National Clinical Guideline Centre

Pneumonia

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

Clinical guideline <…>

Appendix I

June 2014

Draft for consultation

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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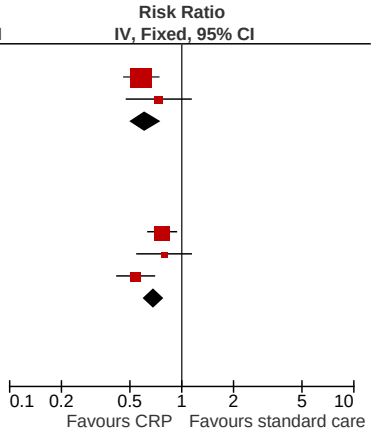
1 Community-acquired pneumonia

1.1 Diagnostic tests

1.1.1.1 CRP compared with standard care

Figure 1: Antibiotic treatment

Study or Subgroup	log[Risk Ratio]	SE	Experimental Total	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.1.1 After index consultation						
Cals 2007 + 2009	-0.5405	0.1193	227	204	77.4%	0.58 [0.46, 0.74]
Cals 2010 - LRTI	-0.3071	0.2205	56	51	22.6%	0.74 [0.48, 1.13]
Subtotal (95% CI)			**283**	**255**	**100.0%**	**0.61 [0.50, 0.75]**
Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 4.65 (P < 0.00001)						
4.1.2 within 28 days						
Cals 2007 + 2009	-0.261	0.0973	227	204	54.0%	0.77 [0.64, 0.93]
Cals 2010 - LRTI	-0.2366	0.1853	56	51	14.9%	0.79 [0.55, 1.13]
Little 2013	-0.6162	0.1282	2224	2040	31.1%	0.54 [0.42, 0.69]
Subtotal (95% CI)			**2507**	**2295**	**100.0%**	**0.69 [0.60, 0.80]**
Heterogeneity: Chi² = 5.46, df = 2 (P = 0.07); I² = 63%						
Test for overall effect: Z = 5.14 (P < 0.00001)						



Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.35), I² = 0%

Figure 2: Mortality

Study or Subgroup	CRP Events	CRP Total	Standard care Events	Standard care Total	Weight	Peto Odds Ratio Peto, Fixed, 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

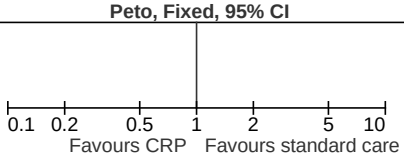
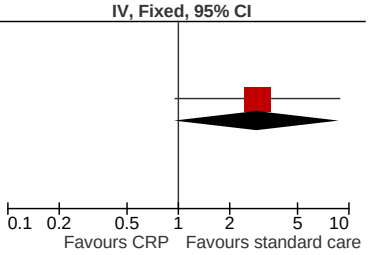


Figure 3: Hospital admission

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.2.1 CRP +/- communication training vs standard care +/- communication training						
Cals 2007 + 2009	0	0	227	204		Not estimable
Cals 2010 - LRTI	0	0	56	54		Not estimable
Little 2013	1.0682	0.5658	2224	2040	100.0%	2.91 [0.96, 8.82]
Subtotal (95% CI)			**2507**	**2298**	**100.0%**	**2.91 [0.96, 8.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						



Test for subgroup differences: Not applicable

Figure 4: Resolution of symptoms

Study or Subgroup	log[Adjusted Hazard Ratio]	SE	CRP Total	Usual care Total	Weight	Adjusted Hazard Ratio IV, Fixed, 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 applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						

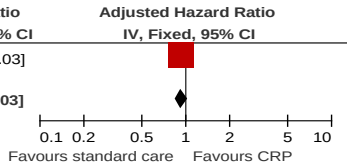


Figure 5: Resolution of symptoms (Feeling recovered as a surrogate at 7 days)

Study or Subgroup	CRP Events	CRP Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 0.63 (P = 0.53)

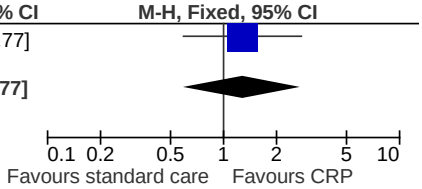


Figure 6: Quality-of-life (patient enablement score)

Study or Subgroup	CRP Mean	CRP SD	CRP Total	Standard care Mean	Standard care SD	Standard care Total	Weight	Mean Difference IV, Random, 95% 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: Tau² = 0.12; Chi² = 2.53, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.46 (P = 0.64)

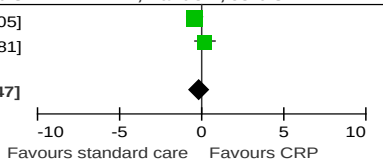
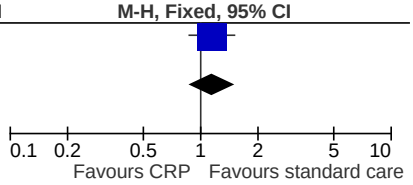


Figure 7: Re-consultation (follow-up 28 days)

Study or Subgroup	CRP Events	CRP Total	Standard care Events	Standard care Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.97 (P = 0.33)



1.1.1.2 PCT compared with standard care

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

Study or Subgroup	log[Adjusted Odds Ratio]	SE	PCT Total	Standard care Total	Weight	Adjusted Odds Ratio IV, Fixed, 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 applicable
Test for overall effect: Z = 15.35 (P < 0.00001)

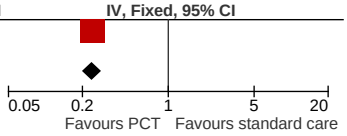


Figure 9: Antibiotic treatment (initiation of antibiotics- primary and ED settings)

Study or Subgroup	log[Adjusted Odds Ratio]	SE	PCT Total	Standard care Total	Weight	Adjusted Odds Ratio IV, Fixed, 95% CI
2.2.2 Primary care						
Schuetz 2012	-2.3026	0.182	507	501	100.0%	0.10 [0.07, 0.14]
Subtotal (95% CI)			**507**	**501**	**100.0%**	**0.10 [0.07, 0.14]**
Heterogeneity: Not applicable						
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 applicable						
Test for overall effect: Z = 10.89 (P < 0.00001)						

Test for subgroup differences: Chi² = 34.87, df = 1 (P < 0.00001), I² = 97.1%

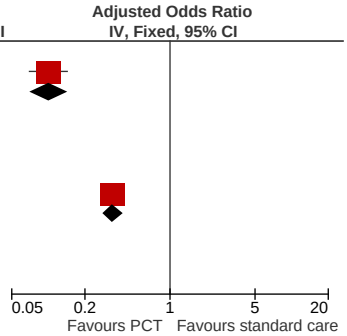


Figure 10: Mortality (all settings)

Study or Subgroup	log[Adjusted Odds Ratio]	SE	Favours PCT Total	Standard care Total	Weight	Adjusted Odds Ratio 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 applicable
Test for overall effect: Z = 0.43 (P = 0.67)

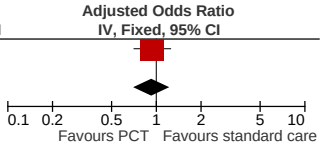
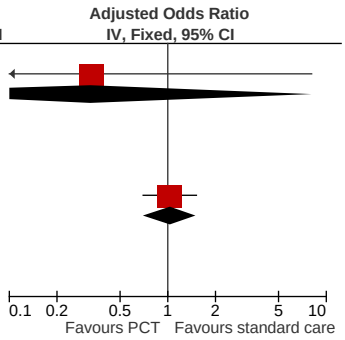


Figure 11: Mortality (Primary and ED settings)

Study or Subgroup	log[Adjusted Odds Ratio]	SE	PCT Total	Standard care Total	Weight	Adjusted Odds Ratio IV, Fixed, 95% CI
2.9.2 Primary care						
Schuetz 2012	-1.1125	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 applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.9.3 ED						
Schuetz 2012	0.0296	0.1971	1291	1314	100.0%	1.03 [0.70, 1.52]
Subtotal (95% CI)			**1291**	**1314**	**100.0%**	**1.03 [0.70, 1.52]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						



Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%

Figure 12: Hospital admission (ED)

Study or Subgroup	PCT Events	PCT Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 ED						
Christ-Crain 2004	101	124	88	119	100.0%	1.10 [0.96, 1.26]
Subtotal (95% CI)		**124**		**119**	**100.0%**	**1.10 [0.96, 1.26]**
Total events	101		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)		**124**		**119**	**100.0%**	**1.10 [0.96, 1.26]**
Total events	101		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Not applicable						

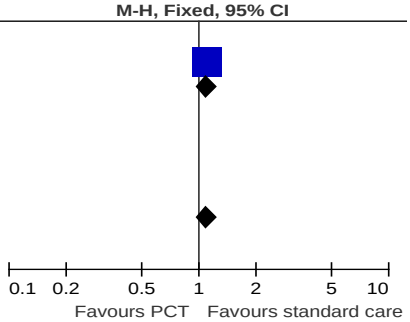
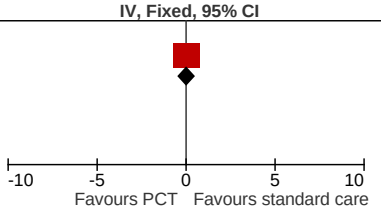


Figure 13: Resolution of symptoms (days with restricted activities for primary care setting)

Study or Subgroup	Risk Difference	SE	PCT Total	Standard care Total	Weight	Risk Difference IV, Fixed, 95% CI
2.6.2 Primary care						
Schuetz 2012	0.05	0.2602	507	501	100.0%	0.05 [-0.46, 0.56]
Subtotal (95% CI)			**507**	**501**	**100.0%**	**0.05 [-0.46, 0.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						



Test for subgroup differences: Not applicable

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

Study or Subgroup	log[Adjusted Odds Ratio]	SE	PCT Total	Standard care Total	Weight	Adjusted Odds Ratio IV, Fixed, 95% CI
Schuetz 2012	-0.1985	0.0857	2085	2126	100.0%	0.82 [0.69, 0.97]
Total (95% CI)			**2085**	**2126**	**100.0%**	**0.82 [0.69, 0.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						

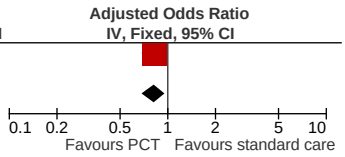
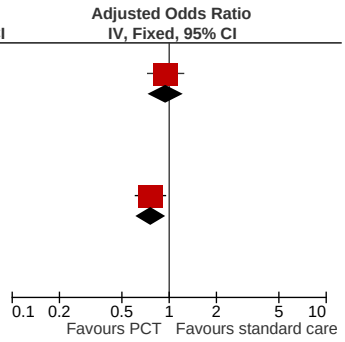


Figure 15: Resolution of symptoms (treatment failure - primary care and ED settings)

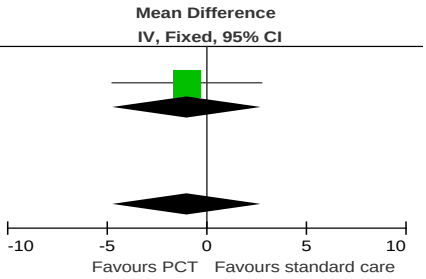
Study or Subgroup	log[Adjusted Odds Ratio]	SE	PCT Total	Standard care Total	Weight	Adjusted Odds Ratio IV, Fixed, 95% CI
2.11.2 Primary care						
Schuetz 2012	-0.0513	0.1344	507	501	100.0%	0.95 [0.73, 1.24]
Subtotal (95% CI)			**507**	**501**	**100.0%**	**0.95 [0.73, 1.24]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
2.11.3 ED						
Schuetz 2012	-0.2744	0.1122	1291	1314	100.0%	0.76 [0.61, 0.95]
Subtotal (95% CI)			**1291**	**1314**	**100.0%**	**0.76 [0.61, 0.95]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.45 (P = 0.01)						



Test for subgroup differences: Chi² = 1.62, df = 1 (P = 0.20), I² = 38.4%

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

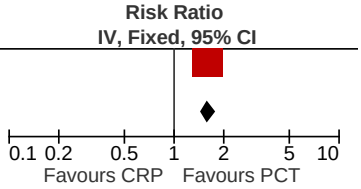
Study or Subgroup	PCT Mean	PCT SD	PCT Total	Standard care Mean	Standard care SD	Standard care Total	Weight	Mean Difference IV, Fixed, 95% CI
3.6.1 ED								
Christ-Crain 2004	21.9	14.7	124	22.9	15.1	119	100.0%	-1.00 [-4.75, 2.75]
Subtotal (95% CI)			**124**			**119**	**100.0%**	**-1.00 [-4.75, 2.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Total (95% CI)			**124**			**119**	**100.0%**	**-1.00 [-4.75, 2.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Test for subgroup differences: Not applicable								



1.1.1.3 CRP compared with PCT (indirect comparison)

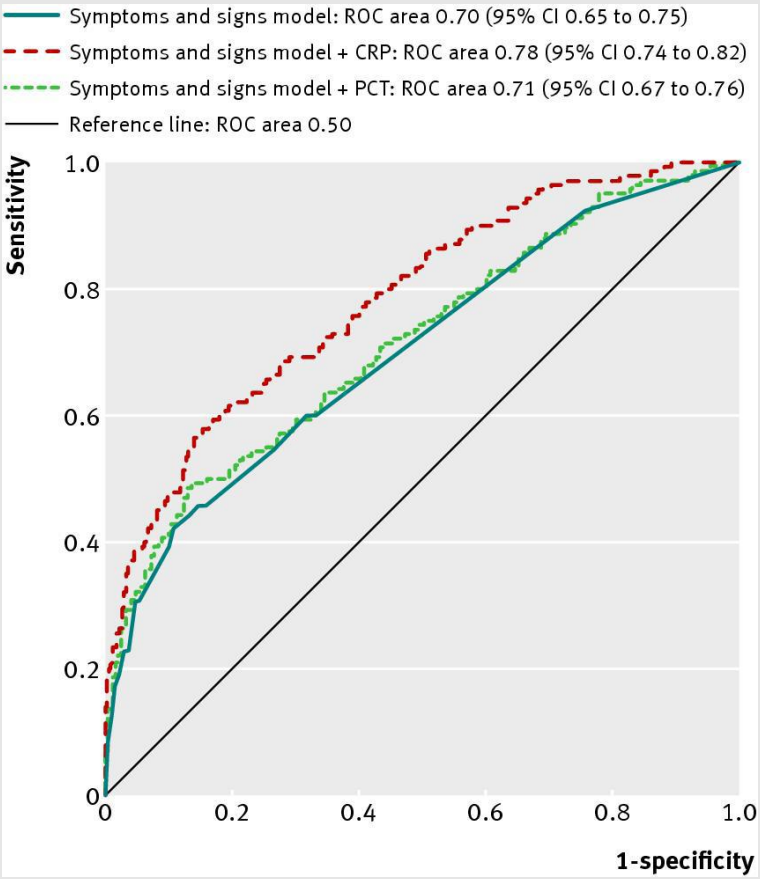
Figure 17: Antibiotic treatment (at index consultation)

Study or Subgroup	log[Risk Ratio]	SE	CRP Total	PCT Total	Weight	Risk Ratio 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 applicable						
Test for overall effect: Z = 9.02 (P < 0.00001)						

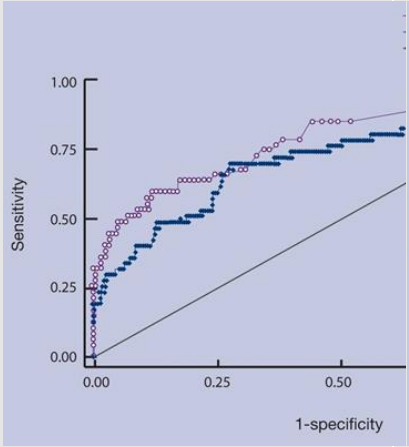
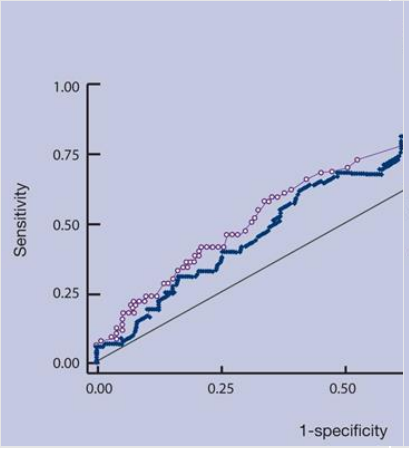
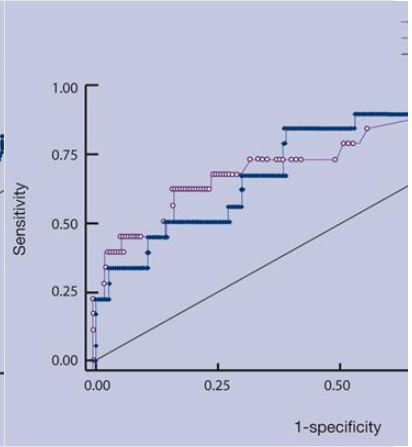


1.1.2 Receiver operating characteristic curves

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

Figure 19:ROC curves of PCT and CRP predicting radiographic pneumonia	Figure 20:ROC curves of PCT and CRP predicting bacterial aetiology	Figure 21:ROC curves of PCT and CRP predicting hospitalisation
		

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

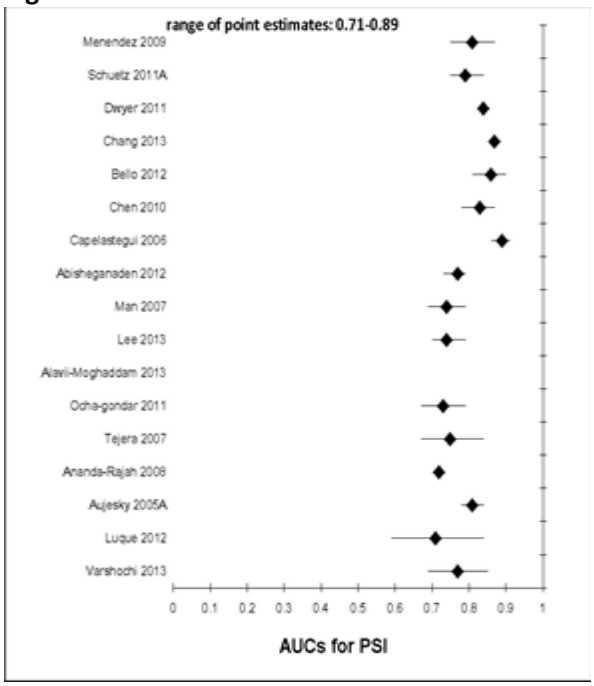


Figure 23: AUCs for CURB65

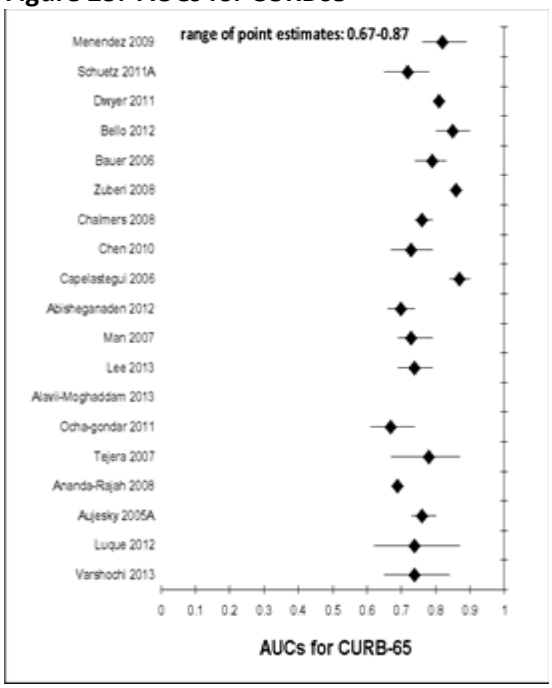


Figure 24: AUCs for CURB

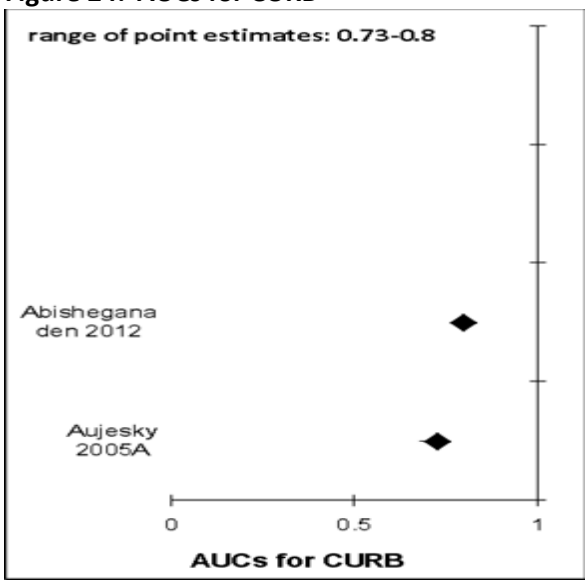


Figure 25: AUCs forCRB65

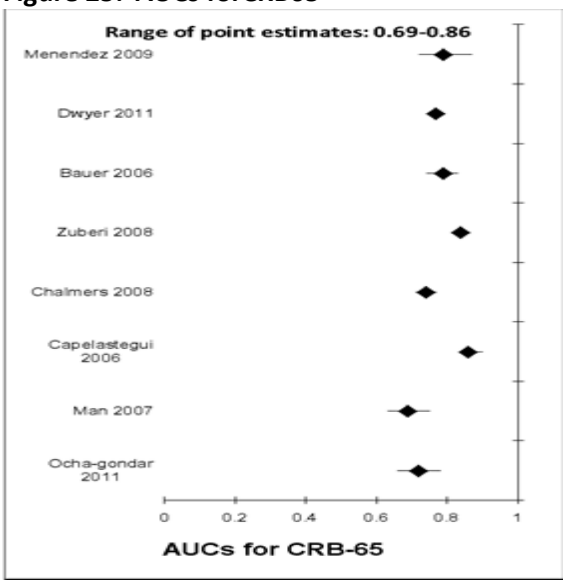


Figure 26: High-risk PSI (≥ IV) compared with low-risk PSI (< IV) to predict mortality

Study or Subgroup	high risk PSI Events	Total	low risk PSI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chang 2013	26	230	10	224	8.3%	2.53 [1.25, 5.13]
Kim 2013	25	323	14	569	8.3%	3.15 [1.66, 5.96]
Ochdagondar 2011	69	369	11	221	11.3%	3.76 [2.03, 6.94]
Man 2007	73	536	14	480	12.1%	4.67 [2.67, 8.16]
Luque 2012	17	114	1	38	1.2%	5.67 [0.78, 41.17]
Ananda-Rajah 2008	59	294	4	114	4.7%	5.72 [2.13, 15.38]
Abisheganaden 2012	158	548	23	504	19.6%	6.32 [4.15, 9.62]
Aujesky 2005A	114	1029	31	2152	16.4%	7.69 [5.21, 11.36]
Varshochi 2013	33	91	2	43	2.2%	7.80 [1.96, 31.00]
Dwyer 2011	31	184	4	191	3.2%	8.04 [2.90, 22.34]
Alavi-Moghaddam 2013	36	180	0	20	0.7%	8.47 [0.54, 133.01]
Lee 2013	94	476	6	268	6.3%	8.82 [3.92, 19.86]
Tejera 2007	27	170	1	56	1.2%	8.89 [1.24, 63.97]
Menendez 2009	34	237	2	216	1.7%	15.49 [3.77, 63.72]
Chen 2010	66	527	2	460	1.7%	28.80 [7.09, 116.95]
Schuetz 2010A	49	502	1	423	0.9%	41.29 [5.73, 297.74]
Total (95% CI)		**5810**		**5979**	**100.0%**	**6.60 [5.46, 7.96]**
Total events	911		126			

