P	< 0.0000	01)				Favours high risk CURB Favours low risk CURB

Figure 35: High-risk CRB65 (≥ 3) compared with low-risk CRB65 (< 3) to predict mortality

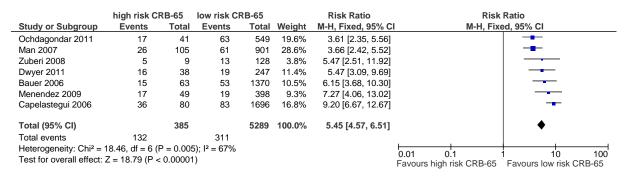


Figure 36: Intermediate-risk CRB65 (= 1 or 2) compared with low-risk CRB65 (= 0) to predict mortality

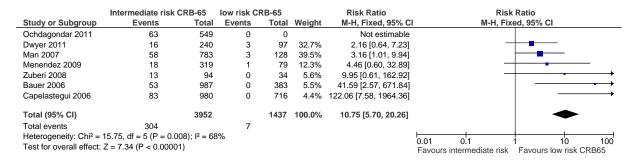


Figure 37: High-risk CRB65 (≥ 3) compared with intermediate-risk CRB65 (= 1 or 2) to predict mortality

	high risk C	RB-65	intermediate risk	CRB-65		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Man 2007	26	105	58	783	26.0%	3.34 [2.21, 5.06]	-
Ochdagondar 2011	17	41	63	549	16.6%	3.61 [2.35, 5.56]	_
Zuberi 2008	5	9	13	94	4.3%	4.02 [1.86, 8.69]	_
Bauer 2006	15	63	53	987	12.0%	4.43 [2.65, 7.41]	
Capelastegui 2006	36	80	83	980	23.7%	5.31 [3.87, 7.30]	-
Menendez 2009	17	49	18	319	9.1%	6.15 [3.41, 11.10]	_
Dwyer 2011	16	38	16	240	8.3%	6.32 [3.46, 11.54]	
Total (95% CI)		385		3952	100.0%	4.52 [3.78, 5.39]	•
Total events	132		304				
Heterogeneity: Chi ² =	6.38, df = 6 (P	= 0.38);	$I^2 = 6\%$				
Test for overall effect:	Z = 16.64 (P <	< 0.0000	1)				0.01 0.1 1 10 10 Favours high risk CRB65 Favours intermediate risk

1.2.2 PSI, CURB65 compared with modified American Thoracic Society 2001 criteria (mATS)

1.2.2.1 Summary of discriminatory analysis (AUCs) for PSI and CURB65 compared with mATS in prediction of mortality

Figure 38: AUCs for PSI

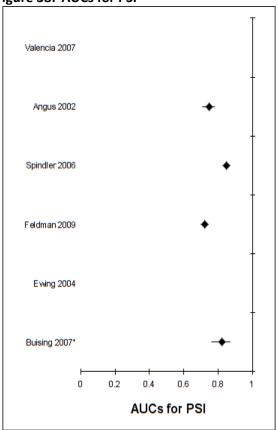
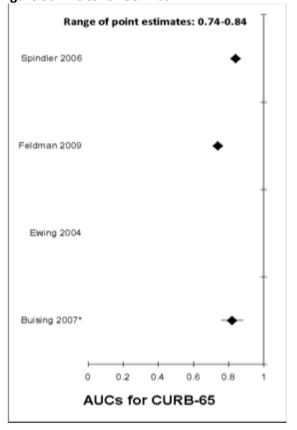
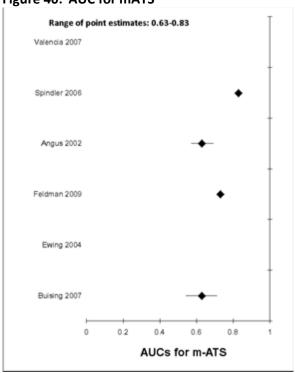


Figure 39: AUCs for CURB65







1.2.2.2 Summary of discriminatory analysis (AUCs) for PSI and CURB65 compared with mATS in prediction of ITU admission

Figure 41: AUCs for PSI

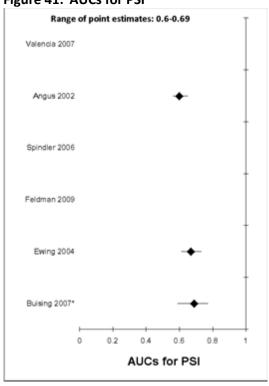
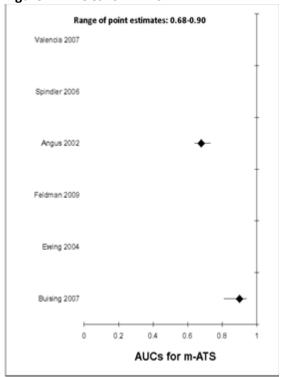


Figure 42: AUCs for mATS



1.2.3 PSI, CURB65 compared with IDSA/ATS

1.2.3.1 Prediction of mortality

Figure 43: High-risk CURB65 (≥ 3) compared with low-risk CURB65 (< 3) groups to predict mortality

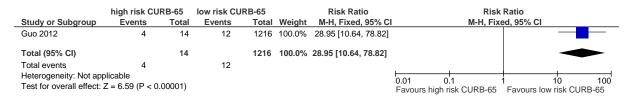
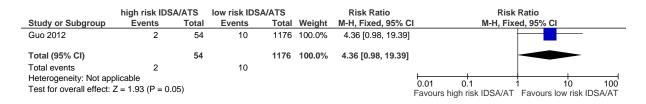


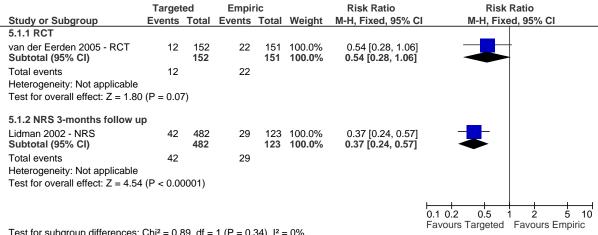
Figure 44: High-risk (≥ 3) groups compared with low-risk IDSA/ATS minor criteria (< 3) to predict mortality



Microbiological tests 1.3

1.3.1.1 Targeted compared with empirical treatment using a combination of tests

Figure 45: Mortality



Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.34), $I^2 = 0\%$

Figure 46: Clinical failure

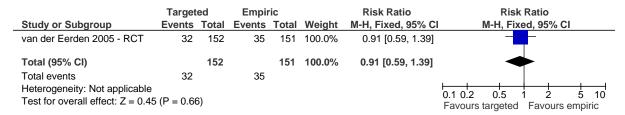


Figure 47: Length of hospital stay

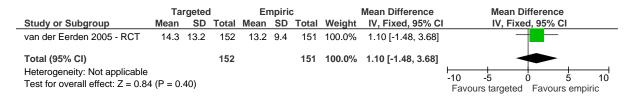


Figure 48: Quality-of-life (SF-36)

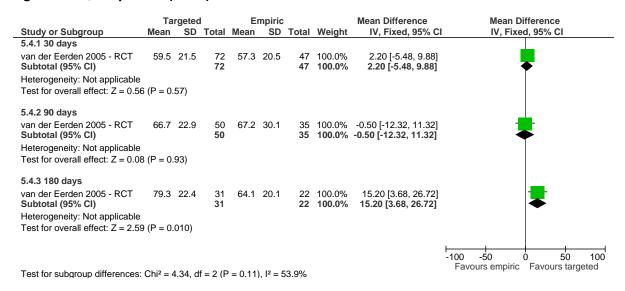
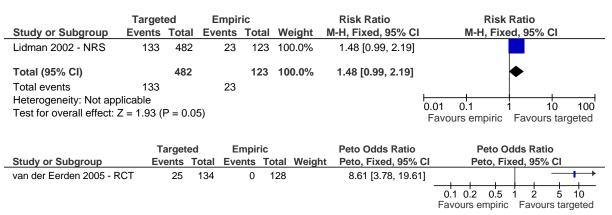


Figure 49: Change in prescription based on test results or clinical judgement



1.3.1.2 Targeted compared with empirical treatment using urinary antigen tests

Figure 50: Mortality

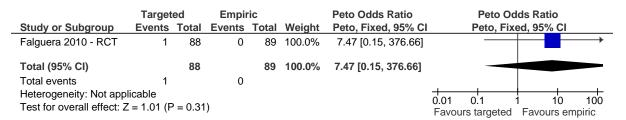


Figure 51: Clinical relapse

	Targete	ed	Empir	ic		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Falguera 2010 - RCT	4	88	2	89	100.0%	2.02 [0.38, 10.76]	
Total (95% CI)		88		89	100.0%	2.02 [0.38, 10.76]	
Total events	4		2				
Heterogeneity: Not appl	icable						0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z	= 0.83 (P	= 0.41)				Favours targeted Favours empiric

Figure 52: Re-admission

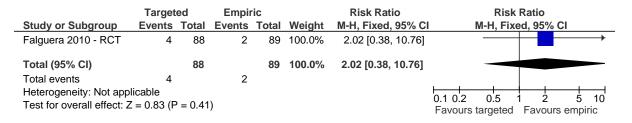


Figure 53: Treatment withdrawal due to adverse events

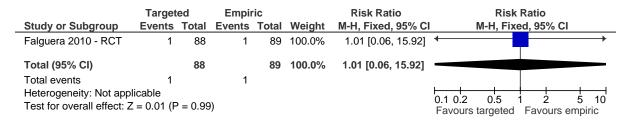
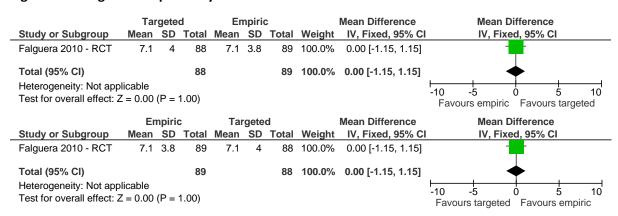


Figure 54: Length of hospital stay



1.3.1.3 Targeted compared with empirical treatment using blood culture

Figure 55: Mortality

	Targeted	Empiric		Risk Ratio	Risk Ratio					
Study or Subgroup	Events Tota	I Events Tot	al Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI					
Benenson 2007 - NRS	32 66	7 8 11	8 14.0%	0.71 [0.33, 1.50]						
Dedier 2001 - NRS	54 84	1 49 15	86.0%	0.20 [0.14, 0.28]	-					
Total (95% CI)	1508	26	8 100.0%	0.27 [0.20, 0.36]	•					
Total events	86	57								
Heterogeneity: Chi ² = 9.5	0.1 0.2 0.5 1 2 5 10									
Test for overall effect: Z =	Heterogeneity: Chi ² = 9.55, df = 1 (P = 0.002); $I^2 = 90\%$ Test for overall effect: Z = 8.42 (P < 0.00001)									

Figure 56: Mortality

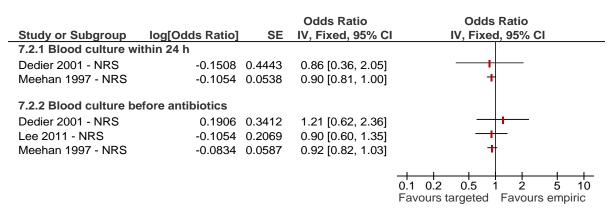


Figure 57: Clinical instability at 48 hours

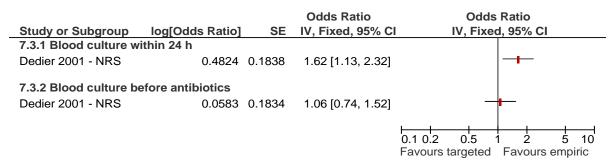


Figure 58: Length of hospital stay

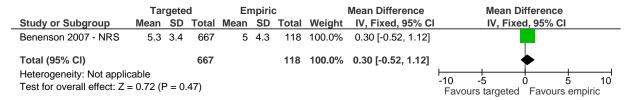
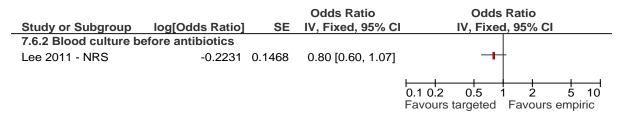


