Finish the course?

Drs. B.M. Roede
Dr. J.M. Prins

Academisch Medisch Centrum – Universiteit van Amsterdam

Zoek een geneesmiddel dat begint met een

a b c d e f g h i
j k l m n o p q r
s t u v w x y z

Zoek een aandoening die begint met een

a b c d e f g h i
j k l m n o p q r
s t u v w x y z

Zoek een geneesmiddel op trefwoord

Zoek

Geneesmiddelen

Dit artikel bevat de volgende onderdelen

Algemeen

Werking en toepassingen

Bijwerkingen

Wisselwerking

Autorijden, alcohol, voeding

Zwangerschap en borstvoeding

Hoe, wanneer, hoe lang?

Dosis vergeten?

Stoppen

amoxicilline

De vergeten dosis moet u alsnog zo snel mogelijk innemen. Duurt het minder dan twee uur voordat u de volgende dosis moet innemen? Sla dan de vergeten dosis over en hervat uw normale schema. De vergeten dosis neemt u aan het eind van de kuur in. U verschuift dus het moment waarop u de kuur beëindigt. Maakt u wel de volledige kuur af!

8. Kan ik zomaar met dit middel stoppen?

Nee, u dient de kuur af te maken. Als u de kuur niet afmaakt, is de bacterie waarschijnlijk nog niet verdwenen en kunt u opnieuw geïnfecteerd raken. Als u allergische reacties of ernstige bijwerkingen krijgt, moet u wel stoppen met de kuur. Neem in dat geval direct contact op met uw arts.

Laatste herziening: 29-4-2004

Deze tekst is opgesteld door het **Wetenschappelijk Instituut Nederlandse Apothekers (WINAp)**. Deze tekst is gebaseerd op de bijsluiter van het beschreven geneesmiddel en op andere, wetenschappelijke bronnen. De officieel geregistreerde gegevens van dit middel bij het College ter Beoordeling van Geneesmiddelen vindt u op: www.cbg-meb.nl.

Don't keep taking the tablets?

H P Lambert

Information about antibiotic drugs and instructions on their proper use usually include an injunction to finish the course. This is found in all patient-information leaflets and package inserts, some of which select the point for special emphasis in bold type or capital letters. "Keep taking the tablets" is a widespread dogma of medical practice. The supposed reasons for completing the course are that the patient either will not recover or will relapse if the course is not finished, and that completing the course will discourage the emergence of antibiotic resistance in the causal organism. Both suppositions are highly suspect. There is very little evidence for the optimum duration of antibiotic treatment for many infections, and courses shorter than those conventionally recommended are often appropriate. The other alleged reason for completing the course—that resistance will be discouraged—is rarely valid; on the contrary, antibiotic resistance is more likely to be encouraged by longer than by shorter courses of antibiotic.

How long is a course of treatment for

prescriptions;[4] for these infections there are great uncertainties and wide variations of opinion and practice about duration of treatment. Indeed, whether antibiotics are needed at all for some syndromes is disputed.

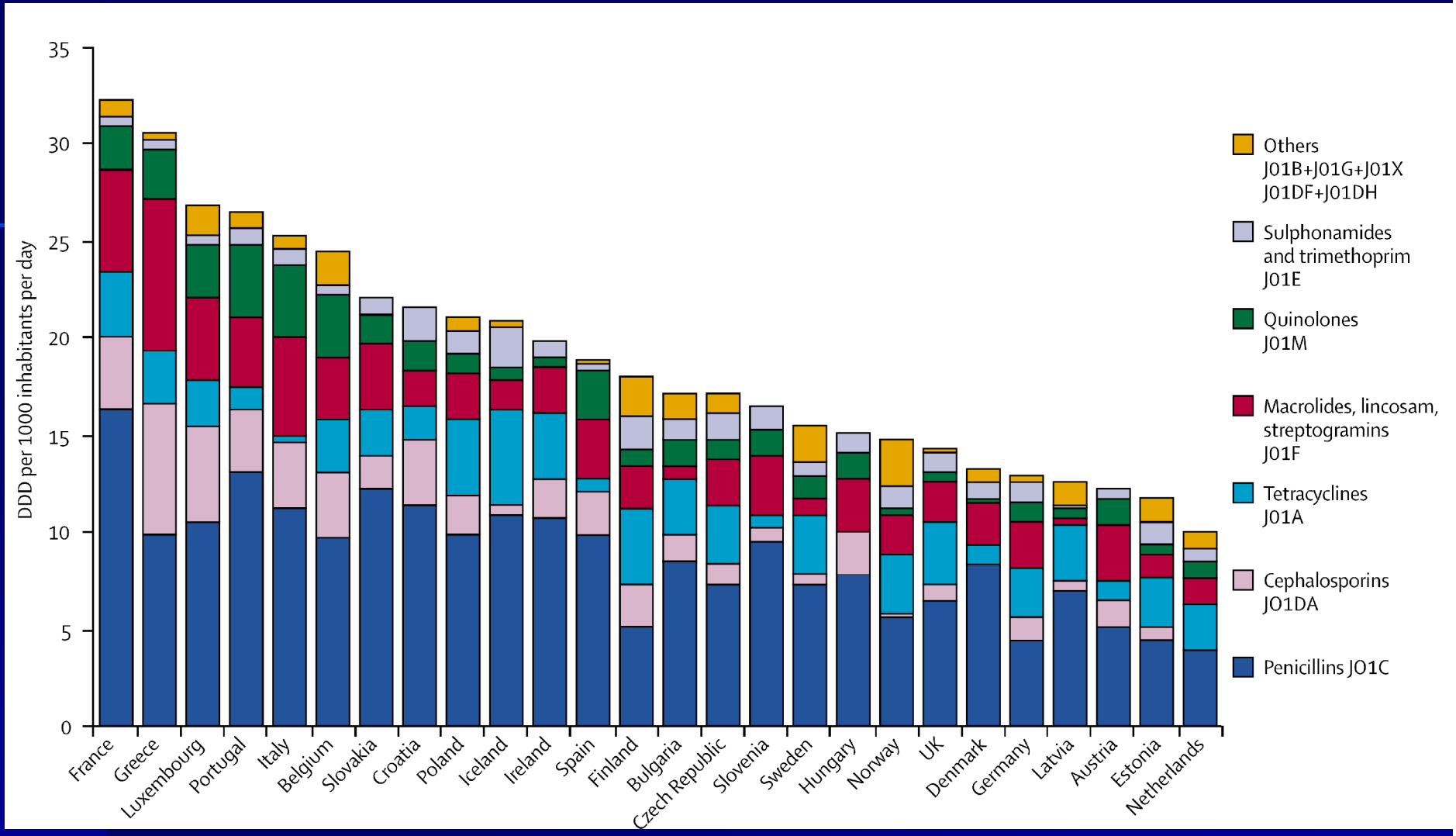
There is much controversy about the treatment of otitis media in children.[5,6] Most British children with a diagnosis of otitis media receive antibiotics, and in the USA this condition is the most common reason for antibiotic use in outpatients. By contrast, antibiotics are not used routinely in otitis media in the Netherlands or Iceland, and there is evidence from several trials that antibiotics provide little or no benefit in this condition.[7] As to duration of treatment, various trials have shown that courses of 2, 3, 5, and 10 days are equally effective (or presumably equally ineffective).

Similar doubts have emerged in acute sinusitis. Some controlled trials have shown the benefit of antibiotics,[8] but 3 days' treatment with trimethoprim-sulphamethoxazole was as effective as 10 days' treatment.[9] Other trials concluded that there is no advantage from

