# Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial

*S L Kenyon, D J Taylor, W Tarnow-Mordi, for the ORACLE Collaborative Group**


## Summary

**Background** Preterm birth after spontaneous preterm labour is associated with death, neonatal disease, and long-term disability. Previous small trials of antibiotics for spontaneous preterm labour have reported inconclusive results. We did a randomised multicentre trial to resolve this issue.

**Methods** 6295 women in spontaneous preterm labour with intact membranes and without evidence of clinical infection were randomly assigned 250 mg erythromycin (n=1611), 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid; n=1550), both (n=1565), or placebo (n=1569) four times daily for 10 days or until delivery, whichever occurred earlier. The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital. Analysis was by intention to treat.

**Findings** None of the trial antibiotics was associated with a lower rate of the composite primary outcome than placebo (erythromycin 90 [5·6%], co-amoxiclav 76 [5·0%], both antibiotics 91 [5·9%], *vs* placebo 78 [5·0%]). However, antibiotic prescription was associated with a lower occurrence of maternal infection.

**Interpretation** This trial provides evidence that antibiotics should not be routinely prescribed for women in spontaneous preterm labour without evidence of clinical infection.


*Lancet* 2001; **357:** 989–94
*See Article page 979*
*See Commentary page 973*

*Members listed in *Lancet* 2001; **357:** 981–90
**Correspondence to:** Sara Kenyon, Department of Obstetrics and Gynaecology, Robert Kilpatrick Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK
(e-mail: oracle@le.ac.uk)

## Introduction

The annual number of preterm births worldwide is estimated at nearly 13 million,[1] of which about a third result from uncomplicated spontaneous preterm labour.[2] Preterm birth is the major cause of neonatal morbidity and mortality, and results in 75–90% of all neonatal deaths not due to lethal congenital malformation, and 50% of childhood neurological disabilities, including cerebral palsy, blindness, and deafness.[3]

Observational evidence suggests that subclinical infection is implicated in the genesis of spontaneous preterm labour. This evidence comes from systemic, intrauterine, and intracervical inoculation studies in pregnant animals,[4,5] from case-control and cohort studies of cervicovaginal microbial colonisation in women with preterm labour, and from the higher rate of histological chorioamnionitis found after spontaneous preterm labour and birth.[6–8] Additionally, microbiological cultures of amniotic fluid taken from women presenting with spontaneous preterm labour have shown that microbial pathogens are present in about 10–15% of cases.[9] The organisms that have the strongest associations with spontaneous preterm labour are *Gardnerella vaginalis*, *Ureaplasma urealyticum*, and the sexually transmitted organisms *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Other organisms such as group B streptococci, *Escherichia coli*, *Klebsiella* spp, *Haemophilus influenzae*, and *Mycoplasma hominis* have also been implicated in the genesis of spontaneous preterm labour. Treatment of pregnant women in spontaneous preterm labour with antibiotics could therefore prolong pregnancy, thereby reducing the frequency of preterm birth and the consequences of prematurity.

A Cochrane meta-analysis[10] of the use of antibiotics on pregnant women in spontaneous preterm labour showed a mixed pattern of results—ie, a decrease in necrotising enterocolitis and trends towards longer time to delivery and reductions in neonatal sepsis and intraventricular haemorrhage, but a trend towards increases in respiratory distress syndrome and perinatal mortality. Additionally, there is debate about whether β-lactam or macrolide antibiotics should be prescribed in this clinical situation. To resolve these uncertainties, we did a randomised trial of antibiotics for spontaneous preterm labour.

## Methods

We enrolled women at less than 37 weeks' gestation who were in suspected or definite preterm labour with intact fetal membranes and in whom there was substantial uncertainty as to whether antibiotics should be prescribed. Since there is no agreed definition of preterm labour or a reliable method of diagnosing it, the diagnosis of labour was left to the clinician caring for the woman. This situation is characteristic of normal clinical practice, and ensured that the results of the trial could be implemented and incorporated into clinical care. Women were randomly assigned to one of four possible treatments: 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid) plus 250 mg erythromycin; co-amoxiclav plus erythromycin placebo; erythromycin plus co-



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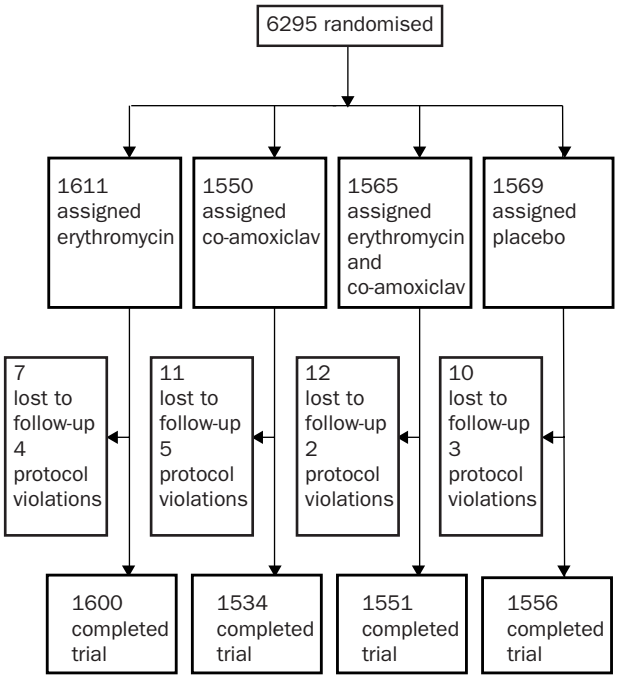