Figure 59: Length of hospital stay

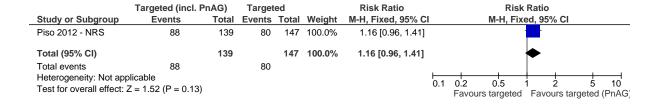
Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% Cl	Odds Ratio IV, Fixed, 95% CI
7.5.1 Blood culture w	ithin 24 h			
Dedier 2001 - NRS	0.0392	0.1876	1.04 [0.72, 1.50]	+
7.5.2 Blood culture be	efore antibiotics			
Dedier 2001 - NRS	-0.1744	0.1717	0.84 [0.60, 1.18]	- -
Lee 2011 - NRS	0	0.0538	1.00 [0.90, 1.11]	<u>†</u>
				0.1 0.2 0.5 1 2 5 10 Favours targeted Favours empiric

Figure 60: Hospital re-admission



1.3.1.4 Targeted treatment following pneumococcal antigen compared with targeted treatment not using pneumococcal antigen

Figure 61: Change in prescription (within 48 to 72 hours)



1.4 Antibiotic therapy

1.4.1 Timing of antibiotic therapy

1.4.1.1 Early compared with late antibiotic therapy (multivariable analysis)

Figure 62: Mortality

	-		Early antibiotics	Later antibiotics	Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	IV, Fixed, 95% C	IV, Fixed, 95% CI
1.1.1 Less than or equ	al to 4 hours versu	s more	than 4 hours			
Houck 2004	-0.16251893	0.057	8388	5383	0.85 [0.76, 0.95]	+
Houck 2004 PSI II-III	-0.478	0.1987	2424	1561	0.62 [0.42, 0.92]	
Houck 2004 PSI IV-V	-0.1393	0.0557	5964	3822	0.87 [0.78, 0.97]	+
Lee 2011	-0.35667494	0.2	1632	444	0.70 [0.47, 1.04]	
Simonetti 2012 - CAP	0.11332868	0.55	477	797	1.12 [0.38, 3.29]	
Waterer 2006	-0.61618614	0.403	222	229	0.54 [0.25, 1.19]	- + +
Wilson 2005	-1.23787436	0.59	70	17	0.29 [0.09, 0.92]	
1.1.2 Less than or equ	al to 8 hours versu	s more	than 8 hours			
Bader 2011	-1.38629436	0.61	155	51	0.25 [0.08, 0.83]	
Dedier 2001	0.52472853	0.394	809	253	1.69 [0.78, 3.66]	++-
Houck 2004	-0.16251893	0.078	11814	1957	0.85 [0.73, 0.99]	+
Meehan 1997	-0.16251893	0.064	0	0	0.85 [0.75, 0.96]	+
Mortensen 2008	0.18232155	0.279	364	56	1.20 [0.69, 2.07]	- +-
Simonetti 2012 - CAP	0.45742485	0.459	0	0	1.58 [0.64, 3.88]	-
1.1.3 Less than or equ	al to 12 hours vers	us more	e than 12 hours			
Houck 2004	-0.03045921	0.105	8388	5383	0.97 [0.79, 1.19]	+
1.1.4 Timing as a cont	inuous variable					
Jo 2012	0	0.001	0	0	1.00 [1.00, 1.00]	
						0.1 0.2 0.5 1 2 5 10 Favours early a/b Favours later a/b

Figure 63: Mortality - full time series

			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	IV, Fixed, 95% CI	
1.7.1 ≤1 h vs. >1 h	log[odds Ratio]		14, 11204, 3576 01	14,11264, 5576 61
Houck 2004	-0.0101	0.1024	0.99 [0.81, 1.21]	+
1.7.2 ≤2 h vs. >2 h				
Houck 2004	-0.0619	0.0635	0.94 [0.83, 1.06]	T
1.7.3 ≤3 h vs. >3 h Houck 2004	-0.1278	0.055	0.88 [0.79, 0.98]	+
1.7.4 ≤4 h vs. >4 h Houck 2004	-0.16251893	0.057	0.85 [0.76, 0.95]	+
1.7.5 ≤5 h vs. >5 h				
Houck 2004	-0.1508	0.0631	0.86 [0.76, 0.97]	+
1.7.6 ≤6 h vs. >6 h Houck 2004	-0.1744	0.0716	0.84 [0.73, 0.97]	-+-
1.7.7 ≤7 h vs. >7 h Houck 2004	-0.1393	0.069	0.87 [0.76, 1.00]	+
1.7.8 ≤8 h vs. >8 h Houck 2004	-0.16251893	0.078	0.85 [0.73, 0.99]	-
1.7.9 ≤9 h vs. >9 h Houck 2004	-0.1508	0.0836	0.86 [0.73, 1.01]	+
1.7.10 ≤10 h vs. >10 h Houck 2004	-0.0943	0.0919	0.91 [0.76, 1.09]	+
1.7.11 ≤11 h vs. >11 h Houck 2004	-0.0726	0.0963	0.93 [0.77, 1.12]	-+-
1.7.12 ≤12 h vs. >12 h Houck 2004	-0.03045921	0.105	0.97 [0.79, 1.19]	_
				0.2 0.5 1 2 5 Favours early a/b Favours later a/b

Figure 64: Prolonged length of stay (above median)

		Early antibiotics	Later antibiotics	Odds Ratio	Odds Ratio
log[Odds Ratio]	SE	Total	Total	IV, Fixed, 95% C	I IV, Fixed, 95% CI
al to 4 hours versi	us more	than 4 hours			
-0.10536052	0.036	8388	5383	0.90 [0.84, 0.97]	+
-0.1508	0.0698	2424	1561	0.86 [0.75, 0.99]	+
-0.0834	0.0464	5964	3822	0.92 [0.84, 1.01]	+
0.1823	0.0464	1632	444	1.20 [1.10, 1.31]	+
al to 8 hours versi	us more	than 8 hours			
-0.11653382	0.16	809	253	0.89 [0.65, 1.22]	+
al to 4 hours versi	us 4-8 h	ours			
0.01980263	0.105	0	0	1.02 [0.83, 1.25]	+
al to 4 hours versi	us more	than 8 hours			
-0.24846136	0.11	0	0	0.78 [0.63, 0.97]	+
					0.2 0.5 1 2 5 Favours early a/b Favours later a/b
	al to 4 hours versi -0.10536052 -0.1508 -0.0834 0.1823 al to 8 hours versi -0.11653382 al to 4 hours versi 0.01980263	al to 4 hours versus more -0.10536052	log[Odds Ratio] SE	al to 4 hours versus more than 4 hours -0.10536052	Total Total IV, Fixed, 95% C

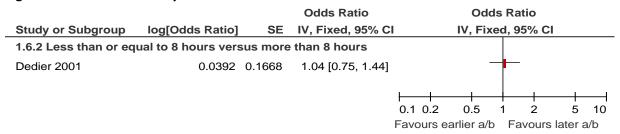
Figure 65: Prolonged length of stay (above 75th percentile)

_			Early antibiotics	Later antibiotics	Odds Ratio	Odds	Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	IV, Fixed, 95% C	IV, Fixed	d, 95% CI	
1.3.1 Less than or eq	ual to 8 hours vers	us m	ore than 8 hours					
Battleman 2002	-0.56211892	0.13	0	0	0.57 [0.44, 0.74]	+		
						0.01 0.1 1	10	100
						Favours early a/b	Favours late	

Figure 66: Re-admission after discharge

			Early a/b	Later antibiotics	Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
1.4.1 Less than or equ	al to 4 hours vers	us more	than 4 hou	ırs		
Houck 2004	-0.05129329	0.055	8388	5383	0.95 [0.85, 1.06]	+
Houck 2004 PSI II-III	-0.1393	0.1109	2424	1561	0.87 [0.70, 1.08]	
Houck 2004 PSI IV-V	-0.0101	0.0601	5964	3822	0.99 [0.88, 1.11]	+
Lee 2011	0.3365	0.2254	1545	416	1.40 [0.90, 2.18]	++-
						0.5 0.7 1 1.5 2
						Favours early a/b Favours later a/l

Figure 67: Clinical instability at 48 hours



1.4.2 In adults with community-acquired pneumonia what is the most clinically- and costeffective empirical antibiotic choice?

1.4.3 Low-severity community-acquired pneumonia

1.4.3.1 Single- compared with other single-antibiotic therapy for low-severity community-acquired pneumonia managed in the community

1.4.3.1.1 Macrolide compared with tetracycline

Figure 68: Clinical cure (end of treatment)

	Othe	r	Tetracy	cline		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.3.2 Macrolide vs tetracyc	line						
Wiesner 1993 - community	9	11	12	13	100.0%	0.89 [0.64, 1.22]	-
Subtotal (95% CI)		11		13	100.0%	0.89 [0.64, 1.22]	•
Total events	9		12				
Heterogeneity: Not applicabl	е						
Test for overall effect: $Z = 0$.	74 (P = 0.4	l 6)					
							0.1 0.2 0.5 1 2 5 10
							avours tetracycline Favours other

Test for subgroup differences: Not applicable

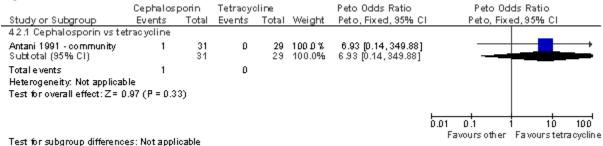
1.4.3.1.2 Cephalosporin compared with tetracycline

Figure 69: Clinical cure at end of treatment

-	Cephalos	porin	Tetracy	cline		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.1.1 Cephalosporin vs tet	tracycline						
Antani 1991 - community Subtotal (95% CI)	9	31 31	9	29 29	100.0% 100.0 %	0.94 [0.43, 2.03] 0.94 [0.43, 2.03]	
Total events Heterogeneity: Not applicab Test for overall effect: Z = 0		7)	9				
						F	0.1 0.2 0.5 1 2 5 10 avours tetracycline Favours other

Test for subgroup differences: Not applicable

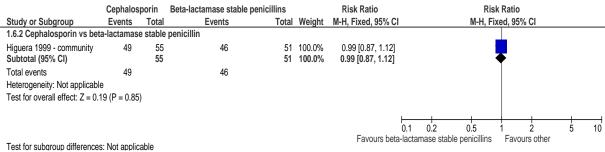
Figure 70: Withdrawals due to adverse events



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1.4.3.1.3 Cephalosporin compared with beta-lactamase-stable penicillin

Figure 71: Clinical cure at the end of follow up



1.4.3.1.4 Macrolide compared with beta-lactam stable penicillin

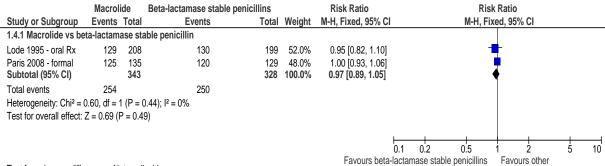
Figure 72: Mortality

Figure 1: Mortality

	Macrol	ide	Beta-lactamase stable per	nicillins		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% CI		
1.1.2 Macrolide vs be	eta-lactam	ase sta	ble penicillin									
Lode 1995 - oral Rx	10	208	4	199	100.0%	2.39 [0.76, 7.50]			_			_
Paris 2008 - formal Subtotal (95% CI)	0	136 344	0	132 331	100.0%	Not estimable 2.39 [0.76, 7.50]			_			_
Total events Heterogeneity: Not ap			4									
Test for overall effect:	Z = 1.50 (I)	P = 0.13	3)									
							0.1	0.2	0.5	1 2	 5	10
T . ()								Fa	avours macrolide	Favours beta-l	actamase s	stable p

Test for subgroup differences: Not applicable Source: <Insert Source text here>

Figure 73: Clinical cure at end of treatment



Test for subgroup differences: Not applicable

Figure 74: Clinical cure at end of follow-up

	Othe	r	Beta-lactamase stable peni	cillins		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
1.4.1 Macrolide vs beta-lac	tamase st	able pe	enicillin								
Bonvehi 2003 - community	114	124	117	129	31.0%	1.01 [0.94, 1.09]			•		
Lode 1995 - oral Rx	129	208	130	199	35.9%	0.95 [0.82, 1.10]		-	-		
Paris 2008 - formal Subtotal (95% CI)	125	135 467	120	129 457	33.1% 100.0%	1.00 [0.93, 1.06] 0.98 [0.93, 1.05]		1			
Total events Heterogeneity: Chi² = 0.90, d Test for overall effect: Z = 0.90	,	,.	367 2 = 0%								
						Favours beta	0.1 0.2	0.5	1 2	5	10

