Antibiotics for pre-term pre-labour rupture of membranes: prevention of neonatal deaths due to complications of pre-term birth and infection

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Background In high-income countries, it is standard practice to give antibiotics to women with pre-term, pre-labour rupture of membranes (pPROM) to delay birth and reduce the risk of infection. In low and middle-income settings, where some 2 million neonatal deaths occur annually due to complications of pre-term birth or infection, many women do not receive antibiotic therapy for pPROM.

Objectives To review the evidence for and estimate the effect on neonatal mortality due to pre-term birth complications or infection, of administration of antibiotics to women with pPROM, in low and middle-income countries.

Methods We performed a systematic review to update a Cochrane review. Standardized abstraction forms were used. The quality of the evidence provided by individual studies and overall was assessed using an adapted GRADE approach.

Results Eighteen RCTs met our inclusion criteria. Most were from high-income countries and provide strong evidence that antibiotics for pPROM reduce the risk of respiratory distress syndrome [risk ratio (RR) = 0.88; confidence interval (CI) 0.80, 0.97], and early onset postnatal infection (RR = 0.61; CI 0.48, 0.77). The data are consistent with a reduction in neonatal mortality (RR = 0.90; CI 0.72, 1.12).

Conclusion Antibiotics for pPROM reduce complications due to pre-term delivery and post-natal infection in high-income settings. There is moderate quality evidence that, in low-income settings, where access to other interventions (antenatal steroids, surfactant therapy, ventilation, antibiotic therapy) may be low, antibiotics for pPROM could prevent 4% of neonatal deaths due to complications of prematurity and 8% of those due to infection.

Keywords Neonatal mortality, newborn care, antibiotics, pre-term birth, prematurity, infection, respiratory distress syndrome

Background

Each year almost 4 million newborns die.[1] Complications of pre-term birth and infections account for more than half of these deaths. Pre-term, pre-labour rupture of membranes (pPROM) occur when the amniotic sac enclosing the fetus ruptures before 37 weeks of gestation (pre-term) and prior to the onset of labour (pre-labour). It is associated with about one-third of pre-term deliveries in high-income countries, and is associated with increased rates of neonatal and maternal infection.[2] Infection may be a cause of or result from pPROM.[3] Empiric antibiotic therapy following pPROM has been demonstrated in high-income countries to increase the time period between pPROM and delivery, and reduce the risks of maternal and neonatal infection.[2] Neonatal infections and prematurity are important causes of neonatal death in low and middle-income countries (LMICs). We therefore reasoned that empiric antibiotic therapy following pPROM may be an efficacious and cost-effective intervention to prevent infection and improve neonatal outcomes in LMICs as well.

A systematic review of randomized trials of antibiotics for pPROM has been published in the Cochrane database.[3] This included 22 trials including over 6000 women and concluded that antibiotic administration following pPROM delays delivery and reduces major markers of neonatal morbidity. The authors conclude that the data support the routine use of antibiotics in pPROM but counsel against the use of co-amoxiclav as this was associated with increased risk of neonatal necrotizing enterocolitis.[3] In this article, we present an update of this review.

Objective

To review the evidence for, and estimate the effect on neonatal mortality due to the direct complications of pre-term birth and due to infections, of antibiotics administered to women with pPROM, compared with no treatment, for low and middle-income countries.

Methods

Searches

We reviewed the 22 trials included in the Cochrane review[3] and abstracted data on the outcomes of interest, namely neonatal mortality, and the incidence of severe morbidity relating to pre-term delivery or infection: necrotizing enterocolitis, intra-ventricular haemorrhage, respiratory distress syndrome (RDS), confirmed sepsis. We excluded two trials in which all women received antibiotic treatment for 3 or 7 days.[4,5] We also excluded three trials which compared co-amoxiclav with placebo or no antibiotic treatment[6–8] and the co-amoxiclav arm of another trial[9] because of the evidence that co-amoxiclav is associated with increased risk of necrotizing enterocolitis. We therefore included 17 trials from the Cochrane review.[9–25]

We also undertook systematic searches in multiple databases to identify studies of antibiotics for pPROM. We searched PubMed, Cochrane Libraries and all World Health Organization Regional Databases, and included publications in any language. Search terms included: 'preterm/premature', 'membranes', 'rupture,' 'antibiotics'. For PubMed, we further restricted the search to randomized/clinical trials. Studies were included if data were reported on mortality or severe morbidity (see above) during the neonatal period.