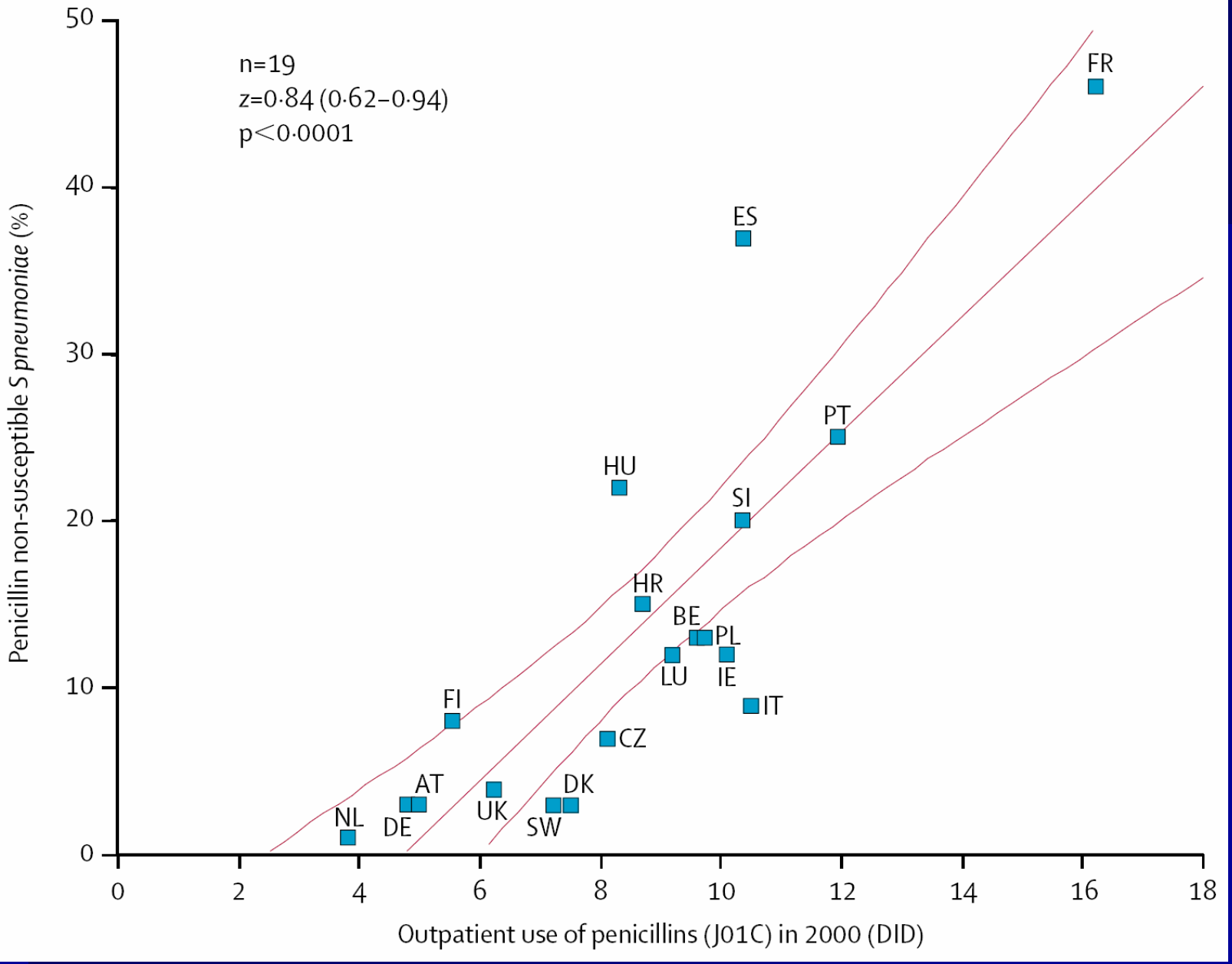
Lancet 1999;354:943

Potential consequences of not completing the course

- Resistance
- Relapse

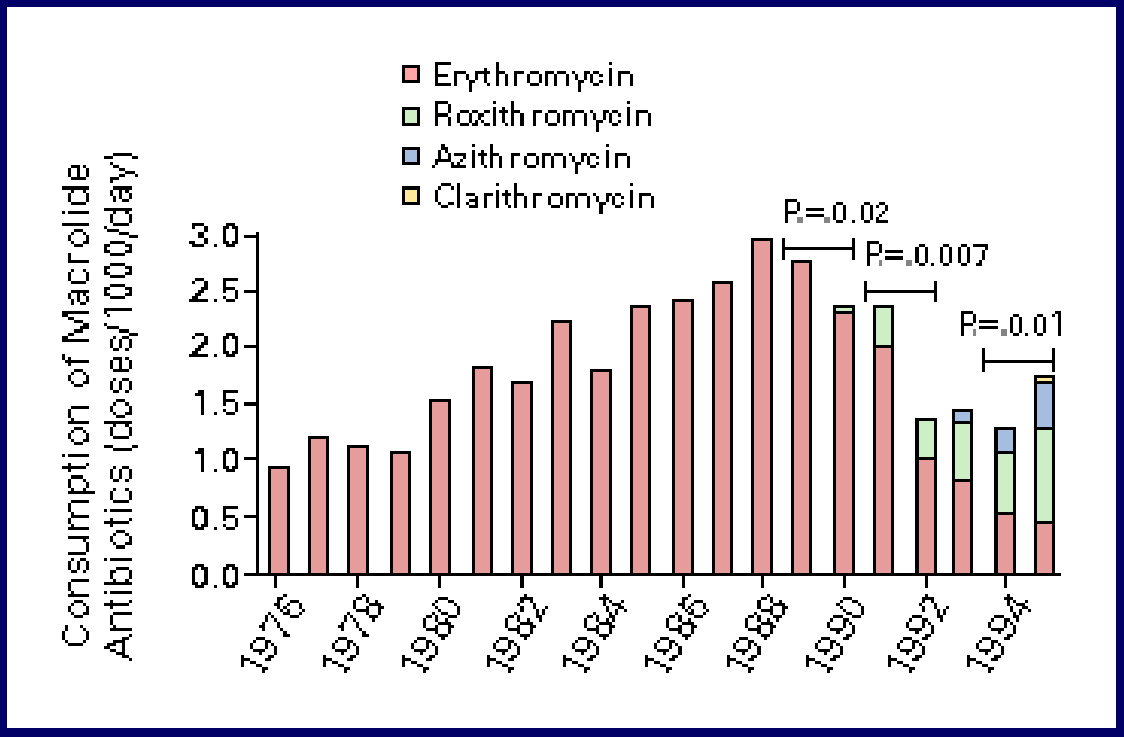


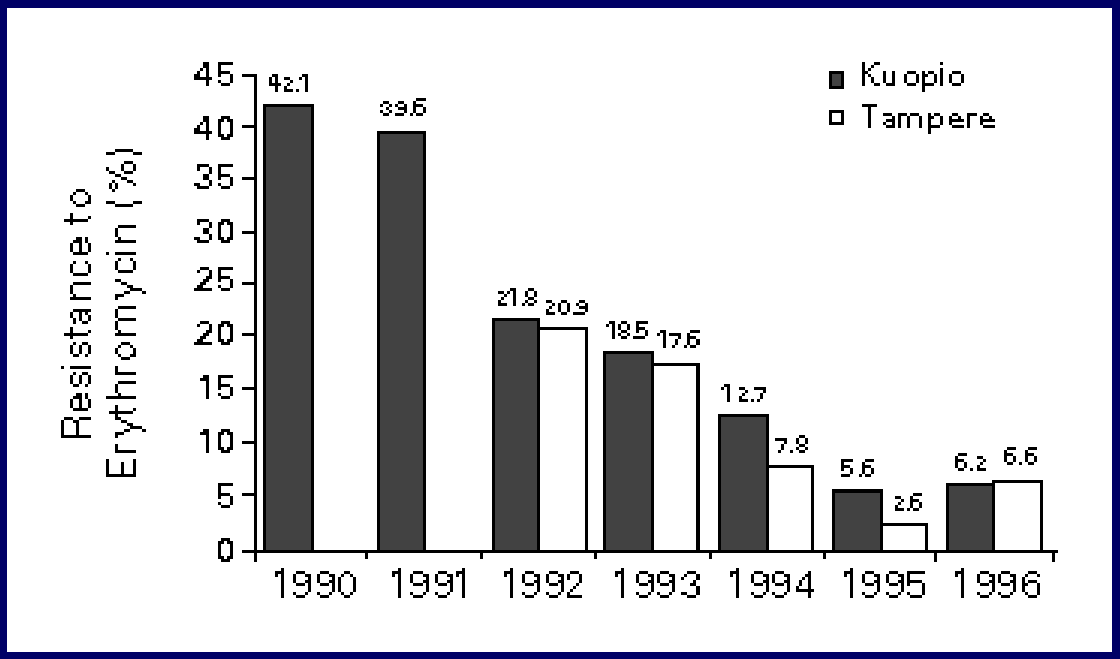
ESAC project, Lancet 2005;365:579


n=19
z=0·84 (0·62–0·94)
p<0·0001
Penicillin non-susceptible S pneumoniae (%)
Outpatient use of penicillins (J01C) in 2000 (DID)
0
10
20
30
40
50
0
2
4
6
8
10
12
14
16
18
FR
ES
PT
HU
SI
HR
BE
PL
LU
IE
IT
FI
CZ
AT
DK
UK
NL
DE
SW

Correlation between antibiotic use and resistance, by organism and year of isolation

	Antibiotic resistance	Antibiotic use, ATC group (year of data)	Number of countries	Spearman correlation (95% CI)	p
S pneumoniae 1999/2000[10]	Erythromycin	Macrolides, J01FA (1998)	16	0·83 (0·67–0·94)	0·0008
S pneumoniae 2001[9]	Penicillin	Penicillins, J01C (2000)	19	0·84 (0·62–0·94)	<0·0001
		Cephalosporins, J01DA (2000)		0·68 (0·33–0·87)	0·0014
S pyogenes 1999/2000[10]	Erythromycin	Macrolides, J01FA and lincosamides, J01FF (1998)	21	0·65 (0·25–0·86)	0·0015
E coli 1999/2000[11]	Ciprofloxacin	Quinolones, J01M (1999)	14	0·74 (0·35–0·91)	0·0023
	Co-trimoxazole	Co-trimoxazole, J01EE01 (1999)		0·71 (0·29–0·90)	0·0048





N Engl J Med
1997;337:441

Carriage PRSP related to dosage and treatment duration

Table 6.—Odds Ratios for Penicillin-Resistant *Streptococcus pneumoniae* (PR*Sp*) Carriage According to Daily Dose and Duration of the Last Antibiotic Used During the Previous 30 Days*

Variable	No. of Children	No. of PR*Sp* Carriers	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Last β-lactam						
Daily dose						
No use†	780	10	1.0		1.0	
Low†	84	6	5.9 (2.1-16.7)	.002	7.5 (2.5-22.8)	<.001
High	54	0	NA	.9	NI	
Missing‡	23	0	NA	.9	NI	
Duration of treatment						
No use†	780	10	1.0		1.0	
Long†	138	6	3.5 (1.3-9.8)	.02	3.9 (1.4-11.2)	.01
Short	23	0	NA	.9	NI	
Last aminopenicillin						

JAMA 1998;279:365

Conclusion

Completing the course does not prevent development of resistance (the shorter, the better)

Longer treatment duration associated with non-compliance

Longer treatment duration means higher costs

Potential consequences of not completing the course

- Resistance
- Relapse

What do we know about the minimal effective treatment duration?

- Upper RTI
  - Otitis media
  - Tonsillo-pharyngitis
- Exacerbation COPD
- Pneumonia

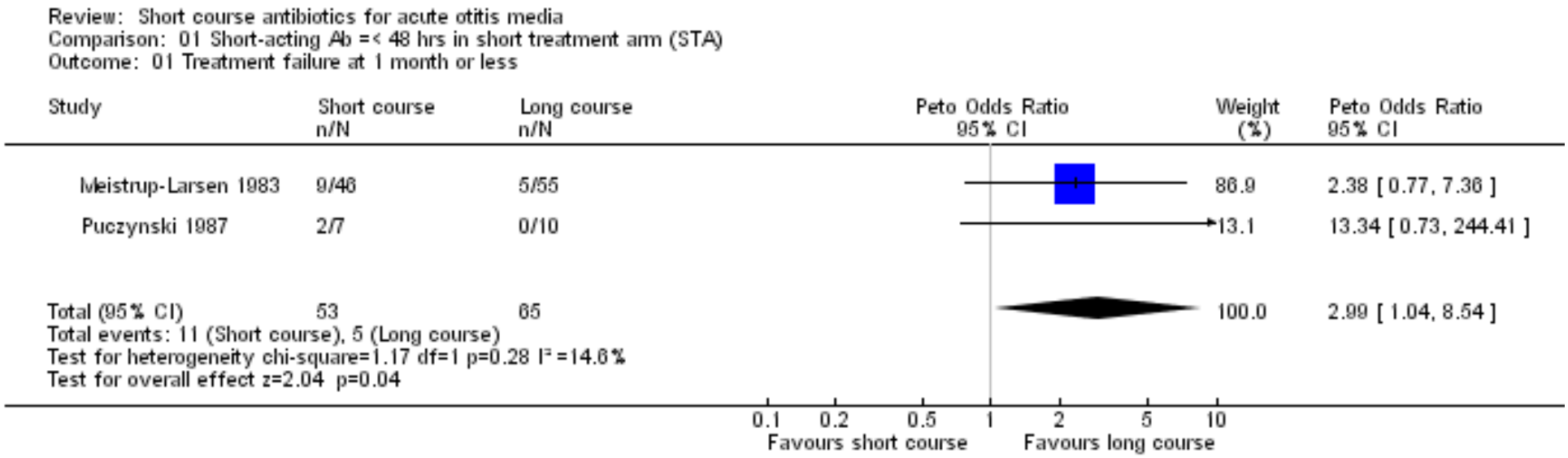
Cochrane: Acute Otitis Media

- 32 randomized studies
  - 8115 children aged 4 weeks - 18 years
- Clinical diagnosis AOM
- No AB at inclusion in study
- Randomization between “short” and “long” treatment duration