Test for subgroup differences: Not applicable

Figure 75: Withdrawal due to adverse events

	Cephalos	porin	Beta-lactamase stable pe	nicillins		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C			M-H, Fixe	ed, 95% CI		
1.5.2 Macrolide vs beta-lact	tamase stab	ole penio	cillin									
Bonvehi 2003 - community	3	160	2	167	17.6%	1.57 [0.27, 9.25]				-		
Lode 1995 - oral Rx	16	208	5	199	45.9%	3.06 [1.14, 8.20]						
Paris 2008 - formal Subtotal (95% CI)	5	136 504	4	132 498	36.5% 100.0%	1.21 [0.33, 4.42] 2.12 [1.05, 4.29]					_	
Total events Heterogeneity: $Chi^2 = 1.36$, d Test for overall effect: $Z = 2.1$			11 0%									
Test for subgroup differences							0.1	0.2	0.5 Favours other	1 2 Favours beta	5 -lactamas	10 e stable

Test for subgroup differences: Not applicable

1.4.3.1.5 Respiratory fluoroquinolone compared with narrow spectrum beta-lactam (class 2)

Figure 76: Mortality

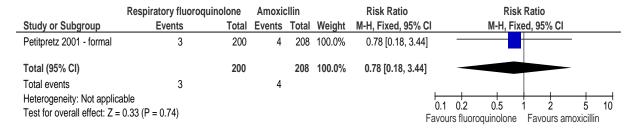


Figure 77: Clinical cure at end of treatment

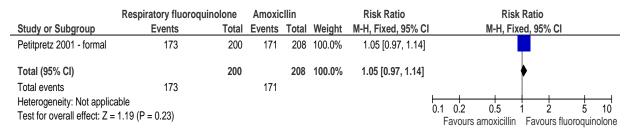


Figure 78: Clinical cure at end of follow-up

	Respiratory fluoroqu	inolone	Amoxic	llin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Petitpretz 2001 - formal	154	200	164	208	100.0%	0.98 [0.88, 1.08]	
Total (95% CI)		200		208	100.0%	0.98 [0.88, 1.08]	•
Total events Heterogeneity: Not applica			164				0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z =	0.45 (P = 0.65)						Favours amoxicillin Favours fluoroquinolone

Figure 79: Complications

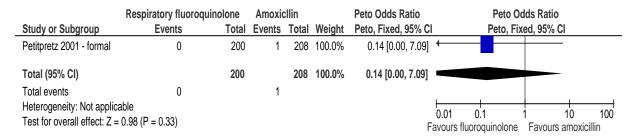


Figure 80: Withdrawal or treatment discontinuation due to adverse events

	Respiratory fluoroqui	inolone	Amoxic	cllin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
Petitpretz 2001 - formal	8	200	8	208	100.0%	1.04 [0.40, 2.72	2]
Total (95% CI)		200		208	100.0%	1.04 [0.40, 2.72	
Total events	8		8				
Heterogeneity: Not applica Test for overall effect: Z =							0.1 0.2 0.5 1 2 5 10 Favours fluoroquinolone Favours amoxicillin

1.4.3.1.6 Respiratory fluoroquinolone compared with beta-lactam stable penicillin

Figure 81: Withdrawal due to adverse events (respiratory fluoroquinolone compared with macrolide)

	Respiratory fluoro	quinolo	Macrol	ide		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI
2.4.1 Respiratory fluoroquir	nolone (new) vs macr	olide						
Fogarty 1999 - community	6	241	12	232	43.6%	0.48 [0.18, 1.26]		
Gotfried 2002 - community	1	143	5	156	17.0%	0.22 [0.03, 1.85]	-	
Hoeffken 2001 - community Subtotal (95% CI)	11	224 608	11	222 610	39.4% 100.0 %	0.99 [0.44, 2.24] 0.64 [0.36, 1.14]	•	
Total events	18		28					
Heterogeneity: Chi ² = 2.42, df	$f = 2 (P = 0.30); I^2 = 17$	%						
Test for overall effect: $Z = 1.5$	62 (P = 0.13)							
							0.1 0.2 0.5	1 2 5 10
T . ()	N						Favours other	Favours macrolide

Test for subgroup differences: Not applicable

1.4.3.1.7 Non-respiratory fluoroquinolone compared with macrolide

Figure 82: Clinical cure at end of treatment

Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed 2.6.3 Non respiratory fluoroquinolone vs macrolide Nielsen 1993 - community 39 69 24 50 79.6% 1.18 [0.83, 1.68] — Peugeot 1991 - community 13 19 6 13 20.4% 1.48 [0.76, 2.87] — Subtotal (95% CI) 88 63 100.0% 1.24 [0.91, 1.69] — Total events 52 30 — — —	ixed, 95% CI
Nielsen 1993 - community 39 69 24 50 79.6% 1.18 [0.83, 1.68] Peugeot 1991 - community 13 19 6 13 20.4% 1.48 [0.76, 2.87] Subtotal (95% CI) 88 63 100.0% 1.24 [0.91, 1.69]	-
Peugeot 1991 - community 13 19 6 13 20.4% 1.48 [0.76, 2.87] Subtotal (95% CI) 88 63 100.0% 1.24 [0.91, 1.69]	+
Subtotal (95% CI) 88 63 100.0% 1.24 [0.91, 1.69]	
Total events 52 30	•
Heterogeneity: $Chi^2 = 0.36$, $df = 1$ ($P = 0.55$); $I^2 = 0\%$ Test for overall effect: $Z = 1.35$ ($P = 0.18$)	

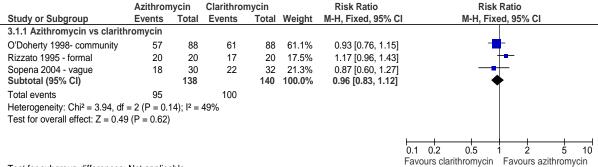
Test for subgroup differences: Not applicable

Figure 83: Withdrawal due to adverse events

N	on-respiratory flu	oroqui	Macrol	ide		Peto Odds Ratio	Peto	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% (CI Peto, F	Fixed, 95% CI	
Peugeot 1991 - community	2	19	0	13	100.0%	5.70 [0.32, 100.37]] —		
Total (95% CI)		19		13	100.0%	5.70 [0.32, 100.37]	-		
Total events	2		0						
Heterogeneity: Not applicable Test for overall effect: Z = 1.19 (I	P = 0.23)						0.01 0.1 Favours non-respirator	1 10 ry Favours macro	100 olide

1.4.3.1.8 Azithromycin compared with other macrolides

Figure 84: Clinical cure at end of treatment (azithromycin compared with clarithromycin)



Test for subgroup differences: Not applicable

Figure 85: Clinical cure at end of follow-up (azithromycin compared with clarithromycin)

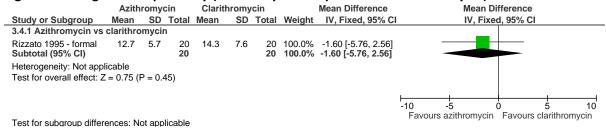
	Azithron	nycin	Clarithron	nycin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
3.2.1 Azithromycin vs clarith	nromycin						
O'Doherty 1998- community	19	24	15	22	36.6%	1.16 [0.82, 1.65]	-
Sopena 2004 - vague Subtotal (95% CI)	28	30 54	28	32 54	63.4% 100.0 %	1.07 [0.91, 1.25] 1.10 [0.93, 1.30]	
Total events Heterogeneity: Chi ² = 0.24, df Test for overall effect: $Z = 1.14$	`	,,	43 0%				
							0.1 0.2 0.5 1 2 5 10 Favours clarithromycin Favours azithromycin

Test for subgroup differences: Not applicable

Figure 86: Withdrawal due to adverse events (azithromycin compared with clarithromycin)

	Azithrom	ycin	Clarithro	mycin		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
3.3.1 Azithromycin vs clarithi	romycin						
O'Doherty 1998- community Subtotal (95% CI)	0	101 101	2	102 102	100.0% 100.0 %	0.14 [0.01, 2.18] 0.14 [0.01 , 2.18]	+
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.41	0 (P = 0.16)		2				
							0.1 0.2 0.5 1 2 5 10 Favours azithromycin Favours clarithromycin

Figure 87: Length of hospital stay (azithromycin compared with clarithromycin)



1.4.3.1.9 Clarithromycin compared with amoxicillin (indirect comparison)

Figure 88: Mortality

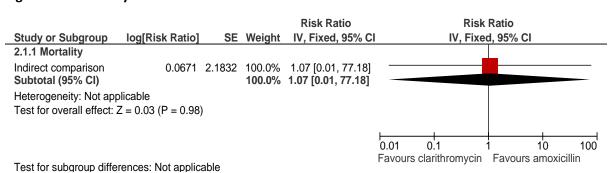
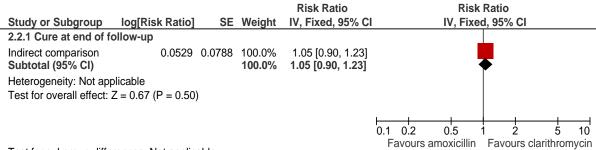
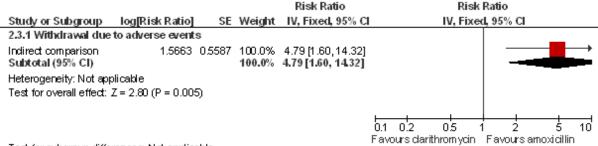


Figure 89: Cure at end of follow up



Test for subgroup differences: Not applicable

Figure 90: Withdrawal due to adverse events



Test for subgroup differences: Not applicable

Source: <Insert Source text here>

1.4.4 Low-severity community-acquired pneumonia managed in hospital

1.4.4.1.1 Macrolide compared with narrow-spectrum beta-lactam (class 1)

Figure 91: Clinical cure

0							
	Macrol	ide	Benzylper	nicillin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
4.1.1 End of treatment							
Bohte 1995 - pneumococcal Subtotal (95% CI)	24	35 35	14	29 29	100.0% 100.0 %	1.42 [0.92, 2.20 1.42 [0.92, 2.20]	
Total events	24		14				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.57	(P = 0.12)	!)					
4.1.2 End of follow-up							<u></u>
Bohte 1995 - pneumococcal Subtotal (95% CI)	29	35 35	19	29 29	100.0% 100.0 %	1.26 [0.93, 1.71 1.26 [0.93, 1.71]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.51	29 (P = 0.13	3)	19				
Test for subgroup differences:	Chi² = 0 1	8 df =	1 (P = 0.67)	l ² = 0%			0.1 0.2 0.5 1 2 5 10 Favours benzylpenicillin Favours macrolide

Figure 92: Withdrawal/switching of treatment due to adverse events

	Macrol	ide	Benzylper	nicillin		Peto Odds Ratio			Peto Oc	lds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI			Peto, Fix	ed, 95% CI		
Bohte 1995 - pneumococcal	2	35	0	29	100.0%	6.41 [0.39, 106.11]						\rightarrow
Total (95% CI)		35		29	100.0%	6.41 [0.39, 106.11]						
Total events	2		0									
Heterogeneity: Not applicable Test for overall effect: Z = 1.30	(P = 0.19))					0.1	0.2 Favours	0.5 macrolide	1 2 Favours be	5 enzylpe	10

1.4.4.1.2 Macrolide compared with beta-lactamase stable penicillin

Figure 93: Mortality

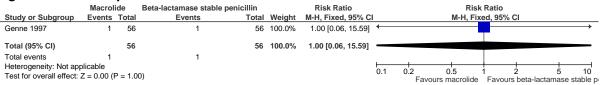


Figure 94: Clinical cure at end of treatment

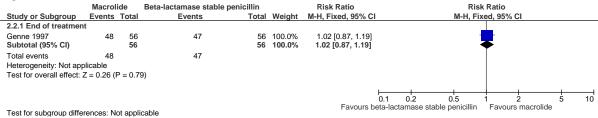
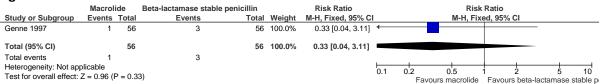


Figure 95: Withdrawal due to adverse events



1.4.4.1.3 Azithromycin compared with other macrolide

Figure 96: Mortality (during treatment)

	Azithrom	nycin	Erythron	nycin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bohte 1995-nonpneumococal	1	20	1	22	100.0%	1.10 [0.07, 16.45]	<u></u>
Total (95% CI)		20		22	100.0%	1.10 [0.07, 16.45]	
Total events	1		1				
Heterogeneity: Not applicable Test for overall effect: Z = 0.07 (P = 0.94)						0.1 0.2 0.5 1 2 5 10 Favours azithromycin Favours erythromycin

Figure 97: Clinical cure

	Azithrom	nycin	Erythron	nycin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
5.2.1 End of treatment							
Bohte 1995-nonpneumococal Subtotal (95% CI)	14	19 19	14	21 21	100.0% 100.0%	1.11 [0.74, 1.66] 1.11 [0.74, 1.66]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.48 (F	14 P = 0.63)		14				
5.2.2 End of follow-up							
Bohte 1995-nonpneumococal Subtotal (95% CI)	15	19 19	15	21 21	100.0% 100.0%	1.11 [0.77, 1.58] 1.11 [0.77, 1.58]	*
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.55 (F	15 P = 0.58)		15				
Test for subgroup differences: C	,						0.1 0.2 0.5 1 2 5 10 Favours erythromycin Favours azithromycin

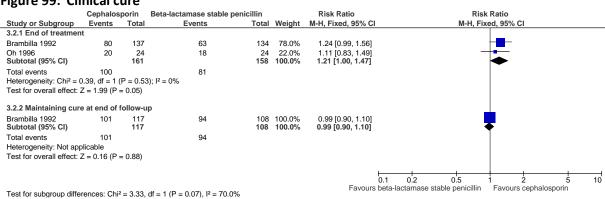
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 1.00), $I^2 = 0\%$

Figure 98: Withdrawal/switching of treatment due to adverse events

0	•	U					
	Azithrom	ycin	Erythron	nycin		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bohte 1995-nonpneumococal	0	19	2	21	100.0%	0.14 [0.01, 2.36]	+
Total (95% CI)		19		21	100.0%	0.14 [0.01, 2.36]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.36 (F	0 P = 0.17)		2				0.1 0.2 0.5 1 2 5 10 Favours azithromycin Favours erythromycin

1.4.4.1.4 Cephalosporin compared with beta-lactamase stable penicillin

Figure 99: Clinical cure



National Clinical Guideline Centre, 2014. Confidential.