**Trial profile**

amoxiclav placebo; or co-amoxiclav placebo plus erythromycin placebo. Reasons for exclusion of patients, method of randomisation, data collection, compliance, comparisons, and statistical methods were the same as for a concurrent trial of the same antibiotics for preterm, pre-labour rupture of the fetal membranes (see page 981).[11]

Some characteristics of the women enrolled were collected: maternal age, gestational age at randomisation, cervical dilatation, and drugs prescribed (β-agonists, corticosteroids, indomethacin, nifedipine, others). No data about past obstetric history and other fetal or maternal disease were collected.

We used a composite primary outcome measure of neonatal death, major adverse outcome—ie, chronic lung disease (defined as receipt of daily supplementary oxygen at 36 weeks post conception), or major cerebral abnormality on ultrasonography before discharge from hospital. These outcomes were also analysed individually.

| | Erythromycin only (n=1600) | Co-amoxiclav only (n=1534) | Erythromycin and co-amoxiclav (n=1551) | Placebo only (n=1556) |
|---|---|---|---|---|
| **Mean (SD) age (years)** | 26·5 (6·1) | 26·1 (5·7) | 26·3 (5·7) | 26·7 (5·7) |
| **Gestational age at entry** | | | | |
| Median (range) gestation (days) | 219 (137–258) | 219 (139–256) | 220 (144–258) | 219 (126–258) |
| <26 weeks | 133 (8·3%) | 121 (7·9%) | 140 (9·0%) | 114 (7·3%) |
| 26–28 weeks | 287 (17·9%) | 301 (19·6%) | 265 (17·1%) | 313 (20·1%) |
| 29–31 weeks | 494 (30·9%) | 456 (29·7%) | 478 (30·8%) | 468 (30·1%) |
| 32–36 weeks | 745 (46·6%) | 698 (45·5%) | 735 (47·4%) | 718 (46·1%) |
| **Cervical dilatation (cm)** | | | | |
| Unknown | 292 (18·3%) | 254 (16·6%) | 274 (17·7%) | 277 (17·8%) |
| 0–1 | 885 (55·3%) | 839 (54·7%) | 907 (58·5%) | 894 (57·5%) |
| >1–2 | 252 (15·8%) | 284 (18.5%) | 236 (15·2%) | 241 (15·5%) |
| >2 | 171 (10·7%) | 157 (10·2%) | 134 (8·6%) | 144 (9·3%) |
| **Drugs prescribed** | | | | |
| β-agonists | 671 (41·9%) | 648 (42·2%) | 624 (40·2%) | 634 (40·7%) |
| Steroids | 1246 (77·9%) | 1251 (81·6%) | 1248 (80·5%) | 1277 (82·1%) |
| Indomethacin | 143 (8·9%) | 139 (9·1%) | 144 (9·3%) | 143 (9·2%) |
| Nifedipine | 95 (5·9%) | 105 (6·8%) | 98 (6·3%) | 101 (6·5%) |
| Others | 190 (11·9%) | 197 (12·8%) | 209 (15·5%) | 204 (13·1%) |

Table 1: **Baseline characteristics**

The secondary outcome measures were: delivery within 48 h; delivery within 7 days; mode of delivery; number of days in hospital; maternal antibiotic prescription after delivery and before discharge (total and within 14 days of randomisation); gestational age at delivery; birthweight less than 2500 g or less than 1500 g; admission to a neonatal intensive-care unit or special-care baby unit; total number of babies ventilated; total number of babies in more than 21% oxygen at 48 h, 7 days, 14 days, and 28 days of age; respiratory distress syndrome confirmed by chest radiography; treatment with exogenous surfactant; oxygen dependence at more than 28 days of age; positive blood culture indicative of clinical infection (total and within 14 days of randomisation); necrotising enterocolitis suspected or proven, and proven (by radiography or surgery).

The endpoint for data collection was discharge from hospital. If more than one outcome was found in a multiple pregnancy, the worst outcome was used in the analysis.

## Results

Enrolment was from July 1, 1994, until May 31, 2000. Of 6295 women randomised, 40 were lost to follow-up and there were 14 protocol violations (four were at more than 37 weeks' gestation, and ten were taking contraindicated drugs); 6241 women were therefore included in the analyses (figure). 4377 women were enrolled in the UK and 1918 from international maternity units. The data set was 100% complete within the UK and 99·3% complete overall.