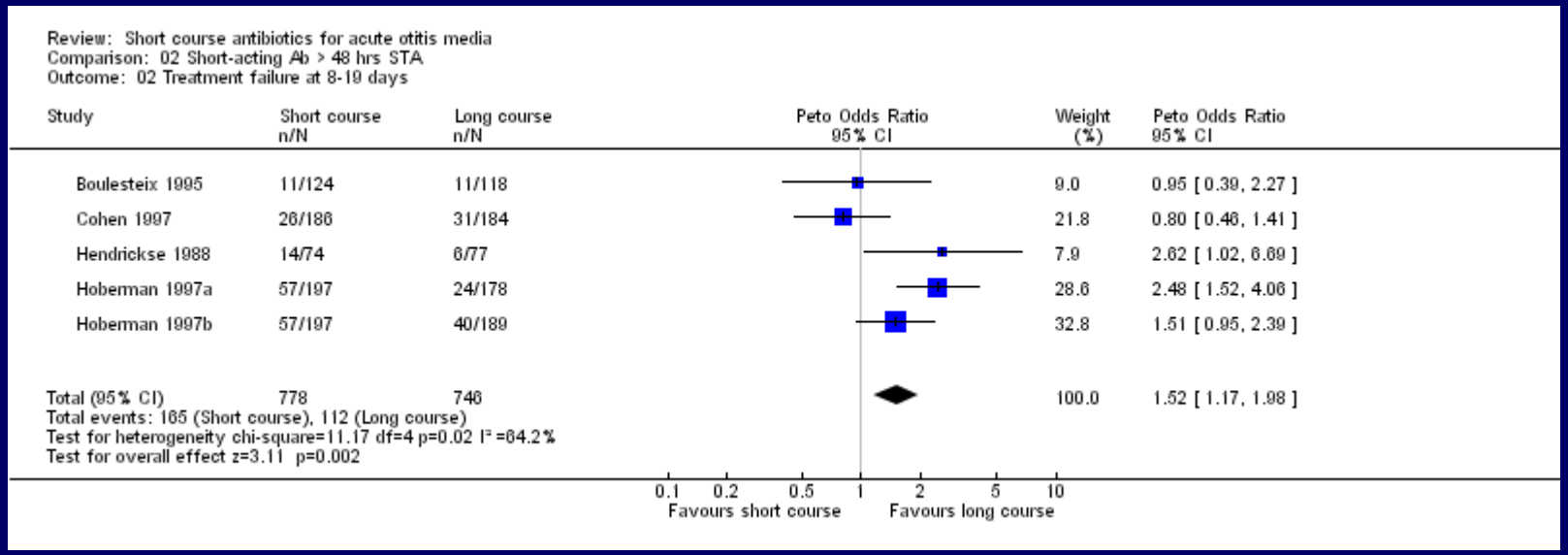
Cochrane 2000

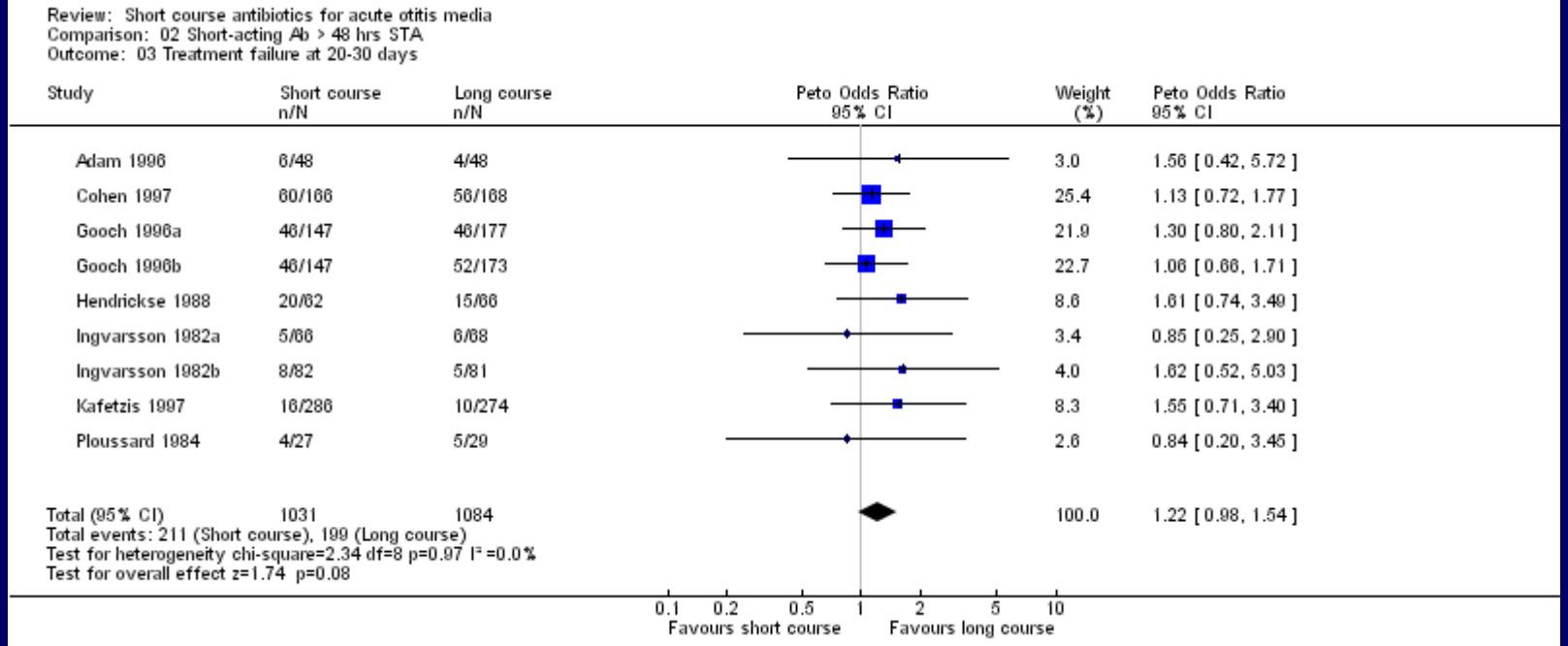
- Therapy:
  - amoxi, peni, cefuroxime, cefaclor
  - oral azytromicin
  - i.m. ceftriaxone