Figure 100: Treatment discontinuation due to adverse events

	Cephalos	porin	Beta-lactamase stable	penicillin		Peto Odds Ratio	Peto Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	ed, 95% CI			
Oh 1996	0	24	2	24	100.0%	0.13 [0.01, 2.13]			-		
Total (95% CI)		24		24	100.0%	0.13 [0.01, 2.13]					
Total events	0		2								
Heterogeneity: Not ap Test for overall effect:		= 0.15)				0.1	0.5	1 2	eta-lactamas	5 se sta	10

1.4.4.1.5 Cephalosporin compared with narrow-spectrum beta-lactam (class 2)

Figure 101: Clinical cure

6	u		•				
	Cephalos	porin	Ampicillin/amox	icillin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
8.2.1 End of treatment							
Leuenberger 1983 Subtotal (95% CI)	15	16 16	16	18 18	100.0% 100.0 %	1.05 [0.86, 1.30] 1.05 [0.86, 1.30]	
Total events Heterogeneity: Not applic Test for overall effect: Z		= 0.61)	16				
Test for subgroup differen	nces: Not	applicab	ole			F	0.1 0.2 0.5 1 2 5 10 avours ampicillin/amoxicillin Favours cephalosporin

1.4.4.1.6 Non-respiratory fluoroquinolone (FQ) compared with tetracycline

Figure 102: Clinical cure at end of treatment



1.4.4.1.7 Macrolide compared with narrow-spectrum beta-lactam (class 1)

Figure 103: Clinical cure

	Macrolide Benzylpenicillin				Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
4.1.1 End of treatment							<u> </u>
Bohte 1995 - pneumococcal Subtotal (95% CI)	24	35 35	14	29 29	100.0% 100.0%	1.42 [0.92, 2.20 1.42 [0.92, 2.20]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.57	24 (P = 0.12	2)	14				
4.1.2 End of follow-up							
Bohte 1995 - pneumococcal Subtotal (95% CI)	29	35 35	19	29 29	100.0% 100.0%	1.26 [0.93, 1.71 1.26 [0.93, 1.71]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.51	29 (P = 0.13	3)	19				
Test for subgroup differences:	Chi2 – 0 1	Ω df =	1 (P = 0.67)	12 – 0%			0.1 0.2 0.5 1 2 5 10 Favours benzylpenicillin Favours macrolide

Test for subgroup differences: $Chi^2 = 0.18$, df = 1 (P = 0.67), $I^2 = 0\%$

Figure 104: Withdrawal/switching of treatment due to adverse events

	Macrol	ide	Benzylpei	nicillin		Peto Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fix	ed, 95% CI		
Bohte 1995 - pneumococcal	2	35	0	29	100.0%	6.41 [0.39, 106.11]					\rightarrow
Total (95% CI)		35		29	100.0%	6.41 [0.39, 106.11]					
Total events	2		0								
Heterogeneity: Not applicable Test for overall effect: Z = 1.30	(P = 0.19	9)					0.1 0.2 Favours	0.5 s macrolide	1 2 Favours b	5 enzylpe	10 nicillin

1.4.4.2 Single- compared with dual-antibiotic therapy

1.4.4.2.1 Macrolide compared with macrolide plus cephalosporin

Figure 105: CAP-related mortality

No forest plot available

Figure 106: Treatment failure

•							
	Single antibiotic the	herapy	Dual antibiotic th	erapy		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% C	I Peto, Fixed, 95% CI
7.2.3 Macrolide vs ma	acrolide + cephalos	oorin					
Rovira 1999 - formal Subtotal (95% CI)	0	45 45	2	45 45		0.13 [0.01, 2.15] 0.13 [0.01 , 2.15]	+
Total events Heterogeneity: Not app Test for overall effect: 2			2				
							0.1 0.2 0.5 1 2 5 10 Favours single antibiotic Favours dual antibiotic

Figure 107: Complications (pleural effusion)

0		, ,		,								
	Single antibiotic	herapy	Dual antibiotic	therapy		Peto Odds Ratio	Peto Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% C	Peto, Fixed, 95% CI					
7.4.3 Macrolide vs ma	crolide + cephalos	porin										
Rovira 1999 - formal Subtotal (95% CI)	1	45 45	0	45 45	100.0% 100.0 %	7.39 [0.15, 372.38] 7.39 [0.15, 372.38]	-					
Total events Heterogeneity: Not app Test for overall effect: Z			0									
							0.1 0.2 0.5 1 2 5 10 Favours single antibiotic Favours dual antibiotic					

1.4.4.2.2 Respiratory fluoroquinolone compared with cephalosporin plus macrolide (azithromycin)

Figure 108: Clinical cure or improvement at end of treatment

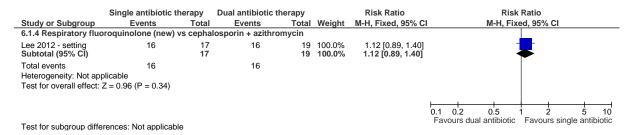


Figure 109: Withdrawal due to adverse events

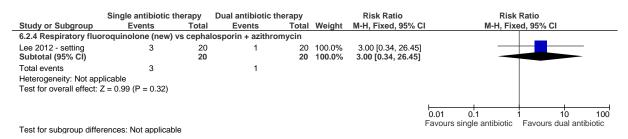
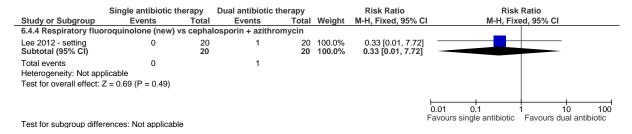


Figure 110: Complications (pleural effusion)



1.4.5 Moderate- to high-severity community-acquired pneumonia

1.4.5.1 Single- compared with other single-antibiotic therapy

1.4.5.1.1 Cephalosporin compared with beta-lactamase stable penicillin

Figure 111: All-cause mortality

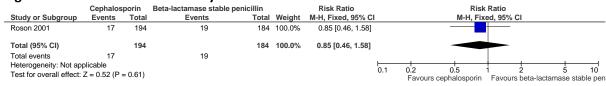
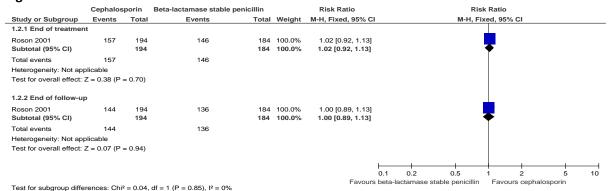


Figure 112: Clinical cure



1000 101 0400g104p 41110101000. 0111 = 0.01; 41 = 1 (1 = 0.00); 1 = 07

Figure 113: ITU admission

	Cephalos	porin	Beta-lactamase stable p		Risk Ratio			Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C			M-H, Fix	ed, 95% C	I		
Roson 2001	14	194	14	184	100.0%	0.95 [0.46, 1.93]							
Total (95% CI)		194		184	100.0%	0.95 [0.46, 1.93]							
Total events	14		14										
Heterogeneity: Not ap Test for overall effect:		= 0.88)					0.1	0.2 Favours	0.5 cephalosporin	1 Favours	 2 beta-lactama:	5 se sta	10 ible pen

Figure 114: Length of hospital stay

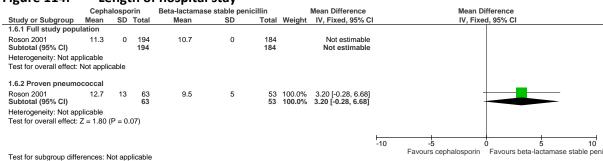


Figure 115: Complications (empyema)



1.4.5.1.2 Cephalosporin compared with narrow-spectrum beta-lactam (class 2)

Figure 116: Mortality

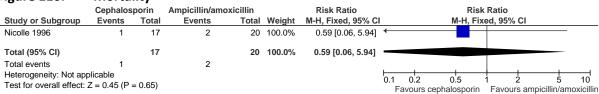


Figure 117: Clinical cure

	Cephalosporin		Ampicillin/amo	xicillin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
2.2.2 End of follow-up	р						<u> </u>
Nicolle 1996 Subtotal (95% CI)	16	17 17	14	20 20	100.0% 100.0 %	1.34 [0.99, 1.83] 1.34 [0.99, 1.83]	
Total events Heterogeneity: Not appress for overall effect:		= 0.06)	14				
Test for subgroup diffe	erences: Not	applicat	ole			F	0.1 0.2 0.5 1 2 5 10 avours ampicillin/amoxicillin Favours cephalosporin

Figure 118: C. difficile-associated diarrhoea

	Cephalos	porin	Ampicillin/amo	oxicillin		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI					
Nicolle 1996	2	17	1	20	100.0%	2.35 [0.23, 23.75]						
Total (95% CI)		17		20	100.0%	2.35 [0.23, 23.75]						
Total events	2		1									
Heterogeneity: Not app Test for overall effect:		0.47)					0.1 0.2 0.5 1 2 5 10					
rest for overall effect.	Z = 0.73 (P =	= 0.47)					Favours cephalosporin Favours ampicillin/amoxicillin					

1.4.5.2 Single- compared with dual-antibiotic therapy

1.4.5.2.1 Macrolide compare with macrolide plus cephalosporin

Figure 119: All-cause mortality

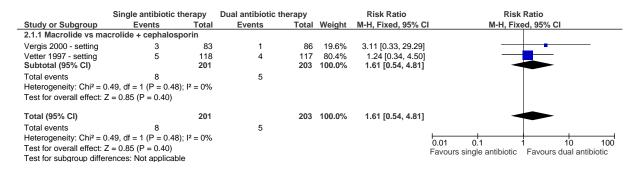


Figure 120: Clinical cure at end of treatment

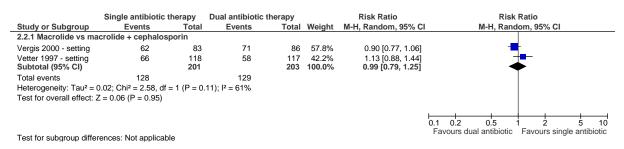


Figure 121: Clinical cure at end of follow-up

	Single antibiotic t	Dual antibiotic	therapy		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.3.1 Macrolide vs ma	acrolide + cephalos	porin					
Vetter 1997 - setting Subtotal (95% CI)	73	118 118	66	117 117	100.0% 100.0%	1.10 [0.89, 1.36] 1.10 [0.89, 1.36]	
Total events Heterogeneity: Not ap	•		66				
Test for overall effect:	Z = 0.85 (P = 0.40)						
Test for subgroup diffe	erences: Not annlicah	ıle					0.1 0.2 0.5 1 2 5 10 Favours dual antibiotic Favours single antibiotic