Heterogeneity: Chi² = 27.43, df = 15 (P = 0.03); I² = 45%
Test for overall effect: Z = 19.63 (P < 0.00001)

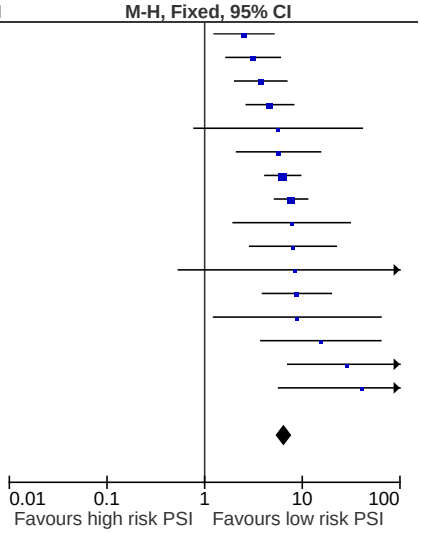


Figure 27: Intermediate-risk PSI (=III) compared with low-risk PSI (< III) to predict mortality

Study or Subgroup	intermediate risk PSI Events	Total	low risk PSI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alavi-Moghaddam 2013	0	13	0	7		Not estimable
Kim 2013	5	213	9	356	27.9%	0.93 [0.32, 2.73]
Luque 2012	1	28	0	10	3.0%	1.14 [0.05, 25.89]
Chen 2010	1	194	1	266	3.5%	1.37 [0.09, 21.79]
Lee 2013	4	136	2	132	8.4%	1.94 [0.36, 10.42]
Ananda-Rajah 2008	3	65	1	49	4.7%	2.26 [0.24, 21.09]
Tejera 2007	1	31	0	25	2.3%	2.44 [0.10, 57.37]
Abisheganaden 2012	20	342	3	162	16.8%	3.16 [0.95, 10.47]
Schuetz 2010A	1	180	0	243	1.8%	4.04 [0.17, 98.70]
Varshochi 2013	2	21	0	22	2.0%	5.23 [0.27, 102.87]
Man 2007	12	238	2	242	8.2%	6.10 [1.38, 26.97]
Menendez 2009	2	95	0	121	1.8%	6.35 [0.31, 130.80]
Ochdagondar 2011	11	160	0	61	3.0%	8.86 [0.53, 148.04]
Aujesky 2005A	26	692	5	1460	13.3%	10.97 [4.23, 28.45]
Dwyer 2011	4	75	0	116	1.6%	13.86 [0.76, 253.69]
Chang 2013	10	90	0	134	1.7%	31.15 [1.85, 525.05]
Total (95% CI)		**2573**		**3406**	**100.0%**	**4.46 [2.93, 6.80]**
Total events	103		23			

Heterogeneity: Chi² = 17.60, df = 14 (P = 0.23); I² = 20%
Test for overall effect: Z = 6.95 (P < 0.00001)

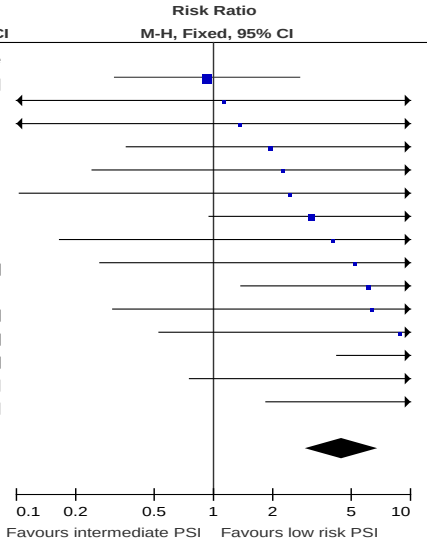


Figure 28: High-risk PSI (≥ IV) compared with intermediate-risk PSI (= III) to predict mortality

Study or Subgroup	high risk PSI Events	Total	intermediate risk PSI Events	Total	Weight	Risk Ratio 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: Chi² = 27.59, df = 15 (P = 0.02); I² = 46%
Test for overall effect: Z = 13.13 (P < 0.00001)

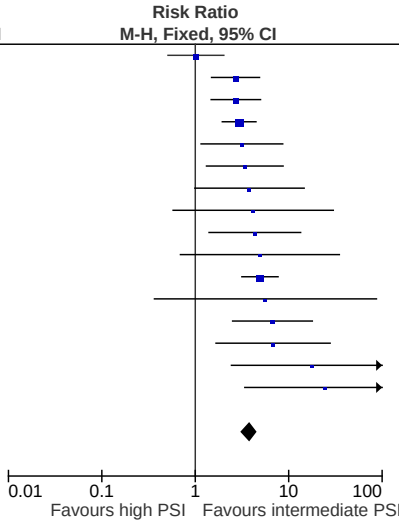


Figure 29: High-risk PSI (≥ IV) compared with low-risk PSI (< IV) to predict ITU admission

Study or Subgroup	high risk PSI Events	Total	low risk PSI Events	Total	Weight	Risk Ratio 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: Chi² = 4.89, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 6.58 (P < 0.00001)

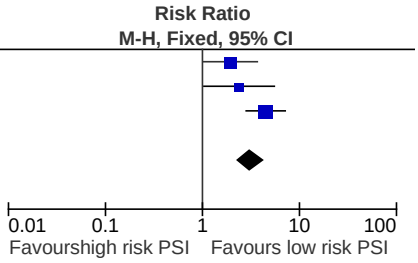


Figure 30: High-risk CURB65 (≥ 3) compared with low-risk CURB65 (< 3) to predict mortality

Study or Subgroup	high risk CURB-65 Events	Total	low risk CURB-65 Events	Total	Weight	Risk Ratio 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: Chi² = 57.02, df = 17 (P < 0.00001); I² = 70%
Test for overall effect: Z = 25.02 (P < 0.00001)

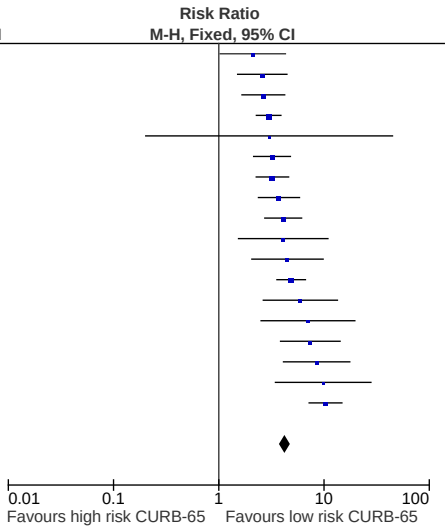


Figure 31: Intermediate-risk CURB65 (= 2) compared with low-risk CURB65 (< 2) to predict mortality

Study or Subgroup	intermediate risk CURB-65 Events	Total	low risk CURB-65 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alavi-Moghaddam 2013	0	3	0	4		Not estimable
Varshochi 2013	3	52	3	22	2.9%	0.42 [0.09, 1.94]
Luque 2012	3	46	2	47	1.4%	1.53 [0.27, 8.75]
Ananda-Rajah 2008	16	133	8	120	5.9%	1.80 [0.80, 4.06]
Kim 2013	13	216	18	560	7.0%	1.87 [0.93, 3.76]
Ochdagondar 2011	32	220	22	293	13.1%	1.94 [1.16, 3.24]
Dwyer 2011	6	100	6	198	2.8%	1.98 [0.66, 5.98]
Tejera 2007	3	72	1	50	0.8%	2.08 [0.22, 19.46]
Man 2007	23	315	13	440	7.6%	2.47 [1.27, 4.80]
Abisheganaden 2012	90	390	45	554	25.9%	2.84 [2.04, 3.97]
Chen 2010	23	295	12	493	6.3%	3.20 [1.62, 6.34]
Lee 2013	36	253	13	310	8.1%	3.39 [1.84, 6.26]
Aujesky 2005A	47	775	33	1952	13.1%	3.59 [2.32, 5.55]
Menendez 2009	7	130	2	205	1.1%	5.52 [1.16, 26.16]
Schuetz 2010A	25	296	4	427	2.3%	9.02 [3.17, 25.64]
Zuberi 2008	4	38	0	63	0.3%	14.77 [0.82, 266.94]
Capelastegui 2006	36	296	4	1006	1.3%	30.59 [10.98, 85.24]
Chang 2013	10	122	0	193	0.3%	33.12 [1.96, 560.16]
Total (95% CI)		**3752**		**6937**	**100.0%**	**3.25 [2.75, 3.83]**
Total events	377		186			

Heterogeneity: Chi² = 44.46, df = 16 (P = 0.0002); I² = 64%
Test for overall effect: Z = 13.88 (P < 0.00001)

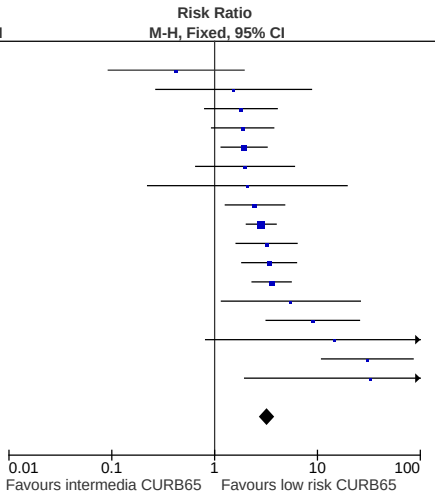


Figure 32: High-risk CURB65 (≥ 3) compared with intermediate-risk CURB65 (= 2) to predict mortality

Study or Subgroup	high risk CURB-65 Events	Total	intermediate risk CURB-65 Events	Total	Weight	Risk Ratio 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: Chi² = 30.23, df = 17 (P = 0.02); I² = 44%
Test for overall effect: Z = 14.04 (P < 0.00001)

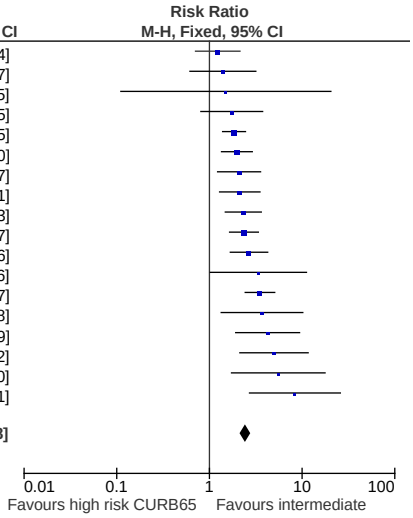


Figure 33: High-risk CURB65 (≥ 3) compared with low-risk CURB65 (< 3) to predict ITU admission

Study or Subgroup	high risk CURB65 Events	Total	low risk CURB65 Events	Total	Weight	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); I² = 9%
Test for overall effect: Z = 3.71 (P = 0.0002)

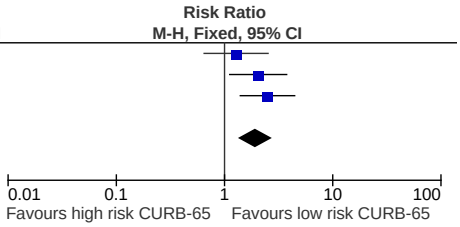


Figure 34: High-risk CURB (≥ 2) compared with low-risk CURB (< 2) to predict mortality

Study or Subgroup	high risk CURB Events	Total	low risk CURB Events	Total	Weight	Risk Ratio 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 = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 12.21 (P < 0.00001)

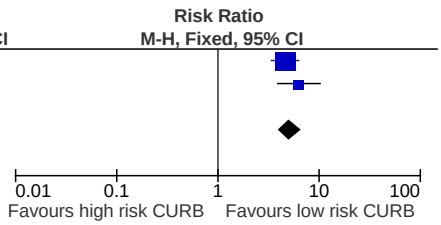


Figure 35: High-risk CRB65 (≥ 3) compared with low-risk CRB65 (< 3) to predict mortality

Study or Subgroup	high risk CRB-65 Events	Total	low risk CRB-65 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ochdagondar 2011	17	41	63	549	19.6%	3.61 [2.35, 5.56]
Man 2007	26	105	61	901	28.6%	3.66 [2.42, 5.52]
Zuberi 2008	5	9	13	128	3.8%	5.47 [2.51, 11.92]
Dwyer 2011	16	38	19	247	11.4%	5.47 [3.09, 9.69]
Bauer 2006	15	63	53	1370	10.5%	6.15 [3.68, 10.30]
Menendez 2009	17	49	19	398	9.3%	7.27 [4.06, 13.02]
Capelastegui 2006	36	80	83	1696	16.8%	9.20 [6.67, 12.67]
Total (95% CI)		**385**		**5289**	**100.0%**	**5.45 [4.57, 6.51]**
Total events	132		311			

Heterogeneity: Chi² = 18.46, df = 6 (P = 0.005); I² = 67%
Test for overall effect: Z = 18.79 (P < 0.00001)

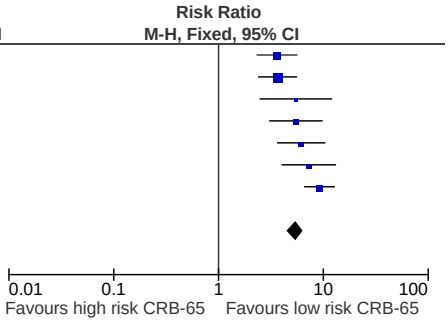


Figure 36: Intermediate-risk CRB65 (= 1 or 2) compared with low-risk CRB65 (= 0) to predict mortality

Study or Subgroup	Intermediate risk CRB-65 Events	Total	low risk CRB-65 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ochdagondar 2011	63	549	0	0		Not estimable
Dwyer 2011	16	240	3	97	32.7%	2.16 [0.64, 7.23]
Man 2007	58	783	3	128	39.5%	3.16 [1.01, 9.94]
Menendez 2009	18	319	1	79	12.3%	4.46 [0.60, 32.89]
Zuberi 2008	13	94	0	34	5.6%	9.95 [0.61, 162.92]
Bauer 2006	53	987	0	383	5.5%	41.59 [2.57, 671.84]
Capelastegui 2006	83	980	0	716	4.4%	122.06 [7.58, 1964.36]
Total (95% CI)		**3952**		**1437**	**100.0%**	**10.75 [5.70, 20.26]**
Total events	304		7			

Heterogeneity: Chi² = 15.75, df = 5 (P = 0.008); I² = 68%
Test for overall effect: Z = 7.34 (P < 0.00001)

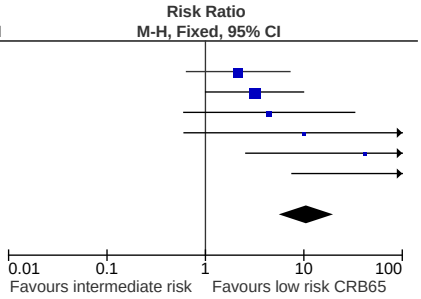
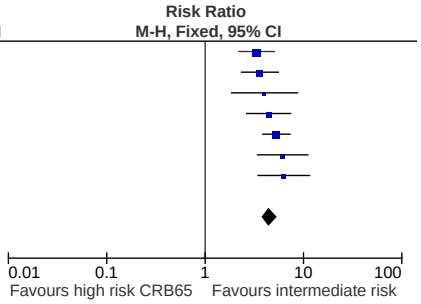


Figure 37: High-risk CRB65 (≥ 3) compared with intermediate-risk CRB65 (= 1 or 2) to predict mortality

Study or Subgroup	high risk CRB-65 Events	Total	intermediate risk CRB-65 Events	Total	Weight	Risk Ratio 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: Chi² = 6.38, df = 6 (P = 0.38); I² = 6%
Test for overall effect: Z = 16.64 (P < 0.00001)



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

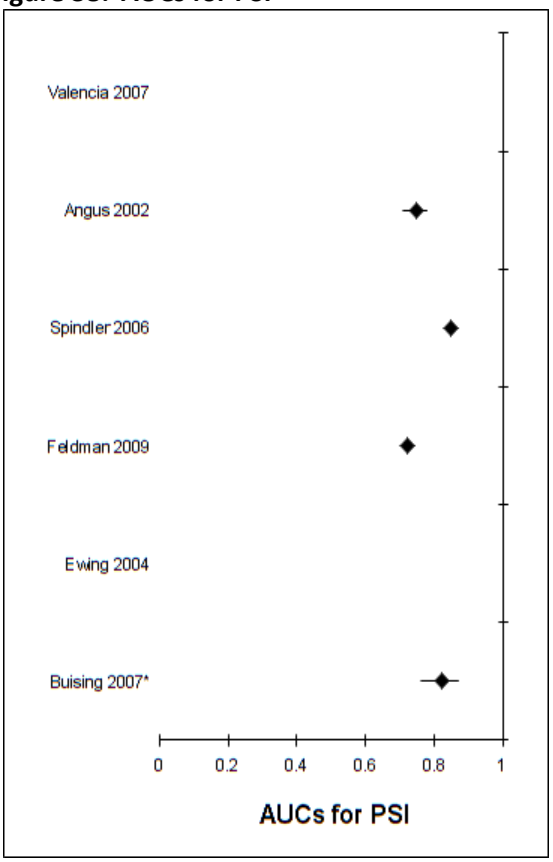


Figure 39: AUCs for CURB65

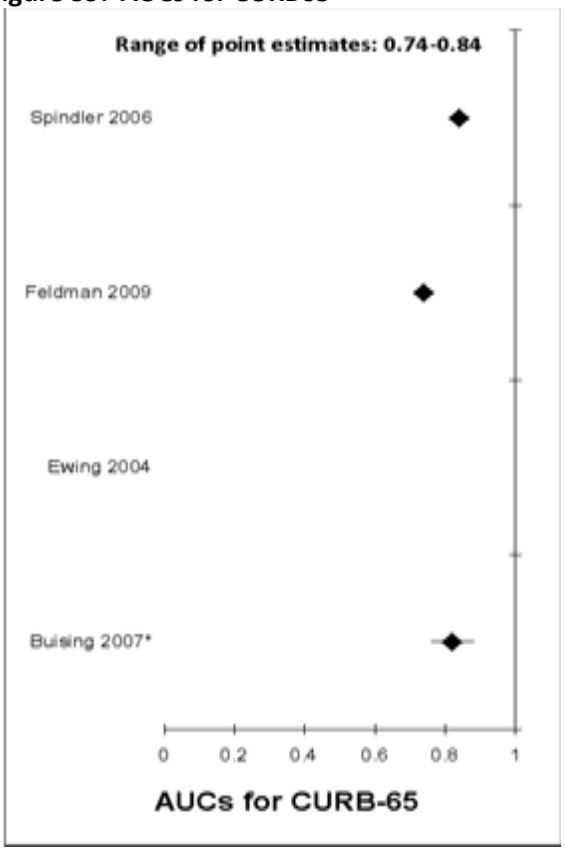
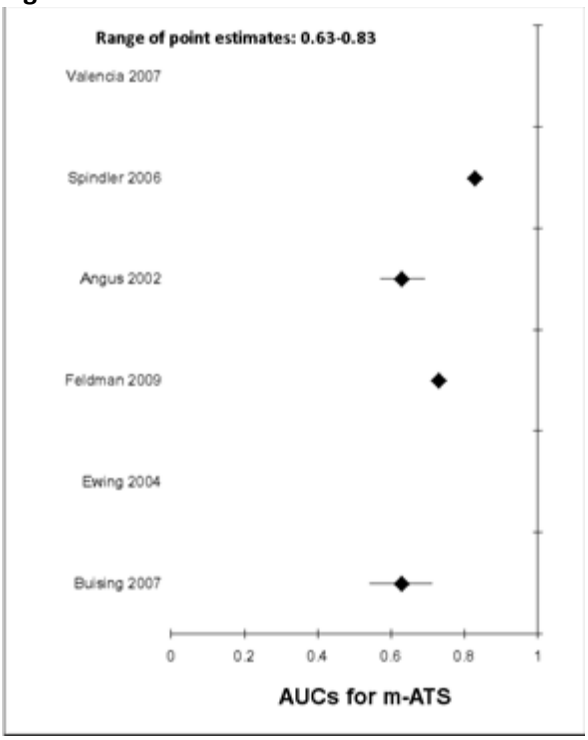


Figure 40: AUC for mATS



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

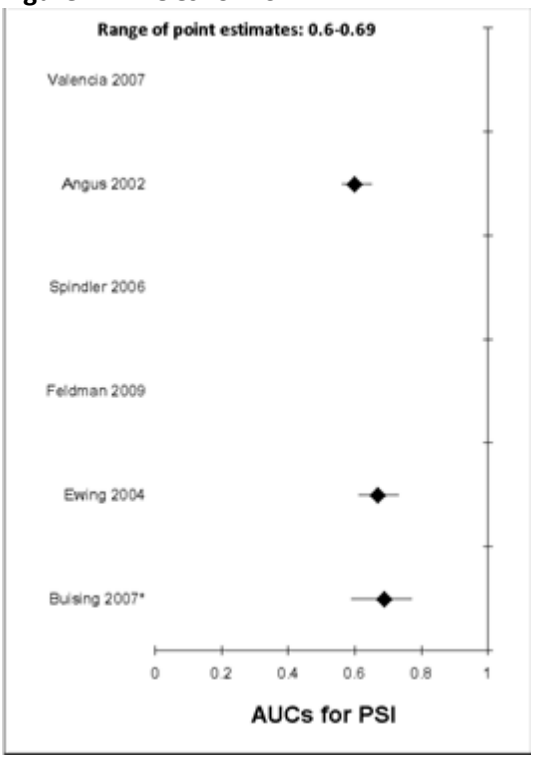
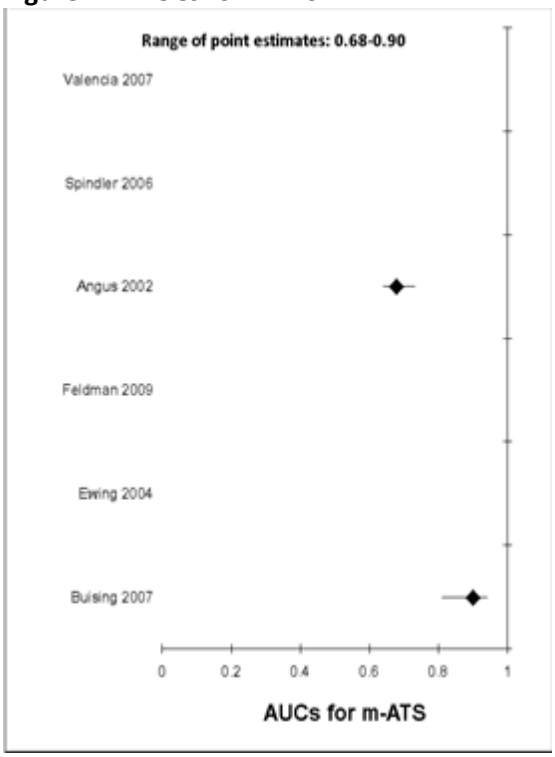


Figure 42: AUCs for mATS



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

Study or Subgroup	high risk CURB-65 Events	Total	low risk CURB-65 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guo 2012	4	14	12	1216	100.0%	28.95 [10.64, 78.82]
Total (95% CI)		**14**		**1216**	**100.0%**	**28.95 [10.64, 78.82]**
Total events	4		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.59 (P < 0.00001)

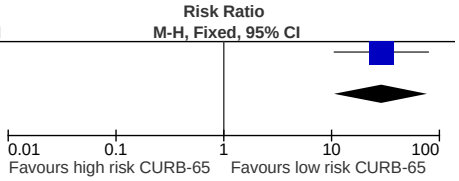
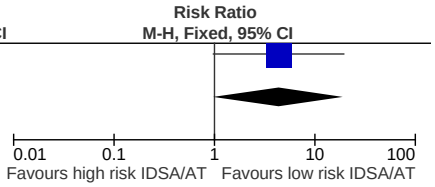