The baseline characteristics in each group were similar (table 1). Gestational age at entry was about 219 days (31 weeks). On recruitment, cervical dilatation of women was usually known, and 54·9% were 0–1 cm dilated. Most women (80·5%) received corticosteroids to mature the fetal lungs. This proportion is consistent with clinical practice in the UK, where about 80% of neonates are exposed to at least one dose of corticosteroids.[12] The use of β-agonists was not as common, with 41·3% of women receiving them.

There was no evidence that use of any antibiotic regimen prolonged pregnancy, or influenced mode of delivery or stay in hospital (tables 2–4). Most women did not deliver within 48 h (89·9%) or 7 days (84·6%), which illustrates the difficulty of reliably predicting which women with a diagnosis of preterm labour will go on to deliver. There was generally less antibiotic prescription (not all of which was significant) in groups assigned any antibiotic regimen compared with placebo. This difference was significant for both antibiotics versus placebo, for any antibiotic (erythromycin alone, co-amoxiclav alone, or erythromycin plus co-amoxiclav) versus placebo (table 4), and for any co-amoxiclav versus no co-amoxiclav within 14 days of delivery (table 3). There was significantly less prescription of antibiotics for caesarean-section wound infection with erythromycin than with placebo (12 [0·8%] *vs* 23 [1·5%], p=0·05); co-amoxiclav versus placebo (11 [0·7%] *vs* 23 [1·5%], p=0·04); both antibiotics versus placebo (11 [0·7%] *vs* 23 [1·5%], p=0·04); any antibiotic versus placebo (35 [0·7%] *vs* 23 [1·5%], p=0·009); and for uterine infection with any co-amoxiclav versus no co-amoxiclav within 14 days (25 [0·8%] *vs* 44 [1·4%], p=0·03).

There were no significant differences between the groups with respect to median birthweight or number of babies admitted to neonatal intensive or special care (tables 5–7). No significant differences were detected between any antibiotic regimen for total number of babies



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| | Erythromycin only (n=1600) | Placebo only (n=1556) | p | Any erythromycin (n=3151) | No erythromycin (n=3090) | p |
|---|---|---|---|---|---|---|
| **Delivery within 48 h** | 166 (10·4%) | 152 (9·8%) | 0·57 | 326 (10·3%) | 304 (9·8%) | 0·50 |
| **Delivery within 7 days** | 253 (15·8%) | 237 (15·2%) | 0·65 | 487 (15·8%) | 474 (15·3%) | 0·90 |
| **Gestational age at delivery** | | | | | | |
| Median (range) gestation (days) | 267 (157–332) | 266 (155–313) | . . | 266 (145–322) | 266 (155–332) | . . |
| <37 weeks | 584 (36·5%) | 559 (35·9%) | 0·34 | 1142 (36·2%) | 1104 (35·7%) | 0·67 |
| <26 weeks (n %) | 23 (1·4%) | 16 (1·0%) | . . | 44 (1·4%) | 36 (1·2%) | . . |
| 26–28[6] weeks | 57 (3·6%) | 51 (3·3%) | . . | 110 (3·5%) | 99 (3·2%) | . . |
| 29–31[6] weeks | 91 (5·7%) | 82 (5·3%) | . . | 164 (5·2%) | 173 (5·6%) | . . |
| 32–36[6] weeks | 413 (25·8%) | 410 (26·3%) | 0·68 | 824 (26·2%) | 796 (25·8%) | 0·69 |
| **Mode of delivery** | | | | | | |
| Spontaneous vaginal | 1159 (72·4%) | 1085 (69·7%) | . . | 2238 (71·0%) | 2206 (71·4%) | . . |
| Forceps/Ventouse | 91 (5·7%) | 113 (7·3%) | . . | 196 (6·2%) | 208 (6·7%) | . . |
| Vaginal breech | 21 (1·3%) | 17 (1·1%) | . . | 40 (1·3%) | 33 (1·1%) | . . |
| Caesarean section | 329 (20·6%) | 341 (21·9%) | 0·18 | 677 (21·5%) | 643 (20·8%) | 0·67 |
| **Median (range) days in hospital** | 3 (0–61) | 3 (0–77) | 0·25 | 3 (0–61) | 3 (0–77) | 0·74 |
| **Maternal antibiotic prescription** | 156 (9·8%) | 183 (11·8%) | 0·07 | 292 (9·3%) | 324 (10·5%) | 0·11 |
| **Maternal antibiotic prescription within 14 days** | 56 (3·5%) | 62 (4·0%) | 0·36 | 95 (3·0%) | 105 (3·4%) | 0·39 |

[6]Number of days

Table 2: **Maternal outcomes of women with preterm labour randomly assigned erythromycin**

ventilated, for total number of babies in more than 21% oxygen, for the number of babies in more than 21% oxygen at 48 h, 7 days, 14 days, and 28 days of age, for reported respiratory distress syndrome, or for treatment with exogenous surfactant (tables 5–7).