Figure 122: Withdrawal due to adverse events

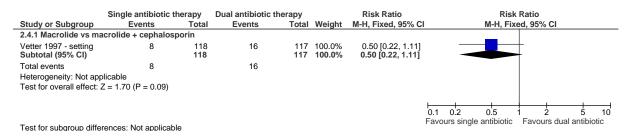
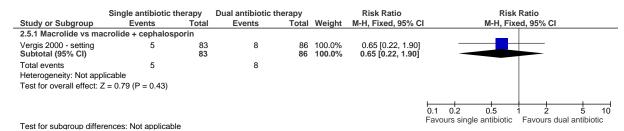


Figure 123: ITU admission



1.4.5.2.2 Respiratory fluoroquinolone compare with cephalosporin plus macrolide

Figure 124: All-cause mortality

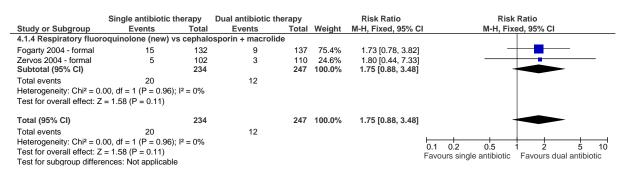


Figure 125: Clinical cure or improvement at end of treatment

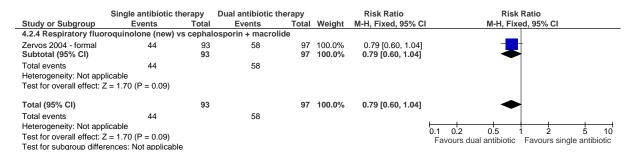


Figure 126: Clinical cure or improvement at end of follow up

	Single antibiotic t	herapy				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
4.7.3 Respiratory fluo	roquinolone (new)	vs cephal	osporin + macro	lide			
Frank 2002 - formal	100	115	97	121	54.1%	1.08 [0.97, 1.22]	=
Zervos 2004 - formal Subtotal (95% CI)	77	92 207	81	94 215	45.9% 100.0 %	0.97 [0.86, 1.10] 1.03 [0.95, 1.12]	*
Total events	177		178				
Heterogeneity: Chi ² =	1.70, df = 1 (P = 0.19)); I ² = 41%)				
Test for overall effect:	Z = 0.76 (P = 0.45)						
Total (95% CI)		207		215	100.0%	1.03 [0.95, 1.12]	•
Total events	177		178				
Heterogeneity: Chi ² =	1.70, df = 1 (P = 0.19)); I ² = 41%)				
Test for overall effect:	Z = 0.76 (P = 0.45)						0.1 0.2 0.5 1 2 5 10 Favours dual antibiotic Favours single antibiotic
Test for subgroup diffe	rences: Not applicable	le					ravours duar aritibiotic Favours single antibiotic

Figure 127: Withdrawal due to adverse events

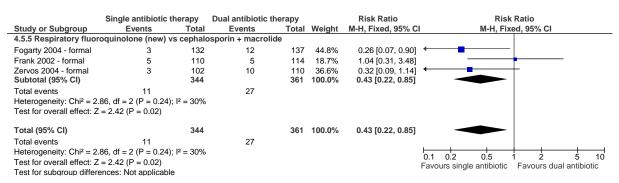
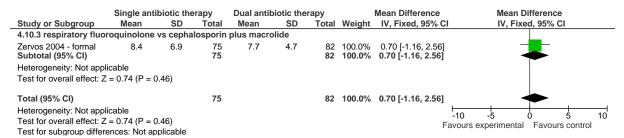


Figure 128: Length of hospital stay



1.4.5.2.3 Respiratory fluoroquinolone compare with beta-lactamase stable penicillin plus macrolide

Figure 129: Clinical cure at end of treatment

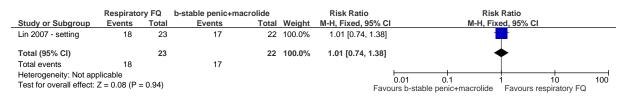


Figure 130: Clinical cure at end of follow-up

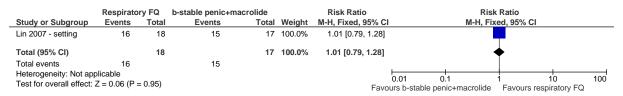


Figure 131: Length of hospital stay

	Respi	ratory FQ b-stable penic+macrolide				olide		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	CI IV, Fixed, 95% CI
Lin 2007 - setting	7.4	3.1	18	6.8	2.1	17	100.0%	0.60 [-1.15, 2.35]	
Total (95% CI)			18			17	100.0%	0.60 [-1.15, 2.35]	
Heterogeneity: Not appropriate Test for overall effect:		(P = 0	.50)					Favo	vours b-stable penic+macrolide Favours respiratory FQ

1.4.5.2.4 Respiratory fluoroquinolone compare with cephalosporin plus respiratory fluoroquinolone

Figure 132: All-cause mortality

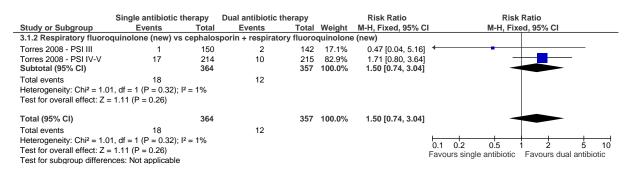


Figure 133: Clinical cure or improvement at end of treatment

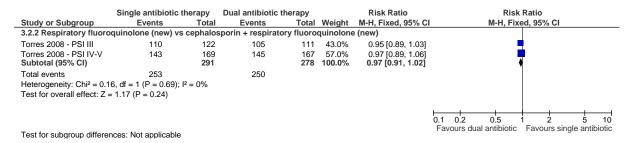


Figure 134: Maintaining clinical cure at end of follow-up

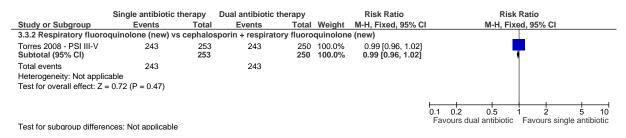
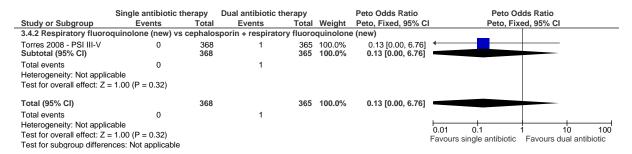


Figure 135: C. difficile-associated diarrhoea



1.4.5.2.5 Respiratory fluoroquinolone compare with cephalosporin plus non-respiratory fluoroquinolone

Figure 136: All-cause mortality

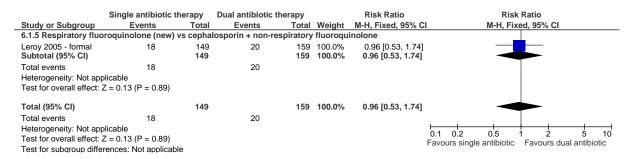


Figure 137: Clinical cure at end of treatment

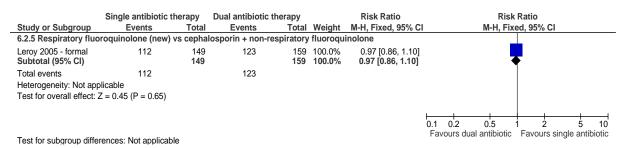


Figure 138: Clinical cure at follow-up

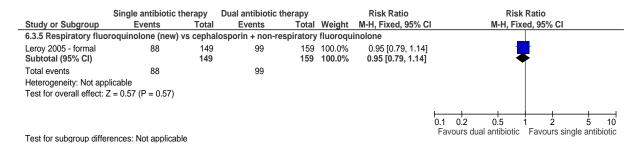


Figure 139: Withdrawal due to adverse events

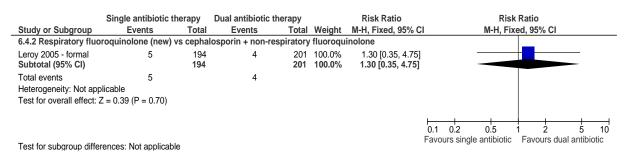
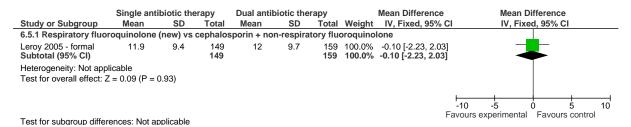


Figure 140: Length of hospital stay



1.4.5.3 Dual-compared with dual-antibiotic therapy

1.4.5.3.1 Non-respiratory fluoroquinolone (FQ) plus narrow spectrum beta-lactam (class 1) compared with macrolide plus beta-lactamase stable penicillin

Figure 141: All-cause mortality

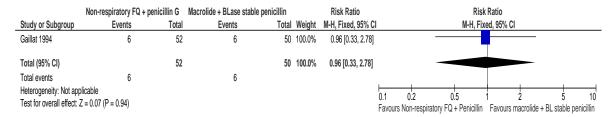


Figure 142: Clinical cure at end of treatment

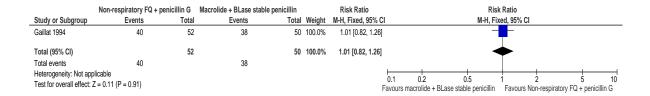
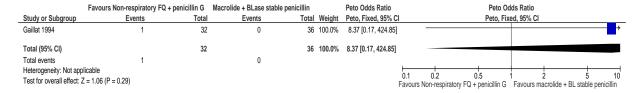


Figure 143: Complications - superinfection



1.4.5.3.2 Azithromycin plus cephalosporin compared with other macrolide plus cephalosporin

Figure 144: Mortality

	Azithromycin + cepha	alosporin	Other macrolide + cephalosporin			Risk Ratio	Risk Ratio						
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C			M-H, Fix	ced, 95% CI			
Tamm 2007	7	135	5	143	100.0%	1.48 [0.48, 4.56]							
Total (95% CI)		135		143	100.0%	1.48 [0.48, 4.56]							
Total events	7		5										
Heterogeneity: Not ap	plicable						0.4	-	0.5	<u> </u>	 	<u> </u>	
Test for overall effect:	Z = 0.69 (P = 0.49)						0.1 Favo	0.2 ours azithromyo	0.5 in + cephalosporin	Favours otl	z her macrolide + (o cephalo	10 osporin

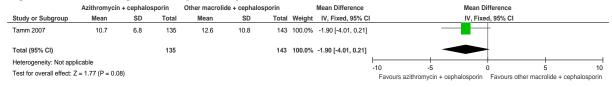
Figure 145: Clinial cure at end of treatment

	Azithromycin + cepha	alosporin	Other macrolide + cep		Risk Ratio			Ris					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI		M-H, F	ixed, 95°	% CI		
Tamm 2007	102	121	104	126	100.0%	1.02 [0.91, 1.14]	I			-			
Total (95% CI)		121		126	100.0%	1.02 [0.91, 1.14]				♦			
Total events	102		104										
Heterogeneity: Not app Test for overall effect:							0.1 Favours	0.2 other macroli	0.5 de + cephalosporin	1 Favo	2 urs azithromyc	5 in + cephalosp	10 porin

Figure 146: Withdrawal due to adverse events



Figure 147: Length of hospital stay



1.4.6 Duration of antibiotic therapy

1.4.6.1 Higher dose of antibiotic therapy with shorter duration compared with lower dose and longer duration of antibiotic therapy

Figure 148: All-cause mortality

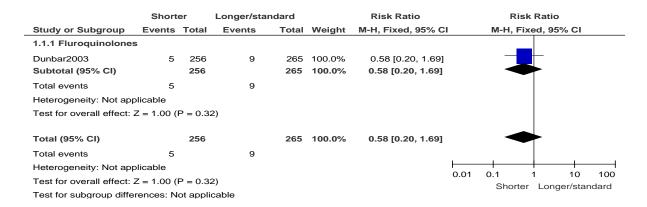


Figure 149: Clinical cure (7 to 14 days after therapy)