Inclusion/exclusion criteria, abstraction

We included randomized trials from any setting and observational studies from low and middle-income settings. Studies were included if antibiotics were given alone or in combination with antenatal steroids and surfactants. For all outcomes, the denominator used was the number of liveborn babies. Data from all studies which met the inclusion criteria were abstracted using a standardized form. We abstracted key variables with regard to the study identifiers and context, study design and limitations, the intervention, application of intention-to-treat analysis and the outcomes of interest (neonatal mortality and the incidence of severe morbidity relating to pre-term delivery or infection). We assessed the quality of the evidence provided by each of these studies using a standard table (webtable) employing an adapted version of GRADE[26] developed by the Child Health Epidemiology Reference Group (CHERG).[27]

Analysis and summary measures

Statistical analyses to summarize results across studies were performed using Stata version 10 software (http://www.stata.com). We performed and presented the results from fixed effects meta-analyses for those outcomes for which the evidence of heterogeneity between studies was weak ($P > 0.1$). Otherwise, we performed and presented the results of random effects meta-analyses. We summarized the overall quality of evidence for each outcome using an adapted version of the GRADE approach.[27]

Results

We identified 498 titles for screening and reviewed the full text of 19 papers (Supplementary Table 1). The search yielded one randomized trial which had been published since the Cochrane review[28] and one observational study from a low-income setting.[29]

Randomized trials

We analysed data from 18 randomized trials and 4581 newborns (Table 1). Most trials were from high-income settings. The exceptions were one

Table 1 Summary of individual studies included in primary analyses

First author	Year of publication	Country	Study design	Study participants	Antibiotics used	Sample size	Reference
Almeida	1996	Mozambique	RCT	30–36 weeks gestation	Amoxicillin	110	[10]
Amon	1988	USA	RCT	20–34 weeks gestation, singleton pregnancies	Ampicillin	78	[11]
Camli	1997	Turkey	RCT	28–34 weeks gestation, singleton pregnancies	Ampicillin	31	[12]
Ernest	1994	USA	RCT	21–37 weeks gestation	Benzylpenicillin, potassium phenoxymethyl penicillin	144	[13]
Fuhr	2006	Germany	RCT	24.0–32.9 weeks gestation	Mezlocillin	105	[28]
Garcia-Burguillo	1996	Spain	RCT	<36 weeks gestation	Erythromycin	58	[14]
Grable	1996	USA	RCT	⩽35 weeks gestation, singleton pregnancies	Ampicillin	60	[15]
Johnston	1990	USA	RCT	20–34 weeks gestation, singleton pregnancies	Mezlocillin and ampicillin	84	[16]
Kenyon	2001	UK and others	RCT	<37 weeks gestation, multiple pregnancies included	Erythromycin	2415	[9]
Kurki	1992	Finland	RCT	23–36 weeks gestation,	Penicillin	115	[17]
Lockwood	1993	USA	RCT	20–34.9 weeks gestation, singleton pregnancies	Piperacillin sodium	70	[18]
McGregor	1991	USA	RCT	23–34 weeks gestation, singleton pregnancies	Erythromycin	54	[19]
Mercer	1992	USA	RCT	20–34.9 weeks gestation, singleton	Erythromycin	216	[21]
Mercer	1997	USA	RCT	24–32.0 weeks gestation, included multiple pregnancies	Ampicillin, erythromycin, amoxicillin	611	[20]
Morales	1989	USA	RCT	26–34 weeks, singleton pregnancies	Ampicillin	165	[22]
Ovalle Salas	1997	Chile	RCT	24–34 weeks gestation	Clindamycin and gentamycin	85	[23]
Owen	1993	USA	RCT	24–33.9 weeks gestation, singleton	Ampicillin	117	[24]
Svare	1997	Denmark	RCT	26 + 0–33.6 weeks gestation, singleton pregnancies	Ampicillin, pivampicillin, metronidazole	67	[25]
Al-Qa'Qa	2005	Pakistan	Observational	28–42 weeks gestation	Unclear	225	[29]