Figure 44: High-risk (≥ 3) groups compared with low-risk IDSA/ATS minor criteria (< 3) to predict mortality

Study or Subgroup	high risk IDSA/ATS Events	Total	low risk IDSA/ATS Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guo 2012	2	54	10	1176	100.0%	4.36 [0.98, 19.39]
Total (95% CI)		**54**		**1176**	**100.0%**	**4.36 [0.98, 19.39]**
Total events	2		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)

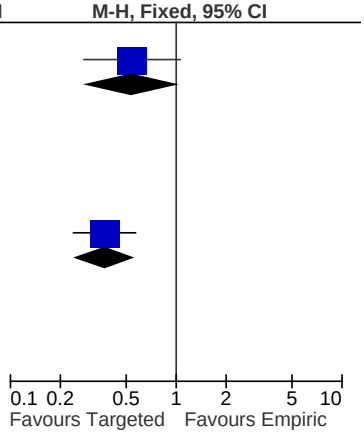


1.3 Microbiological tests

1.3.1.1 Targeted compared with empirical treatment using a combination of tests

Figure 45: Mortality

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 RCT						
van der Eerden 2005 - RCT	12	152	22	151	100.0%	0.54 [0.28, 1.06]
Subtotal (95% CI)		**152**		**151**	**100.0%**	**0.54 [0.28, 1.06]**
Total events	12		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.80 (P = 0.07)						
5.1.2 NRS 3-months follow up						
Lidman 2002 - NRS	42	482	29	123	100.0%	0.37 [0.24, 0.57]
Subtotal (95% CI)		**482**		**123**	**100.0%**	**0.37 [0.24, 0.57]**
Total events	42		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.54 (P < 0.00001)						



Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.34), I² = 0%

Figure 46: Clinical failure

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio M-H, Fixed, 95% CI
van der Eerden 2005 - RCT	32	152	35	151	100.0%	0.91 [0.59, 1.39]
Total (95% CI)		**152**		**151**	**100.0%**	**0.91 [0.59, 1.39]**
Total events	32		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.66)						

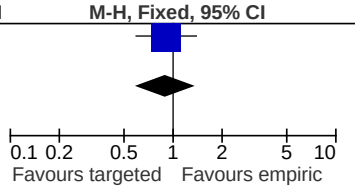


Figure 47: Length of hospital stay

Study or Subgroup	Targeted Mean	Targeted SD	Targeted Total	Empiric Mean	Empiric SD	Empiric Total	Weight	Mean Difference IV, Fixed, 95% CI
van der Eerden 2005 - RCT	14.3	13.2	152	13.2	9.4	151	100.0%	1.10 [-1.48, 3.68]
Total (95% CI)			**152**			**151**	**100.0%**	**1.10 [-1.48, 3.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								

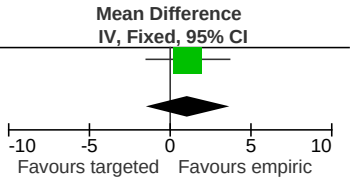
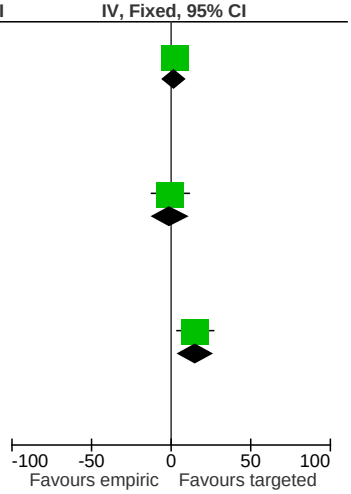


Figure 48: Quality-of-life (SF-36)

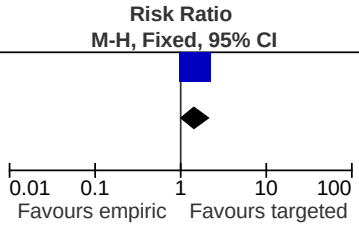
Study or Subgroup	Targeted Mean	Targeted SD	Targeted Total	Empiric Mean	Empiric SD	Empiric Total	Weight	Mean Difference IV, Fixed, 95% CI
5.4.1 30 days								
van der Eerden 2005 - RCT	59.5	21.5	72	57.3	20.5	47	100.0%	2.20 [-5.48, 9.88]
Subtotal (95% CI)			**72**			**47**	**100.0%**	**2.20 [-5.48, 9.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.57)								
5.4.2 90 days								
van der Eerden 2005 - RCT	66.7	22.9	50	67.2	30.1	35	100.0%	-0.50 [-12.32, 11.32]
Subtotal (95% CI)			**50**			**35**	**100.0%**	**-0.50 [-12.32, 11.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.93)								
5.4.3 180 days								
van der Eerden 2005 - RCT	79.3	22.4	31	64.1	20.1	22	100.0%	15.20 [3.68, 26.72]
Subtotal (95% CI)			**31**			**22**	**100.0%**	**15.20 [3.68, 26.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.59 (P = 0.010)								



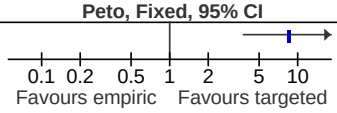
Test for subgroup differences: Chi² = 4.34, df = 2 (P = 0.11), I² = 53.9%

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

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lidman 2002 - NRS	133	482	23	123	100.0%	1.48 [0.99, 2.19]
Total (95% CI)		**482**		**123**	**100.0%**	**1.48 [0.99, 2.19]**
Total events	133		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						



Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
van der Eerden 2005 - RCT	25	134	0	128		8.61 [3.78, 19.61]



1.3.1.2 Targeted compared with empirical treatment using urinary antigen tests

Figure 50: Mortality

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Falguera 2010 - RCT	1	88	0	89	100.0%	7.47 [0.15, 376.66]
Total (95% CI)		**88**		**89**	**100.0%**	**7.47 [0.15, 376.66]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						

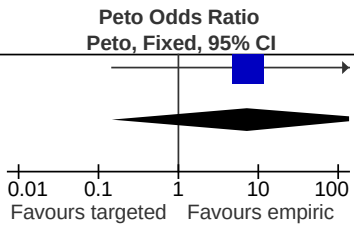


Figure 51: Clinical relapse

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.83 (P = 0.41)

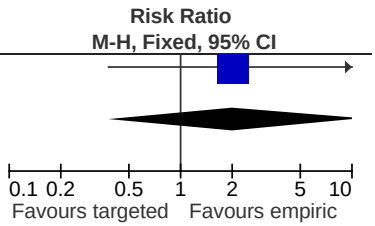


Figure 52: Re-admission

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.83 (P = 0.41)

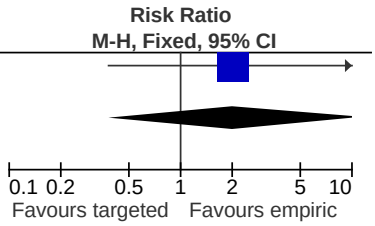


Figure 53: Treatment withdrawal due to adverse events

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Falguera 2010 - RCT	1	88	1	89	100.0%	1.01 [0.06, 15.92]
Total (95% CI)		**88**		**89**	**100.0%**	**1.01 [0.06, 15.92]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)

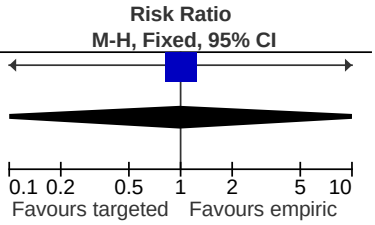
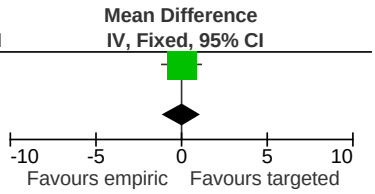


Figure 54: Length of hospital stay

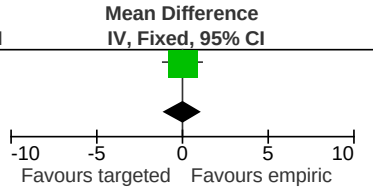
Study or Subgroup	Targeted Mean	Targeted SD	Targeted Total	Empiric Mean	Empiric SD	Empiric Total	Weight	Mean Difference IV, Fixed, 95% CI
Falguera 2010 - RCT	7.1	4	88	7.1	3.8	89	100.0%	0.00 [-1.15, 1.15]
Total (95% CI)			**88**			**89**	**100.0%**	**0.00 [-1.15, 1.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Study or Subgroup	Empiric Mean	Empiric SD	Empiric Total	Targeted Mean	Targeted SD	Targeted Total	Weight	Mean Difference IV, Fixed, 95% CI
Falguera 2010 - RCT	7.1	3.8	89	7.1	4	88	100.0%	0.00 [-1.15, 1.15]
Total (95% CI)			**89**			**88**	**100.0%**	**0.00 [-1.15, 1.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



1.3.1.3 Targeted compared with empirical treatment using blood culture

Figure 55: Mortality

Study or Subgroup	Targeted Events	Targeted Total	Empiric Events	Empiric Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Benenson 2007 - NRS	32	667	8	118	14.0%	0.71 [0.33, 1.50]
Dedier 2001 - NRS	54	841	49	150	86.0%	0.20 [0.14, 0.28]
Total (95% CI)		**1508**		**268**	**100.0%**	**0.27 [0.20, 0.36]**
Total events	86		57			

Heterogeneity: Chi² = 9.55, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 8.42 (P < 0.00001)

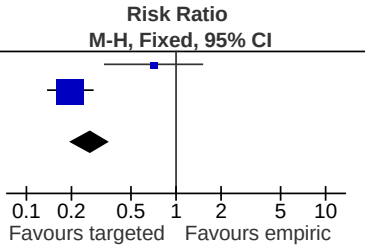


Figure 56: Mortality

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
7.2.1 Blood culture within 24 h			
Dedier 2001 - NRS	-0.1508	0.4443	0.86 [0.36, 2.05]
Meehan 1997 - NRS	-0.1054	0.0538	0.90 [0.81, 1.00]
7.2.2 Blood culture before antibiotics			
Dedier 2001 - NRS	0.1906	0.3412	1.21 [0.62, 2.36]
Lee 2011 - NRS	-0.1054	0.2069	0.90 [0.60, 1.35]
Meehan 1997 - NRS	-0.0834	0.0587	0.92 [0.82, 1.03]

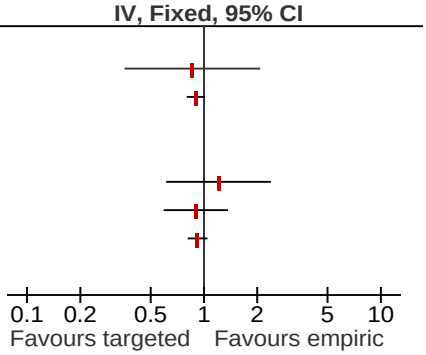


Figure 57: Clinical instability at 48 hours

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
7.3.1 Blood culture within 24 h			
Dedier 2001 - NRS	0.4824	0.1838	1.62 [1.13, 2.32]
7.3.2 Blood culture before antibiotics			
Dedier 2001 - NRS	0.0583	0.1834	1.06 [0.74, 1.52]

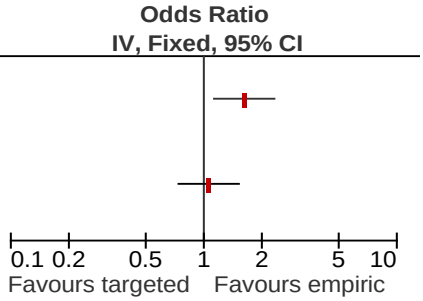


Figure 58: Length of hospital stay

Study or Subgroup	Targeted Mean	Targeted SD	Targeted Total	Empiric Mean	Empiric SD	Empiric Total	Weight	Mean Difference IV, Fixed, 95% CI
Benenson 2007 - NRS	5.3	3.4	667	5	4.3	118	100.0%	0.30 [-0.52, 1.12]
Total (95% CI)			**667**			**118**	**100.0%**	**0.30 [-0.52, 1.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

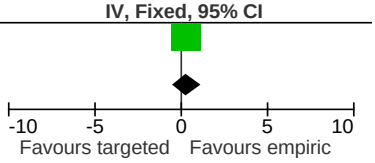


Figure 59: Length of hospital stay

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
7.5.1 Blood culture within 24 h			
Dedier 2001 - NRS	0.0392	0.1876	1.04 [0.72, 1.50]
7.5.2 Blood culture before 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]

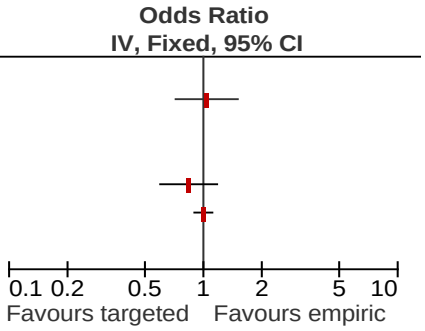
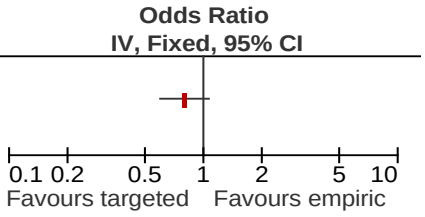


Figure 60: Hospital re-admission

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
7.6.2 Blood culture before antibiotics			
Lee 2011 - NRS	-0.2231	0.1468	0.80 [0.60, 1.07]

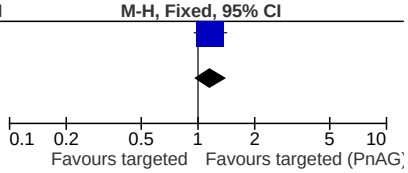


1.3.1.4 Targeted treatment following pneumococcal antigen compared with targeted treatment not using pneumococcal antigen

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

Study or Subgroup	Targeted (incl. PnAG) Events	Total	Targeted Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piso 2012 - NRS	88	139	80	147	100.0%	1.16 [0.96, 1.41]
Total (95% CI)		**139**		**147**	**100.0%**	**1.16 [0.96, 1.41]**
Total events	88		80			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)



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

Study or Subgroup	log[Odds Ratio]	SE	Early antibiotics Total	Later antibiotics Total	Odds Ratio IV, Fixed, 95% CI
1.1.1 Less than or equal to 4 hours versus 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 equal to 8 hours versus 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 equal to 12 hours versus more than 12 hours					
Houck 2004	-0.03045921	0.105	8388	5383	0.97 [0.79, 1.19]
1.1.4 Timing as a continuous variable					
Jo 2012	0	0.001	0	0	1.00 [1.00, 1.00]

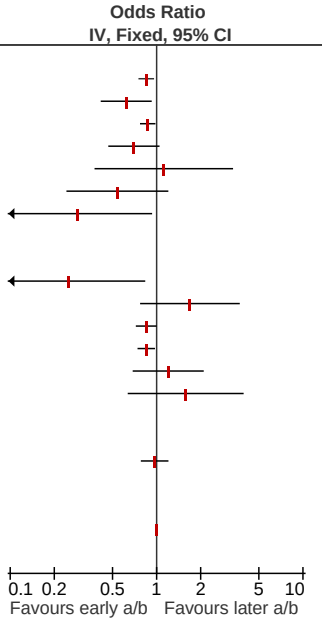


Figure 63: Mortality - full time series

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
1.7.1 ≤1 h vs. >1 h			
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]
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]

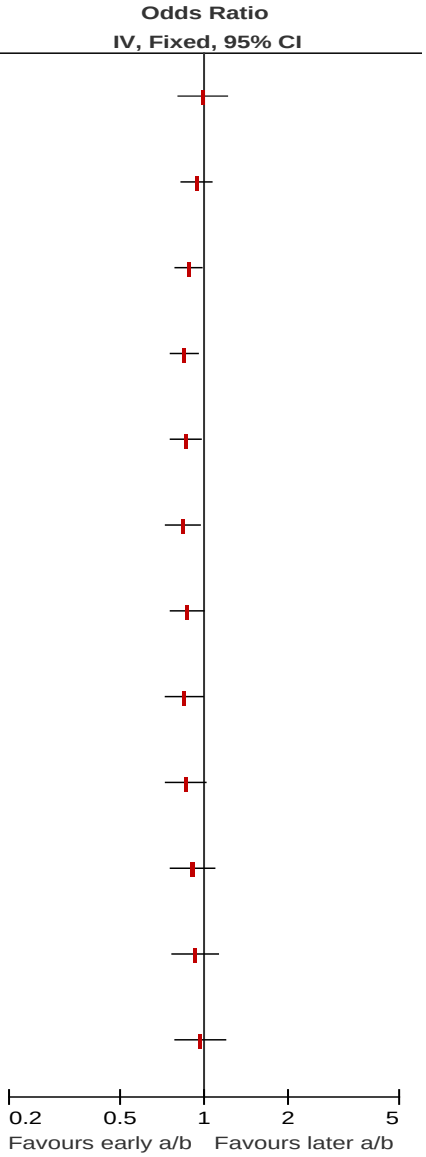


Figure 64: Prolonged length of stay (above median)

Study or Subgroup	log[Odds Ratio]	SE	Early antibiotics Total	Later antibiotics Total	Odds Ratio IV, Fixed, 95% CI
1.3.1 Less than or equal to 4 hours versus more than 4 hours					
Houck 2004	-0.10536052	0.036	8388	5383	0.90 [0.84, 0.97]
Houck 2004 PSI II-III	-0.1508	0.0698	2424	1561	0.86 [0.75, 0.99]
Houck 2004 PSI IV-V	-0.0834	0.0464	5964	3822	0.92 [0.84, 1.01]
Lee 2011	0.1823	0.0464	1632	444	1.20 [1.10, 1.31]
1.3.2 Less than or equal to 8 hours versus more than 8 hours					
Dedier 2001	-0.11653382	0.16	809	253	0.89 [0.65, 1.22]
1.3.3 Less than or equal to 4 hours versus 4-8 hours					
Huang 2006	0.01980263	0.105	0	0	1.02 [0.83, 1.25]
1.3.4 Less than or equal to 4 hours versus more than 8 hours					
Huang 2006	-0.24846136	0.11	0	0	0.78 [0.63, 0.97]

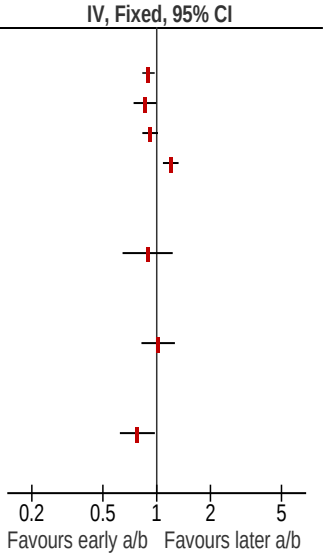


Figure 65: Prolonged length of stay (above 75th percentile)

Study or Subgroup	log[Odds Ratio]	SE	Early antibiotics Total	Later antibiotics Total	Odds Ratio IV, Fixed, 95% CI
1.3.1 Less than or equal to 8 hours versus more than 8 hours					
Battleman 2002	-0.56211892	0.13	0	0	0.57 [0.44, 0.74]

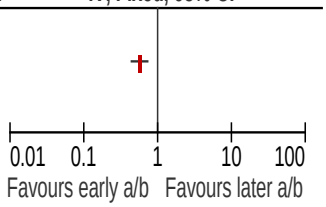


Figure 66: Re-admission after discharge

Study or Subgroup	log[Odds Ratio]	SE	Early a/b Total	Later antibiotics Total	Odds Ratio IV, Fixed, 95% CI
1.4.1 Less than or equal to 4 hours versus more than 4 hours					
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]

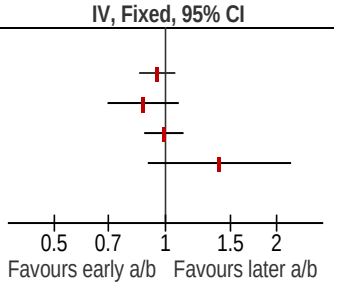
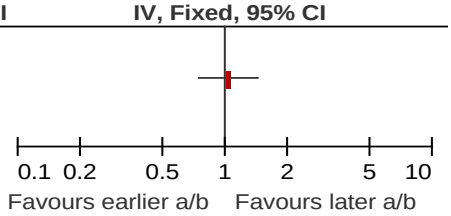


Figure 67: Clinical instability at 48 hours

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
1.6.2 Less than or equal to 8 hours versus more than 8 hours			
Dedier 2001	0.0392	0.1668	1.04 [0.75, 1.44]



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

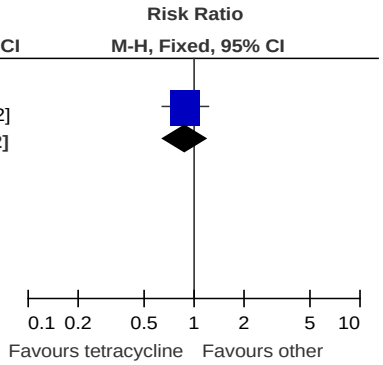
1.4.3 Low-severity community-acquired pneumonia

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)

Study or Subgroup	Other Events	Other Total	Tetracycline Events	Tetracycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.2 Macrolide vs tetracycline						
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 applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						

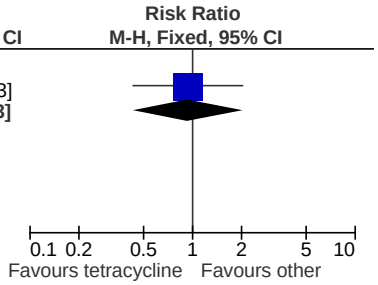


Test for subgroup differences: Not applicable

1.4.3.1.2 Cephalosporin compared with tetracycline

Figure 69: Clinical cure at end of treatment

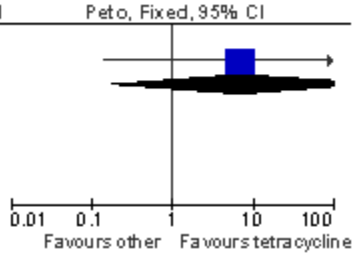
Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Tetracycline Events	Tetracycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Cephalosporin vs tetracycline						
Antani 1991 - community	9	31	9	29	100.0%	0.94 [0.43, 2.03]
Subtotal (95% CI)		**31**		**29**	**100.0%**	**0.94 [0.43, 2.03]**
Total events	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						



Test for subgroup differences: Not applicable

Figure 70: Withdrawals due to adverse events

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Tetracycline Events	Tetracycline Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.2.1 Cephalosporin vs tetracycline						
Antani 1991 - community	1	31	0	29	100.0%	6.93 [0.14, 349.88]
Subtotal (95% CI)		31		29	100.0%	6.93 [0.14, 349.88]
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						

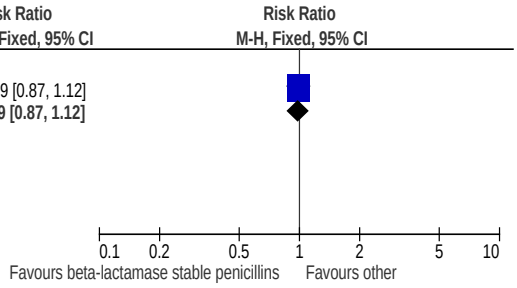


Test for subgroup differences: Not applicable

1.4.3.1.3 Cephalosporin compared with beta-lactamase-stable penicillin

Figure 71: Clinical cure at the end of follow up

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillins Events	Beta-lactamase stable penicillins Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.2 Cephalosporin vs beta-lactamase stable penicillin						
Higuera 1999 - community	49	55	46	51	100.0%	0.99 [0.87, 1.12]
Subtotal (95% CI)		**55**		**51**	**100.0%**	**0.99 [0.87, 1.12]**
Total events	49		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						