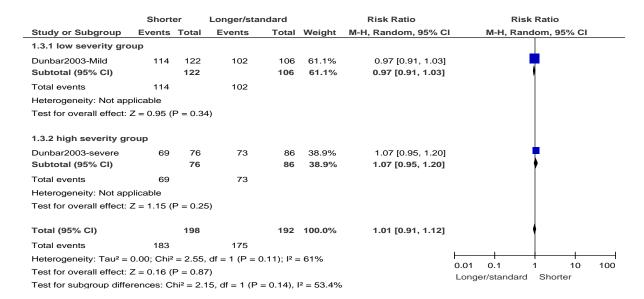
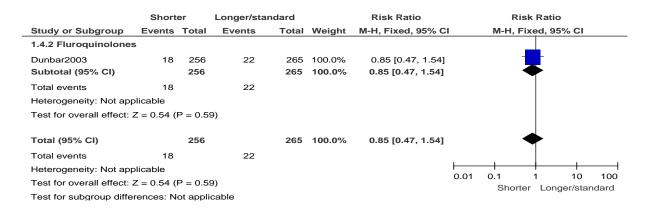
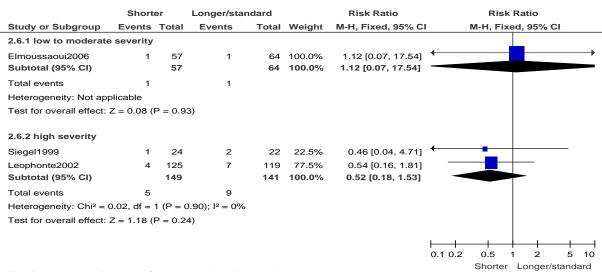


Figure 150: Withdrawal due to treatment-related adverse events



1.4.6.2 Shorter duration compared with longer duration of antibiotic therapy

Figure 151: All-cause 30-day mortality



Test for subgroup differences: $Chi^2 = 0.26$, df = 1 (P = 0.61), $I^2 = 0\%$

Figure 152: Clinical cure

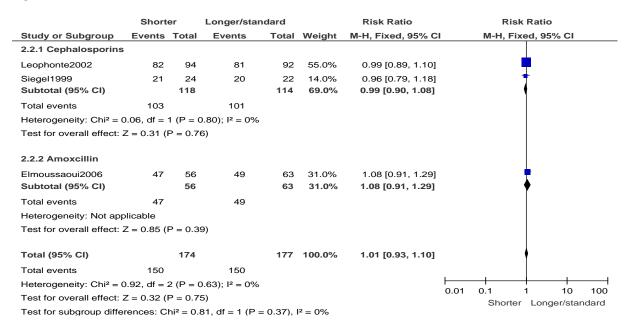


Figure 153: Withdrawal due to adverse events

	Short	er	Longer/star	ndard		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.3.1 Amoxicillin							
Elmoussaoui2006	0	57	0	64		Not estimable	
Subtotal (95% CI)		57		64		Not estimable	
Total events	0		0				
Heterogeneity: Not app	olicable						
Test for overall effect:	Not applic	able					
2.3.2 Cephalosporins	;						
Siegel1999	0	24	0	22		Not estimable	
Subtotal (95% CI)		24		22		Not estimable	
Total events	0		0				
Heterogeneity: Not app	olicable						
Test for overall effect:	Not applic	able					
Total (95% CI)		81		86		Not estimable	
Total events	0		0				
Heterogeneity: Not app	olicable						
Test for overall effect:	Not applic	able					0.01 0.1 1 10 100 Shorter Longer/standard
Test for subgroup diffe	rences: N	ot appli	icable				Chorter Eorigei/standard

Figure 154: Complications (worsening infection, abscess, metastatic infection, MODS)

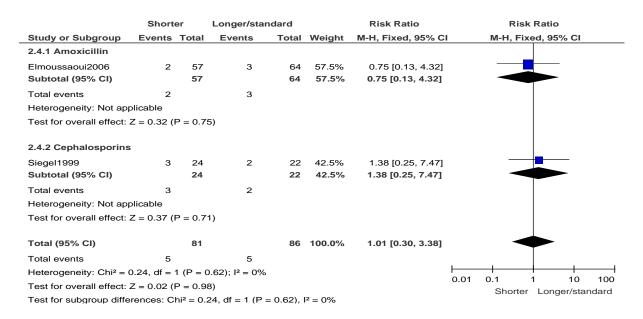
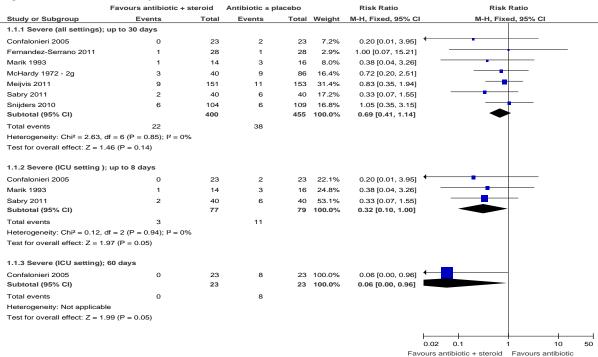


Figure 155: C. difficile-associated diarrhoea

	Short	er	Longer/star	ndard		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.5.2 Cephalosporins	;						
Leophonte2002 Subtotal (95% CI)	0	125 125	1	119 119	100.0% 100.0 %	0.32 [0.01, 7.72] 0.32 [0.01, 7.72]	
Total events	0		1				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.70 (P = 0.4	8)				
Total (95% CI)		125		119	100.0%	0.32 [0.01, 7.72]	
Total events	0		1				
Heterogeneity: Not app	olicable						0.01 0.1 1 10 100
Test for overall effect:	,		,				0.01 0.1 1 10 100 Shorter Longer/standard

1.5 Glucocorticosteroid treatment

Figure 156: Mortality



Test for subgroup differences: Chi² = 4.06, df = 2 (P = 0.13), I^2 = 50.8%

Figure 157: Mechanical ventilation

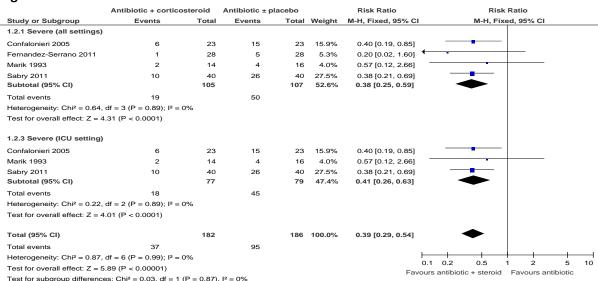


Figure 158: Clinical cure (time to clinical stability)

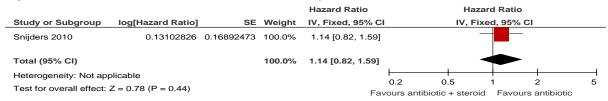


Figure 159: Length of hospital stay

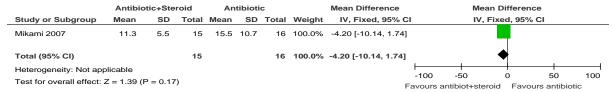
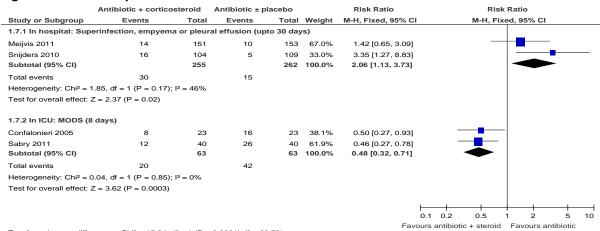


Figure 160: Hyperglycaemia

	Antibiotic + cortico	steroid	Antibiotic ± p	olacebo		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI	M-H, Fix	ed, 95% CI		
Meijvis 2011	67	151	35	153	94.7%	1.94 [1.38, 2.73]					
Snijders 2010	5	104	2	109	5.3%	2.62 [0.52, 13.21]			-		→
Total (95% CI)		255		262	100.0%	1.98 [1.41, 2.76]			•		
Total events	72		37								
Heterogeneity: Chi ² =	, , ,	$I^2 = 0\%$					0.1 0.2	0.5	1 2		10
Test for overall effect:	Z = 3.98 (P < 0.0001)					Fa	vours antibiot		Favours ar	ntibiotic	

Figure 161: **Complications**

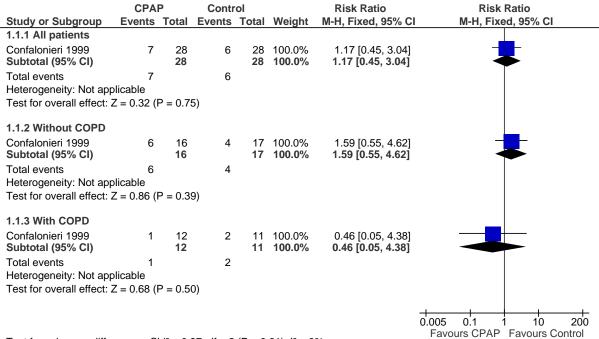


Test for subgroup differences: $Chi^2 = 15.94$, df = 1 (P < 0.0001), $I^2 = 93.7\%$

1.6 Gas exchange

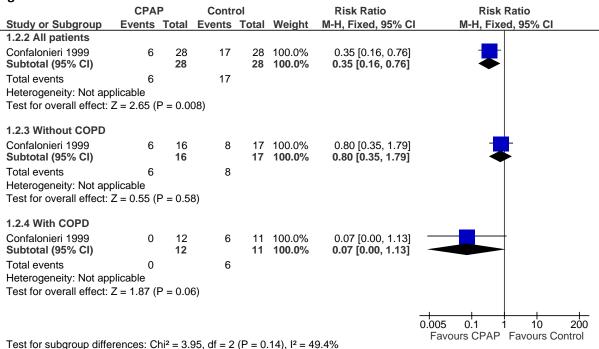
1.6.1 CPAP compared with usual care

Figure 162: Hospital mortality



Test for subgroup differences: Chi² = 0.97, df = 2 (P = 0.61), I^2 = 0%

Figure 163: Need for intubation



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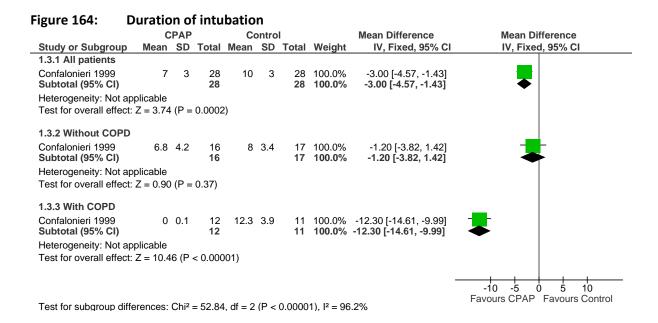
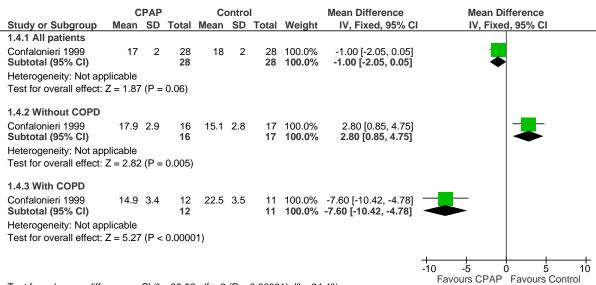


Figure 165: Duration of hospital stay



Test for subgroup differences: $Chi^2 = 35.52$, df = 2 (P < 0.00001), $I^2 = 94.4\%$

Figure 166: Duration of ITU stay

		•.		,					
	C	PAP		Co	ontro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	IV, Fixed, 95% CI
1.5.1 All patients									
Confalonieri 1999 Subtotal (95% CI)	1.8	0.7	28 28	6	2	28 28		-4.20 [-4.98, -3.42] -4.20 [-4.98, -3.42]	
Heterogeneity: Not app	olicable		20			20	100.0 /6	-4.20 [-4.90, -3.42]	~
Test for overall effect:		19 (P	< 0.000	001)					
rest for overall effect.	10	1) (1	< 0.000	,01)					
1.5.2 Without COPD									
Confalonieri 1999	0.25	2.1	16	7.6	2.2	17		-7.35 [-8.82, -5.88]	-
Subtotal (95% CI)			16			17	100.0%	-7.35 [-8.82, -5.88]	•
Heterogeneity: Not app									
Test for overall effect: 2	Z = 9.82	2 (P <	0.0000	01)					
1.5.3 With COPD									
Confalonieri 1999	2.9	1.8	12	4.8	1.7	11	100.0%	-1.90 [-3.33, -0.47]	
Subtotal (95% CI)			12			11	100.0%	-1.90 [-3.33, -0.47]	•
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 2.60) (P =	0.009)						
									-10 -5 0 5 10
		-							Favours CPAP Favours Control
Test for subgroup diffe	rences:	Chi ²	= 27.47	', df = 2	(P <	0.0000	1), $I^2 = 92$	2.7%	