The rate of oxygen dependence at 36 weeks post conception was higher with the use of any erythromycin than with no erythromycin (table 5). The other measure of chronic lung disease—ie, oxygen dependence at more than 28 days of age—did not show this difference. There were no significant differences between the groups with respect to the number of babies with a positive blood culture, either overall or if they were born within 14 days of randomisation.

There was a higher proportion of babies with suspected or proven necrotising enterocolitis or proven necrotising entercolitis for use of any co-amoxiclav versus no co-amoxiclav, although these differences were not significant (table 6).

No significant differences were detected between any antibiotic regimen for the number of babies who died or who were diagnosed as having abnormal cerebral ultrasound scans before discharge. Analysis of the effect of any antibiotic regimen on the composite primary outcome of death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital also showed no significant differences.

Subgroup analyses were done on women who were enrolled at less than 32 weeks' gestation. No significant differences between antibiotics and placebo could be found with respect to prolongation of pregnancy or the composite primary outcome (data not shown). Neither were any differences in prolongation of pregnancy or in neonatal outcomes found between antibiotics and placebo when stratified by singleton or multiple pregnancy, or by recruitment centre (UK or international).

## Discussion

The results of this trial of 6241 women indicate that neither β-lactam nor macrolide antibiotics prolong pregnancy or improve neonatal health when prescribed to women in spontaneous preterm labour with intact membranes and without clinical evidence of infection.

There are a number of possible explanations for these results including antibiotic activity, maternal compliance, timing of the intervention, post-randomisation prescription of antibiotics, and over-estimation of the role of subclinical infection in spontaneous preterm labour. The first of these possibilities is unlikely to be true because the antibiotics were

| | Co-amoxiclav only (n=1534) | Placebo only (n=1556) | p | Any co-amoxiclav (n=3085) | No co-amoxiclav (n=3156) | p |
|---|---|---|---|---|---|---|
| **Delivery within 48 h** | 152 (9·9%) | 152 (9·7%) | 0·90 | 312 (10·1%) | 318 (10·1%) | 0·96 |
| **Delivery within 7 days** | 237 (15·4%) | 237 (15·2%) | 0·87 | 471 (15·3%) | 490 (15·5%) | 0·78 |
| **Gestational age at delivery** | | | | | | |
| Median (range) gestation (days) | 267 (145–312) | 266 (155–313) | .. | 267 (145–332) | 266 (155–322) | . . |
| <37 weeks | 545 (35·5%) | 559 (35·9%) | 0·82 | 1103 (35·8%) | 1143 (36·2%) | 0·70 |
| <26 weeks | 20 (1·3%) | 16 (1·0%) | . . | 41 (1·3%) | 39 (1·2%) | . . |
| 26–28[6] weeks | 48 (3·1%) | 51 (3·3%) | . . | 101 (3·3%) | 108 (3·4%) | . . |
| 29–31[6] weeks | 91 (5·9%) | 82 (5·3%) | . . | 164 (5·3%) | 173 (5·5%) | . . |
| 32–36[6] weeks | 386 (25·2%) | 410 (26·3%) | 0·67 | 797 (25·8%) | 823 (26·0%) | 0·97 |
| **Mode of delivery** | | | | | | |
| Spontaneous vaginal | 1121 (73·1%) | 1085 (69·7%) | . . | 2200 (71·3%) | 2244 (71·1%) | . . |
| Forceps/Ventouse | 95 (6·2%) | 113 (7·3%) | . . | 202 (6·5%) | 204 (6·5%) | . . |
| Vaginal breech | 16 (1·0%) | 17 (1·1%) | . . | 35 (1·1%) | 38 (1·2%) | . . |
| Caesarean section | 302 (19·7%) | 341 (21·9%) | 0·92 | 650 (21·1%) | 670 (21·2%) | 0·35 |
| **Median (range) days in hospital** | 2 (0–76) | 3 (0–77) | 0·08 | 3 (0–76) | 3 (0–77) | 0.47 |
| **Maternal antibiotic prescription** | 141 (9·2%) | 183 (11·8%) | 0·02 | 277 (9·0%) | 339 (10·7%) | 0.02 |
| **Maternal antibiotic prescription within 14 days** | 43 (2·8%) | 62 (4·0%) | 0·07 | 84 (2·7%) | 116 (3·7%) | 0.03 |

[6]Number of days

Table 3: **Maternal outcomes of women with preterm labour randomly assigned co-amoxiclav**