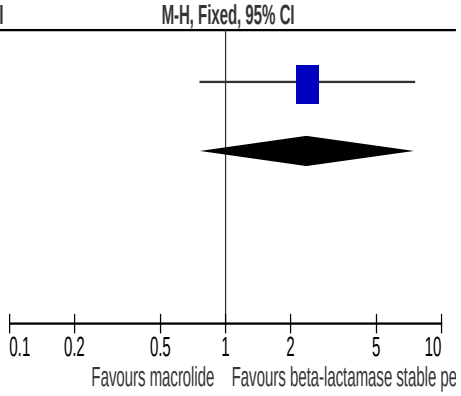
Test for subgroup differences: Not applicable

1.4.3.1.4 Macrolide compared with beta-lactam stable penicillin

Figure 72: Mortality

Figure 1: Mortality

Study or Subgroup	Macrolide Events	Macrolide Total	Beta-lactamase stable penicillins Events	Beta-lactamase stable penicillins Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.2 Macrolide vs beta-lactamase stable penicillin						
Lode 1995 - oral Rx	10	208	4	199	100.0%	2.39 [0.76, 7.50]
Paris 2008 - formal	0	136	0	132		Not estimable
Subtotal (95% CI)		**344**		**331**	**100.0%**	**2.39 [0.76, 7.50]**
Total events	10		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						



Test for subgroup differences: Not applicable

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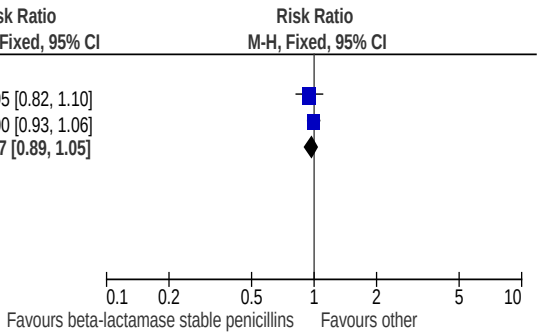
Figure 73: Clinical cure at end of treatment

Study or Subgroup	Macrolide Events	Macrolide Total	Beta-lactamase stable penicillins Events	Beta-lactamase stable penicillins Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Macrolide vs beta-lactamase stable penicillin						
Lode 1995 - oral Rx	129	208	130	199	52.0%	0.95 [0.82, 1.10]
Paris 2008 - formal	125	135	120	129	48.0%	1.00 [0.93, 1.06]
Subtotal (95% CI)		**343**		**328**	**100.0%**	**0.97 [0.89, 1.05]**
Total events	254		250			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						

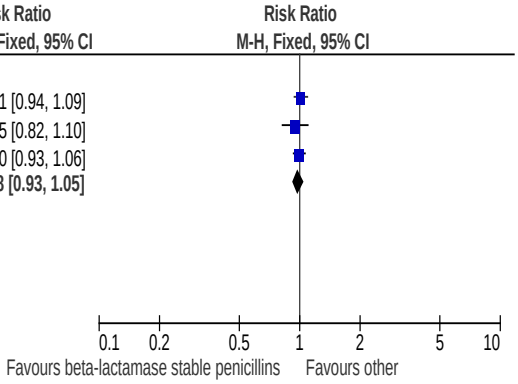


Test for subgroup differences: Not applicable

Figure 74: Clinical cure at end of follow-up

Study or Subgroup	Other Events	Other Total	Beta-lactamase stable penicillins Events	Beta-lactamase stable penicillins Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Macrolide vs beta-lactamase stable penicillin						
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	125	135	120	129	33.1%	1.00 [0.93, 1.06]
Subtotal (95% CI)		**467**		**457**	**100.0%**	**0.98 [0.93, 1.05]**
Total events	368		367			

Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0% ; Test for overall effect: Z = 0.50 (P = 0.62)

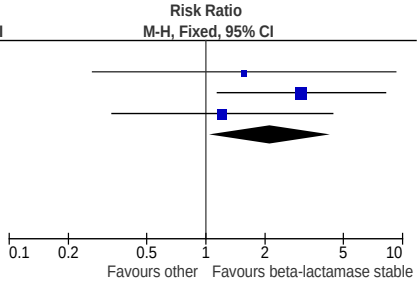


Test for subgroup differences: Not applicable

Figure 75: Withdrawal due to adverse events

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillins Events	Beta-lactamase stable penicillins Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.2 Macrolide vs beta-lactamase stable penicillin						
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	5	136	4	132	36.5%	1.21 [0.33, 4.42]
Subtotal (95% CI)		**504**		**498**	**100.0%**	**2.12 [1.05, 4.29]**
Total events	24		11			

Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0% ; Test for overall effect: Z = 2.10 (P = 0.04)



Test for subgroup differences: Not applicable

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

Figure 76: Mortality

Study or Subgroup	Respiratory fluoroquinolone Events	Respiratory fluoroquinolone Total	Amoxicllin Events	Amoxicllin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Petitpretz 2001 - formal	3	200	4	208	100.0%	0.78 [0.18, 3.44]
Total (95% CI)		**200**		**208**	**100.0%**	**0.78 [0.18, 3.44]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

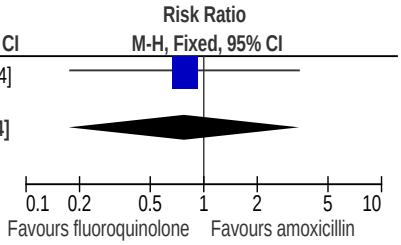


Figure 77: Clinical cure at end of treatment

Study or Subgroup	Respiratory fluoroquinolone Events	Respiratory fluoroquinolone Total	Amoxicllin Events	Amoxicllin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Petitpretz 2001 - formal	173	200	171	208	100.0%	1.05 [0.97, 1.14]
Total (95% CI)		**200**		**208**	**100.0%**	**1.05 [0.97, 1.14]**
Total events	173		171			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)

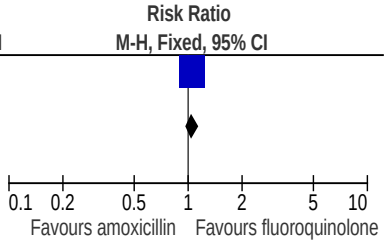


Figure 78: Clinical cure at end of follow-up

Study or Subgroup	Respiratory fluoroquinolone Events	Total	Amoxicllin Events	Total	Weight	Risk Ratio 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	154		164			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

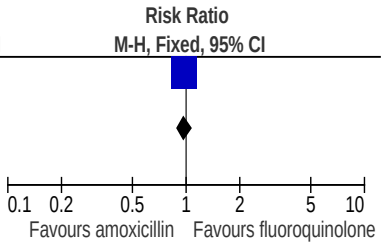


Figure 79: Complications

Study or Subgroup	Respiratory fluoroquinolone Events	Total	Amoxicllin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Petitpretz 2001 - formal	0	200	1	208	100.0%	0.14 [0.00, 7.09]
Total (95% CI)		**200**		**208**	**100.0%**	**0.14 [0.00, 7.09]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

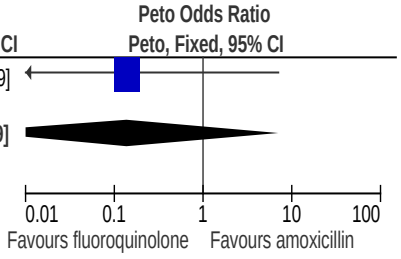
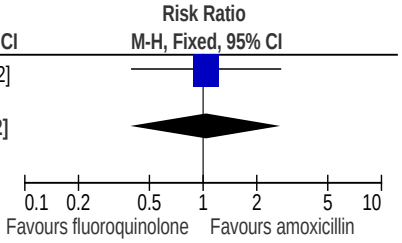


Figure 80: Withdrawal or treatment discontinuation due to adverse events

Study or Subgroup	Respiratory fluoroquinolone Events	Total	Amoxicllin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Petitpretz 2001 - formal	8	200	8	208	100.0%	1.04 [0.40, 2.72]
Total (95% CI)		**200**		**208**	**100.0%**	**1.04 [0.40, 2.72]**
Total events	8		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)

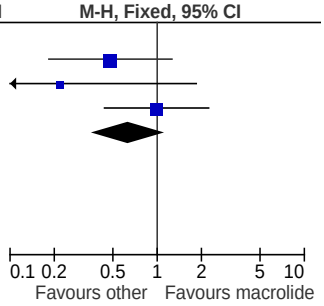


1.4.3.1.6 *Respiratory fluoroquinolone compared with beta-lactam stable penicillin*

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

Study or Subgroup	Respiratory fluoroquinolo Events	Total	Macrolide Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Respiratory fluoroquinolone (new) vs macrolide						
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	11	224	11	222	39.4%	0.99 [0.44, 2.24]
Subtotal (95% CI)		**608**		**610**	**100.0%**	**0.64 [0.36, 1.14]**
Total events	18		28			

Heterogeneity: Chi² = 2.42, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 1.52 (P = 0.13)



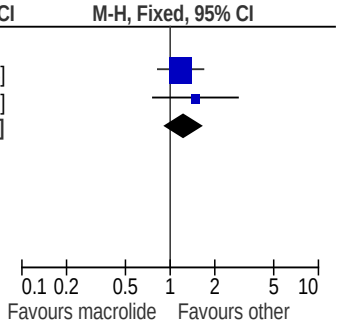
Test for subgroup differences: Not applicable

1.4.3.1.7 *Non-respiratory fluoroquinolone compared with macrolide*

Figure 82: Clinical cure at end of treatment

Study or Subgroup	Non-respiratory fluoroqui Events	Total	Macrolide Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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			

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)

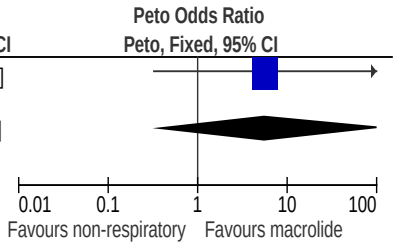


Test for subgroup differences: Not applicable

Figure 83: Withdrawal due to adverse events

Study or Subgroup	Non-respiratory fluoroqui Events	Total	Macrolide Events	Total	Weight	Peto Odds Ratio Peto, 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 (P = 0.23)

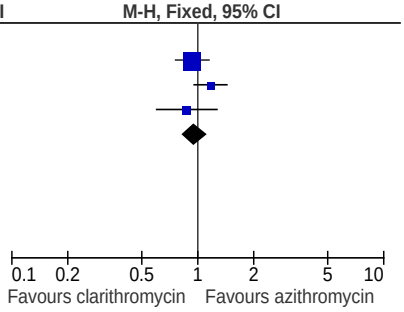


1.4.3.1.8 *Azithromycin compared with other macrolides*

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

Study or Subgroup	Azithromycin Events	Total	Clarithromycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Azithromycin vs clarithromycin						
O'Doherty 1998- community	57	88	61	88	61.1%	0.93 [0.76, 1.15]
Rizzato 1995 - formal	20	20	17	20	17.5%	1.17 [0.96, 1.43]
Sopena 2004 - vague	18	30	22	32	21.3%	0.87 [0.60, 1.27]
Subtotal (95% CI)		**138**		**140**	**100.0%**	**0.96 [0.83, 1.12]**
Total events	95		100			

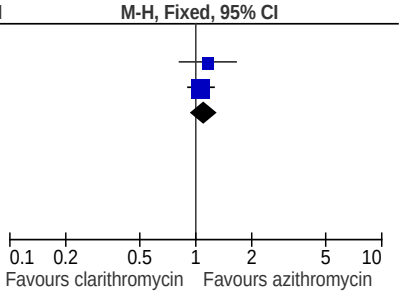
Heterogeneity: Chi² = 3.94, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 0.49 (P = 0.62)



Test for subgroup differences: Not applicable

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

Study or Subgroup	Azithromycin Events	Azithromycin Total	Clarithromycin Events	Clarithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Azithromycin vs clarithromycin						
O'Doherty 1998- community	19	24	15	22	36.6%	1.16 [0.82, 1.65]
Sopena 2004 - vague	28	30	28	32	63.4%	1.07 [0.91, 1.25]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**1.10 [0.93, 1.30]**
Total events	47		43			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.26)						



Test for subgroup differences: Not applicable

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

Study or Subgroup	Azithromycin Events	Azithromycin Total	Clarithromycin Events	Clarithromycin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.3.1 Azithromycin vs clarithromycin						
O'Doherty 1998- community	0	101	2	102	100.0%	0.14 [0.01, 2.18]
Subtotal (95% CI)		**101**		**102**	**100.0%**	**0.14 [0.01, 2.18]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						

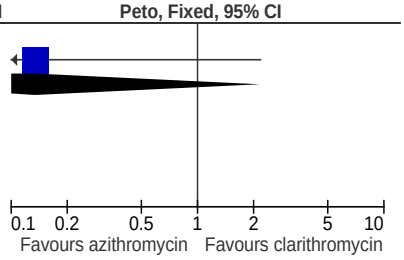
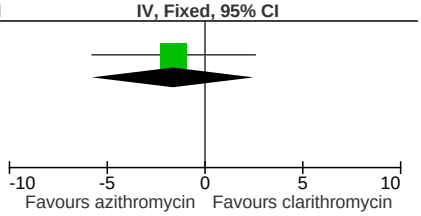


Figure 87: Length of hospital stay (azithromycin compared with clarithromycin)

Study or Subgroup	Azithromycin Mean	Azithromycin SD	Azithromycin Total	Clarithromycin Mean	Clarithromycin SD	Clarithromycin Total	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 Azithromycin vs clarithromycin								
Rizzato 1995 - formal	12.7	5.7	20	14.3	7.6	20	100.0%	-1.60 [-5.76, 2.56]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.60 [-5.76, 2.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.75 (P = 0.45)								

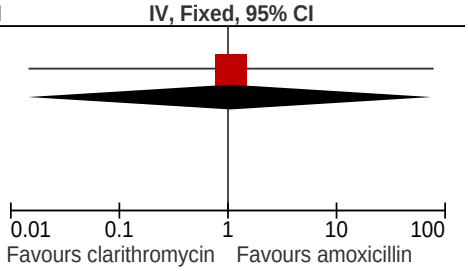


Test for subgroup differences: Not applicable

1.4.3.1.9 Clarithromycin compared with amoxicillin (indirect comparison)

Figure 88: Mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
2.1.1 Mortality				
Indirect comparison	0.0671	2.1832	100.0%	1.07 [0.01, 77.18]
Subtotal (95% CI)			**100.0%**	**1.07 [0.01, 77.18]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.03 (P = 0.98)				



Test for subgroup differences: Not applicable

Figure 89: Cure at end of follow up

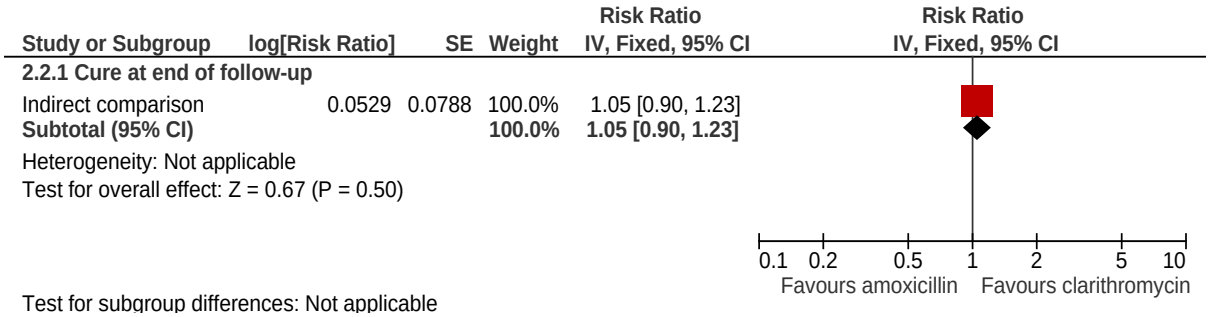
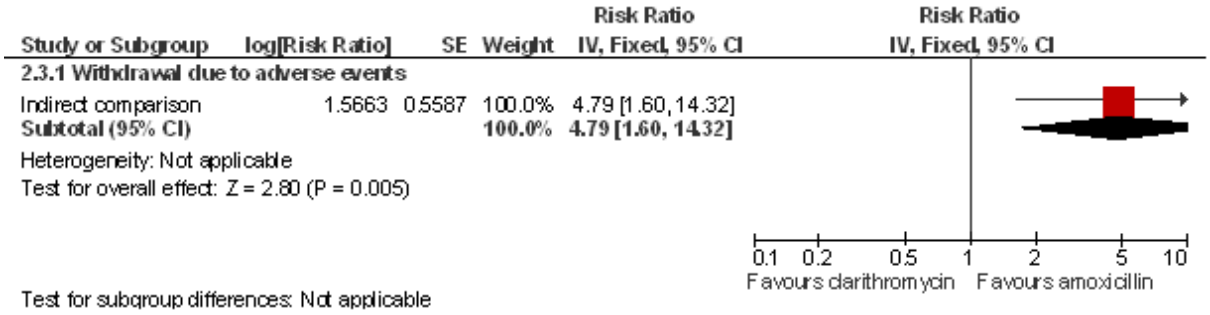


Figure 90: Withdrawal due to adverse events



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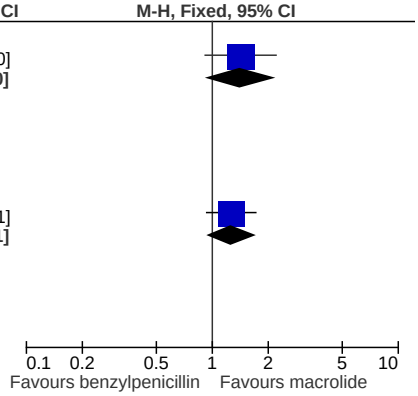
1.4.4 Low-severity community-acquired pneumonia managed in hospital

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

Figure 91: Clinical cure

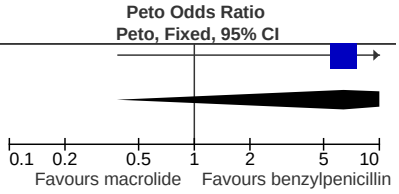
Study or Subgroup	Macrolide Events	Macrolide Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 End of treatment						
Bohte 1995 - pneumococcal	24	35	14	29	100.0%	1.42 [0.92, 2.20]
Subtotal (95% CI)		**35**		**29**	**100.0%**	**1.42 [0.92, 2.20]**
Total events	24		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
4.1.2 End of follow-up						
Bohte 1995 - pneumococcal	29	35	19	29	100.0%	1.26 [0.93, 1.71]
Subtotal (95% CI)		**35**		**29**	**100.0%**	**1.26 [0.93, 1.71]**
Total events	29		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						



Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

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

Study or Subgroup	Macrolide Events	Macrolide Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bohte 1995 - pneumococcal	2	35	0	29	100.0%	6.41 [0.39, 106.11]
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)						



1.4.4.1.2 Macrolide compared with beta-lactamase stable penicillin

Figure 93: Mortality

Study or Subgroup	Macrolide Events	Macrolide Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Genne 1997	1	56	1	56	100.0%	1.00 [0.06, 15.59]
Total (95% CI)		**56**		**56**	**100.0%**	**1.00 [0.06, 15.59]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						

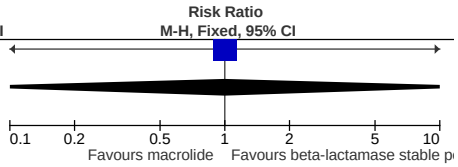
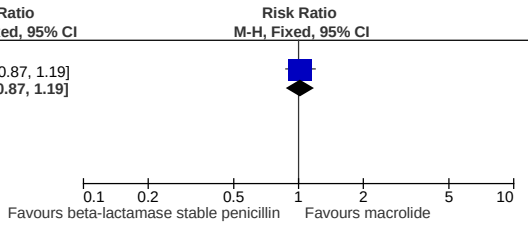


Figure 94: Clinical cure at end of treatment

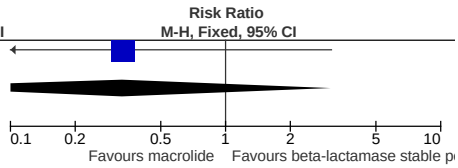
Study or Subgroup	Macrolide Events	Macrolide Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 End of treatment						
Genne 1997	48	56	47	56	100.0%	1.02 [0.87, 1.19]
Subtotal (95% CI)		**56**		**56**	**100.0%**	**1.02 [0.87, 1.19]**
Total events	48		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						



Test for subgroup differences: Not applicable

Figure 95: Withdrawal due to adverse events

Study or Subgroup	Macrolide Events	Macrolide Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Genne 1997	1	56	3	56	100.0%	0.33 [0.04, 3.11]
Total (95% CI)		**56**		**56**	**100.0%**	**0.33 [0.04, 3.11]**
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.33)						



1.4.4.1.3 *Azithromycin compared with other macrolide*

Figure 96: Mortality (during treatment)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Erythromycin Events	Erythromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bohte 1995-nonpneumococal	1	20	1	22	100.0%	1.10 [0.07, 16.45]
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)

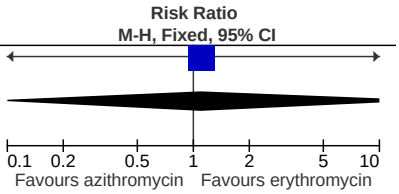


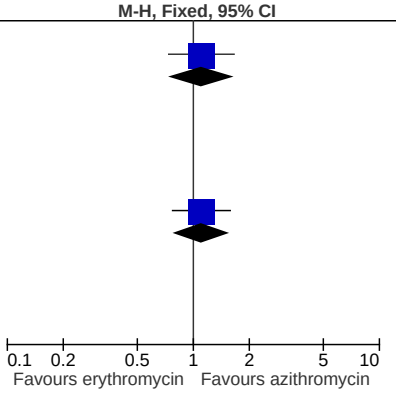
Figure 97: Clinical cure

Study or Subgroup	Azithromycin Events	Azithromycin Total	Erythromycin Events	Erythromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 End of treatment						
Bohte 1995-nonpneumococal	14	19	14	21	100.0%	1.11 [0.74, 1.66]
Subtotal (95% CI)		**19**		**21**	**100.0%**	**1.11 [0.74, 1.66]**
Total events	14		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

5.2.2 End of follow-up						
Bohte 1995-nonpneumococal	15	19	15	21	100.0%	1.11 [0.77, 1.58]
Subtotal (95% CI)		**19**		**21**	**100.0%**	**1.11 [0.77, 1.58]**
Total events	15		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)

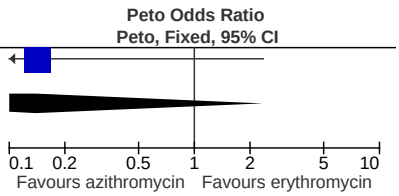


Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%

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

Study or Subgroup	Azithromycin Events	Azithromycin Total	Erythromycin Events	Erythromycin Total	Weight	Peto Odds Ratio 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	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



1.4.4.1.4 *Cephalosporin compared with beta-lactamase stable penicillin*

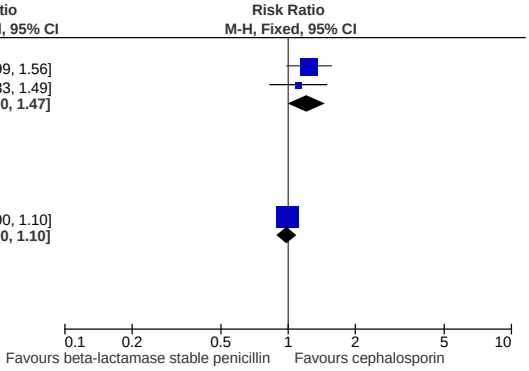
Figure 99: Clinical cure

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 End of treatment						
Brambilla 1992	80	137	63	134	78.0%	1.24 [0.99, 1.56]
Oh 1996	20	24	18	24	22.0%	1.11 [0.83, 1.49]
Subtotal (95% CI)		**161**		**158**	**100.0%**	**1.21 [1.00, 1.47]**
Total events	100		81			