trial from Turkey (31 newborns),[12] one trial from Mozambique (106 newborns)[10] and one trial in Chile (85 newborns).[23] Most (14) trials were blinded through the use of a placebo, but most were small with half involving fewer than 100 women. The largest trial[9] contributed more than half of the total mothers (2415) after exclusion of the arms receiving co-amoxiclav. The studies are summarized in Table 1 and described in more detail in the Supplementary table.

Description of the intervention

Women with pre-term rupture of membranes were treated with antibiotics. The antibiotic used, dose and duration varied between trials. Six trials used ampicillin, four erythromycin, two penicillin and one each used amoxicillin, mezlocillin, piperacillin. Two studies used combinations of two or more of these antibiotics, whereas one trial used a combination of clindamycin and gentamycin.
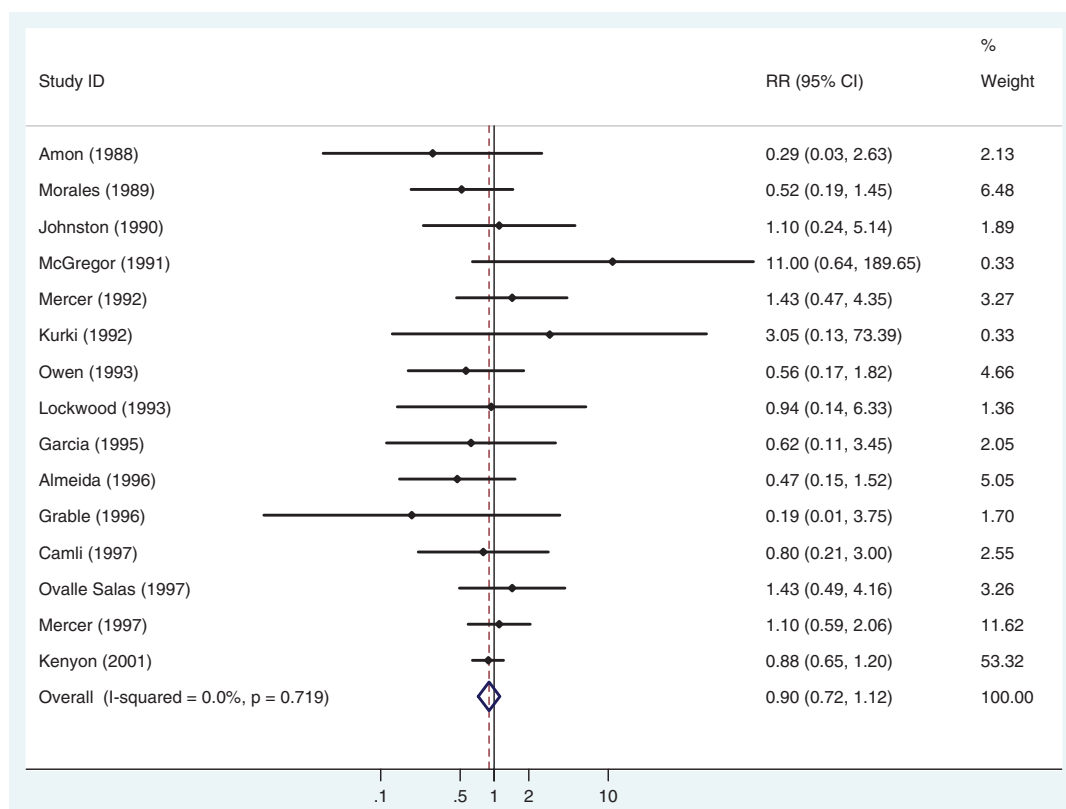
Figure 1 Fixed effects meta-analysis of the effect of antibiotics for pPROM on neonatal mortality