Acute Otitis Media
< 48 h versus ≥ 7 days

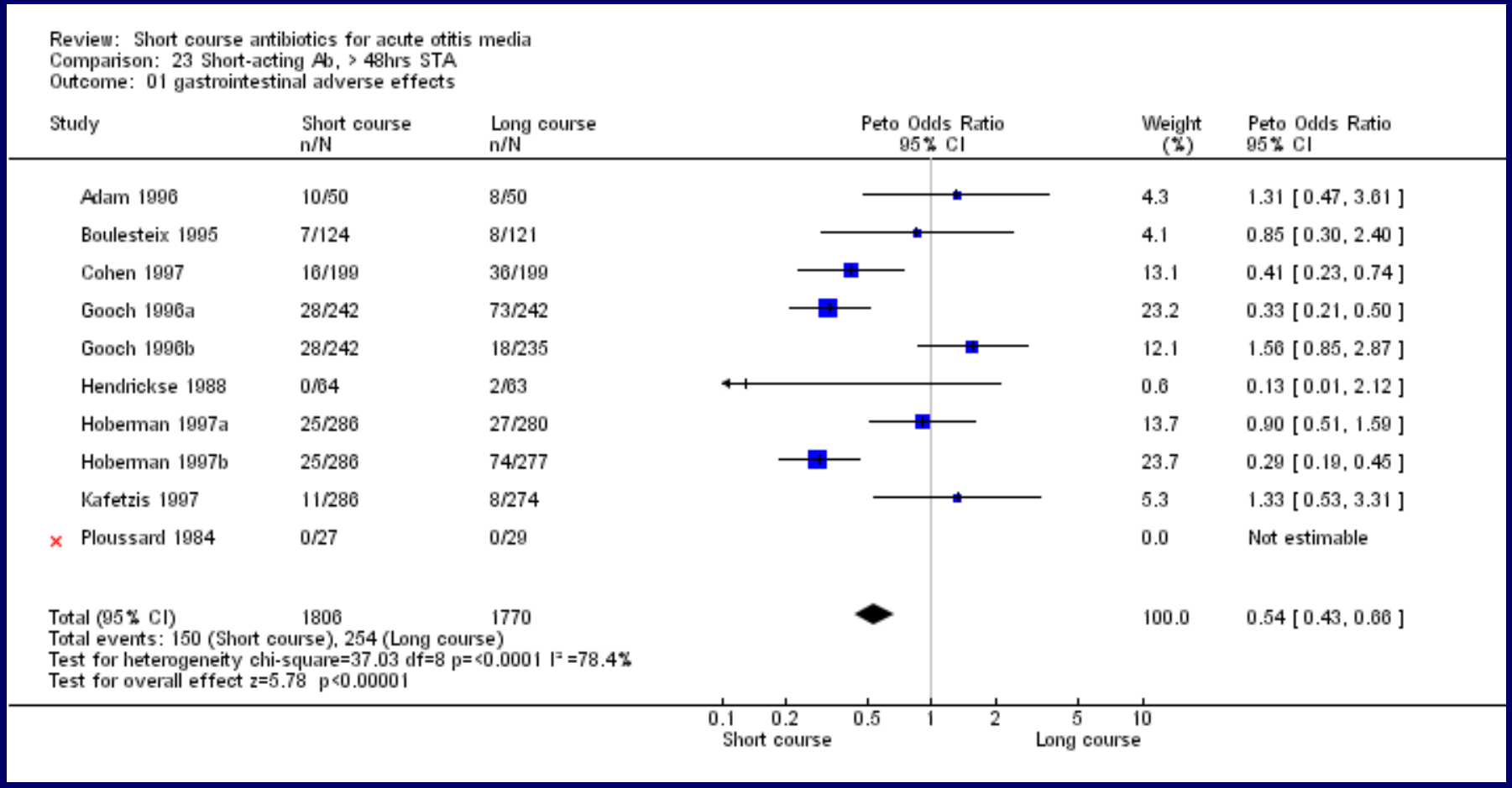


≤ 5 days versus ≥ 7 days





Side effects

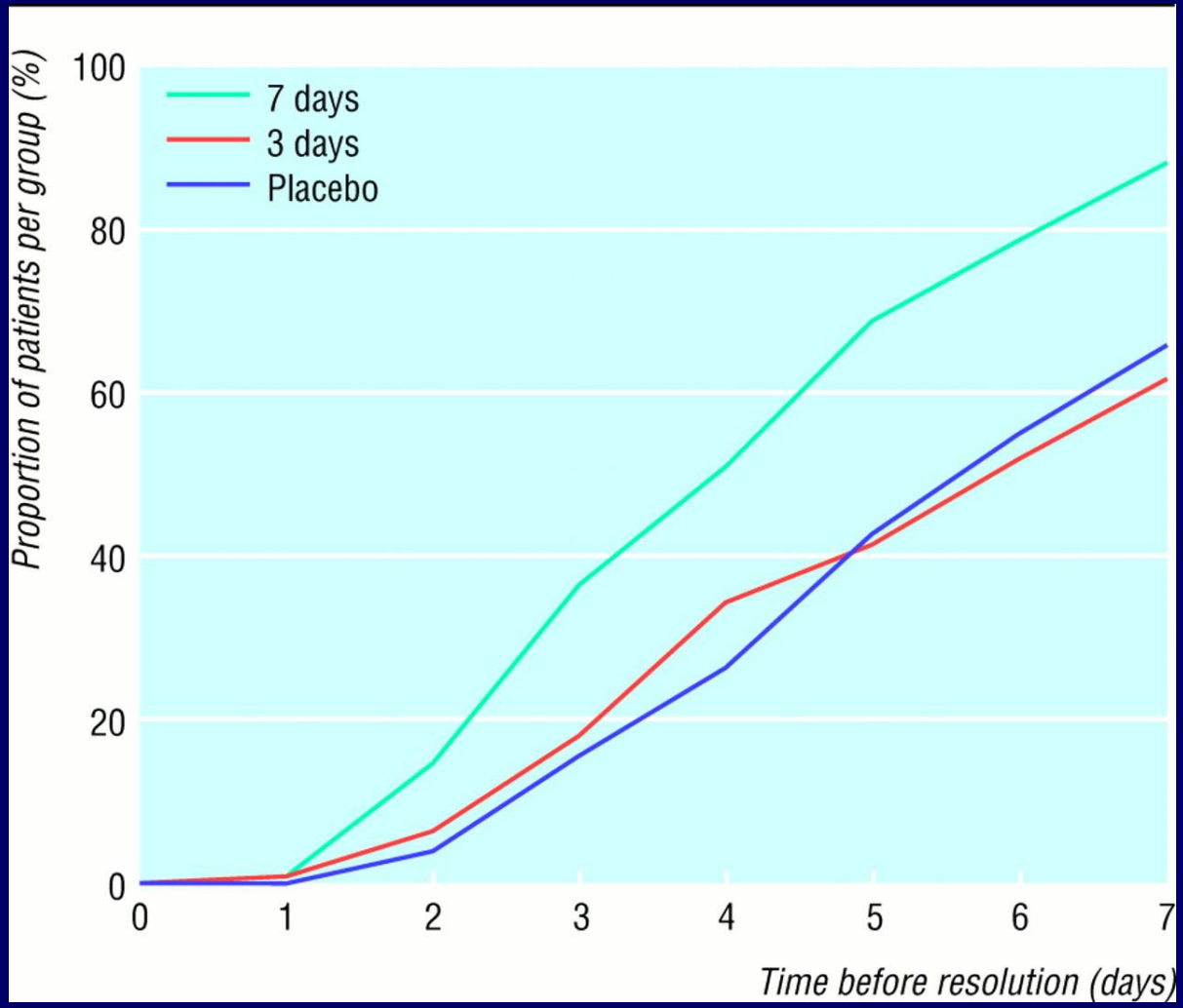


Tonsillo-pharyngitis

- Most important bacterial cause:

  β-hemolytic streptococcus

Kaplan-Meier plot for resolution of symptoms of sore throat in patients treated with penicillin for seven days, three days or placebo



Zwart S, BMJ 2000;320(7228):150-4.

Meta-analysis

- 22 randomized trials, 7470 patients:
  - Cephalosporin in short arm (n=14 trials)
  - Macrolide in short arm (n = 6 trials)
  - Penicillin in short arm (n = 2 trials)

Pediatric Infectious Disease Journal 2005; 24(10):909-917.

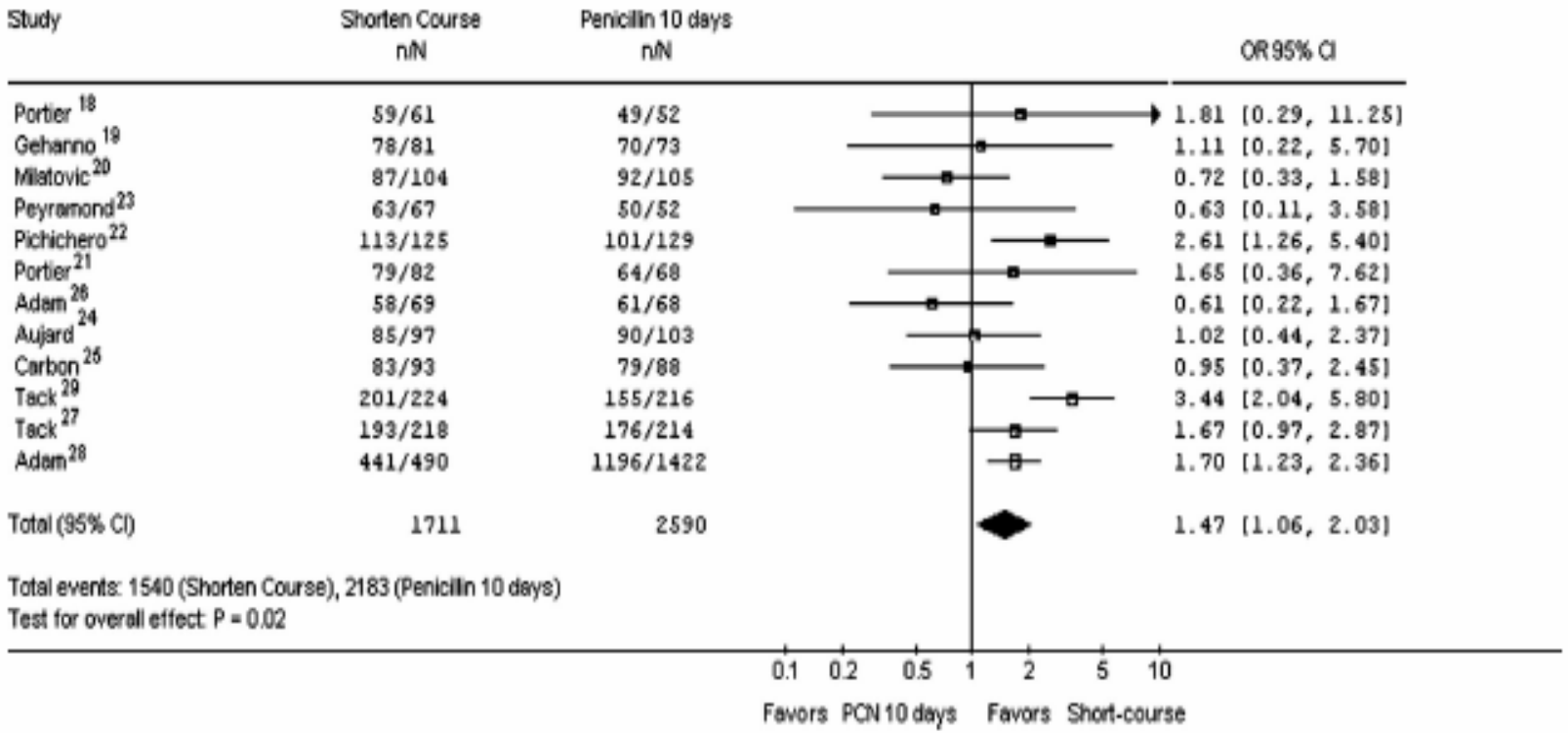


FIGURE 1. Short course cephalosporin therapy versus 10 days penicillin therapy for GAS tonsillopharyngitis. Bacterial cure rate.

- Short course of cephalosporin is superior to long course of penicillin
- Short course of macrolides equally effective as long course of penicillin
- Short course of penicillin is inferior

Why does penicillin fail?

- Inactivation by co-pathogens in pharynx
- Non-compliance
- Resistance?