Figure 167:	Patients w	ho re	ached F	PaO ₂ /	FiO ₂ ≥ 3	15		
	CPA	Р	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgro	up Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Cosentini 2010	19	20	8	27	100.0%	3.21 [1.78, 5.78]	-	
Total (95% CI)		20		27	100.0%	3.21 [1.78, 5.78]	•	
Total events	19		8					
Heterogeneity: No	t applicable						0.005 0.1 1 10	200
Test for overall eff	fect: $Z = 3.87$ (P = 0.0	001)				Favours Control Favours CP	

1.7 Monitoring

1.7.1 PCT to guide antibiotic administration and monitoring decisions compared with standard care (randomised data)

Figure 168: Mortality

			PCT	Standard care		Odds Ratio			Odds	Rati د	io		
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI			IV, Fixe	d, 95	% CI		
Schuetz 2012	-0.1165	0.1682	999	1028	100.0%	0.89 [0.64, 1.24]			-	-			
Total (95% CI)			999	1028	100.0%	0.89 [0.64, 1.24]			⋖				
Heterogeneity: Not app Test for overall effect: 2							0.1	0.2 Fav	0.5 vours PCT	1 Fav	2 ours s	5 tandar	10 d care

Figure 169: Treatment failure

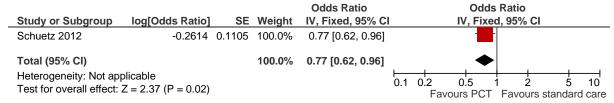


Figure 170: Median duration of antibiotic therapy

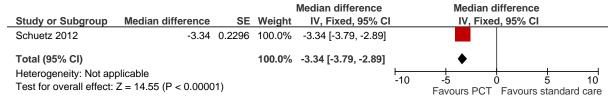


Figure 171: Total exposure to antibiotics

				Median difference		Median	difference		
Study or Subgroup	Median difference	SE	Weight	IV, Fixed, 95% CI		IV, Fix	red, 95% CI		
Schuetz 2012	-3.98	0.2347	100.0%	-3.98 [-4.44, -3.52]					
Total (95% CI)			100.0%	-3.98 [-4.44, -3.52]		♦			
Heterogeneity: Not approper Test for overall effect:		01)			-10	-5 Favours PC	0 T Favours	5 stand	10 lard care

1.7.2 PCT to guide antibiotic administration and monitoring decisions compared with standard care for the subgroup of patients with community-acquired pneumonia who received antibiotic therapy (unpublished data)

Figure 172: Mortality

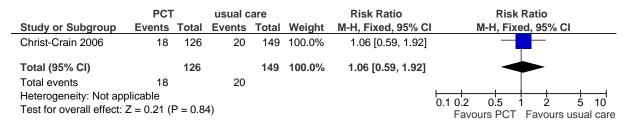


Figure 173: Length of hospital stay

		PCT		usı	ıal car	е		Mean Difference		Mea	n Differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, F	ixed, 95	5% CI	
Christ-Crain 2006	12.54	9.46	126	13.06	8.94	149	100.0%	-0.52 [-2.71, 1.67]		-	+		
Total (95% CI)			126			149	100.0%	-0.52 [-2.71, 1.67]					
Heterogeneity: Not app Test for overall effect:		(P = 0	0.64)						-10 F	-5 Favours P	O CT Fav	5 vours usu	10 ial care

Figure 174: Treatment failure

	PCT	•	Usual o	are		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI	
Christ-Crain 2006	23	126	27	149	100.0%	1.01 [0.55, 1.87]	-	
Total (95% CI)		126		149	100.0%	1.01 [0.55, 1.87]	•	
Total events Heterogeneity: Not app Test for overall effect:		P = 0.9	27 8)				0.01 0.1 1 10 Favours PCT Favours usua	100 I care

Figure 175: Duration of antibiotics

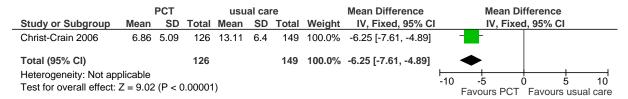


Figure 176: ITU admission



1.7.3 CRP or PCT to guide monitoring decisions (non-randomised data)

Figure 177: Mortality

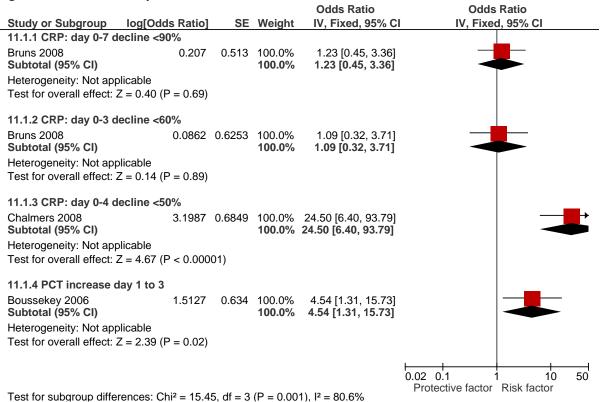


Figure 178: ITU mortality

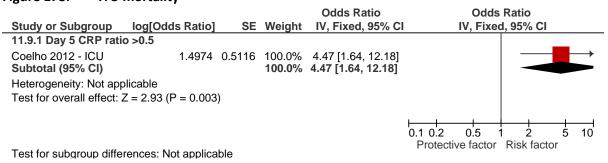
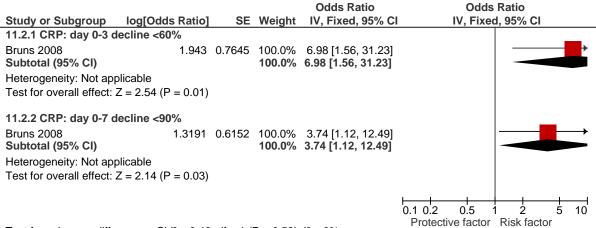


Figure 179: Inappropriate antibiotic therapy



Test for subgroup differences: $Chi^2 = 0.40$, df = 1 (P = 0.52), $I^2 = 0\%$

Figure 180: Overall treatment failure

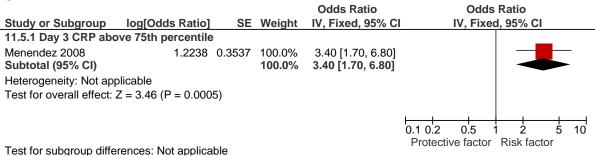
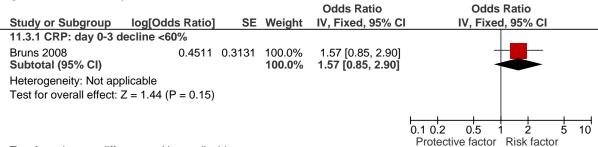


Figure 181: Early treatment failure



Test for subgroup differences: Not applicable

Figure 182: Late treatment failure

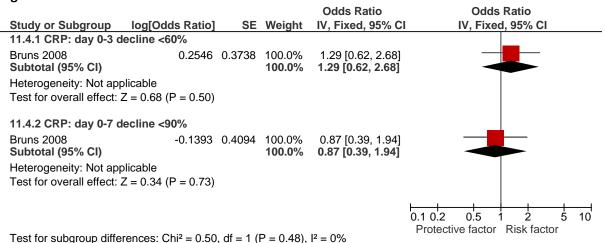


Figure 183: Late treatment failure (after 72 hours)

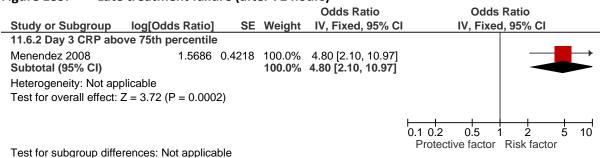
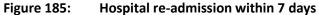


Figure 184: Severe complications after 72 hours

	or a comprisation	J 4	, – ou.	•	
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
11.7.1 Day 3 PCT <0.2	25 ng/ml				
Menendez 2009	0.157	0.2069	100.0%	1.17 [0.78, 1.76]	-
Subtotal (95% CI)			100.0%	1.17 [0.78, 1.76]	*
Heterogeneity: Not app	plicable				
Test for overall effect:	Z = 0.76 (P = 0.45)				
44.50.0.000.0					
11.7.2 Day 3 CRP <3	mg/dl				
Menendez 2009	-0.1508	0.0564		0.86 [0.77, 0.96]	
Subtotal (95% CI)			100.0%	0.86 [0.77, 0.96]	▼
Heterogeneity: Not app					
Test for overall effect:	Z = 2.67 (P = 0.008)				
11.7.3 Day 3 'clinical	stability'				
Menendez 2009	-0.2485	0.048	100.0%	0.78 [0.71, 0.86]	
Subtotal (95% CI)			100.0%	0.78 [0.71, 0.86]	<u>▼</u>
Heterogeneity: Not app	plicable				
Test for overall effect:	Z = 5.18 (P < 0.0000	01)			
					0.1 0.2 0.5 1 2 5 10
					Protective factor Risk factor
Test for subgroup diffe	erences: $Chi^2 = 4.75$,	df = 2 (I	P = 0.09),	$I^2 = 57.9\%$	1 TOLOGRAPO TAGIOT TAGIOTAGIO



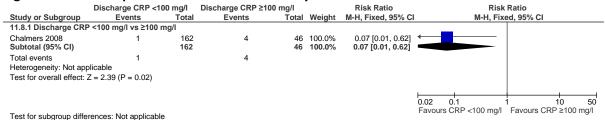
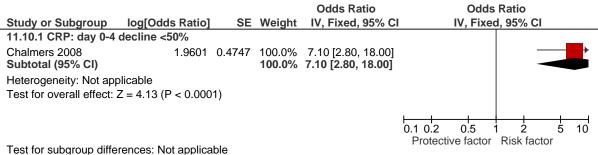
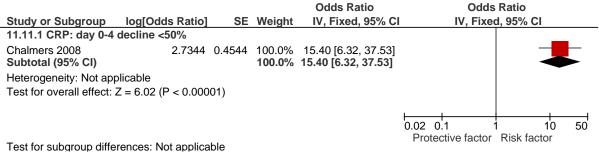


Figure 186: Need for invasive ventilation or ionotropic support



. cotto: cabqicap amotoricot tot approaci

Figure 187: Complicated pneumonia



. cot to caballoap amore more that applicable

1.8 Safe discharge

1.8.1 Clinical outcomes of patients who reached clinical stability according to ATS 2001 and ATS/IDSA 2007 criteria of clinical stability or number of instabilities

Figure 188: Hospital re-admission 30 days after discharge

	ATS 20	01	ATD/IDSA	2007		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Aliberti 2013	62	429	59	410	100.0%	1.00 [0.72, 1.40]	-
Total (95% CI)		429		410	100.0%	1.00 [0.72, 1.40]	*
Total events Heterogeneity: Not app Test for overall effect:		P = 0.98	59 8)			Fa	0.1 0.2 0.5 1 2 5 10 vours ATS/IDSA 20007 Favours ATS 2001

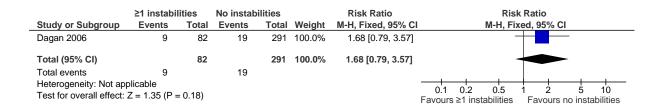
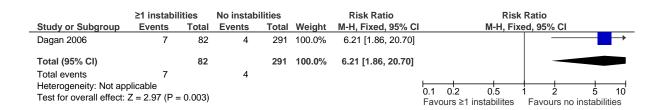


Figure 189: Mortality 30 days after discharge

	ATS 20	001	ATD/IDSA	2007		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H, Fixe	ed, 95% CI		
Aliberti 2013	14	429	14	410	100.0%	0.96 [0.46, 1.98]					
Total (95% CI)		429		410	100.0%	0.96 [0.46, 1.98]					
Total events	14		14								
Heterogeneity: Not ap	plicable						0.1 0.	2 0.5		<u> </u>	10
Test for overall effect:	Z = 0.12 (P = 0.90	0)			F:			ı ∠ Favours A	TS 200	



1.9 Patient information

No forest plots were generated for this question.

2 HAP

2.1 Diagnostic tests

No data available.

2.2 Severity assessment

No data available.

2.3 Microbiological tests

No data available.