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.99 (P = 0.05)

3.2.2 Maintaining cure at end of follow-up						
Brambilla 1992	101	117	94	108	100.0%	0.99 [0.90, 1.10]
Subtotal (95% CI)		**117**		**108**	**100.0%**	**0.99 [0.90, 1.10]**
Total events	101		94			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)

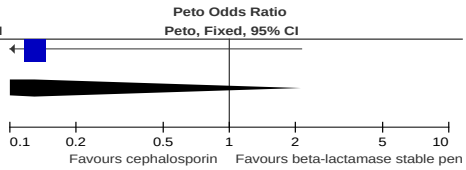


Test for subgroup differences: Chi² = 3.33, df = 1 (P = 0.07), I² = 70.0%

Figure 100: Treatment discontinuation due to adverse events

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Peto Odds Ratio Peto, Fixed, 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 applicable
Test for overall effect: Z = 1.43 (P = 0.15)

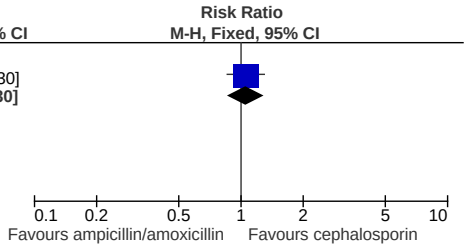


1.4.4.1.5 Cephalosporin compared with narrow-spectrum beta-lactam (class 2)

Figure 101: Clinical cure

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Ampicillin/amoxicillin Events	Ampicillin/amoxicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 End of treatment						
Leuenberger 1983	15	16	16	18	100.0%	1.05 [0.86, 1.30]
Subtotal (95% CI)		**16**		**18**	**100.0%**	**1.05 [0.86, 1.30]**
Total events	15		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)



Test for subgroup differences: Not applicable

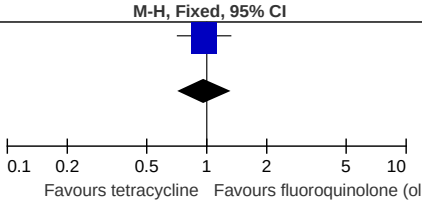
1.4.4.1.6 Non-respiratory fluoroquinolone (FQ) compared with tetracycline

Figure 102: Clinical cure at end of treatment

Study or Subgroup	Fluoroquinolone (old) Events	Total	Tetracycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harazim 1987	34	62	39	69	100.0%	0.97 [0.71, 1.32]
Total (95% CI)		**62**		**69**	**100.0%**	**0.97 [0.71, 1.32]**
Total events	34		39			

Heterogeneity: Not applicable

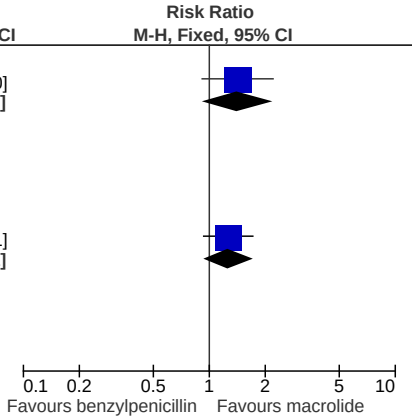
Test for overall effect: Z = 0.19 (P = 0.85)



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

Figure 103: Clinical cure

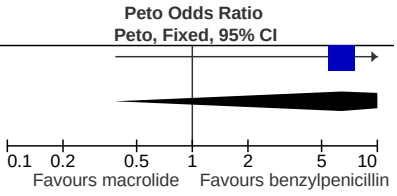
Study or Subgroup	Macrolide Events	Macrolide Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 End of treatment						
Bohte 1995 - pneumococcal	24	35	14	29	100.0%	1.42 [0.92, 2.20]
Subtotal (95% CI)		**35**		**29**	**100.0%**	**1.42 [0.92, 2.20]**
Total events	24		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
4.1.2 End of follow-up						
Bohte 1995 - pneumococcal	29	35	19	29	100.0%	1.26 [0.93, 1.71]
Subtotal (95% CI)		**35**		**29**	**100.0%**	**1.26 [0.93, 1.71]**
Total events	29		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						



Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

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

Study or Subgroup	Macrolide Events	Macrolide Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bohte 1995 - pneumococcal	2	35	0	29	100.0%	6.41 [0.39, 106.11]
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)						



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

Study or Subgroup	Single antibiotic therapy Events	Single antibiotic therapy Total	Dual antibiotic therapy Events	Dual antibiotic therapy Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.2.3 Macrolide vs macrolide + cephalosporin						
Rovira 1999 - formal	0	45	2	45	100.0%	0.13 [0.01, 2.15]
Subtotal (95% CI)		**45**		**45**	**100.0%**	**0.13 [0.01, 2.15]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.15)						

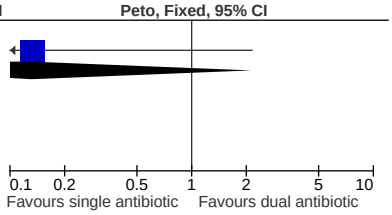
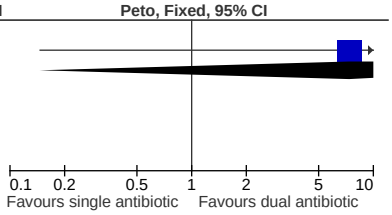


Figure 107: Complications (pleural effusion)

Study or Subgroup	Single antibiotic therapy Events	Single antibiotic therapy Total	Dual antibiotic therapy Events	Dual antibiotic therapy Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.4.3 Macrolide vs macrolide + cephalosporin						
Rovira 1999 - formal	1	45	0	45	100.0%	7.39 [0.15, 372.38]
Subtotal (95% CI)		**45**		**45**	**100.0%**	**7.39 [0.15, 372.38]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						

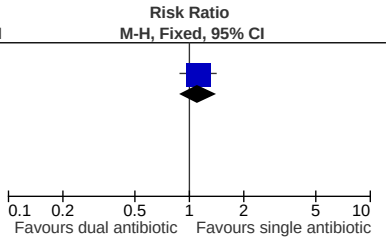


1.4.4.2.2 Respiratory fluoroquinolone compared with cephalosporin plus macrolide (azithromycin)

Figure 108: Clinical cure or improvement at end of treatment

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.4 Respiratory fluoroquinolone (new) vs cephalosporin + azithromycin						
Lee 2012 - setting	16	17	16	19	100.0%	1.12 [0.89, 1.40]
Subtotal (95% CI)		**17**		**19**	**100.0%**	**1.12 [0.89, 1.40]**
Total events	16		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

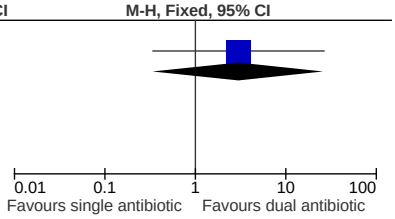


Test for subgroup differences: Not applicable

Figure 109: Withdrawal due to adverse events

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.4 Respiratory fluoroquinolone (new) vs cephalosporin + azithromycin						
Lee 2012 - setting	3	20	1	20	100.0%	3.00 [0.34, 26.45]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.34, 26.45]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

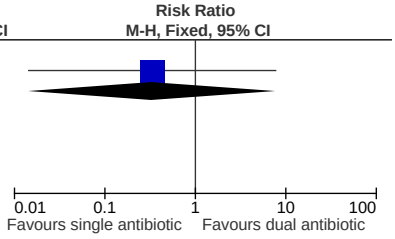


Test for subgroup differences: Not applicable

Figure 110: Complications (pleural effusion)

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.4 Respiratory fluoroquinolone (new) vs cephalosporin + azithromycin						
Lee 2012 - setting	0	20	1	20	100.0%	0.33 [0.01, 7.72]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.33 [0.01, 7.72]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



Test for subgroup differences: Not applicable

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

Study or Subgroup	Cephalosporin Events	Total	Beta-lactamase stable penicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Roson 2001	17	194	19	184	100.0%	0.85 [0.46, 1.58]
Total (95% CI)		**194**		**184**	**100.0%**	**0.85 [0.46, 1.58]**
Total events	17		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.61)

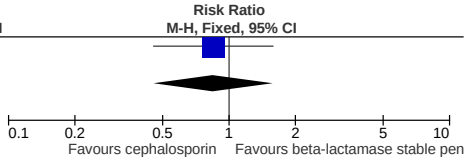
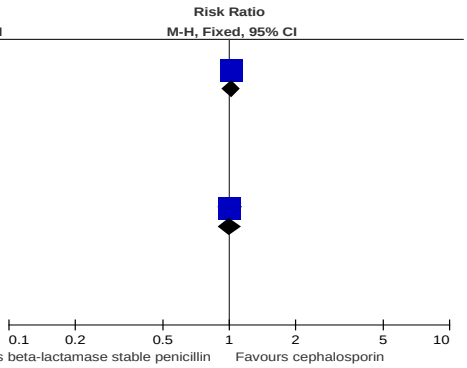


Figure 112: Clinical cure

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 End of treatment						
Roson 2001	157	194	146	184	100.0%	1.02 [0.92, 1.13]
Subtotal (95% CI)		**194**		**184**	**100.0%**	**1.02 [0.92, 1.13]**
Total events	157		146			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
1.2.2 End of follow-up						
Roson 2001	144	194	136	184	100.0%	1.00 [0.89, 1.13]
Subtotal (95% CI)		**194**		**184**	**100.0%**	**1.00 [0.89, 1.13]**
Total events	144		136			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						



Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%

Figure 113: ITU admission

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						

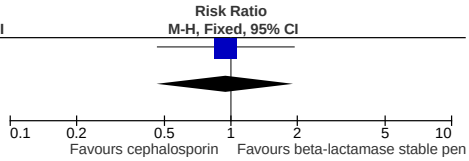
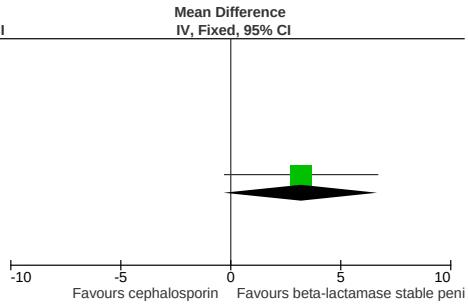


Figure 114: Length of hospital stay

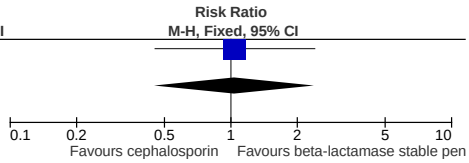
Study or Subgroup	Cephalosporin Mean	Cephalosporin SD	Cephalosporin Total	Beta-lactamase stable penicillin Mean	Beta-lactamase stable penicillin SD	Beta-lactamase stable penicillin Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Full study population								
Roson 2001	11.3	0	194	10.7	0	184		Not estimable
Subtotal (95% CI)			**194**			**184**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.6.2 Proven pneumococcal								
Roson 2001	12.7	13	63	9.5	5	53	100.0%	3.20 [-0.28, 6.68]
Subtotal (95% CI)			**63**			**53**	**100.0%**	**3.20 [-0.28, 6.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.80 (P = 0.07)								



Test for subgroup differences: Not applicable

Figure 115: Complications (empyema)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Beta-lactamase stable penicillin Events	Beta-lactamase stable penicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Roson 2001	11	194	10	184	100.0%	1.04 [0.45, 2.40]
Total (95% CI)		**194**		**184**	**100.0%**	**1.04 [0.45, 2.40]**
Total events	11		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						



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

Figure 116: Mortality

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Ampicillin/amoxicillin Events	Ampicillin/amoxicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Nicolle 1996	1	17	2	20	100.0%	0.59 [0.06, 5.94]
Total (95% CI)		**17**		**20**	**100.0%**	**0.59 [0.06, 5.94]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						

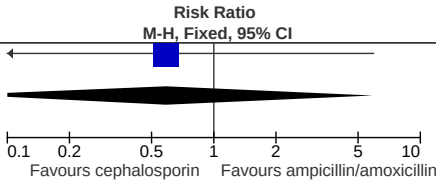


Figure 117: Clinical cure

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Ampicillin/amoxicillin Events	Ampicillin/amoxicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.2 End of follow-up						
Nicolle 1996	16	17	14	20	100.0%	1.34 [0.99, 1.83]
Subtotal (95% CI)		**17**		**20**	**100.0%**	**1.34 [0.99, 1.83]**
Total events	16		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)

Test for subgroup differences: Not applicable

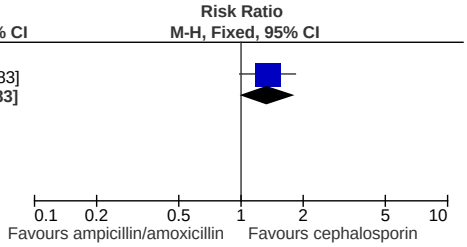
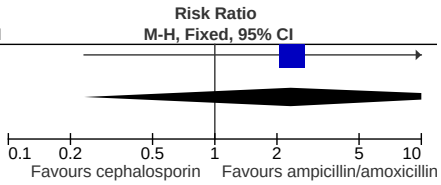


Figure 118: C. difficile-associated diarrhoea

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Ampicillin/amoxicillin Events	Ampicillin/amoxicillin Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.73 (P = 0.47)



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

Study or Subgroup	Single antibiotic therapy Events	Single antibiotic therapy Total	Dual antibiotic therapy Events	Dual antibiotic therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Macrolide vs macrolide + cephalosporin						
Vergis 2000 - setting	3	83	1	86	19.6%	3.11 [0.33, 29.29]
Vetter 1997 - setting	5	118	4	117	80.4%	1.24 [0.34, 4.50]
Subtotal (95% CI)		**201**		**203**	**100.0%**	**1.61 [0.54, 4.81]**
Total events	8		5			

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)

Total (95% CI)		**201**		**203**	**100.0%**	**1.61 [0.54, 4.81]**
Total events	8		5			

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable

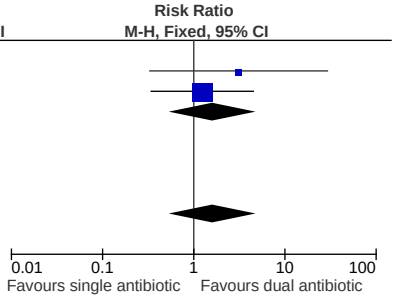


Figure 120: Clinical cure at end of treatment

Study or Subgroup	Single antibiotic therapy Events	Single antibiotic therapy Total	Dual antibiotic therapy Events	Dual antibiotic therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Macrolide vs macrolide + cephalosporin						
Vergis 2000 - setting	62	83	71	86	57.8%	0.90 [0.77, 1.06]
Vetter 1997 - setting	66	118	58	117	42.2%	1.13 [0.88, 1.44]
Subtotal (95% CI)		**201**		**203**	**100.0%**	**0.99 [0.79, 1.25]**
Total events	128		129			

Heterogeneity: Tau² = 0.02; Chi² = 2.58, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable

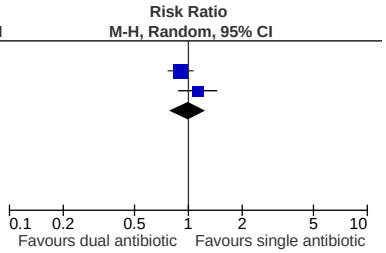


Figure 121: Clinical cure at end of follow-up

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Macrolide vs macrolide + cephalosporin						
Vetter 1997 - setting	73	118	66	117	100.0%	1.10 [0.89, 1.36]
Subtotal (95% CI)		**118**		**117**	**100.0%**	**1.10 [0.89, 1.36]**
Total events	73		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						

Test for subgroup differences: Not applicable

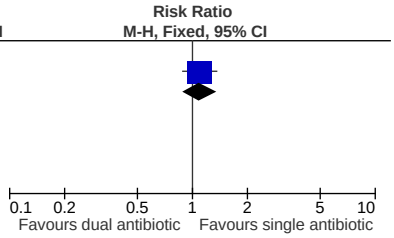


Figure 122: Withdrawal due to adverse events

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Macrolide vs macrolide + cephalosporin						
Vetter 1997 - setting	8	118	16	117	100.0%	0.50 [0.22, 1.11]
Subtotal (95% CI)		**118**		**117**	**100.0%**	**0.50 [0.22, 1.11]**
Total events	8		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						

Test for subgroup differences: Not applicable

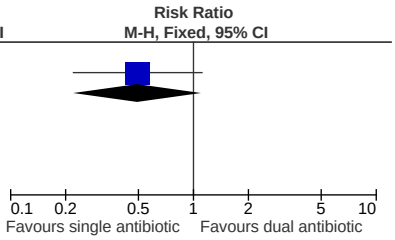
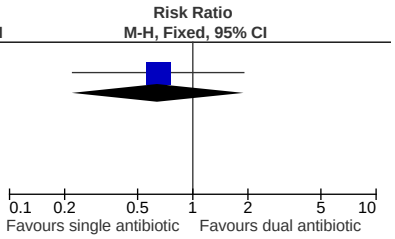


Figure 123: ITU admission

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Macrolide vs macrolide + cephalosporin						
Vergis 2000 - setting	5	83	8	86	100.0%	0.65 [0.22, 1.90]
Subtotal (95% CI)		**83**		**86**	**100.0%**	**0.65 [0.22, 1.90]**
Total events	5		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						

Test for subgroup differences: Not applicable



1.4.5.2.2 Respiratory fluoroquinolone compare with cephalosporin plus macrolide

Figure 124: All-cause mortality

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.4 Respiratory fluoroquinolone (new) vs cephalosporin + macrolide						
Fogarty 2004 - formal	15	132	9	137	75.4%	1.73 [0.78, 3.82]
Zervos 2004 - formal	5	102	3	110	24.6%	1.80 [0.44, 7.33]
Subtotal (95% CI)		**234**		**247**	**100.0%**	**1.75 [0.88, 3.48]**
Total events	20		12			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**234**		**247**	**100.0%**	**1.75 [0.88, 3.48]**
Total events	20		12			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						

Test for subgroup differences: Not applicable

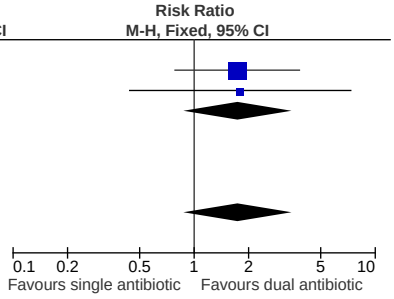


Figure 125: Clinical cure or improvement at end of treatment

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.4 Respiratory fluoroquinolone (new) vs cephalosporin + macrolide						
Zervos 2004 - formal	44	93	58	97	100.0%	0.79 [0.60, 1.04]
Subtotal (95% CI)		**93**		**97**	**100.0%**	**0.79 [0.60, 1.04]**
Total events	44		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
Total (95% CI)		**93**		**97**	**100.0%**	**0.79 [0.60, 1.04]**
Total events	44		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: Not applicable						

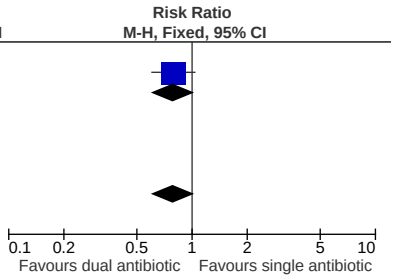


Figure 126: Clinical cure or improvement at end of follow up

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.3 Respiratory fluoroquinolone (new) vs cephalosporin + macrolide						
Frank 2002 - formal	100	115	97	121	54.1%	1.08 [0.97, 1.22]
Zervos 2004 - formal	77	92	81	94	45.9%	0.97 [0.86, 1.10]
Subtotal (95% CI)		**207**		**215**	**100.0%**	**1.03 [0.95, 1.12]**
Total events	177		178			
Heterogeneity: Chi² = 1.70, df = 1 (P = 0.19); I² = 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: Chi² = 1.70, df = 1 (P = 0.19); I² = 41%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Not applicable						

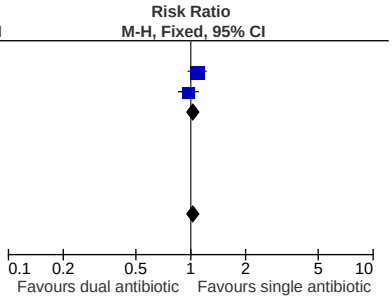


Figure 127: Withdrawal due to adverse events

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.5 Respiratory fluoroquinolone (new) vs cephalosporin + macrolide						
Fogarty 2004 - formal	3	132	12	137	44.8%	0.26 [0.07, 0.90]
Frank 2002 - formal	5	110	5	114	18.7%	1.04 [0.31, 3.48]
Zervos 2004 - formal	3	102	10	110	36.6%	0.32 [0.09, 1.14]
Subtotal (95% CI)		**344**		**361**	**100.0%**	**0.43 [0.22, 0.85]**
Total events	11		27			
Heterogeneity: Chi² = 2.86, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 2.42 (P = 0.02)						
Total (95% CI)		**344**		**361**	**100.0%**	**0.43 [0.22, 0.85]**
Total events	11		27			
Heterogeneity: Chi² = 2.86, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 2.42 (P = 0.02)						
Test for subgroup differences: Not applicable						

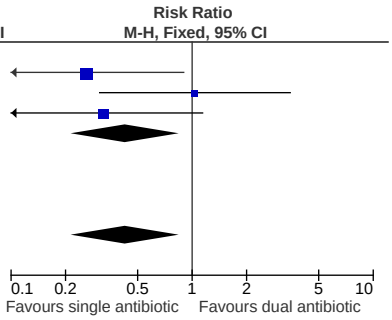
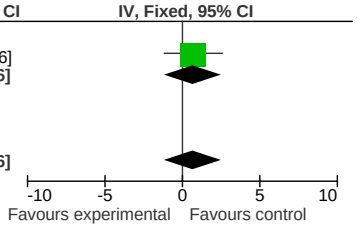


Figure 128: Length of hospital stay

Study or Subgroup	Single antibiotic therapy Mean	SD	Total	Dual antibiotic therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.10.3 respiratory fluoroquinolone vs cephalosporin plus macrolide								
Zervos 2004 - formal	8.4	6.9	75	7.7	4.7	82	100.0%	0.70 [-1.16, 2.56]
Subtotal (95% CI)			**75**			**82**	**100.0%**	**0.70 [-1.16, 2.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
Total (95% CI)			**75**			**82**	**100.0%**	**0.70 [-1.16, 2.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
Test for subgroup differences: Not applicable								



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

Figure 129: Clinical cure at end of treatment

Study or Subgroup	Respiratory FQ Events	Total	b-stable penic+macrolide Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lin 2007 - setting	18	23	17	22	100.0%	1.01 [0.74, 1.38]
Total (95% CI)		**23**		**22**	**100.0%**	**1.01 [0.74, 1.38]**
Total events	18		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						

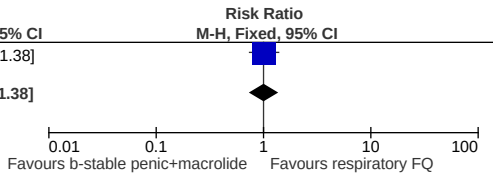


Figure 130: Clinical cure at end of follow-up

Study or Subgroup	Respiratory FQ Events	Total	b-stable penic+macrolide Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lin 2007 - setting	16	18	15	17	100.0%	1.01 [0.79, 1.28]
Total (95% CI)		**18**		**17**	**100.0%**	**1.01 [0.79, 1.28]**
Total events	16		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						