Meta-analysis chronic bronchitis and COPD

Criteria

- Patients ≥ 18 years
- Type 1 or 2 exacerbation of chronic bronchitis, COPD or emphysema
- No antibiotics at diagnosis
- Antibiotic therapy ≤ 5 days vs > 5 days
- Double-blind

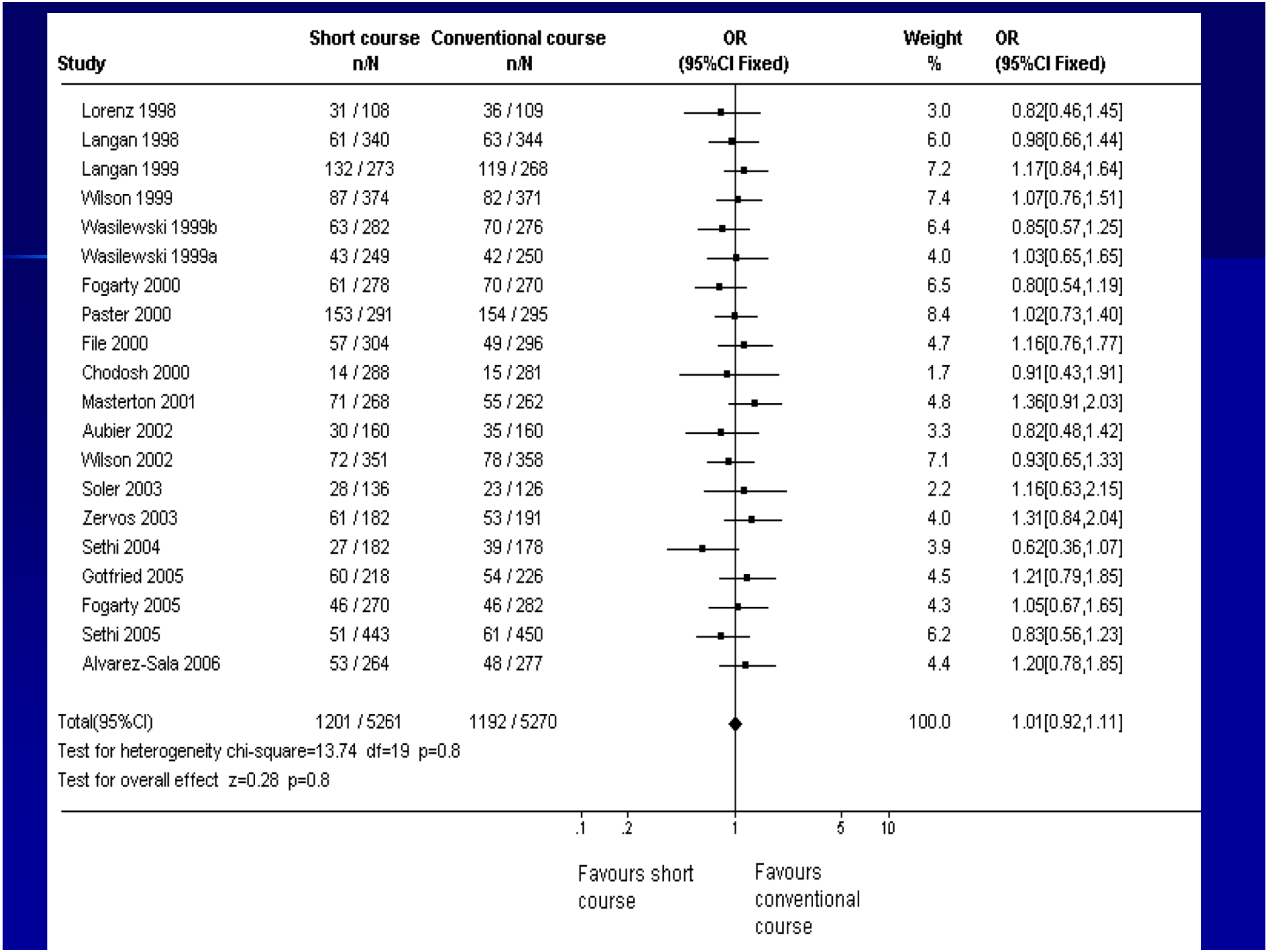
El Moussaoui R, et al. submitted

Primary outcome

- Clinical failure during early follow-up

Secundary outcomes

- Clinical failure at late follow-up
- Bacteriological failure


Study
Short course n/N
Conventional course n/N
OR (95%CI Fixed)
Weight %
OR (95%CI Fixed)
Lorenz 1998 31 / 108 36 / 109 3.0 0.82[0.46,1.45]
Langan 1998 61 / 340 63 / 344 6.0 0.98[0.66,1.44]
Langan 1999 132 / 273 119 / 268 7.2 1.17[0.84,1.64]
Wilson 1999 87 / 374 82 / 371 7.4 1.07[0.76,1.51]
Wasilewski 1999b 63 / 282 70 / 276 6.4 0.85[0.57,1.25]
Wasilewski 1999a 43 / 249 42 / 250 4.0 1.03[0.65,1.65]
Fogarty 2000 61 / 278 70 / 270 6.5 0.80[0.54,1.19]
Paster 2000 153 / 291 154 / 295 8.4 1.02[0.73,1.40]
File 2000 57 / 304 49 / 296 4.7 1.16[0.76,1.77]
Chodosh 2000 14 / 288 15 / 281 1.7 0.91[0.43,1.91]
Masterton 2001 71 / 268 55 / 262 4.8 1.36[0.91,2.03]
Aubier 2002 30 / 160 35 / 160 3.3 0.82[0.48,1.42]
Wilson 2002 72 / 351 78 / 358 7.1 0.93[0.65,1.33]
Soler 2003 28 / 136 23 / 126 2.2 1.16[0.63,2.15]
Zervos 2003 61 / 182 53 / 191 4.0 1.31[0.84,2.04]
Sethi 2004 27 / 182 39 / 178 3.9 0.62[0.36,1.07]
Gotfried 2005 60 / 218 54 / 226 4.5 1.21[0.79,1.85]
Fogarty 2005 46 / 270 46 / 282 4.3 1.05[0.67,1.65]
Sethi 2005 51 / 443 61 / 450 6.2 0.83[0.56,1.23]
Alvarez-Sala 2006 53 / 264 48 / 277 4.4 1.20[0.78,1.85]
Total(95%CI) 1201 / 5261 1192 / 5270 100.0 1.01[0.92,1.11]
Test for heterogeneity chi-square=13.74 df=19 p=0.8
Test for overall effect z=0.28 p=0.8
.1
.2
1
5
10
Favours short course
Favours conventional course