2.4 Antibiotic therapy

2.4.1 Single- compared with other single-antibiotic therapy

2.4.1.1 Respiratory fluoroquinolone compared with cephalosporin

Figure 190: All-cause mortality

	KOITIXOIVI	acın	Certriax	cone		RISK Ratio	RISK RATIO
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Hoffken 2007	8	77	11	82	100.0%	0.77 [0.33, 1.82]	
Total (95% CI)		77		82	100.0%	0.77 [0.33, 1.82]	
Total events	8		11				
Heterogeneity: Not a	pplicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect	t: Z = 0.59 (F	P = 0.56)				Favours moxifloxacin Favours ceftriaxone

Figure 191: Clinical cure or improvement at end of follow-up

-	Moxifloxacin Ceftriaxone					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hoffken 2007	56	77	56	82	100.0%	1.06 [0.87, 1.30]	—
Total (95% CI)		77		82	100.0%	1.06 [0.87, 1.30]	•
Total events	56		56				
Heterogeneity: Not ap Test for overall effect:		9 = 0.54))				0.1 0.2 0.5 1 2 5 10 Favours ceftriaxone Favours moxifloxacin

Figure 192: Withdrawal due to adverse events

	Moxiflox	oxifloxacin Ceftriaxone Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Hoffken 2007	4	78	2	83	100.0%	2.13 [0.40, 11.29]	
Total (95% CI)		78		83	100.0%	2.13 [0.40, 11.29]	
Total events	4		2				
Heterogeneity: Not ap Test for overall effect:	•	9 = 0.38)	ı				0.1 0.2 0.5 1 2 5 10 Favours moxifloxacin Favours ceftriaxone

2.4.1.2 Beta-lactamase-stable penicillin compared with carbapenem

Figure 193: All cause mortality

	Favours piperacillin-taze	bactam	Imipenem-cila	astatin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Schmitt 2006	17	110	11	111	100.0%	1.56 [0.77, 3.18]	
Total (95% CI)		110		111	100.0%	1.56 [0.77, 3.18]	
Total events	17		11				
Heterogeneity: Not app							0.1 0.2 0.5 1 2 5 10
Test for overall effect: 2	Z = 1.22 (P = 0.22)						Favours piperacillin-tazobactam Favours imipenem-cilastatin

Figure 194: Clinical cure at end of treatment

	Piperacillin-tazob	actam	Imipenem-cila	astatin		Risk Ratio			Risk	(Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% C	ı		
Schmitt 2006	76	107	85	110	100.0%	0.92 [0.78, 1.08]			-	-			
Total (95% CI)		107		110	100.0%	0.92 [0.78, 1.08]				\			
Total events	76		85										
Heterogeneity: Not ap Test for overall effect:							0.1 Fav	0.2 ours imipen	0.5 em-cilastatin	1 2 Favours	l 2 piperacilli	5 in-tazob	10 actam

Figure 195: Clinical cure at end of follow-up

	Piperacillin-tazol	oactam	Imipenem-cil	astatin		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% C	:1		
Schmitt 2006	64	107	73	110	100.0%	0.90 [0.73, 1.11]			-	-			
Total (95% CI)		107		110	100.0%	0.90 [0.73, 1.11]				+			
Total events	64		73										
Heterogeneity: Not app Test for overall effect:							0.1 Fav	0.2 rours imipen	0.5 em-cilastatin	1 Favours	l 2 piperacillin-t	5 azob	10 actam

Figure 196: Withdrawal due to adverse events

	Piperacillin-tazob	actam	Imipenem-cil	astatin		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	i .		M-H, Fix	ed, 95% C	:1		
Schmitt 2006	13	110	9	111	100.0%	1.46 [0.65, 3.27]							
Total (95% CI)		110		111	100.0%	1.46 [0.65, 3.27]			-				
Total events	13		9										
Heterogeneity: Not app Test for overall effect:							0.1 Favour	0.2 s piperacillir	0.5 n-tazobactam	1 2 Favours	 2 imipenen	5 n-cilasta	10 tin

2.4.2 Single- compared with dual-antibiotic therapy

2.4.2.1 Cephalosporin compared with cephalosporin plus aminoglycoside

Table 1: All-cause mortality

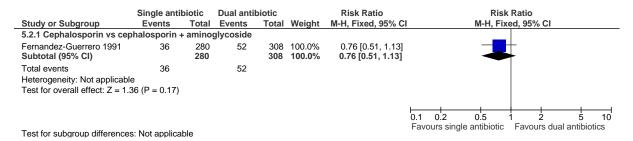
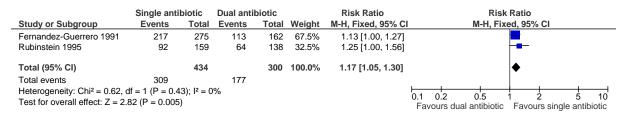
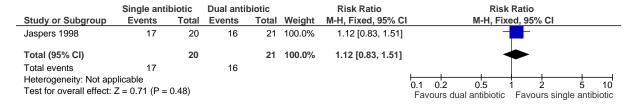


Table 2: Clincal cure at end of treatment



2.4.2.2 Carbapenem versus cephalosporin plus aminoglycoside

Figure 197: Clinical cure at end of treatment



Clinical cure at end of treatment (comparison subgroups from Fernandez-Guerrero 1991)

tudy or Subgroup			Dual antib Events		Weight	Risk Ratio M-H, Fixed, 95% C	Risk Ratio I M-H, Fixed, 95% CI
.1.1 Cefotaxime + aminog	•	075	00		100.001	4.00.50.00.4.1==	<u> </u>
ernandez-Guerrero 1991 ubtotal (95% CI)	217	275 275	60		100.0% 100.0%	1.03 [0.90, 1.18] 1.03 [0.90, 1.18]	-
otal events	217	2.0	60		100.070	1.00 [0.00, 1.10]	Ť
leterogeneity: Not applicable			00				
est for overall effect: Z = 0.3	87 (P = 0.71)						
.1.2 Cefotaxime + other							
ernandez-Guerrero 1991 ubtotal (95% CI)	217	275 275	10		100.0% 100.0%	1.03 [0.76, 1.39]	
otal events	217	2/3	10	13	100.076	1.03 [0.76, 1.39]	
leterogeneity: Not applicable			10				
est for overall effect: $Z = 0.7$							
.1.3 Broad-spectrum peni	cillins + amino	glycos	ides				<u>L</u>
ernandez-Guerrero 1991	217	275	23		100.0%	1.06 [0.86, 1.32]	
ubtotal (95% CI)	0.47	275		31	100.0%	1.06 [0.86, 1.32]	—
otal events leterogeneity: Not applicable	217		23				
est for overall effect: Z = 0.5							
1.4 Cephalosporins (gran	n-nositive activ	vitv) + a	aminoalyc	osides			
ernandez-Guerrero 1991	217	275	10		100.0%	1.66 [1.05, 2.61]	
ubtotal (95% CI)	=	275			100.0%	1.66 [1.05, 2.61]	
otal events	217		10				
eterogeneity: Not applicable est for overall effect: $Z = 2.7$							
	,	alas-V		!-!-			
.1.5 Cephalosporins (gran	-	-,				1.18 [0.89, 1.58]	
ernandez-Guerrero 1991 ubtotal (95% CI)	217	275 275	16		100.0% 100.0%	1.18 [0.89, 1.58] 1.18 [0.89, 1.58]	
otal events	217		16				
leterogeneity: Not applicable	Э						
est for overall effect: Z = 1.	14 (P = 0.25)						
.1.6 Cephalosporins (Pseu		-,				4 0 4 50 04 4 001	
ernandez-Guerrero 1991 ubtotal (95% CI)	217	275 275	16		100.0% 1 00.0 %	1.04 [0.81, 1.33] 1.04 [0.81, 1.33]	
otal events	217	2.0	16		100.070	1.04 [0.01, 1.00]	T
leterogeneity: Not applicable			10				
est for overall effect: Z = 0.2							
.1.7 Cephalosporins (anae	robe activity)	+ amin	oglycoside	es			<u></u>
ernandez-Guerrero 1991	217	275	11		100.0%	1.29 [0.89, 1.88]	+
ubtotal (95% CI)		275		18	100.0%	1.29 [0.89, 1.88]	
otal events	217		11				
leterogeneity: Not applicable est for overall effect: Z = 1.3							
.1.8 Clindamycin + amino	alveneidne						
ernandez-Guerrero 1991	217	275	7	12	100.0%	1.35 [0.84, 2.19]	
ubtotal (95% CI)	217	275	,		100.0%	1.35 [0.84, 2.19]	
otal events	217		7				
leterogeneity: Not applicable est for overall effect: Z = 1.2							
	, ,						
.1.9 Narrow-spectrum pen ernandez-Guerrero 1991	icillin (gram-p	ositive 275	activity) + 13		glycosides 100.0%	1.09 [0.82, 1.46]	
ubtotal (95% CI)	411	275 275	13			1.09 [0.82, 1.46]	-
otal events	217		13			- /	
leterogeneity: Not applicable							
est for overall effect: Z = 0.5	os (P = 0.55)						
.1.10 Other + aminoglycos							<u>L</u>
ernandez-Guerrero 1991	217	275	11		100.0%	1.08 [0.79, 1.47]	
otal events	247	275	4.4	15	100.0%	1.08 [0.79, 1.47]	
otal events leterogeneity: Not applicable	217		11				
est for overall effect: Z = 0.4							
.1.11 Other combination							
	217	275	16	22	100.0%	1.08 [0.83, 1.41]	
ernangez-Guerrero 1991		275			100.0%	1.08 [0.83, 1.41]	-
	217		16			_	
ernandez-Guerrero 1991 Jubtotal (95% CI) Jotal events	_						
ubtotal (95% CI) otal events leterogeneity: Not applicable							
subtotal (95% CI) otal events leterogeneity: Not applicable lest for overall effect: Z = 0.6							
subtotal (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 0.6 .1.12 All combinations	61 (P = 0.54)	275	102	272	100.09/	1 12 [1 04 4 22]	—
otational (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 0.6 .1.12 All combinations ernandez-Guerrero 1991		275 275	193		100.0% 100.0 %	1.12 [1.01, 1.23] 1.12 [1.01, 1.23]	
subtotal (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 0.6 .1.12 All combinations	61 (P = 0.54)		193 193			1.12 [1.01, 1.23] 1.12 [1.01, 1.23]	•
subtotal (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 0.6 .1.12 All combinations ernandez-Guerrero 1991 subtotal (95% CI) otal events leterogeneity: Not applicable	217 217						•
ubtotal (95% CI) otal events eterogeneity: Not applicable est for overall effect: Z = 0.6 1.12 All combinations ernandez-Guerrero 1991 ubtotal (95% CI) otal events	217 217						•
ubtotal (95% CI) tal events esterogeneity: Not applicable est for overall effect: Z = 0.6 1.12 All combinations ernandez-Guerrero 1991 ubtotal (95% CI) tal events eterogeneity: Not applicable	217 217						0.1 0.2 0.5 1 2 5

2.4.3 Dual- compared with other dual-antibiotic therapy

2.4.3.1 Beta-lactamase stable penicillin plus aminoglycoside compared with cephalosporin plus aminoglycoside

Figure 198: All-cause mortality



Figure 199: Clinical cure or improvement at end of follow-up

	BL + A	AG	C + A	G		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Joshi 1999	115	155	84	145	100.0%	1.28 [1.08, 1.51]	
Total (95% CI)		155		145	100.0%	1.28 [1.08, 1.51]	•
Total events	115		84				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 2.91 (I	P = 0.0	04)				0.1 0.2 0.5 1 2 5 10 Favours C + AG Favours BL + AG

Figure 200: Withdrawal due to adverse events

	BL + A	4G	C + A	G		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Joshi 1999	4	155	7	145	100.0%	0.53 [0.16, 1.79]	
Total (95% CI)		155		145	100.0%	0.53 [0.16, 1.79]	
Total events	4		7				
Heterogeneity: Not ap	plicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 1.02 (F	P = 0.3	1)				0.1 0.2 0.5 1 2 5 10 Favours BL + AG Favours C + AG

Figure 201: C. diffiile-associated diarrhoea

	BL + A	٩G	C + A	G		Peto Odds Ratio	Peto Oc	lds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	ed, 95% CI
Joshi 1999	0	155	0	145		Not estimable		
Total (95% CI)		155		145		Not estimable		
Total events	0		0					
Heterogeneity: Not app	olicable						0.1 0.2 0.5	1 2 5 10
Test for overall effect:	Not applic	able						Favours C + AG

2.4.4 Duration of antibiotic therapy

No data available.

2.4.5 Timing of antibiotic therapy

No data available.

2.5 Glucocorticosteroid treatment

No data available.

2.6 Gas exchange

No data available.

2.7 Monitoring

No data available.

2.8 Safe discharge

No data available.

2.9 Patient information

No data available.