Effect on all-cause neonatal mortality

Fifteen studies (4265 newborns) reported on neonatal mortality (or mortality prior to discharge). A total of 284 deaths were reported (NMR = 66/1000 livebirths). There was no evidence of heterogeneity between studies (I^2 = 0%, P = 0.7). The summary, fixed effects, risk ratio (RR) was 0.90 [95% confidence interval (CI) 0.72, 1.12; P = 0.33] (Figure 1, Table 2).

Effects on severe morbidity

Thirteen studies (4104 newborns) reported on the occurrence of respiratory distress syndrome (1105 cases). There was no evidence of heterogeneity between studies (I^2 = 0%, P = 0.7). The summary, fixed effects, risk ratio (RR) was 0.88 (95% CI 0.80, 0.97; P = 0.009) (Figure 2, Table 2).

Thirteen studies (4126 newborns) reported on the risk of necrotizing enterocolitis (148 cases). There was no evidence of heterogeneity between studies (I^2 = 0%, P = 0.7). The summary, fixed effects, risk ratio was 0.76 (95% CI 0.56, 1.05; P = 0.09) (Figure 3, Table 2).

Twelve studies (1702 newborns) reported on the risk of intra-ventricular haemorrhage (149 cases). One study[15] reported no cases and did not contribute to the analysis. There was no evidence of heterogeneity between studies (I^2 = 0%, P = 0.6). The summary,

fixed effects, risk ratio was 0.67 (95% CI 0.49, 0.92; P = 0.01) (Figure 4, Table 2).

Thirteen studies (3693 newborns) reported on the risk of confirmed sepsis (260 cases). There was no evidence of heterogeneity between studies (I^2 = 0%, P = 0.6). The summary, fixed effects, risk ratio was 0.61 (95% CI 0.48, 0.77; P < 0.001) (Figure 5, Table 2).

In 6 of the 18 trials (2860 babies),[9,10,12,14,19,21] only oral antibiotics were used. In meta-regression analyses, there was no strong evidence that any of the above effects differed between trials using IV antibiotics and those using oral antibiotics only (P > 0.15 for all outcomes).

Studies in low and middle-income countries

Very few data are available from low and middle-income countries. One trial in Mozambique[10] included 106 newborns and reported 11 deaths and 12 cases of confirmed sepsis. Both the risk of death (RR = 0.47) and risk of sepsis (RR = 0.17) appeared lower in the treated arm. A trial in a middle-income setting (Turkey,[12]) included 31 newborns and reported a total of seven deaths and seven cases of confirmed sepsis. Again, both the risk of death (RR = 0.80) and the risk of sepsis (RR = 0.43) appeared lower in the treated arm. Excluding one death which occurred 10 min after delivery in a baby with multiple malformations, the trial in

Table 2 Assessment of the quality of the evidence with respect to the effect of antibiotics for pPROM on severe neonatal morbidity and mortality in low and middle-income settings

		Assessment of quality of evidence				Summary of Findings		
				Directness		No. of events in total		
No. of studies	Design	Limitations	Consistency	Generalizability to low/middle-income settings	Generalizability to mortality outcomes	Inter-vention	Control	RR (95% CI)
Neonatal mortality: Quality of evidence: low								
15	RCT	No major	Yes	Low, mostly high-income	Direct (all-cause)	133	151	RR = 0.90 (0.72, 1.12)
Severe morbidity (RDS): Quality of evidence: moderate								
13	RCT	No major	Yes	Low, mostly high-income	Indirect (severe morbidity)	509	596	RR = 0.88 (0.80, 0.97)
Severe morbidity (necrotizing enterocolitis): Quality of evidence: low								
13	RCT	No major	Yes	Low, mostly high-income	Indirect (severe morbidity)	63	85	RR = 0.76 (0.56, 1.05)
Severe morbidity (intra-ventricular haemorrhage): Quality of evidence: moderate								
11	RCT	No major	Yes	Low, mostly high-income	Indirect (severe morbidity)	59	90	RR = 0.67 (0.49, 0.92)
Severe morbidity (confirmed sepsis): Quality of evidence: moderate								
13	RCT	No major	Yes	Low, mostly high-income	Indirect (severe morbidity)	97	163	RR = 0.61 (0.48, 0.78)