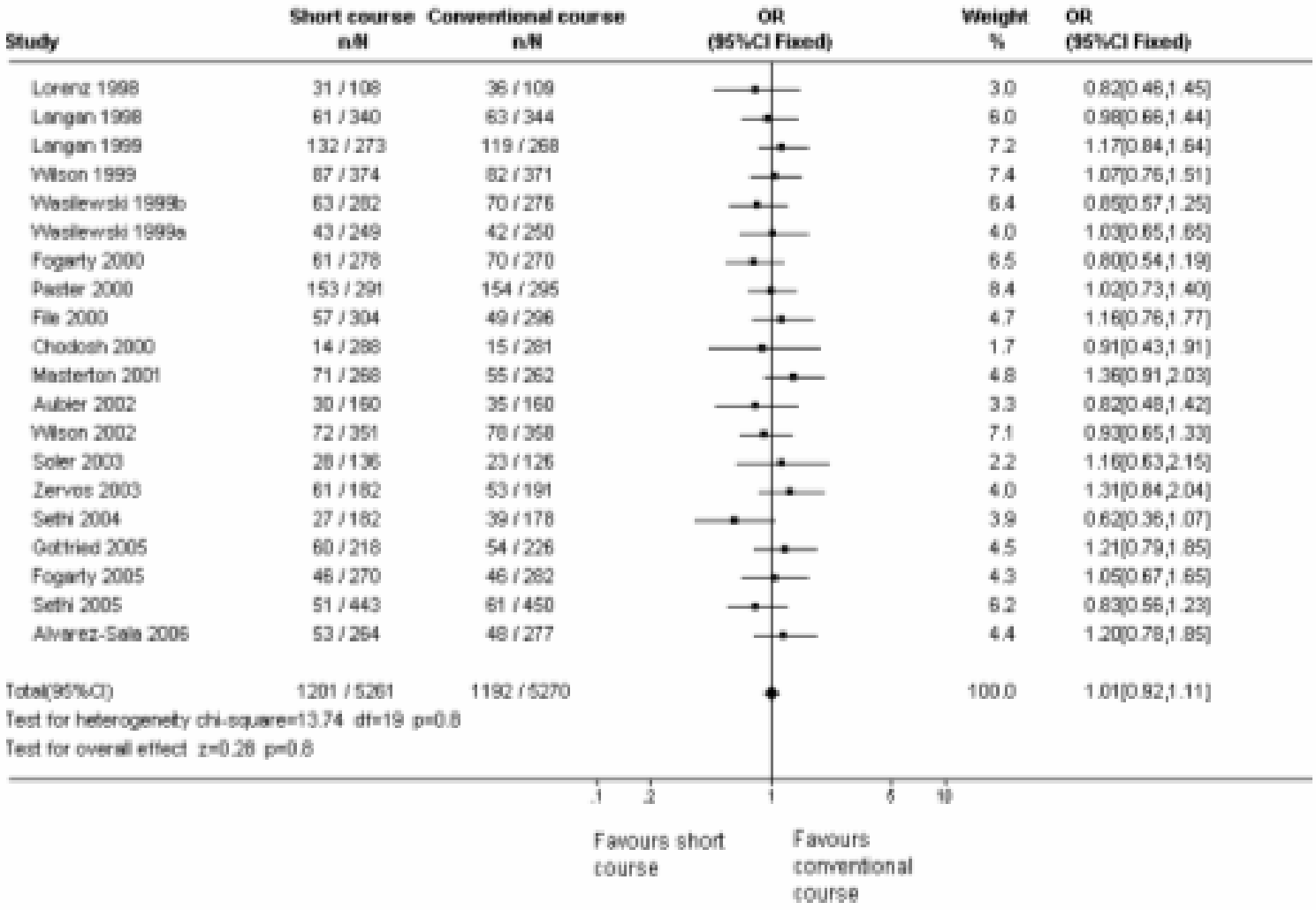


Figure 2 Clinical failure at early follow-up

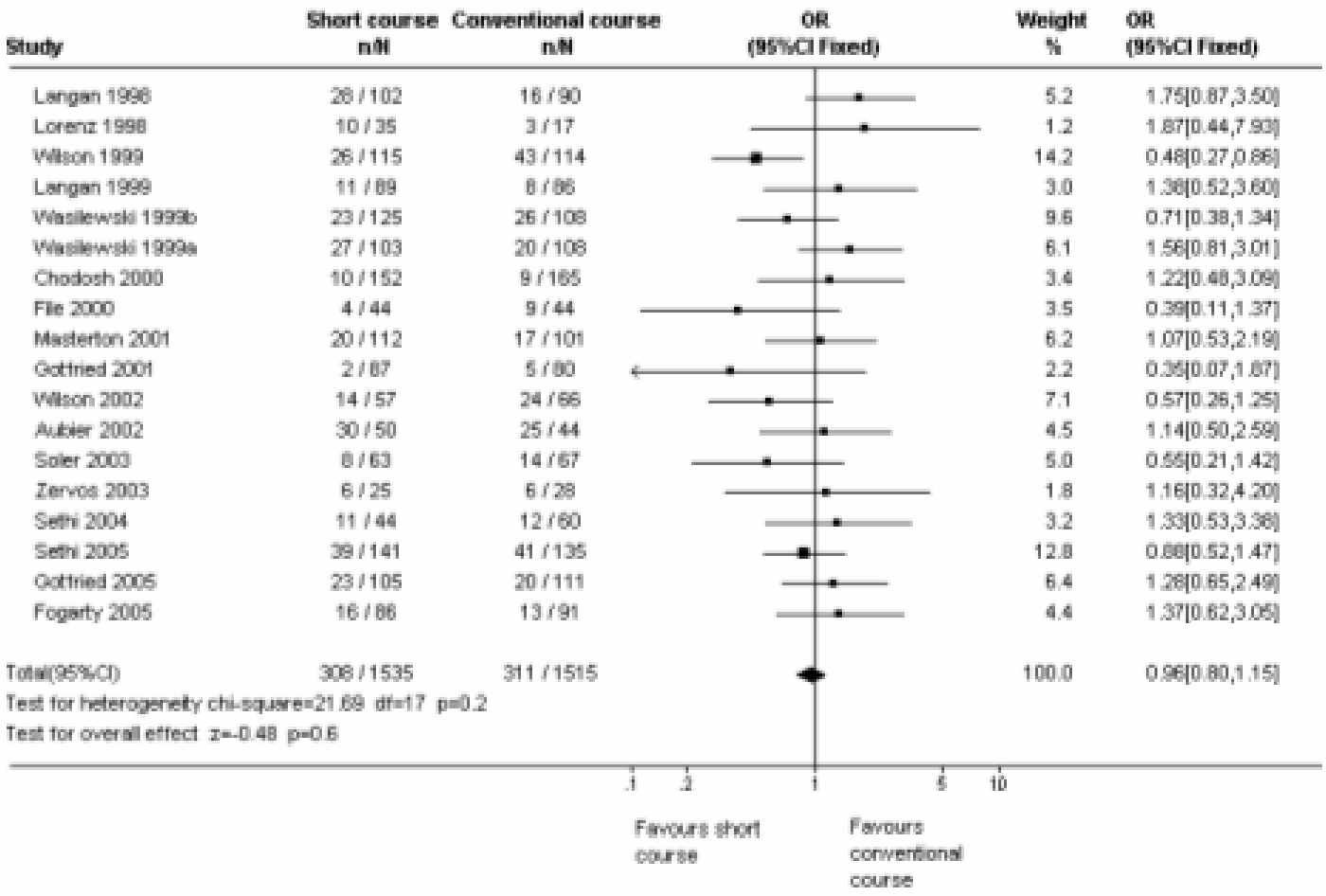
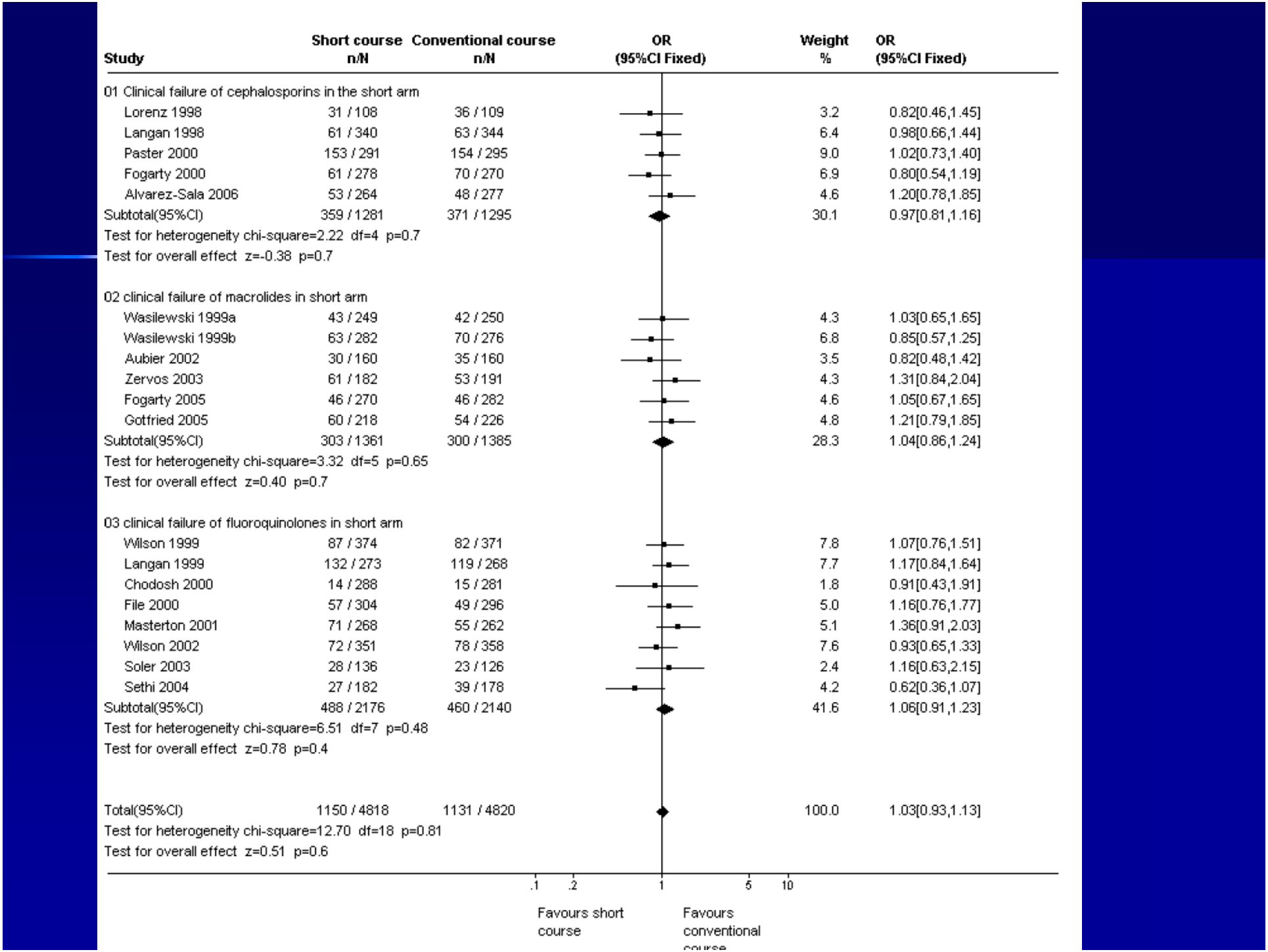


Figure 3 Bacteriological failure


Study
Short course n/N
Conventional course n/N
OR (95%CI Fixed)
Weight %
OR (95%CI Fixed)
01 Clinical failure of cephalosporins in the short arm
Lorenz 1998 31 / 108 36 / 109 3.2 0.82[0.46,1.45]
Langan 1998 61 / 340 63 / 344 6.4 0.98[0.66,1.44]
Paster 2000 153 / 291 154 / 295 9.0 1.02[0.73,1.40]
Fogarty 2000 61 / 278 70 / 270 6.9 0.80[0.54,1.19]
Alvarez-Sala 2006 53 / 264 48 / 277 4.6 1.20[0.78,1.85]
Subtotal(95%CI) 359 / 1281 371 / 1295 30.1 0.97[0.81,1.16]
Test for heterogeneity chi-square=2.22 df=4 p=0.7
Test for overall effect z=-0.38 p=0.7
02 clinical failure of macrolides in short arm
Wasilewski 1999a 43 / 249 42 / 250 4.3 1.03[0.65,1.65]
Wasilewski 1999b 63 / 282 70 / 276 6.8 0.85[0.57,1.25]
Aubier 2002 30 / 160 35 / 160 3.5 0.82[0.48,1.42]
Zervos 2003 61 / 182 53 / 191 4.3 1.31[0.84,2.04]
Fogarty 2005 46 / 270 46 / 282 4.6 1.05[0.67,1.65]
Gotfried 2005 60 / 218 54 / 226 4.8 1.21[0.79,1.85]
Subtotal(95%CI) 303 / 1361 300 / 1385 28.3 1.04[0.86,1.24]
Test for heterogeneity chi-square=3.32 df=5 p=0.65
Test for overall effect z=0.40 p=0.7
03 clinical failure of fluoroquinolones in short arm
Wilson 1999 87 / 374 82 / 371 7.8 1.07[0.76,1.51]
Langan 1999 132 / 273 119 / 268 7.7 1.17[0.84,1.64]
Chodosh 2000 14 / 288 15 / 281 1.8 0.91[0.43,1.91]
File 2000 57 / 304 49 / 296 5.0 1.16[0.76,1.77]
Masterton 2001 71 / 268 55 / 262 5.1 1.36[0.91,2.03]
Wilson 2002 72 / 351 78 / 358 7.6 0.93[0.65,1.33]
Soler 2003 28 / 136 23 / 126 2.4 1.16[0.63,2.15]
Sethi 2004 27 / 182 39 / 178 4.2 0.62[0.36,1.07]
Subtotal(95%CI) 488 / 2176 460 / 2140 41.6 1.06[0.91,1.23]
Test for heterogeneity chi-square=6.51 df=7 p=0.48
Test for overall effect z=0.78 p=0.4
Total(95%CI) 1150 / 4818 1131 / 4820 100.0 1.03[0.93,1.13]
Test for heterogeneity chi-square=12.70 df=18 p=0.81
Test for overall effect z=0.51 p=0.6
.1
.2
1
5
10
Favours short course
Favours conventional course