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| | Erythromycin and co-amoxiclav (n=1551) | p | Placebo only (n=1556) | p | Any antibiotic* (n=4685) |
|---|---|---|---|---|---|
| **Delivery within 48 h** | 166 (10·7%) | 0·39 | 152 (9·8%) | 0·62 | 478 (10·2%) |
| **Delivery within 7 days** | 234 (15·1%) | 0·91 | 237 (15·2%) | 0·83 | 724 (15·5%) |
| **Gestation at delivery** | | | | | |
| Median (range) gestation (days) | 267 (145–312) | . . | 266 (155–313) | . . | 266 (145–332) |
| <37 weeks | 558 (36·0%) | 0·76 | 559 (35·9%) | 0·95 | 1687 (36·0%) |
| <26 weeks | 21 (1·4%) | . . | 16 (1·0%) | . . | 64 (1·4%) |
| 26–28[6] weeks | 53 (3·4%) | . . | 51 (3·3%) | . . | 158 (3·4%) |
| 29–31[6] weeks | 73 (4·7%) | . . | 82 (5·3%) | . . | 255 (5·4%) |
| 32–36[6] weeks | 411 (26·5%) | 0·74 | 410 (26·3%) | 0·74 | 1210 (25·8%) |
| **Mode of delivery** | | | | | |
| Spontaneous vaginal | 1079 (69·6%) | . . | 1085 (69·7%) | . . | 3359 (71·6%) |
| Forceps/Ventouse | 105 (6·8%) | . . | 113 (7·3%) | . . | 291 (6·2%) |
| Vaginal breech | 19 (1·2%) | . . | 17 (1·1%) | . . | 56 (1·2%) |
| Caesarean section | 348 (22·4%) | 0·92 | 341 (21·9%) | 0·35 | 979 (20·9%) |
| **Median (range) days in hospital** | 3 (0–49) | 0·17 | 3 (0–77) | 0·17 | 3 (0–76) |
| **Maternal antibiotic prescription** | 136 (8·8%) | 0·006 | 183 (11·8%) | 0·004 | 433 (9·2%) |
| **Maternal antibiotic prescription within 14 days** | 41 (2·6%) | 0·06 | 62 (4·0%) | 0·05 | 140 (3·0%) |

[6]Number of days. *Erythromycin alone, co-amoxiclav alone, or both.

Table 4: **Maternal outcomes of women with preterm labour randomly assigned both co-amoxiclav and erythromycin or any antibiotic**

specifically chosen on the basis of their activity against the micro-organisms implicated by observational studies of spontaneous preterm labour, and are effective in preterm, prelabour rupture of the membranes, in which similar micro-organisms are pathogenic.[11] Neither can the results be explained by poor maternal compliance, since the rate of maternal infection after delivery was reduced in the women taking antibiotics. The third possible explanation is that the timing of the administration of antibiotics was too late for them to have any beneficial effect—ie, when clinical symptoms and signs of labour were already established. We analysed the effect of antibiotics stratified by cervical dilatation and still could not discern any beneficial effect from antibiotics on the prolongation of pregnancy. The fourth explanation for these results is that any benefit from the trial antibiotics could have been diluted by the widespread prescription of antibiotics after randomisation. We collected data on prescription after randomisation and before 10 days or delivery (ie, within the treatment period). This information was collected by the midwives in 77 UK maternity units on all 619 women randomised over 4 months. There was inappropriate antibiotic prescription to only a 15 women (2·4%). This finding provides evidence that the results of the trial were not compromised by a dilution effect.

Therefore, the results of this trial suggest that the role played by subclinical infection in the cause of spontaneous preterm labour has been overestimated. From microbial culture studies of amniotic fluid taken by amniocentesis during spontaneous preterm labour, 10–15% of cases in deprived, urban populations, mainly from the USA, are estimated to be associated with subclinical infection.[9,13] The role of subclinical infection in spontaneous preterm labour should be reassessed in different populations.