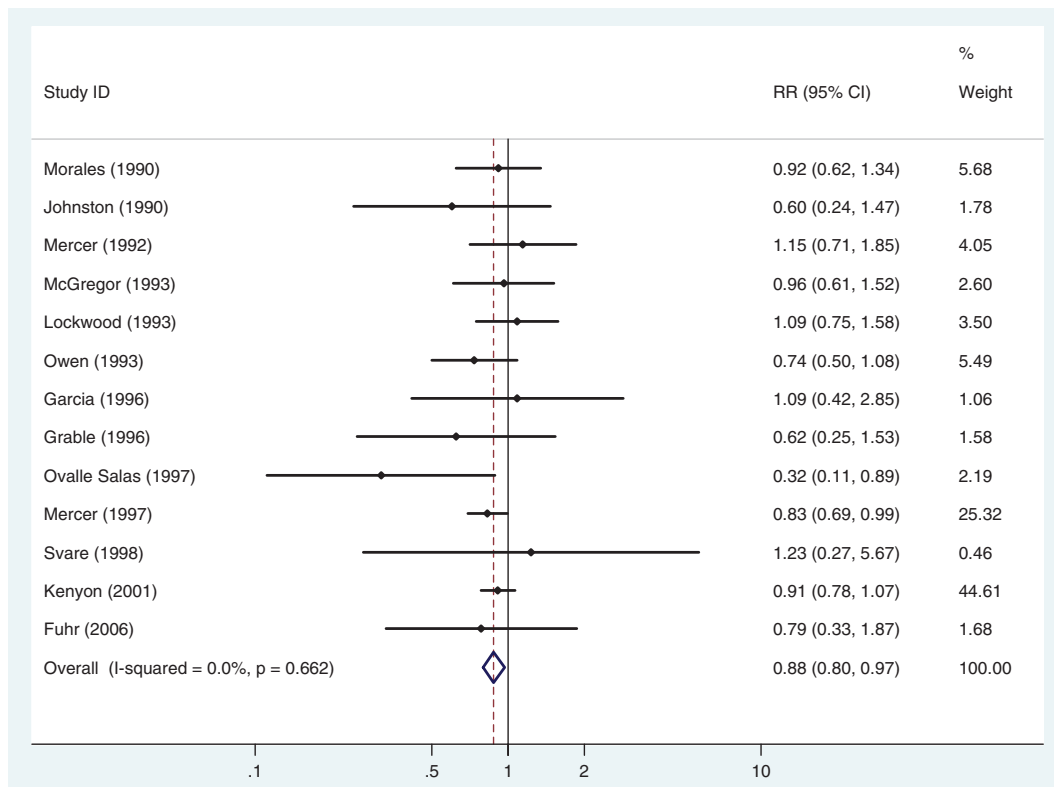| Study ID	RR (95% CI)	% Weight
Morales (1990)	0.92 (0.62, 1.34)	5.68
Johnston (1990)	0.60 (0.24, 1.47)	1.78
Mercer (1992)	1.15 (0.71, 1.85)	4.05
McGregor (1993)	0.96 (0.61, 1.52)	2.60
Lockwood (1993)	1.09 (0.75, 1.58)	3.50
Owen (1993)	0.74 (0.50, 1.08)	5.49
Garcia (1996)	1.09 (0.42, 2.85)	1.06
Grable (1996)	0.62 (0.25, 1.53)	1.58
Ovalle Salas (1997)	0.32 (0.11, 0.89)	2.19
Mercer (1997)	0.83 (0.69, 0.99)	25.32
Svare (1998)	1.23 (0.27, 5.67)	0.46
Kenyon (2001)	0.91 (0.78, 1.07)	44.61
Fuhr (2006)	0.79 (0.33, 1.87)	1.68
Overall (I-squared = 0.0%, p = 0.662)	0.88 (0.80, 0.97)	100.00