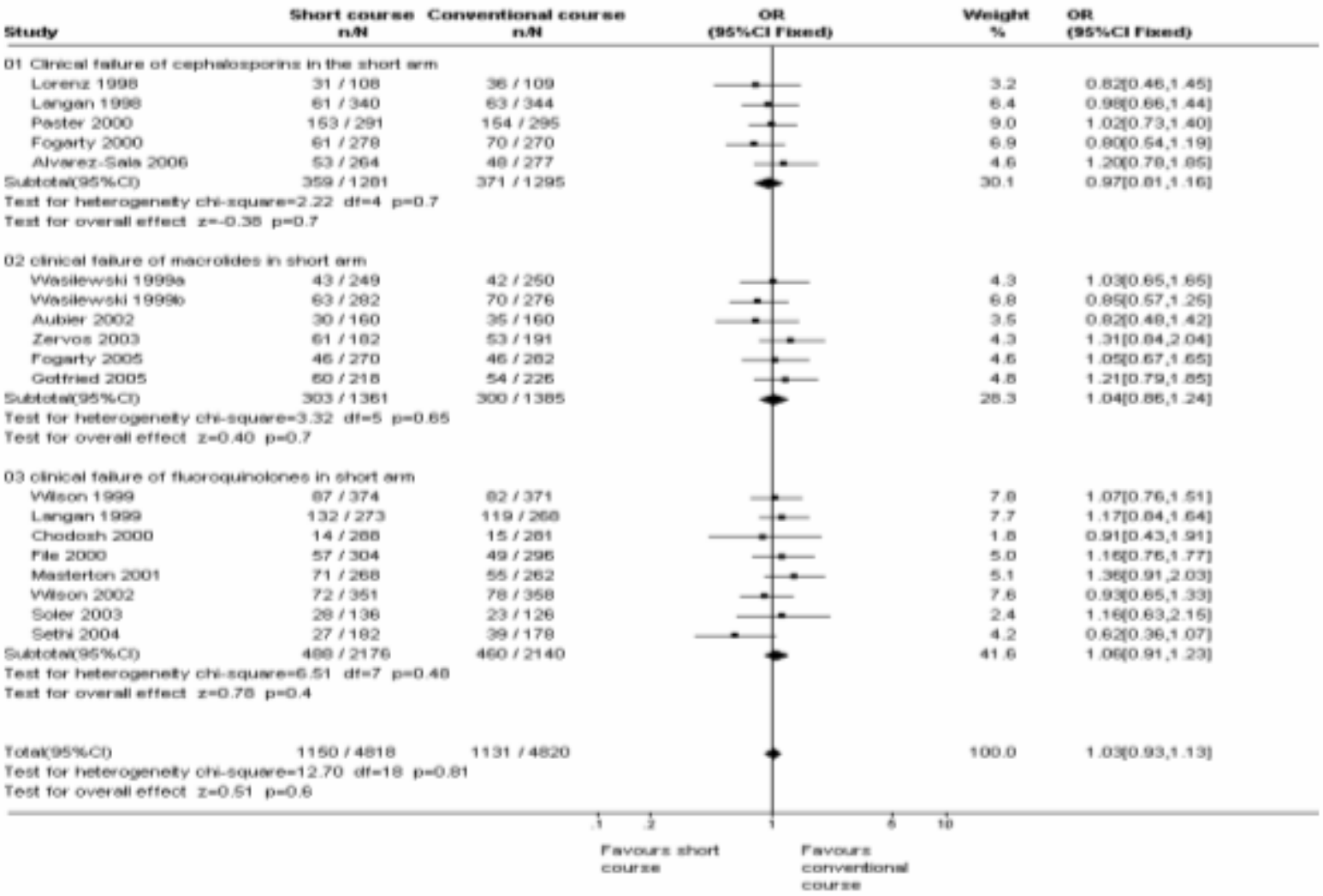


Figure 4 Clinical failure of studies grouped by the antibiotic class

Conclusion meta-analysis:

- Short antibiotic therapy (≤ 5 d) as effective as "traditional" long therapy (> 5 d) in the treatment of type 1 or 2 exacerbations:

- 'Clinical cure rates' comparable
  - at early follow-up
  - at late follow-up
  - including bacteriological failure rate

Pneumonia

Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial

*Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group**

Summary

Background For most infections, especially acute respiratory infections (ARIs), the recommended duration of therapy is not based on strong scientific or clinical criteria. Shorter courses of antibiotics for non-severe pneumonia would result in lower costs, enhance patient compliance, and might help to contain antimicrobial resistance. We aimed to compare the clinical efficacy of 3-day and 5-day courses of amoxicillin in children with non-severe pneumonia.

Methods We recruited 2000 children, aged 2–59 months, with non-severe pneumonia (WHO criteria) diagnosed in the outpatient departments of seven hospitals. Patients were randomly assigned to 3 days or 5 days of treatment with oral amoxicillin. The primary outcome was treatment failure.

Introduction

Pneumonia is one of the major causes of death in children aged younger than 5 years in less-developed countries.[1] To reduce the number of people dying from pneumonia, WHO developed standard guidelines[2] for management of patients with this disease. These guidelines have been used widely in several less-developed countries for many years and recommend 5 days of oral co-trimoxazole or amoxicillin for treatment of non-severe pneumonia. This recommendation is based on data from less-developed countries, which show that *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causes of bacterial pneumonia.[3] These guidelines have effectively reduced death from pneumonia in less-developed countries.[4]

Conventionally, antibiotics are continued until the patient no longer has a fever or laboratory measurements of

Lancet 2002;360:835-41

Conclusion: percentage failures (21% vs 20%) and relapses (1%) in both arms comparable

Research

BMJ

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

Abstract

Objective To compare the effectiveness of discontinuing treatment with amoxicillin after three days or eight days in adults admitted to hospital with mild to moderate-severe community acquired pneumonia who substantially improved after an initial three days' treatment.

Design Randomised, double blind, placebo controlled

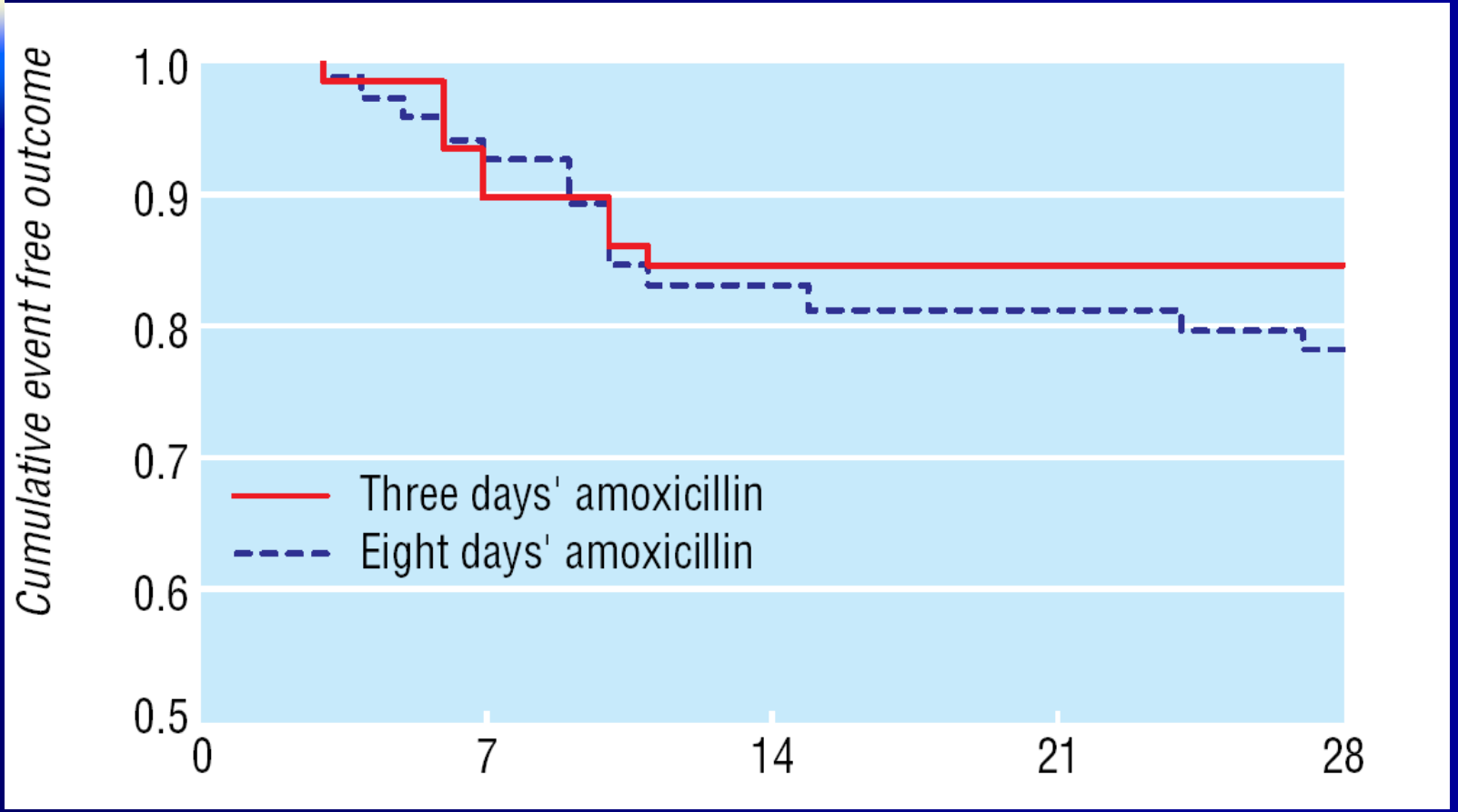
7-10 days for uncomplicated pneumonia is not based on scientific evidence but has nevertheless gained acceptance over the years. Two older studies in adults have suggested that a significantly shorter duration than 7-10 days might be justified.[4 5] These studies do not, however, meet the required standards of clinical trials.

If a shorter duration of therapy is equally effective, this can be of major importance in decreasing antibiotic consumption. On a