| | Erythromycin only (n=1600) | Placebo only (n=1556) | p | Any erythromycin (n=3151) | No erythromycin (n=3090) | p |
|---|---|---|---|---|---|---|
| **Birthweight (g)** | | | | | | |
| Mean (SD) | 2823 (788) | 2857 (775) | 0·22 | 2837 (791) | 2850 (792) | 0·52 |
| Median (range) | 2950 (450–5120) | 2980 (570–5127) | . . | 2970 (275–5300) | 2970 (440–5520) | . . |
| <2500 | 468 (29·3%) | 419 (26·9%) | 0·15 | 894 (28·4%) | 867 (28·1%) | 0·78 |
| <1500 | 121 (7·6%) | 107 (6·9%) | 0·46 | 235 (7·5%) | 229 (7·4%) | 0·94 |
| **Admission to NICU/SCBU** | 424 (26·5%) | 380 (24·4%) | 0·18 | 813 (25·8%) | 783 (25·3%) | 0·67 |
| **Total babies ventilated** | 126 (7·9%) | 121 (7·8%) | 0·92 | 252 (8·0%) | 240 (7·8%) | 0·73 |
| **Total babies in >21% $O_2$** | 216 (13·5%) | 207 (13·3%) | 0·87 | 426 (13·5%) | 410 (13·3%) | 0·77 |
| At 48 h | 185 (11·6%) | 178 (11·4%) | 0·91 | 372 (11·8%) | 348 (11·0%) | 0·50 |
| At 7 days | 86 (5·4%) | 88 (5·6%) | 0·73 | 173 (5·5%) | 173 (5·6%) | 0·85 |
| At 14 days | 64 (4·0%) | 63 (4·0%) | 0·94 | 123 (3·9%) | 125 (4·0%) | 0·77 |
| At 28 days | 52 (3·3%) | 49 (3·1%) | 0·87 | 96 (3·0%) | 96 (3·1%) | 0·89 |
| **RDS confirmed by chest radiography** | 133 (8·3%) | 138 (8·9%) | 0·58 | 272 (8·6%) | 265 (8·6%) | 0·94 |
| **Treatment with exogenous surfactant** | 89 (5·6%) | 88 (5·7%) | 0·91 | 179 (5·7%) | 170 (5·5%) | 0·76 |
| **$O_2$ dependence >28 days** | 51 (3·2%) | 48 (3·1%) | 0·87 | 93 (3·0%) | 94 (3·0%) | 0·83 |
| **$O_2$ at 36 weeks post conception** | 36 (2·3%) | 29 (1·9%) | 0·45 | 78 (2·5%) | 53 (1·7%) | 0·04 |
| **Positive blood culture** | | | | | | |
| Overall | 34 (2·1%) | 31 (2·0%) | 0·79 | 68 (2·2%) | 59 (1·9%) | 0·48 |
| If born within 14 days | 24 (1·5%) | 25 (1·6%) | 0·81 | 52 (1·7%) | 45 (1·5%) | 0·54 |
| **Necrotising enterocolitis** | | | | | | |
| Suspected or proven | 16 (1·0%) | 12 (0·8%) | 0·49 | 39 (1·2%) | 31 (1·0%) | 0·38 |
| Proven | 6 (0·4%) | 4 (0·3%) | 0·56 | 17 (0·5%) | 13 (0·4%) | 0·50 |
| **Abnormal cerebral ultrasonography** | 26 (1·6%) | 29 (1·9%) | 0·61 | 60 (1·9%) | 56 (1·8%) | 0·77 |
| **Death** | 43 (2·7%) | 39 (2·5%) | 0·75 | 90 (2·9%) | 77 (2·5%) | 0·37 |
| **Composite primary outcome** | 90 (5·6%) | 78 (5·0%) | 0·44 | 181 (5·7%) | 154 (5·0%) | 0·18 |

NICU=neonatal intensive-care unit. SCBU=special-care baby unit.

Table 5: **Neonatal outcomes of babies born to women with preterm labour randomly assigned erythromycin**



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| | Co-amoxiclav only (n=1534) | Placebo only (n=1556) | p | Any co-amoxiclav (n=3085) | No co-amoxiclav (n=3156) | p |
|---|---|---|---|---|---|---|
| **Birthweight (g)** | | | | | | |
| Mean (SD) | 2842 (810) | 2857 (775) | 0·60 | 2847 (802) | 2840 (782) | 0·74 |
| Median (range) | 2960 (440–5520) | 2980 (570–5127) | . . | 2890 (275–5520) | 2960 (450–5127) | . . |
| <2500 | 448 (29·2%) | 419 (26·9%) | 0·16 | 874 (28·3%) | 887 (28·1%) | 0·84 |
| <1500 | 122 (8·0%) | 107 (6·9%) | 0·16 | 236 (7·6%) | 228 (7·2%) | 0·52 |
| **Admission to NICU/SCBU** | 403 (26·3%) | 380 (24·4%) | 0·24 | 792 (25·7%) | 804 (25·5%) | 0·86 |
| **Total babies ventilated** | 119 (7·8%) | 121 (7·8%) | 0·98 | 245 (7·9%) | 247 (7·8%) | 0·87 |
| **Total babies in >21% $O_2$** | 203 (13·2%) | 207 (13·3%) | 0·95 | 413 (13·4%) | 423 (13·4%) | 0·98 |
| At 48 h | 170 (11·1%) | 178 (11·4%) | 0·76 | 357 (11·6%) | 363 (11·5%) | 0·93 |
| At 7 days | 85 (5·5%) | 88 (5·7%) | 0·89 | 172 (5·6%) | 174 (5·5%) | 0·91 |
| At 14 days | 62 (4·0%) | 63 (4·0%) | 0·99 | 121 (3·9%) | 127 (4·0%) | 0·83 |
| At 28 days | 47 (3·1%) | 49 (3·1%) | 0·89 | 91 (2·9%) | 101 (3·2%) | 0·57 |
| **RDS confirmed by chest radiography** | 127 (8·3%) | 138 (8·9%) | 0·56 | 266 (8·6%) | 271 (8·6%) | 0·96 |
| **Treatment with exogenous surfactant** | 82 (5·3%) | 88 (5·7%) | 0·70 | 172 (5·6%) | 177 (5·6%) | 0·95 |
| **$O_2$ dependence >28 days** | 46 (3·0%) | 48 (3·1%) | 0·89 | 88 (2·9%) | 99 (3·1%) | 0·51 |
| **$O_2$ at 36 weeks post conception** | 24 (1·6%) | 29 (1·9%) | 0·52 | 66 (2·1%) | 65 (2·1%) | 0·83 |
| **Positive blood culture** | | | | | | |
| Overall | 28 (1·8%) | 31 (2·0%) | 0·73 | 62 (2·0%) | 65 (2·1%) | 0·89 |
| If born within 14 days of randomisation | 20 (1·3%) | 25 (1·6%) | 0·48 | 48 (1·6%) | 49 (1·6%) | 0·99 |
| **Necrotising enterocolitis** | | | | | | |
| Suspected or proven | 19 (1·2%) | 12 (0·8%) | 0·19 | 42 (1·4%) | 28 (0·9%) | 0·08 |
| Proven | 9 (0·6%) | 4 (0·3%) | 0·16 | 20 (0·6%) | 10 (0·3%) | 0·06 |
| **Abnormal cerebral ultrasonography** | 27 (1·8%) | 29 (1·9%) | 0·83 | 61 (2·0%) | 55 (1·7%) | 0·49 |
| **Death** | 38 (2·5%) | 39 (2·5%) | 0·96 | 85 (2·8%) | 82 (2·6%) | 0·70 |
| **Composite primary outcome** | 76 (5·0%) | 78 (5·0%) | 0·94 | 167 (5·4%) | 168 (5·3%) | 0·87 |