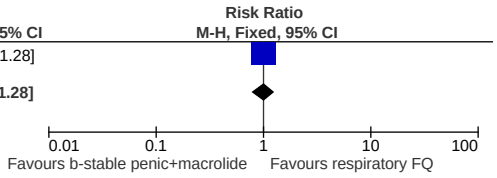
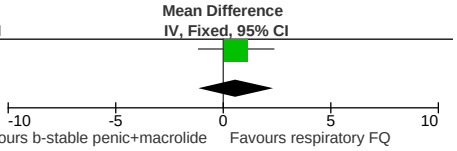


Figure 131: Length of hospital stay

Study or Subgroup	Respiratory FQ Mean	SD	Total	b-stable penic+macrolide Mean	SD	Total	Weight	Mean Difference 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 applicable
Test for overall effect: Z = 0.67 (P = 0.50)



1.4.5.2.4 Respiratory fluoroquinolone compare with cephalosporin plus respiratory fluoroquinolone

Figure 132: All-cause mortality

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.2 Respiratory fluoroquinolone (new) vs cephalosporin + respiratory fluoroquinolone (new)						
Torres 2008 - PSI III	1	150	2	142	17.1%	0.47 [0.04, 5.16]
Torres 2008 - PSI IV-V	17	214	10	215	82.9%	1.71 [0.80, 3.64]
Subtotal (95% CI)		**364**		**357**	**100.0%**	**1.50 [0.74, 3.04]**
Total events	18		12			
Heterogeneity: Chi² = 1.01, df = 1 (P = 0.32); I² = 1%						
Test for overall effect: Z = 1.11 (P = 0.26)						
Total (95% CI)		**364**		**357**	**100.0%**	**1.50 [0.74, 3.04]**
Total events	18		12			
Heterogeneity: Chi² = 1.01, df = 1 (P = 0.32); I² = 1%						
Test for overall effect: Z = 1.11 (P = 0.26)						
Test for subgroup differences: Not applicable						

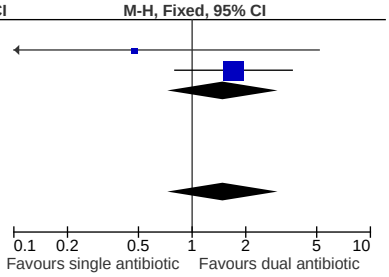


Figure 133: Clinical cure or improvement at end of treatment

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.2 Respiratory fluoroquinolone (new) vs cephalosporin + respiratory fluoroquinolone (new)						
Torres 2008 - PSI III	110	122	105	111	43.0%	0.95 [0.89, 1.03]
Torres 2008 - PSI IV-V	143	169	145	167	57.0%	0.97 [0.89, 1.06]
Subtotal (95% CI)		**291**		**278**	**100.0%**	**0.97 [0.91, 1.02]**
Total events	253		250			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Not applicable						

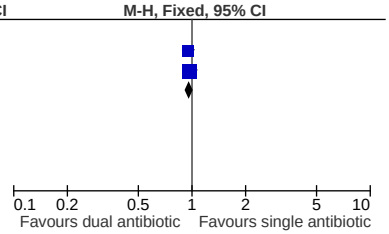


Figure 134: Maintaining clinical cure at end of follow-up

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.2 Respiratory fluoroquinolone (new) vs cephalosporin + respiratory fluoroquinolone (new)						
Torres 2008 - PSI III-V	243	253	243	250	100.0%	0.99 [0.96, 1.02]
Subtotal (95% CI)		**253**		**250**	**100.0%**	**0.99 [0.96, 1.02]**
Total events	243		243			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Not applicable						

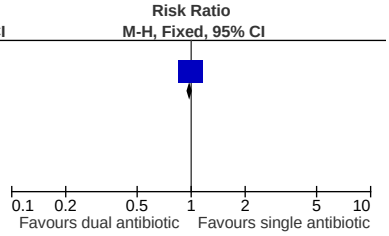
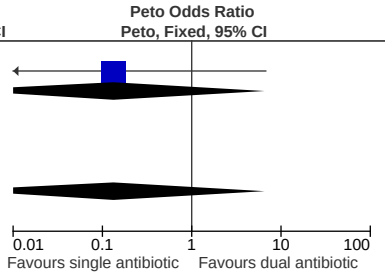


Figure 135: *C. difficile*-associated diarrhoea

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.4.2 Respiratory fluoroquinolone (new) vs cephalosporin + respiratory fluoroquinolone (new)						
Torres 2008 - PSI III-V	0	368	1	365	100.0%	0.13 [0.00, 6.76]
Subtotal (95% CI)		**368**		**365**	**100.0%**	**0.13 [0.00, 6.76]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**368**		**365**	**100.0%**	**0.13 [0.00, 6.76]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						



1.4.5.2.5 Respiratory fluoroquinolone compare with cephalosporin plus non-respiratory fluoroquinolone

Figure 136: All-cause mortality

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.5 Respiratory fluoroquinolone (new) vs cephalosporin + non-respiratory fluoroquinolone						
Leroy 2005 - formal	18	149	20	159	100.0%	0.96 [0.53, 1.74]
Subtotal (95% CI)		**149**		**159**	**100.0%**	**0.96 [0.53, 1.74]**
Total events	18		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
Total (95% CI)		**149**		**159**	**100.0%**	**0.96 [0.53, 1.74]**
Total events	18		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Not applicable						

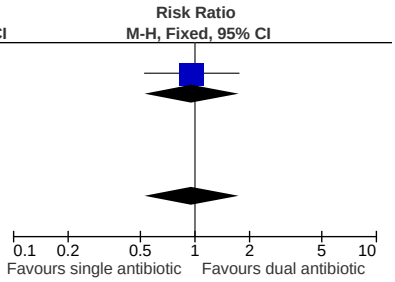


Figure 137: Clinical cure at end of treatment

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.5 Respiratory fluoroquinolone (new) vs cephalosporin + non-respiratory fluoroquinolone						
Leroy 2005 - formal	112	149	123	159	100.0%	0.97 [0.86, 1.10]
Subtotal (95% CI)		**149**		**159**	**100.0%**	**0.97 [0.86, 1.10]**
Total events	112		123			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Not applicable						

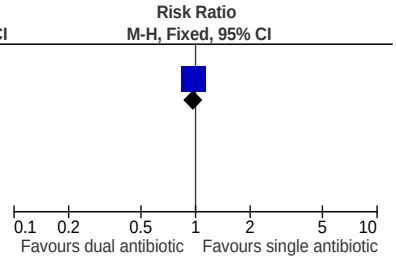


Figure 138: Clinical cure at follow-up

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.5 Respiratory fluoroquinolone (new) vs cephalosporin + non-respiratory fluoroquinolone						
Leroy 2005 - formal	88	149	99	159	100.0%	0.95 [0.79, 1.14]
Subtotal (95% CI)		**149**		**159**	**100.0%**	**0.95 [0.79, 1.14]**
Total events	88		99			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Not applicable						

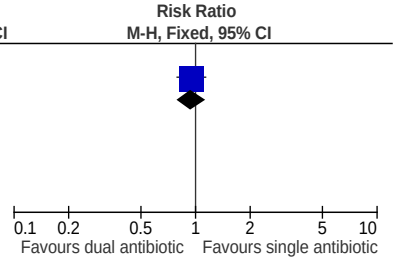


Figure 139: Withdrawal due to adverse events

Study or Subgroup	Single antibiotic therapy Events	Total	Dual antibiotic therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.2 Respiratory fluoroquinolone (new) vs cephalosporin + non-respiratory fluoroquinolone						
Leroy 2005 - formal	5	194	4	201	100.0%	1.30 [0.35, 4.75]
Subtotal (95% CI)		**194**		**201**	**100.0%**	**1.30 [0.35, 4.75]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						

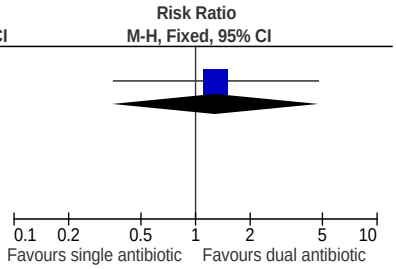
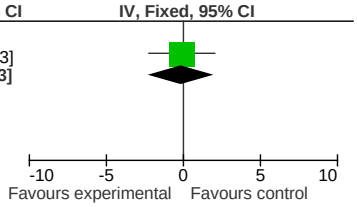


Figure 140: Length of hospital stay

Study or Subgroup	Single antibiotic therapy Mean	SD	Total	Dual antibiotic therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.5.1 Respiratory fluoroquinolone (new) vs cephalosporin + non-respiratory fluoroquinolone								
Leroy 2005 - formal	11.9	9.4	149	12	9.7	159	100.0%	-0.10 [-2.23, 2.03]
Subtotal (95% CI)			**149**			**159**	**100.0%**	**-0.10 [-2.23, 2.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
Test for subgroup differences: Not applicable								



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

Study or Subgroup	Non-respiratory FQ + penicillin G Events	Total	Macrolide + BLase stable penicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gaillat 1994	6	52	6	50	100.0%	0.96 [0.33, 2.78]
Total (95% CI)		**52**		**50**	**100.0%**	**0.96 [0.33, 2.78]**
Total events	6		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)

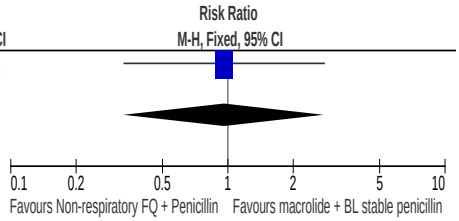


Figure 142: Clinical cure at end of treatment

Study or Subgroup	Non-respiratory FQ + penicillin G Events	Total	Macrolide + BLase stable penicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gaillat 1994	40	52	38	50	100.0%	1.01 [0.82, 1.26]
Total (95% CI)		**52**		**50**	**100.0%**	**1.01 [0.82, 1.26]**
Total events	40		38			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

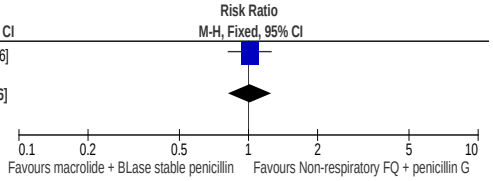
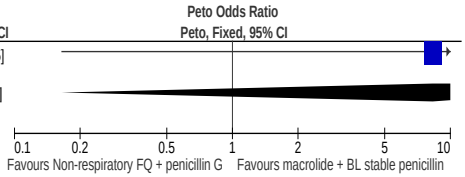


Figure 143: Complications - superinfection

Study or Subgroup	Favours Non-respiratory FQ + penicillin G Events	Total	Macrolide + BLase stable penicillin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gaillat 1994	1	32	0	36	100.0%	8.37 [0.17, 424.85]
Total (95% CI)		**32**		**36**	**100.0%**	**8.37 [0.17, 424.85]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



1.4.5.3.2 Azithromycin plus cephalosporin compared with other macrolide plus cephalosporin

Figure 144: Mortality

Study or Subgroup	Azithromycin + cephalosporin Events	Total	Other macrolide + cephalosporin Events	Total	Weight	Risk Ratio M-H, Fixed, 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 applicable
Test for overall effect: Z = 0.69 (P = 0.49)

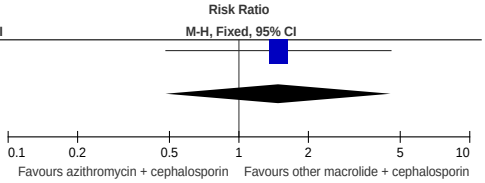


Figure 145: Clinial cure at end of treatment

Study or Subgroup	Azithromycin + cephalosporin Events	Total	Other macrolide + cephalosporin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tamm 2007	102	121	104	126	100.0%	1.02 [0.91, 1.14]
Total (95% CI)		**121**		**126**	**100.0%**	**1.02 [0.91, 1.14]**
Total events	102		104			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

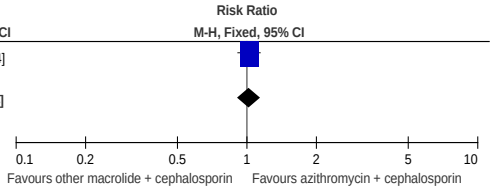


Figure 146: Withdrawal due to adverse events

Study or Subgroup	Azithromycin + cephalosporin Events	Total	Other macrolide + cephalosporin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tamm 2007	1	135	4	143	100.0%	0.26 [0.03, 2.34]
Total (95% CI)		**135**		**143**	**100.0%**	**0.26 [0.03, 2.34]**
Total events	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

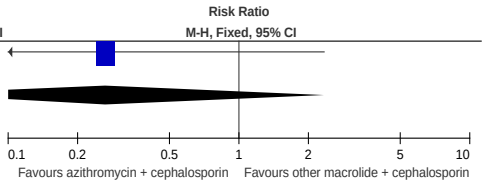
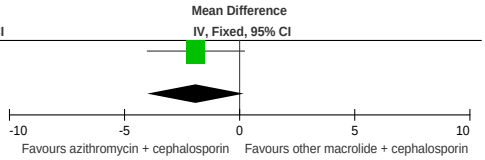


Figure 147: Length of hospital stay

Study or Subgroup	Azithromycin + cephalosporin Mean	SD	Total	Other macrolide + cephalosporin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tamm 2007	10.7	6.8	135	12.6	10.8	143	100.0%	-1.90 [-4.01, 0.21]
Total (95% CI)			**135**			**143**	**100.0%**	**-1.90 [-4.01, 0.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)



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

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Fluroquinolones						
Dunbar2003	5	256	9	265	100.0%	0.58 [0.20, 1.69]
Subtotal (95% CI)		**256**		**265**	**100.0%**	**0.58 [0.20, 1.69]**
Total events	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**256**		**265**	**100.0%**	**0.58 [0.20, 1.69]**
Total events	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						

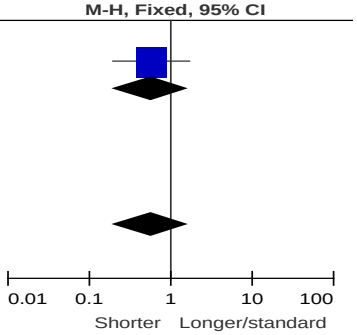


Figure 149: Clinical cure (7 to 14 days after therapy)

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 low severity group						
Dunbar2003-Mild	114	122	102	106	61.1%	0.97 [0.91, 1.03]
Subtotal (95% CI)		**122**		**106**	**61.1%**	**0.97 [0.91, 1.03]**
Total events	114		102			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.3.2 high severity group						
Dunbar2003-severe	69	76	73	86	38.9%	1.07 [0.95, 1.20]
Subtotal (95% CI)		**76**		**86**	**38.9%**	**1.07 [0.95, 1.20]**
Total events	69		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**198**		**192**	**100.0%**	**1.01 [0.91, 1.12]**
Total events	183		175			
Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Chi² = 2.15, df = 1 (P = 0.14), I² = 53.4%						

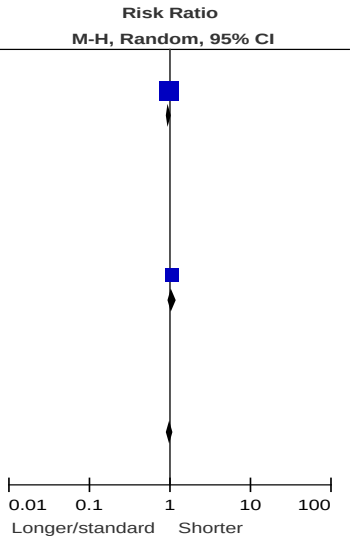
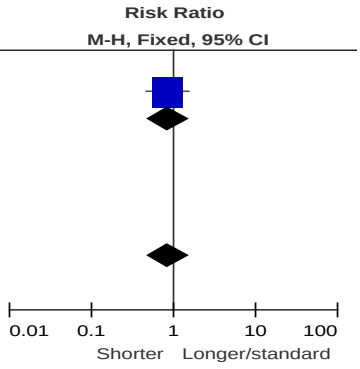


Figure 150: Withdrawal due to treatment-related adverse events

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.2 Fluroquinolones						
Dunbar2003	18	256	22	265	100.0%	0.85 [0.47, 1.54]
Subtotal (95% CI)		**256**		**265**	**100.0%**	**0.85 [0.47, 1.54]**
Total events	18		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**256**		**265**	**100.0%**	**0.85 [0.47, 1.54]**
Total events	18		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Not applicable						



1.4.6.2 Shorter duration compared with longer duration of antibiotic therapy

Figure 151: All-cause 30-day mortality

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 low to moderate severity						
Elmoussaoui2006	1	57	1	64	100.0%	1.12 [0.07, 17.54]
Subtotal (95% CI)		**57**		**64**	**100.0%**	**1.12 [0.07, 17.54]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
2.6.2 high severity						
Siegel1999	1	24	2	22	22.5%	0.46 [0.04, 4.71]
Leophonte2002	4	125	7	119	77.5%	0.54 [0.16, 1.81]
Subtotal (95% CI)		**149**		**141**	**100.0%**	**0.52 [0.18, 1.53]**
Total events	5		9			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						

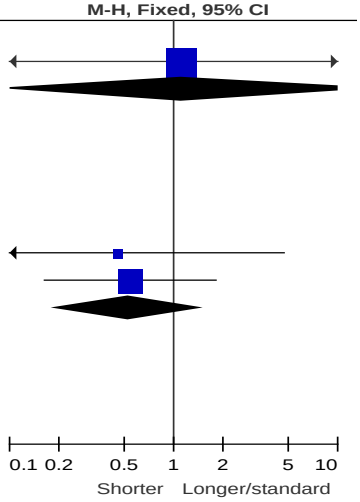


Figure 152: Clinical cure

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Cephalosporins						
Leophonte2002	82	94	81	92	55.0%	0.99 [0.89, 1.10]
Siegel1999	21	24	20	22	14.0%	0.96 [0.79, 1.18]
Subtotal (95% CI)		**118**		**114**	**69.0%**	**0.99 [0.90, 1.08]**
Total events	103		101			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
2.2.2 Amoxcillin						
Elmoussaoui2006	47	56	49	63	31.0%	1.08 [0.91, 1.29]
Subtotal (95% CI)		**56**		**63**	**31.0%**	**1.08 [0.91, 1.29]**
Total events	47		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
Total (95% CI)		**174**		**177**	**100.0%**	**1.01 [0.93, 1.10]**
Total events	150		150			
Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%						

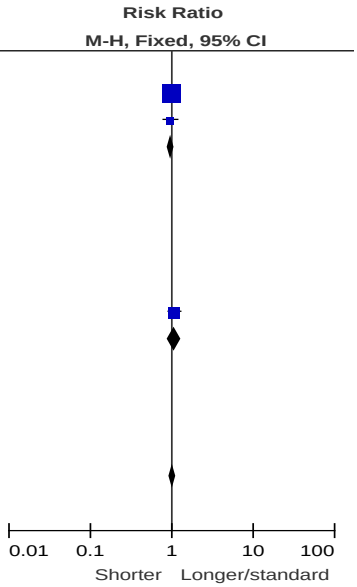


Figure 153: Withdrawal due to adverse events

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio 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 applicable						
Test for overall effect: Not applicable						
2.3.2 Cephalosporins						
Siegel1999	0	24	0	22		Not estimable
Subtotal (95% CI)		**24**		**22**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**81**		**86**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

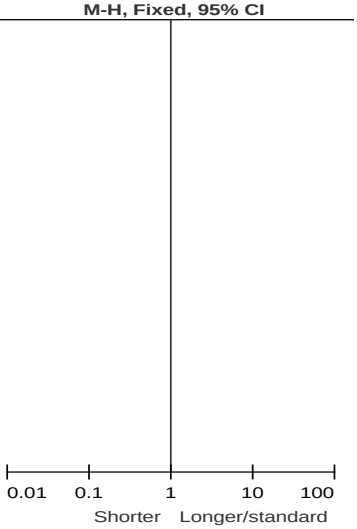


Figure 154: Complications (worsening infection, abscess, metastatic infection, MODS)

Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Amoxicillin						
Elmoussaoui2006	2	57	3	64	57.5%	0.75 [0.13, 4.32]
Subtotal (95% CI)		**57**		**64**	**57.5%**	**0.75 [0.13, 4.32]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.4.2 Cephalosporins						
Siegel1999	3	24	2	22	42.5%	1.38 [0.25, 7.47]
Subtotal (95% CI)		**24**		**22**	**42.5%**	**1.38 [0.25, 7.47]**
Total events	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**81**		**86**	**100.0%**	**1.01 [0.30, 3.38]**
Total events	5		5			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%						

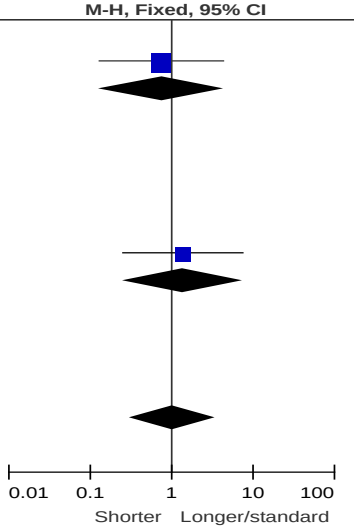
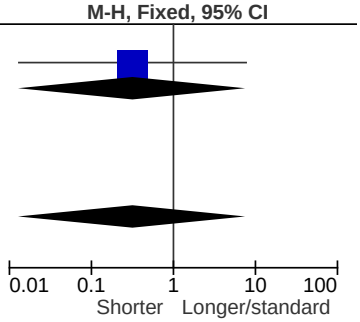


Figure 155: *C. difficile*-associated diarrhoea

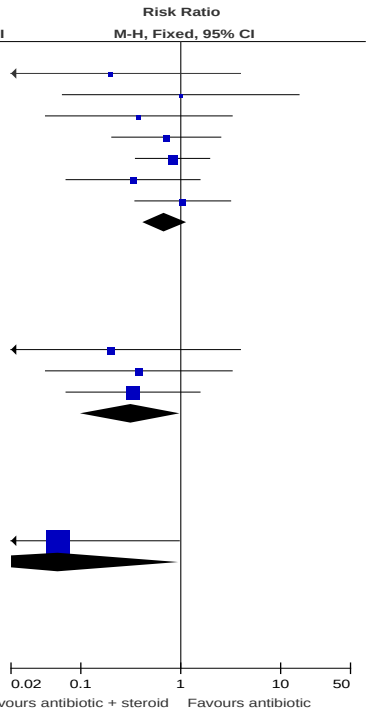
Study or Subgroup	Shorter Events	Shorter Total	Longer/standard Events	Longer/standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.2 Cephalosporins						
Leophonte2002	0	125	1	119	100.0%	0.32 [0.01, 7.72]
Subtotal (95% CI)		**125**		**119**	**100.0%**	**0.32 [0.01, 7.72]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**125**		**119**	**100.0%**	**0.32 [0.01, 7.72]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						



1.5 Glucocorticosteroid treatment

Figure 156: Mortality

Study or Subgroup	Favours antibiotic + steroid Events	Total	Antibiotic ± placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Severe (all settings); up to 30 days						
Confalonieri 2005	0	23	2	23	7.2%	0.20 [0.01, 3.95]
Fernandez-Serrano 2011	1	28	1	28	2.9%	1.00 [0.07, 15.21]
Marik 1993	1	14	3	16	8.0%	0.38 [0.04, 3.26]
McHardy 1972 - 2g	3	40	9	86	16.4%	0.72 [0.20, 2.51]
Meijvis 2011	9	151	11	153	31.4%	0.83 [0.35, 1.94]
Sabry 2011	2	40	6	40	17.2%	0.33 [0.07, 1.55]
Snijders 2010	6	104	6	109	16.8%	1.05 [0.35, 3.15]
Subtotal (95% CI)		**400**		**455**	**100.0%**	**0.69 [0.41, 1.14]**
Total events	22		38			
Heterogeneity: Chi² = 2.63, df = 6 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
1.1.2 Severe (ICU setting); up to 8 days						
Confalonieri 2005	0	23	2	23	22.1%	0.20 [0.01, 3.95]
Marik 1993	1	14	3	16	24.8%	0.38 [0.04, 3.26]
Sabry 2011	2	40	6	40	53.1%	0.33 [0.07, 1.55]
Subtotal (95% CI)		**77**		**79**	**100.0%**	**0.32 [0.10, 1.00]**
Total events	3		11			
Heterogeneity: Chi² = 0.12, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.97 (P = 0.05)						
1.1.3 Severe (ICU setting); 60 days						
Confalonieri 2005	0	23	8	23	100.0%	0.06 [0.00, 0.96]
Subtotal (95% CI)		**23**		**23**	**100.0%**	**0.06 [0.00, 0.96]**
Total events	0		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						