Figure 2 Fixed effects meta-analysis of the effect of antibiotics for pPROM on the risk of respiratory distress syndrome
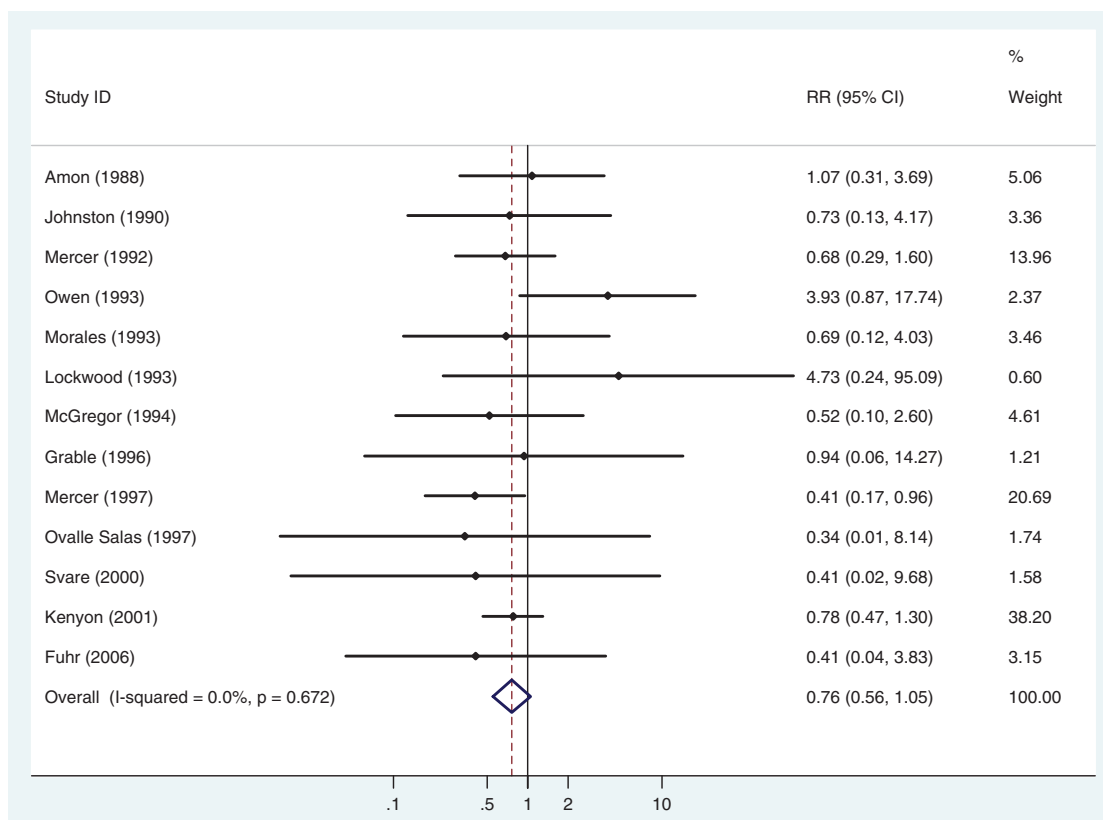