NICU=neonatal intensive-care unit. SCBU=special-care baby unit.

Table 6: **Neonatal outcomes of babies born to women with preterm labour randomly assigned co-amoxiclav**

We should consider the results of this trial in the context of previous trials that assessed the effects of broad-spectrum antibiotic prescription to women in spontaneous preterm labour with intact membranes. The Cochrane review[10] showed a decrease in the rate of neonatal necrotising enterocolitis, trends towards reductions in prolongation of pregnancy and the rates of neonatal sepsis and intraventricular haemorrhage, and increases in the rates of respiratory distress syndrome and perinatal death. Most of the trials in that review were small, the largest being the one by Romero and colleagues,[14] which enrolled 227 women, and their small size may have led, in part, to the confusing picture. Additionally, some small trials either with a null result or that found negative effects might not have been published. This trial, by its size and quality, overcomes the uncertainties of the previous Cochrane review.

| | Erythromycin and co-amoxiclav (n=1551) | p | Placebo only (n=1556) | p | Any antibiotic* (n=4685) |
|---|---|---|---|---|---|
| **Birthweight (g)** | | | | | |
| Mean (SD) | 2851 (794) | 0·83 | 2857 (775) | 0·42 | 2839 (797) |
| Median (range) | 2990 (275–5300) | . . | 2980 (570–5127) | . . | 2960 (275–5320) |
| <2500 | 426 (27·5%) | 0·73 | 419 (26·9%) | 0·19 | 1342 (28·6%) |
| <1500 | 114 (7·4%) | 0·61 | 107 (6·9%) | 0·33 | 357 (7·6%) |
| **Admission to NICU/SCBU** | 389 (25·1%) | 0·67 | 380 (24·4%) | 0·23 | 1216 (26·0%) |
| **Total babies ventilated** | 126 (8·1%) | 0·72 | 121 (7·8%) | 0·86 | 371 (7·9%) |
| **Total babies in >21% $O_2$** | 210 (13·5%) | 0·85 | 207 (13·3%) | 0·90 | 629 (13·4%) |
| At 48 h | 187 (12·1%) | 0·60 | 178 (11·4%) | 0·89 | 542 (11·6%) |
| At 7 days | 87 (5·6%) | 0·95 | 88 (5·7%) | 0·83 | 258 (5·5%) |
| At 14 days | 59 (3·8%) | 0·73 | 63 (4·0%) | 0·86 | 185 (3·9%) |
| At 28 days | 44 (2·8%) | 0·61 | 49 (3·1%) | 0·85 | 143 (3·1%) |
| **RDS confirmed by chest radiography** | 139 (9·0%) | 0·93 | 138 (8·9%) | 0·67 | 399 (8·5%) |
| **Treatment with exogenous surfactant** | 90 (5·8%) | 0·86 | 88 (5·7%) | 0·90 | 261 (5·6%) |
| **$O_2$ dependence >28 days** | 42 (2·7%) | 0·53 | 48 (3·1%) | 0·81 | 139 (3·0%) |
| **$O_2$ at 36 weeks post conception** | 42 (2·7%) | 0·12 | 29 (1·9%) | 0·45 | 102 (2·2%) |
| **Positive blood cultures** | | | | | |
| Overall | 34 (2·2%) | 0·70 | 31 (2·0%) | 0·89 | 96 (2·0%) |
| If born within 14 days | 28 (1·8%) | 0·67 | 25 (1·6%) | 0·85 | 72 (1·5%) |
| **Necrotising enterocolitis** | | | | | |
| Suspected or proven | 23 (1·5%) | 0·06 | 12 (0·8%) | 0·13 | 58 (1·2%) |
| Proven | 11 (0·7%) | 0·07 | 4 (0·3%) | 0·14 | 26 (0·6%) |
| **Abnormal cerebral ultrasonography** | 34 (2·2%) | 0·52 | 29 (1·9%) | 0·98 | 87 (1·9%) |
| **Death** | 47 (3·0%) | 0·37 | 39 (2·5%) | 0·63 | 128 (2·7%) |
| **Composite primary outcome** | 91 (5·9%) | 0·29 | 78 (5·0%) | 0·47 | 257 (5·5%) |