Test for subgroup differences: Chi² = 4.06, df = 2 (P = 0.13), I² = 50.8%

Figure 157: Mechanical ventilation

Study or Subgroup	Antibiotic + corticosteroid Events	Total	Antibiotic ± placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Severe (all settings)						
Confalonieri 2005	6	23	15	23	15.9%	0.40 [0.19, 0.85]
Fernandez-Serrano 2011	1	28	5	28	5.3%	0.20 [0.02, 1.60]
Marik 1993	2	14	4	16	4.0%	0.57 [0.12, 2.66]
Sabry 2011	10	40	26	40	27.5%	0.38 [0.21, 0.69]
Subtotal (95% CI)		**105**		**107**	**52.6%**	**0.38 [0.25, 0.59]**
Total events	19		50			
Heterogeneity: Chi² = 0.64, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 4.31 (P < 0.0001)						
1.2.3 Severe (ICU setting)						
Confalonieri 2005	6	23	15	23	15.9%	0.40 [0.19, 0.85]
Marik 1993	2	14	4	16	4.0%	0.57 [0.12, 2.66]
Sabry 2011	10	40	26	40	27.5%	0.38 [0.21, 0.69]
Subtotal (95% CI)		**77**		**79**	**47.4%**	**0.41 [0.26, 0.63]**
Total events	18		45			
Heterogeneity: Chi² = 0.22, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 4.01 (P < 0.0001)						
Total (95% CI)		**182**		**186**	**100.0%**	**0.39 [0.29, 0.54]**
Total events	37		95			
Heterogeneity: Chi² = 0.87, df = 6 (P = 0.99); I² = 0%						
Test for overall effect: Z = 5.89 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						

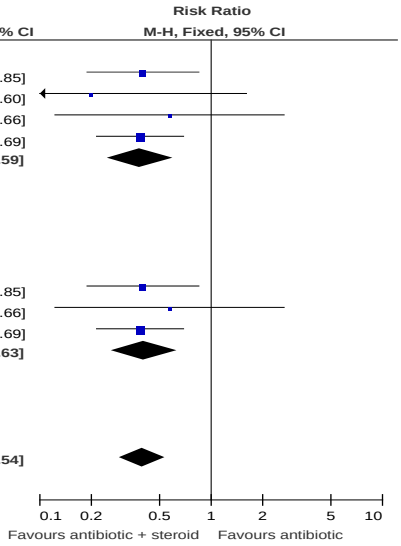


Figure 158: Clinical cure (time to clinical stability)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Snijders 2010	0.13102826	0.16892473	100.0%	1.14 [0.82, 1.59]
Total (95% CI)			**100.0%**	**1.14 [0.82, 1.59]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.78 (P = 0.44)				

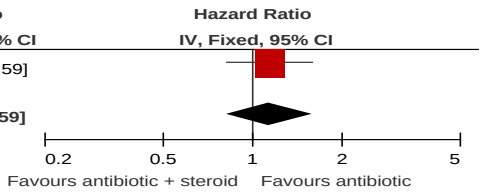


Figure 159: Length of hospital stay

Study or Subgroup	Antibiotic+Steroid Mean	SD	Total	Antibiotic Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mikami 2007	11.3	5.5	15	15.5	10.7	16	100.0%	-4.20 [-10.14, 1.74]
Total (95% CI)			**15**			**16**	**100.0%**	**-4.20 [-10.14, 1.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.17)

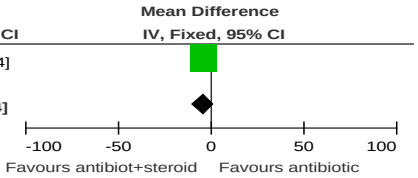


Figure 160: Hyperglycaemia

Study or Subgroup	Antibiotic + corticosteroid Events	Total	Antibiotic ± placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 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: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.98 (P < 0.0001)

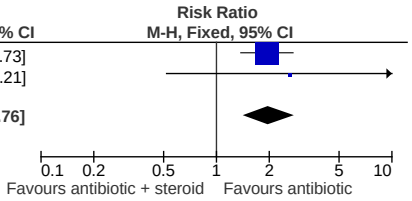


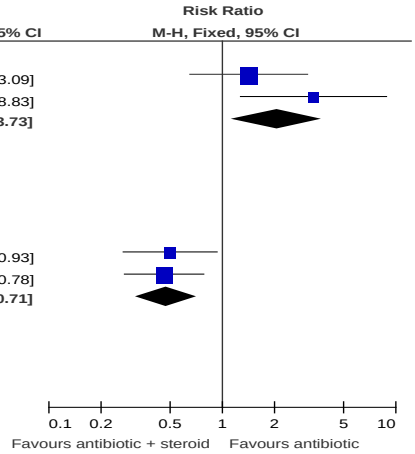
Figure 161: Complications

Study or Subgroup	Antibiotic + corticosteroid Events	Total	Antibiotic ± placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 In hospital: Superinfection, empyema or pleural effusion (upto 30 days)						
Meijvis 2011	14	151	10	153	67.0%	1.42 [0.65, 3.09]
Snijders 2010	16	104	5	109	33.0%	3.35 [1.27, 8.83]
Subtotal (95% CI)		**255**		**262**	**100.0%**	**2.06 [1.13, 3.73]**
Total events	30		15			

Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 2.37 (P = 0.02)

1.7.2 In ICU: MODS (8 days)						
Confalonieri 2005	8	23	16	23	38.1%	0.50 [0.27, 0.93]
Sabry 2011	12	40	26	40	61.9%	0.46 [0.27, 0.78]
Subtotal (95% CI)		**63**		**63**	**100.0%**	**0.48 [0.32, 0.71]**
Total events	20		42			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 3.62 (P = 0.0003)



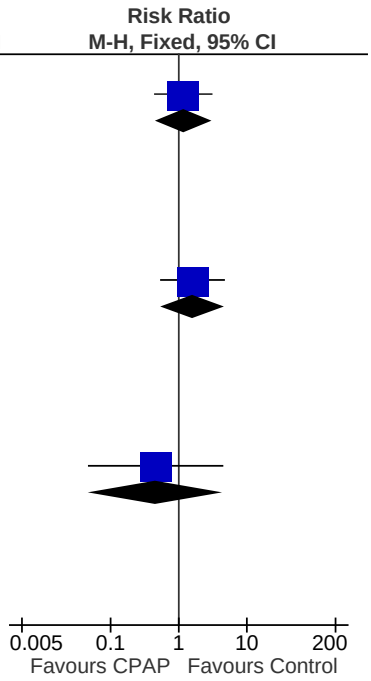
Test for subgroup differences: Chi² = 15.94, df = 1 (P < 0.0001), I² = 93.7%

1.6 Gas exchange

1.6.1 CPAP compared with usual care

Figure 162: Hospital mortality

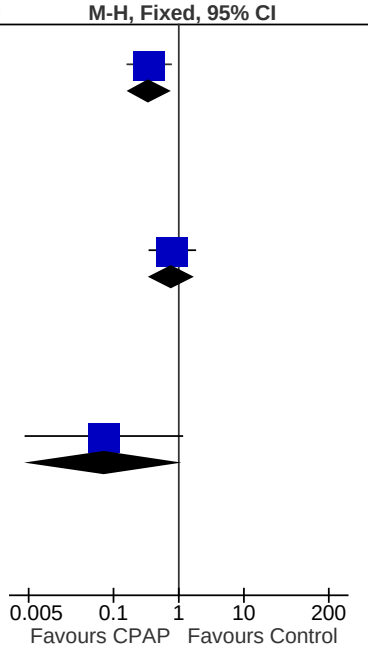
Study or Subgroup	CPAP Events	CPAP Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 All patients						
Confalonieri 1999	7	28	6	28	100.0%	1.17 [0.45, 3.04]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**1.17 [0.45, 3.04]**
Total events	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.1.2 Without COPD						
Confalonieri 1999	6	16	4	17	100.0%	1.59 [0.55, 4.62]
Subtotal (95% CI)		**16**		**17**	**100.0%**	**1.59 [0.55, 4.62]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.1.3 With COPD						
Confalonieri 1999	1	12	2	11	100.0%	0.46 [0.05, 4.38]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**0.46 [0.05, 4.38]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						



Test for subgroup differences: Chi² = 0.97, df = 2 (P = 0.61), I² = 0%

Figure 163: Need for intubation

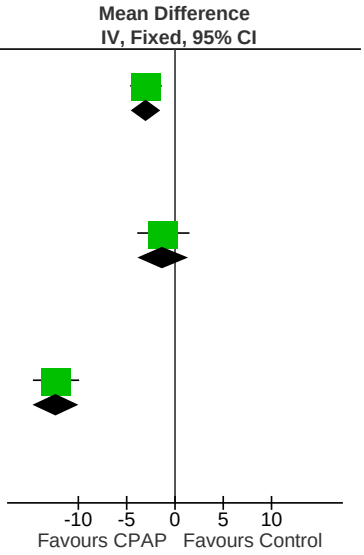
Study or Subgroup	CPAP Events	CPAP Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.2 All patients						
Confalonieri 1999	6	28	17	28	100.0%	0.35 [0.16, 0.76]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**0.35 [0.16, 0.76]**
Total events	6		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.65 (P = 0.008)						
1.2.3 Without COPD						
Confalonieri 1999	6	16	8	17	100.0%	0.80 [0.35, 1.79]
Subtotal (95% CI)		**16**		**17**	**100.0%**	**0.80 [0.35, 1.79]**
Total events	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.2.4 With COPD						
Confalonieri 1999	0	12	6	11	100.0%	0.07 [0.00, 1.13]
Subtotal (95% CI)		**12**		**11**	**100.0%**	**0.07 [0.00, 1.13]**
Total events	0		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						



Test for subgroup differences: Chi² = 3.95, df = 2 (P = 0.14), I² = 49.4%

Figure 164: Duration of intubation

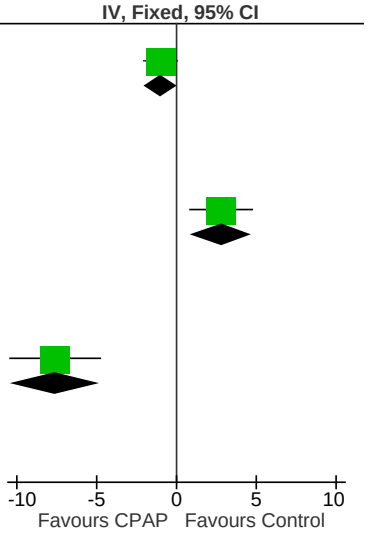
Study or Subgroup	CPAP Mean	CPAP SD	CPAP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 All patients								
Confalonieri 1999	7	3	28	10	3	28	100.0%	-3.00 [-4.57, -1.43]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-3.00 [-4.57, -1.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.74 (P = 0.0002)								
1.3.2 Without COPD								
Confalonieri 1999	6.8	4.2	16	8	3.4	17	100.0%	-1.20 [-3.82, 1.42]
Subtotal (95% CI)			**16**			**17**	**100.0%**	**-1.20 [-3.82, 1.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.90 (P = 0.37)								
1.3.3 With COPD								
Confalonieri 1999	0	0.1	12	12.3	3.9	11	100.0%	-12.30 [-14.61, -9.99]
Subtotal (95% CI)			**12**			**11**	**100.0%**	**-12.30 [-14.61, -9.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.46 (P < 0.00001)								



Test for subgroup differences: Chi² = 52.84, df = 2 (P < 0.00001), I² = 96.2%

Figure 165: Duration of hospital stay

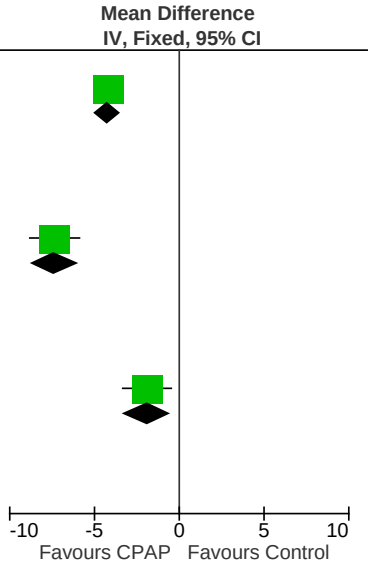
Study or Subgroup	CPAP Mean	CPAP SD	CPAP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 All patients								
Confalonieri 1999	17	2	28	18	2	28	100.0%	-1.00 [-2.05, 0.05]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-1.00 [-2.05, 0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								
1.4.2 Without COPD								
Confalonieri 1999	17.9	2.9	16	15.1	2.8	17	100.0%	2.80 [0.85, 4.75]
Subtotal (95% CI)			**16**			**17**	**100.0%**	**2.80 [0.85, 4.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.82 (P = 0.005)								
1.4.3 With COPD								
Confalonieri 1999	14.9	3.4	12	22.5	3.5	11	100.0%	-7.60 [-10.42, -4.78]
Subtotal (95% CI)			**12**			**11**	**100.0%**	**-7.60 [-10.42, -4.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.27 (P < 0.00001)								



Test for subgroup differences: Chi² = 35.52, df = 2 (P < 0.00001), I² = 94.4%

Figure 166: Duration of ITU stay

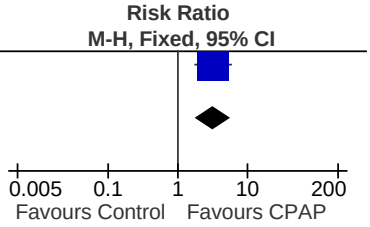
Study or Subgroup	CPAP Mean	CPAP SD	CPAP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 All patients								
Confalonieri 1999	1.8	0.7	28	6	2	28	100.0%	-4.20 [-4.98, -3.42]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-4.20 [-4.98, -3.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.49 (P < 0.00001)								
1.5.2 Without COPD								
Confalonieri 1999	0.25	2.1	16	7.6	2.2	17	100.0%	-7.35 [-8.82, -5.88]
Subtotal (95% CI)			**16**			**17**	**100.0%**	**-7.35 [-8.82, -5.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.82 (P < 0.00001)								
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 applicable								
Test for overall effect: Z = 2.60 (P = 0.009)								



Test for subgroup differences: Chi² = 27.47, df = 2 (P < 0.00001), I² = 92.7%

Figure 167: Patients who reached $PaO_2/FiO_2 \geq 315$

Study or Subgroup	CPAP Events	CPAP Total	Control Events	Control Total	Weight	Risk Ratio 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: Not applicable						
Test for overall effect: Z = 3.87 (P = 0.0001)						



1.7 Monitoring

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

Figure 168: Mortality

Study or Subgroup	log[Odds Ratio]	SE	PCT Total	Standard care Total	Weight	Odds Ratio IV, Fixed, 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 applicable
Test for overall effect: Z = 0.69 (P = 0.49)

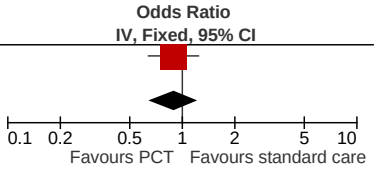


Figure 169: Treatment failure

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Schuetz 2012	-0.2614	0.1105	100.0%	0.77 [0.62, 0.96]
Total (95% CI)			**100.0%**	**0.77 [0.62, 0.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)

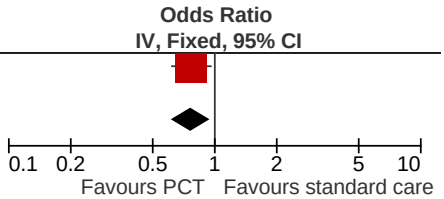


Figure 170: Median duration of antibiotic therapy

Study or Subgroup	Median difference	SE	Weight	Median difference IV, Fixed, 95% CI
Schuetz 2012	-3.34	0.2296	100.0%	-3.34 [-3.79, -2.89]
Total (95% CI)			**100.0%**	**-3.34 [-3.79, -2.89]**

Heterogeneity: Not applicable
Test for overall effect: Z = 14.55 (P < 0.00001)

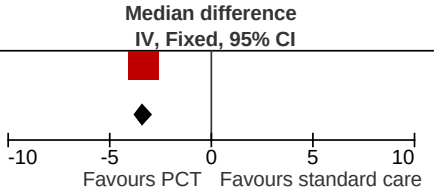
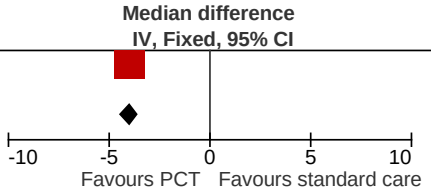


Figure 171: Total exposure to antibiotics

Study or Subgroup	Median difference	SE	Weight	Median difference IV, Fixed, 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 applicable
Test for overall effect: Z = 16.96 (P < 0.00001)



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

Study or Subgroup	PCT Events	PCT Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Christ-Crain 2006	18	126	20	149	100.0%	1.06 [0.59, 1.92]
Total (95% CI)		**126**		**149**	**100.0%**	**1.06 [0.59, 1.92]**
Total events	18		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)

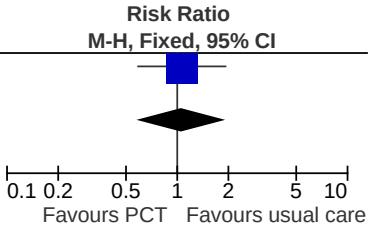


Figure 173: Length of hospital stay

Study or Subgroup	PCT Mean	PCT SD	PCT Total	usual care Mean	usual care SD	usual care Total	Weight	Mean Difference IV, Fixed, 95% 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 applicable
Test for overall effect: Z = 0.47 (P = 0.64)

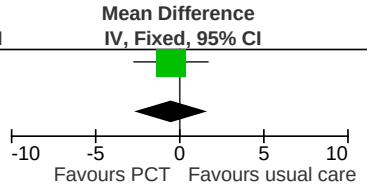


Figure 174: Treatment failure

Study or Subgroup	PCT Events	PCT Total	Usual care Events	Usual care Total	Weight	Odds Ratio 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	23		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)

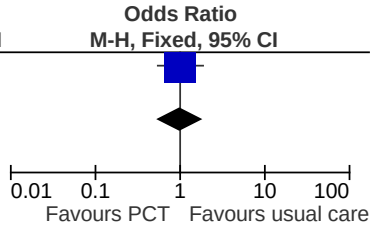


Figure 175: Duration of antibiotics

Study or Subgroup	PCT Mean	PCT SD	PCT Total	usual care Mean	usual care SD	usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Christ-Crain 2006	6.86	5.09	126	13.11	6.4	149	100.0%	-6.25 [-7.61, -4.89]
Total (95% CI)			**126**			**149**	**100.0%**	**-6.25 [-7.61, -4.89]**

Heterogeneity: Not applicable
Test for overall effect: Z = 9.02 (P < 0.00001)

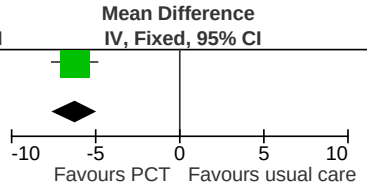
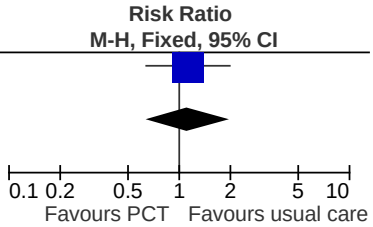


Figure 176: ITU admission

Study or Subgroup	PCT Events	PCT Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Christ-Crain 2006	20	126	21	149	100.0%	1.13 [0.64, 1.98]
Total (95% CI)		**126**		**149**	**100.0%**	**1.13 [0.64, 1.98]**
Total events	20		21			

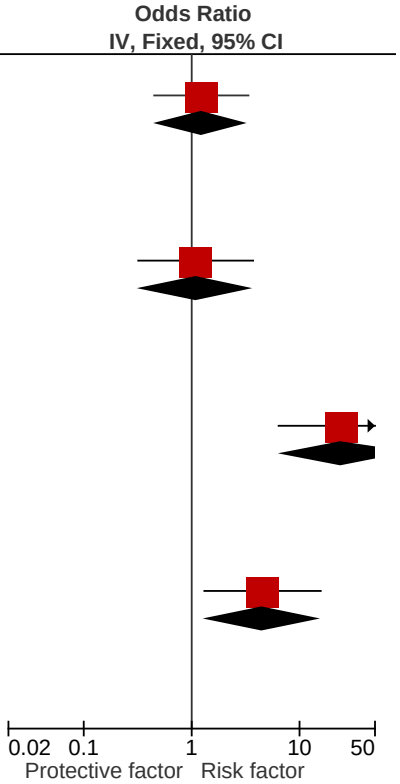
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



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

Figure 177: Mortality

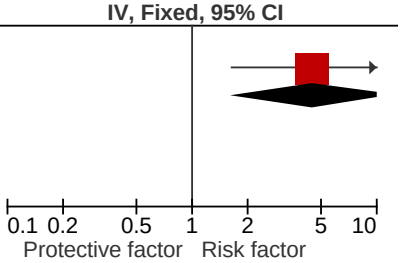
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.1.1 CRP: day 0-7 decline <90%				
Bruns 2008	0.207	0.513	100.0%	1.23 [0.45, 3.36]
Subtotal (95% CI)			**100.0%**	**1.23 [0.45, 3.36]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.40 (P = 0.69)				
11.1.2 CRP: day 0-3 decline <60%				
Bruns 2008	0.0862	0.6253	100.0%	1.09 [0.32, 3.71]
Subtotal (95% CI)			**100.0%**	**1.09 [0.32, 3.71]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.14 (P = 0.89)				
11.1.3 CRP: day 0-4 decline <50%				
Chalmers 2008	3.1987	0.6849	100.0%	24.50 [6.40, 93.79]
Subtotal (95% CI)			**100.0%**	**24.50 [6.40, 93.79]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.67 (P < 0.00001)				
11.1.4 PCT increase day 1 to 3				
Boussekey 2006	1.5127	0.634	100.0%	4.54 [1.31, 15.73]
Subtotal (95% CI)			**100.0%**	**4.54 [1.31, 15.73]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.39 (P = 0.02)				



Test for subgroup differences: Chi² = 15.45, df = 3 (P = 0.001), I² = 80.6%

Figure 178: ITU mortality

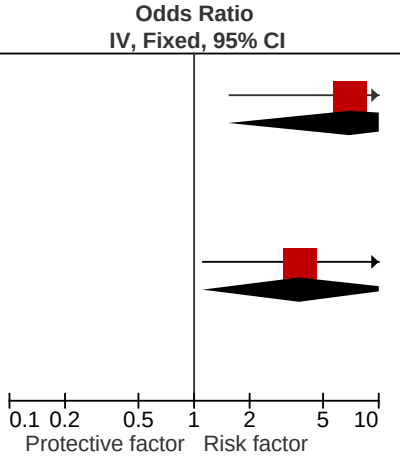
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.9.1 Day 5 CRP ratio >0.5				
Coelho 2012 - ICU	1.4974	0.5116	100.0%	4.47 [1.64, 12.18]
Subtotal (95% CI)			**100.0%**	**4.47 [1.64, 12.18]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.93 (P = 0.003)				