Figure 3 Fixed effects meta-analysis of the effect of antibiotics for pPROM on the risk of necrotizing enterocolitis
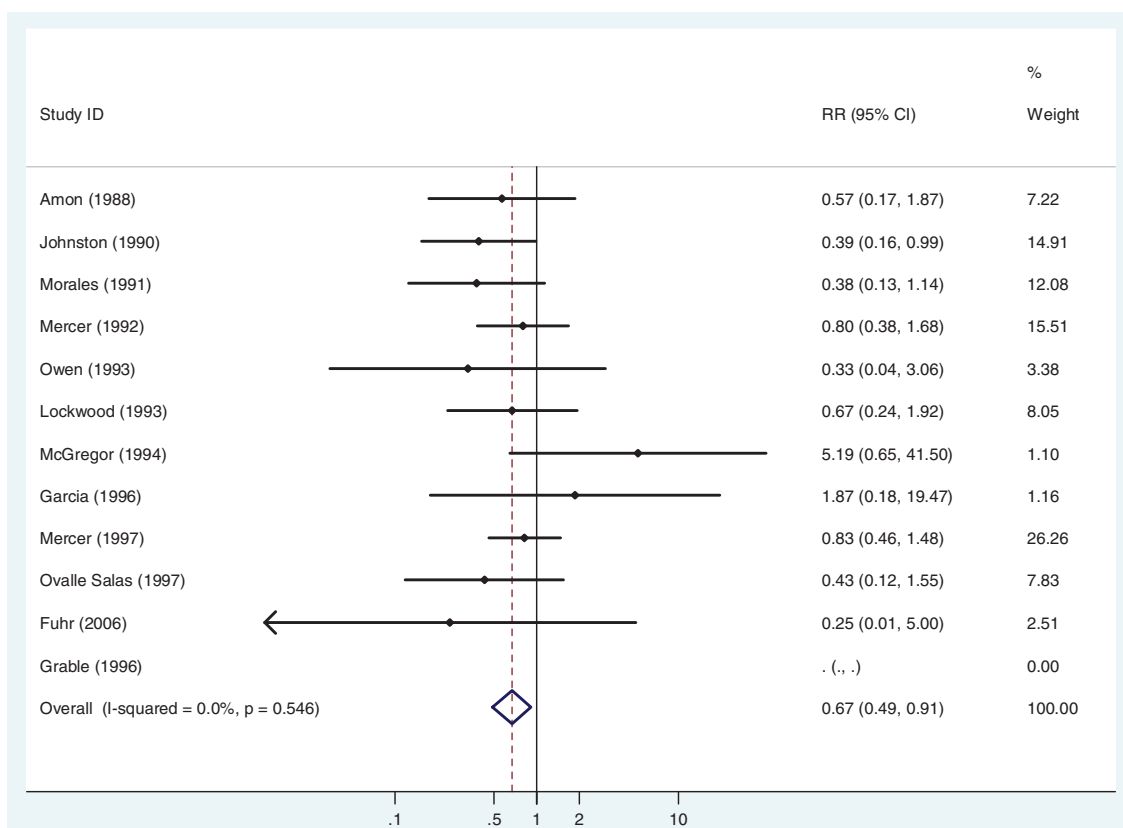