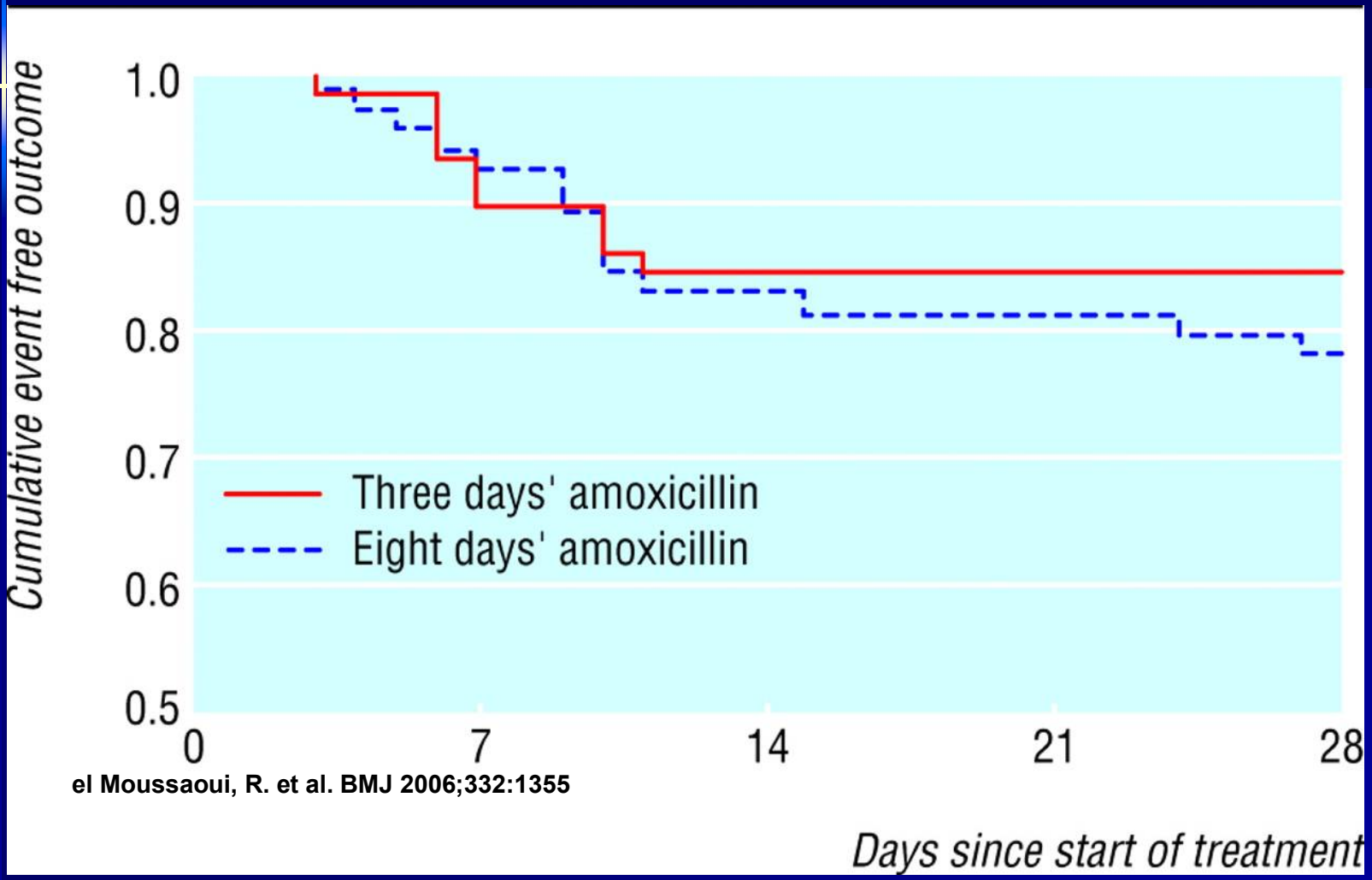
Inclusion criteria

- Adult patients ≥ 18 years
- Clinical signs of pneumonia
- Radiological evidence of a new infiltrate
- Pneumonia severity score (Fine) ≤110

Proportion of patients considered clinical successes in intention to treat population



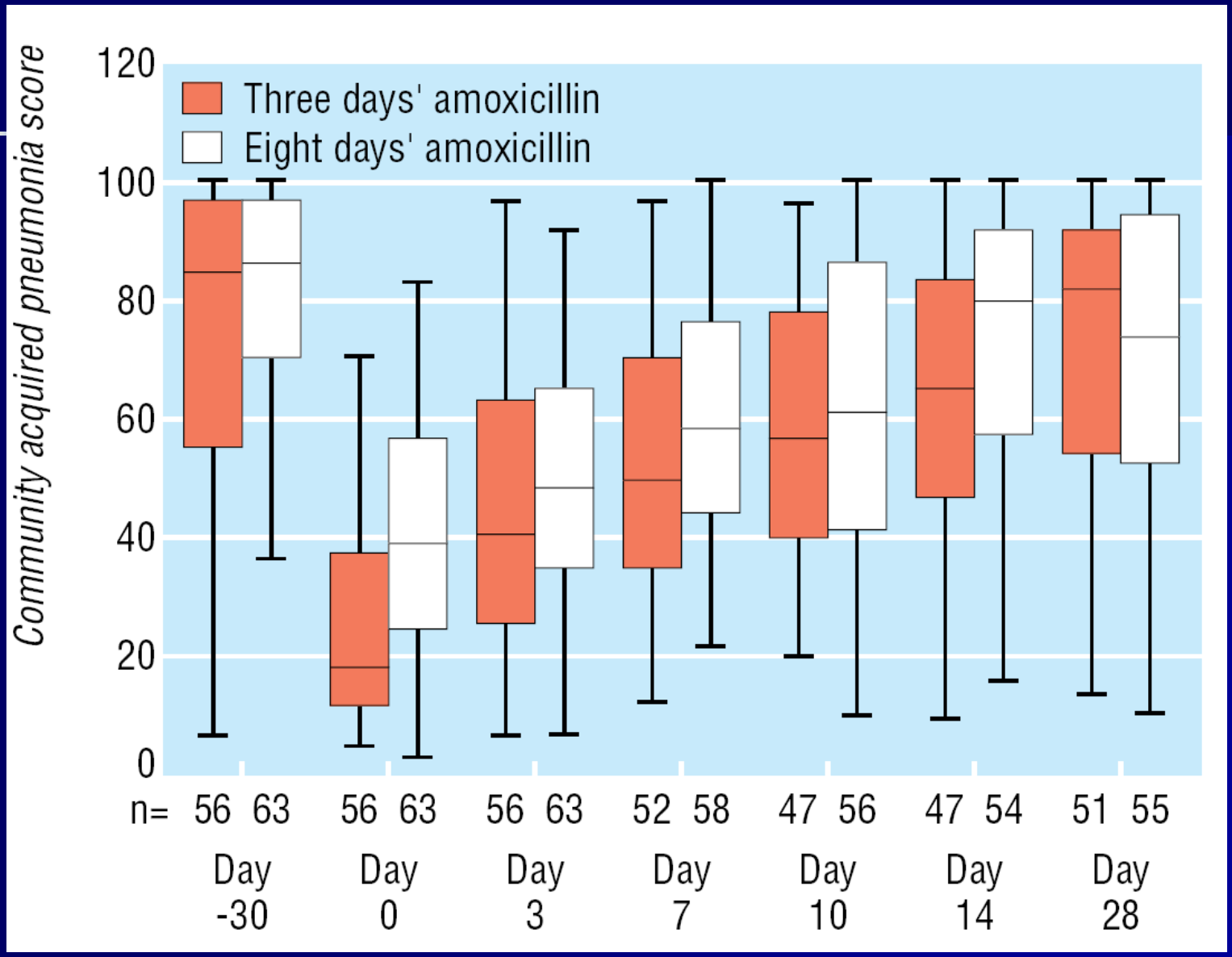
Proportion of patients considered clinical successes in intention to treat population



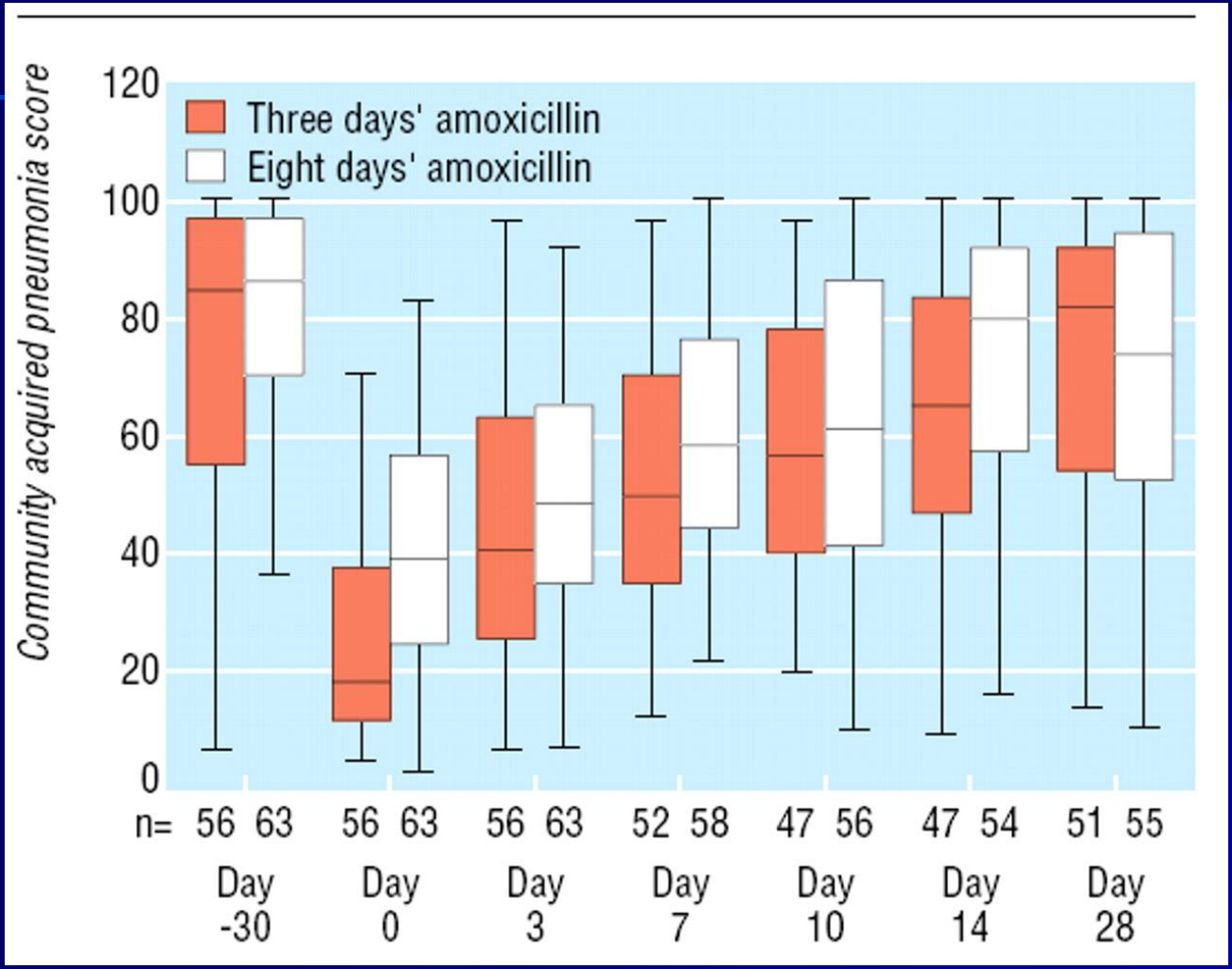
el Moussaoui, R. et al. BMJ 2006;332:1355

bmj.com

CAP-scores during treatment and follow-up



CAP-scores during treatment and follow-up



el Moussaoui, R. et al. BMJ 2006;332:1355

Conclusions

"Short" therapy justified in:

Acute otitis media

Tonsillo-pharyngitis

Exacerbations chronic bronchitis and COPD

Conclusions

- Finish the course: not to prevent resistance
- Finish the course: to prevent relapse
- But look for minimal effective treatment duration