Test for subgroup differences: Not applicable

Figure 179: Inappropriate antibiotic therapy

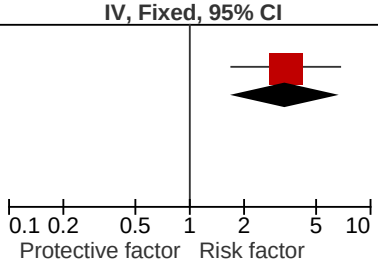
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.2.1 CRP: day 0-3 decline <60%				
Bruns 2008	1.943	0.7645	100.0%	6.98 [1.56, 31.23]
Subtotal (95% CI)			**100.0%**	**6.98 [1.56, 31.23]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.54 (P = 0.01)				
11.2.2 CRP: day 0-7 decline <90%				
Bruns 2008	1.3191	0.6152	100.0%	3.74 [1.12, 12.49]
Subtotal (95% CI)			**100.0%**	**3.74 [1.12, 12.49]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.14 (P = 0.03)				



Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.52), I² = 0%

Figure 180: Overall treatment failure

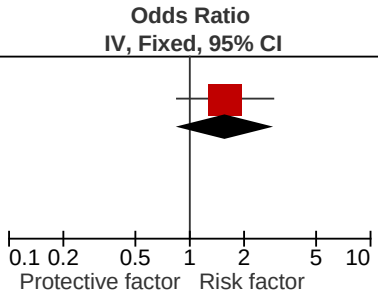
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.5.1 Day 3 CRP above 75th percentile				
Menendez 2008	1.2238	0.3537	100.0%	3.40 [1.70, 6.80]
Subtotal (95% CI)			**100.0%**	**3.40 [1.70, 6.80]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.46 (P = 0.0005)				



Test for subgroup differences: Not applicable

Figure 181: Early treatment failure

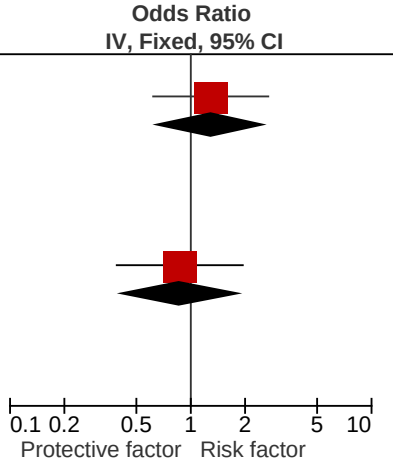
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.3.1 CRP: day 0-3 decline <60%				
Bruns 2008	0.4511	0.3131	100.0%	1.57 [0.85, 2.90]
Subtotal (95% CI)			**100.0%**	**1.57 [0.85, 2.90]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.44 (P = 0.15)				



Test for subgroup differences: Not applicable

Figure 182: Late treatment failure

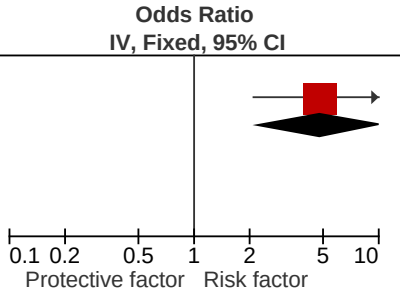
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.4.1 CRP: day 0-3 decline <60%				
Bruns 2008	0.2546	0.3738	100.0%	1.29 [0.62, 2.68]
Subtotal (95% CI)			**100.0%**	**1.29 [0.62, 2.68]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.68 (P = 0.50)				
11.4.2 CRP: day 0-7 decline <90%				
Bruns 2008	-0.1393	0.4094	100.0%	0.87 [0.39, 1.94]
Subtotal (95% CI)			**100.0%**	**0.87 [0.39, 1.94]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.34 (P = 0.73)				



Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%

Figure 183: Late treatment failure (after 72 hours)

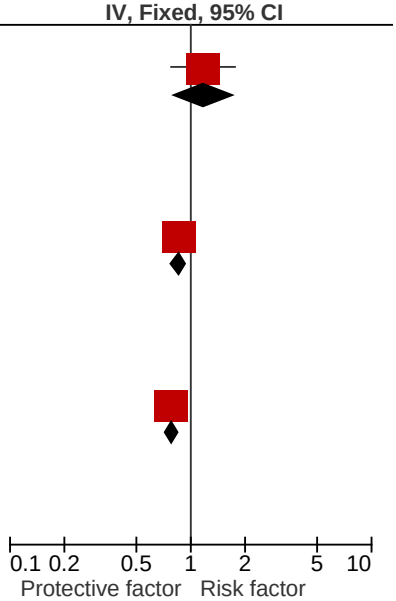
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.6.2 Day 3 CRP above 75th percentile				
Menendez 2008	1.5686	0.4218	100.0%	4.80 [2.10, 10.97]
Subtotal (95% CI)			**100.0%**	**4.80 [2.10, 10.97]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.72 (P = 0.0002)				



Test for subgroup differences: Not applicable

Figure 184: Severe complications after 72 hours

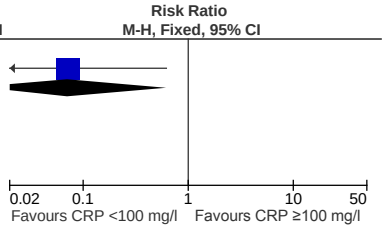
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.7.1 Day 3 PCT <0.25 ng/ml				
Menendez 2009	0.157	0.2069	100.0%	1.17 [0.78, 1.76]
Subtotal (95% CI)			**100.0%**	**1.17 [0.78, 1.76]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.76 (P = 0.45)				
11.7.2 Day 3 CRP <3 mg/dl				
Menendez 2009	-0.1508	0.0564	100.0%	0.86 [0.77, 0.96]
Subtotal (95% CI)			**100.0%**	**0.86 [0.77, 0.96]**
Heterogeneity: Not applicable				
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]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.18 (P < 0.00001)				



Test for subgroup differences: Chi² = 4.75, df = 2 (P = 0.09), I² = 57.9%

Figure 185: Hospital re-admission within 7 days

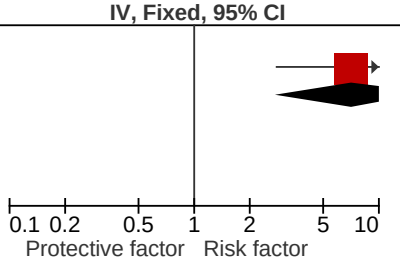
Study or Subgroup	Discharge CRP <100 mg/l Events	Total	Discharge CRP ≥100 mg/l Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.8.1 Discharge CRP <100 mg/l vs ≥100 mg/l						
Chalmers 2008	1	162	4	46	100.0%	0.07 [0.01, 0.62]
Subtotal (95% CI)		**162**		**46**	**100.0%**	**0.07 [0.01, 0.62]**
Total events	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.39 (P = 0.02)						



Test for subgroup differences: Not applicable

Figure 186: Need for invasive ventilation or ionotropic support

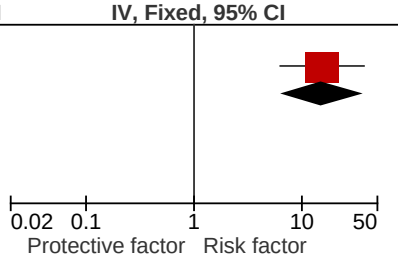
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.10.1 CRP: day 0-4 decline <50%				
Chalmers 2008	1.9601	0.4747	100.0%	7.10 [2.80, 18.00]
Subtotal (95% CI)			**100.0%**	**7.10 [2.80, 18.00]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.13 (P < 0.0001)				



Test for subgroup differences: Not applicable

Figure 187: Complicated pneumonia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.11.1 CRP: day 0-4 decline <50%				
Chalmers 2008	2.7344	0.4544	100.0%	15.40 [6.32, 37.53]
Subtotal (95% CI)			**100.0%**	**15.40 [6.32, 37.53]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 6.02 (P < 0.00001)				



Test for subgroup differences: Not applicable

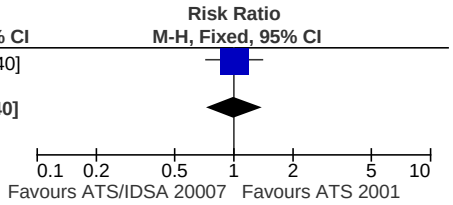
1.8 Safe discharge

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

Study or Subgroup	ATS 2001 Events	ATS 2001 Total	ATD/IDSA 2007 Events	ATD/IDSA 2007 Total	Weight	Risk Ratio 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	62		59			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



Study or Subgroup	≥1 instabilities Events	≥1 instabilities Total	No instabilities Events	No instabilities Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dagan 2006	9	82	19	291	100.0%	1.68 [0.79, 3.57]
Total (95% CI)		**82**		**291**	**100.0%**	**1.68 [0.79, 3.57]**
Total events	9		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

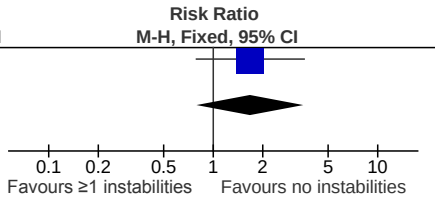
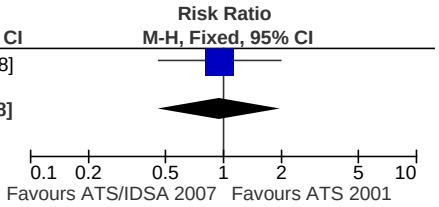


Figure 189: Mortality 30 days after discharge

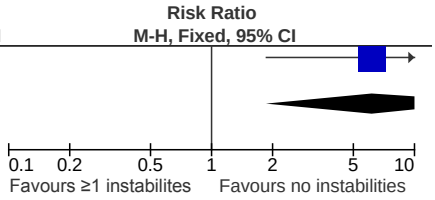
Study or Subgroup	ATS 2001 Events	ATS 2001 Total	ATD/IDSA 2007 Events	ATD/IDSA 2007 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aliberti 2013	14	429	14	410	100.0%	0.96 [0.46, 1.98]
Total (95% CI)		**429**		**410**	**100.0%**	**0.96 [0.46, 1.98]**
Total events	14		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)



Study or Subgroup	≥1 instabilities Events	≥1 instabilities Total	No instabilities Events	No instabilities Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dagan 2006	7	82	4	291	100.0%	6.21 [1.86, 20.70]
Total (95% CI)		**82**		**291**	**100.0%**	**6.21 [1.86, 20.70]**
Total events	7		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.97 (P = 0.003)



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

Study or Subgroup	Moxifloxacin Events	Moxifloxacin Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.59 (P = 0.56)

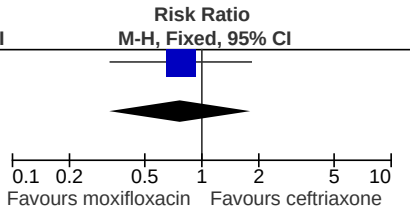


Figure 191: Clinical cure or improvement at end of follow-up

Study or Subgroup	Moxifloxacin Events	Moxifloxacin Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.61 (P = 0.54)

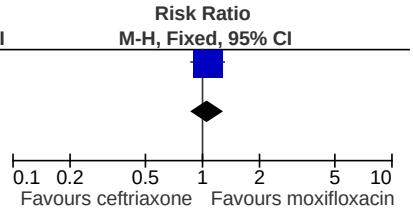
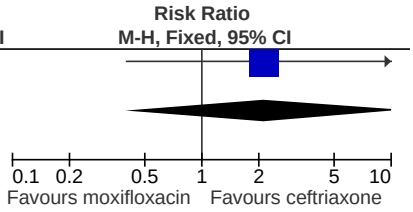


Figure 192: Withdrawal due to adverse events

Study or Subgroup	Moxifloxacin Events	Moxifloxacin Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 0.89 (P = 0.38)



2.4.1.2 Beta-lactamase-stable penicillin compared with carbapenem

Figure 193: All cause mortality

Study or Subgroup	Favours piperacillin-tazobactam Events	Total	Imipenem-cilastatin Events	Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 1.22 (P = 0.22)

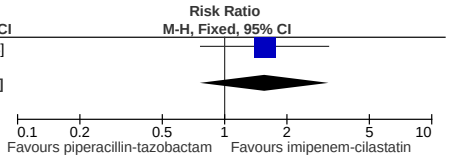


Figure 194: Clinical cure at end of treatment

Study or Subgroup	Piperacillin-tazobactam Events	Total	Imipenem-cilastatin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 1.05 (P = 0.30)

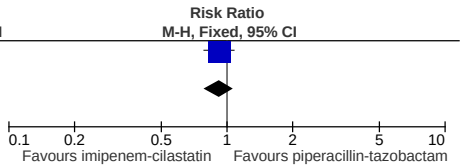


Figure 195: Clinical cure at end of follow-up

Study or Subgroup	Piperacillin-tazobactam Events	Total	Imipenem-cilastatin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 1.00 (P = 0.32)

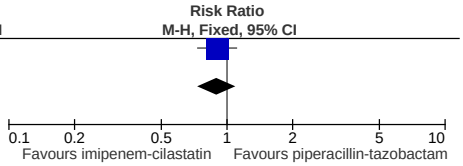
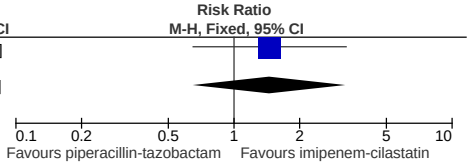


Figure 196: Withdrawal due to adverse events

Study or Subgroup	Piperacillin-tazobactam Events	Total	Imipenem-cilastatin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 0.91 (P = 0.36)



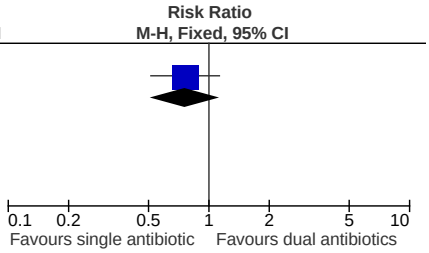
2.4.2 Single- compared with dual-antibiotic therapy

2.4.2.1 Cephalosporin compared with cephalosporin plus aminoglycoside

Table 1: All-cause mortality

Study or Subgroup	Single antibiotic Events	Total	Dual antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Cephalosporin vs cephalosporin + aminoglycoside						
Fernandez-Guerrero 1991	36	280	52	308	100.0%	0.76 [0.51, 1.13]
Subtotal (95% CI)		**280**		**308**	**100.0%**	**0.76 [0.51, 1.13]**
Total events	36		52			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)

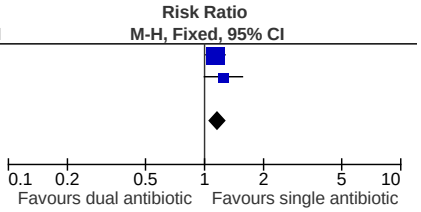


Test for subgroup differences: Not applicable

Table 2: Clincal cure at end of treatment

Study or Subgroup	Single antibiotic Events	Total	Dual antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez-Guerrero 1991	217	275	113	162	67.5%	1.13 [1.00, 1.27]
Rubinstein 1995	92	159	64	138	32.5%	1.25 [1.00, 1.56]
Total (95% CI)		**434**		**300**	**100.0%**	**1.17 [1.05, 1.30]**
Total events	309		177			

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)



2.4.2.2 Carbapenem versus cephalosporin plus aminoglycoside

Figure 197: Clinical cure at end of treatment

Study or Subgroup	Single antibiotic Events	Total	Dual antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jaspers 1998	17	20	16	21	100.0%	1.12 [0.83, 1.51]
Total (95% CI)		**20**		**21**	**100.0%**	**1.12 [0.83, 1.51]**
Total events	17		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

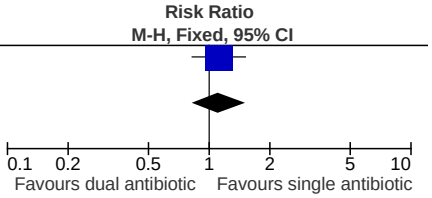
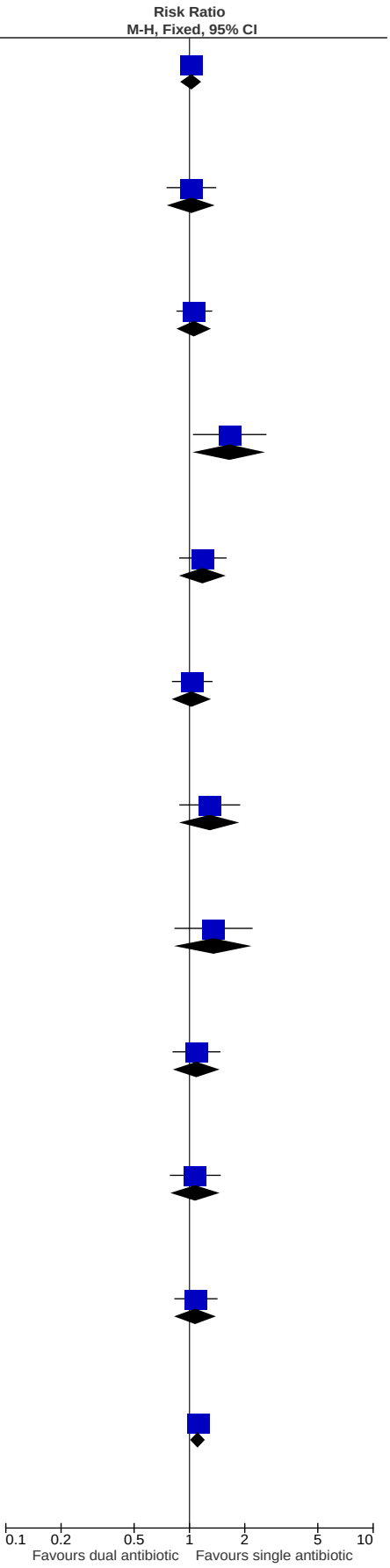


Table 3: Clinical cure at end of treatment (comparison subgroups from Fernandez-Guerrero 1991)

Study or Subgroup	Single antibiotic Events	Total	Dual antibiotic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Cefotaxime + aminoglycosides						
Fernandez-Guerrero 1991	217	275	60	78	100.0%	1.03 [0.90, 1.18]
Subtotal (95% CI)		**275**		**78**	**100.0%**	**1.03 [0.90, 1.18]**
Total events	217		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
3.1.2 Cefotaxime + other						
Fernandez-Guerrero 1991	217	275	10	13	100.0%	1.03 [0.76, 1.39]
Subtotal (95% CI)		**275**		**13**	**100.0%**	**1.03 [0.76, 1.39]**
Total events	217		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
3.1.3 Broad-spectrum penicillins + aminoglycosides						
Fernandez-Guerrero 1991	217	275	23	31	100.0%	1.06 [0.86, 1.32]
Subtotal (95% CI)		**275**		**31**	**100.0%**	**1.06 [0.86, 1.32]**
Total events	217		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
3.1.4 Cephalosporins (gram-positive activity) + aminoglycosides						
Fernandez-Guerrero 1991	217	275	10	21	100.0%	1.66 [1.05, 2.61]
Subtotal (95% CI)		**275**		**21**	**100.0%**	**1.66 [1.05, 2.61]**
Total events	217		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.19 (P = 0.03)						
3.1.5 Cephalosporins (gram-negative activity) + aminoglycosides						
Fernandez-Guerrero 1991	217	275	16	24	100.0%	1.18 [0.89, 1.58]
Subtotal (95% CI)		**275**		**24**	**100.0%**	**1.18 [0.89, 1.58]**
Total events	217		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
3.1.6 Cephalosporins (Pseudomonas activity) + aminoglycosides						
Fernandez-Guerrero 1991	217	275	16	21	100.0%	1.04 [0.81, 1.33]
Subtotal (95% CI)		**275**		**21**	**100.0%**	**1.04 [0.81, 1.33]**
Total events	217		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
3.1.7 Cephalosporins (anaerobe activity) + aminoglycosides						
Fernandez-Guerrero 1991	217	275	11	18	100.0%	1.29 [0.89, 1.88]
Subtotal (95% CI)		**275**		**18**	**100.0%**	**1.29 [0.89, 1.88]**
Total events	217		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
3.1.8 Clindamycin + aminoglycosides						
Fernandez-Guerrero 1991	217	275	7	12	100.0%	1.35 [0.84, 2.19]
Subtotal (95% CI)		**275**		**12**	**100.0%**	**1.35 [0.84, 2.19]**
Total events	217		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
3.1.9 Narrow-spectrum penicillin (gram-positive activity) + aminoglycosides						
Fernandez-Guerrero 1991	217	275	13	18	100.0%	1.09 [0.82, 1.46]
Subtotal (95% CI)		**275**		**18**	**100.0%**	**1.09 [0.82, 1.46]**
Total events	217		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
3.1.10 Other + aminoglycosides						
Fernandez-Guerrero 1991	217	275	11	15	100.0%	1.08 [0.79, 1.47]
Subtotal (95% CI)		**275**		**15**	**100.0%**	**1.08 [0.79, 1.47]**
Total events	217		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
3.1.11 Other combination						
Fernandez-Guerrero 1991	217	275	16	22	100.0%	1.08 [0.83, 1.41]
Subtotal (95% CI)		**275**		**22**	**100.0%**	**1.08 [0.83, 1.41]**
Total events	217		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
3.1.12 All combinations						
Fernandez-Guerrero 1991	217	275	193	273	100.0%	1.12 [1.01, 1.23]
Subtotal (95% CI)		**275**		**273**	**100.0%**	**1.12 [1.01, 1.23]**
Total events	217		193			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						



Test for subgroup differences: Chi² = 6.46, df = 11 (P = 0.84), I² = 0%

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

Study or Subgroup	BL + AG Events	BL + AG Total	C + AG Events	C + AG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Joshi 1999	12	155	24	145	100.0%	0.47 [0.24, 0.90]
Total (95% CI)		**155**		**145**	**100.0%**	**0.47 [0.24, 0.90]**
Total events	12		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)

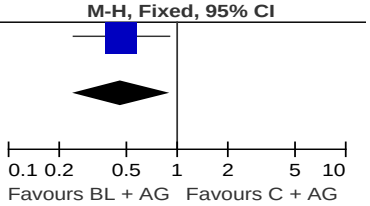


Figure 199: Clinical cure or improvement at end of follow-up

Study or Subgroup	BL + AG Events	BL + AG Total	C + AG Events	C + AG Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 2.91 (P = 0.004)

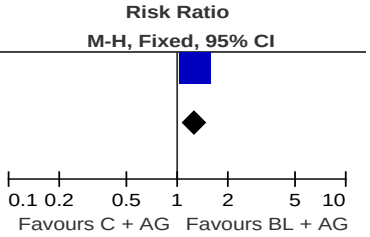


Figure 200: Withdrawal due to adverse events

Study or Subgroup	BL + AG Events	BL + AG Total	C + AG Events	C + AG Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 1.02 (P = 0.31)

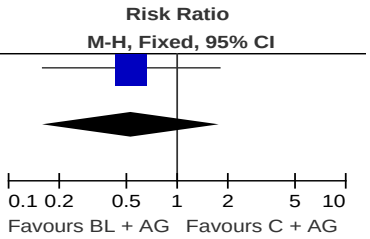
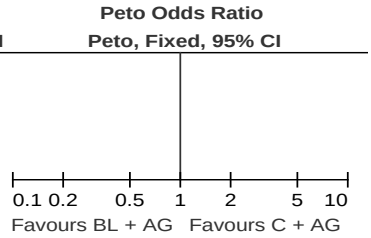


Figure 201: C. diffiile-associated diarrhoea

Study or Subgroup	BL + AG Events	BL + AG Total	C + AG Events	C + AG Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Joshi 1999	0	155	0	145		Not estimable
Total (95% CI)		**155**		**145**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



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.