NICU=neonatal intensive-care unit. SCBU=special-care baby unit. *Erythromycin alone, co-amoxiclav alone, or both.

Table 7: **Neonatal outcomes of women with preterm labour randomly assigned both co-amoxiclav and erythromycin or any antibiotic**



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The trial, however, does raise concern about the prescription of co-amoxiclav in this clinical situation, since it was associated with a (non-significant) doubling in the risk of neonatal necrotising enterocolitis. These results taken together with the results from the concurrent trial of antibiotics of pPROM[11] provide strong evidence that co-amoxiclav should not be routinely prescribed for women in spontaneous preterm labour nor for those with pPROM, and that caution should be exercised in prescribing it as a prophylactic antibiotic at the time of caesarean section for a preterm delivery.[15] The observational evidence surrounding the rate of neonatal necrotising enterocolitis and co-amoxiclav prescription at caesarean section for preterm delivery should be reviewed. These results must also raise concerns about the prescription of co-amoxiclav to neonates.

The results of this trial suggest the need for research in other areas. The results have emphasised that the clinical symptoms and signs of preterm labour are poor predictors of preterm delivery and birth.[16] A reliable predictive test of preterm delivery and birth is therefore vital for appropriate targeting of therapeutic interventions.

There is some evidence that if women who have had a previous preterm birth are screened for abnormal microbial colonisation of the genital tract and treated with antibiotics, some preterm births can be prevented. Morales and colleagues[17] did a small randomised controlled trial of oral metronidazole in 80 women who had a past history of preterm birth and who had bacterial vaginosis at between 13 and 20 weeks of gestation. Metronidazole reduced the admission rate from 78% to 27%, the preterm birth rate from 39% to 18%, and the rate of pPROM from 33% to 5%. Hauth and colleagues[18] did a much larger study, which involved 616 women who had previously had preterm birth or who were of low bodyweight and had bacterial vaginosis at 22 weeks' gestation. The women were randomly assigned either ampicillin plus erythromycin, or placebo. The antibiotics reduced the preterm birth rate from 49% in the placebo group to 31% in the antibiotic group. Further evidence comes from McDonald and colleagues,[19] who did a post-hoc analysis of 424 women who had had a previous preterm birth and who were taking part in a randomised trial of metronidazole in a group of 879 women with a heavy growth of *Gardnerella vaginalis*. They reported a reduction of the preterm birth rate in this subclass of women. The summation of the evidence from these trials does suggest that a large trial of screening for abnormal microbial colonisation of the genital tract during the prenatal period in women who have had previous preterm birth, and subsequent treatment with antibiotics is needed.

Our trial indicates that antibiotics should not be routinely prescribed to women in spontaneous preterm labour without clinical evidence of infection or preterm, prelabour rupture of the membranes.

*Contributors*

Sara Kenyon (Leicester, UK), David Taylor, (Leicester), Richard Peto (Oxford, UK), and William Tarnow-Mordi (Sydney, Australia) designed the study protocol. David Taylor and Sara Kenyon supervised the study. Sara Kenyon and the trial team took responsibility for the day-to-day contact with the centres, the organisation of the drug supplies, and the management of the data. The statistical analysis was done by Ann Blackburn, supported by Richard Peto.

*Acknowledgments*

We thank all the women who joined the study, Barbara Farrell, Richard Peto, Peter Brocklehurst, David Field, Steve Gould, Peter Howie, David Isaacs, Roberto Lede, Paul Lewis, Rona McCandlish, Jim Neilson, Gabriella Phillips, and the UK National Childbirth Trust (Gill Gyte and Sandy Oliver). Co-amoxiclav (Augmentin) and co-amoxiclav placebo were supplied free of charge by Smith Kline Beecham, and erythromycin (Erymax) and erythromycin placebo were supplied by Parke Davis. The study was supported by a strategic project grant from the UK Medical Research Council (ISCRT number 53995660).

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