Figure 4 Fixed effects meta-analysis of the effect of antibiotics for pPROM on the risk of intra-ventricular haemorrhage
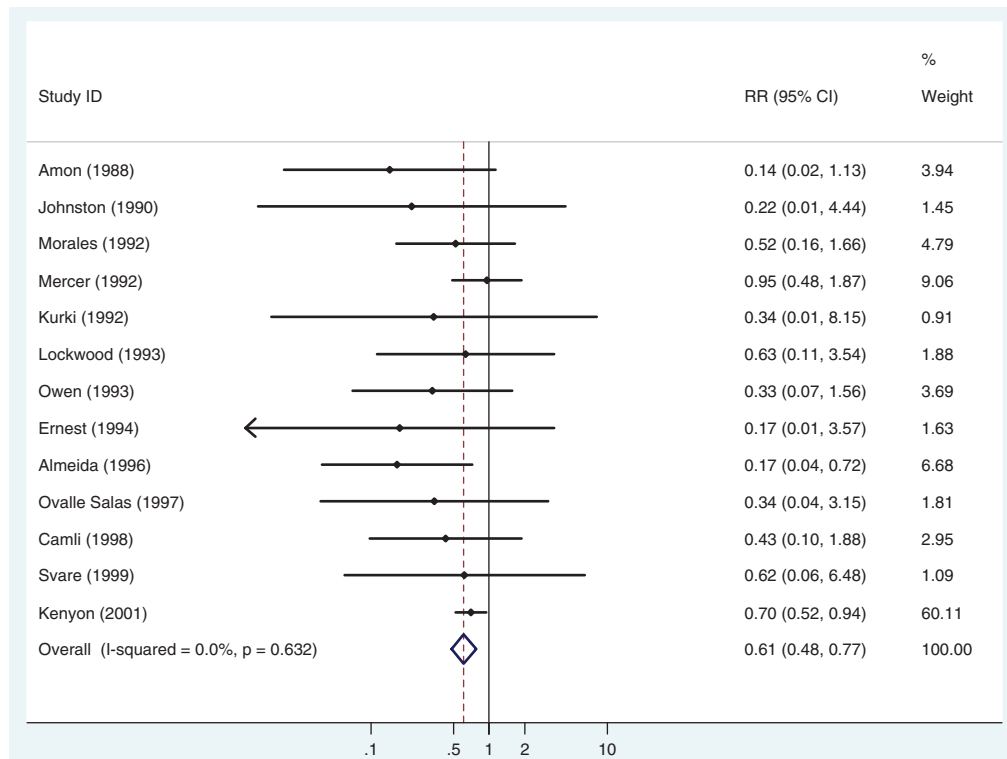
Study ID	RR (95% CI)	% Weight
Amon (1988)	0.14 (0.02, 1.13)	3.94
Johnston (1990)	0.22 (0.01, 4.44)	1.45
Morales (1992)	0.52 (0.16, 1.66)	4.79
Mercer (1992)	0.95 (0.48, 1.87)	9.06
Kurki (1992)	0.34 (0.01, 8.15)	0.91
Lockwood (1993)	0.63 (0.11, 3.54)	1.88
Owen (1993)	0.33 (0.07, 1.56)	3.69
Ernest (1994)	0.17 (0.01, 3.57)	1.63
Almeida (1996)	0.17 (0.04, 0.72)	6.68
Ovalle Salas (1997)	0.34 (0.04, 3.15)	1.81
Camli (1998)	0.43 (0.10, 1.88)	2.95
Svare (1999)	0.62 (0.06, 6.48)	1.09
Kenyon (2001)	0.70 (0.52, 0.94)	60.11
Overall (I-squared = 0.0%, p = 0.632)	0.61 (0.48, 0.77)	100.00

Figure 5 Fixed effects meta-analysis of the effect of antibiotics for pPROM on the risk of confirmed sepsis

Chile[23] reported 12 neonatal deaths, 7 of which occurred in the group receiving antibiotics (RR = 1.43). RDS (17 cases, RR = 0.32), necrotizing enterocolitis (1 case, control arm), intra-ventricular haemorrhage (10 cases, RR = 0.43) and early onset sepsis (4 cases, RR = 0.34) were all, if anything, less common in the intervention arm.

These data are consistent with one trial and one observational study from low and middle-income countries that we excluded from our primary analysis. We excluded from our main analyses a trial conducted in Zimbabwe[8] because it used co-amoxiclav, This trial included 168 newborns and reported 19 deaths and 34 cases of unconfirmed clinical sepsis. Both the risk of death (RR = 0.76) and the risk of unconfirmed sepsis (RR = 0.65) appeared lower in the treated arm. In an observational study conducted in Pakistan,[29] 225 newborns were studied, of whom 140 were pre-term. It is not clear what antibiotics mothers received though all newborns received antibiotics until a negative blood culture was obtained. The risks of a positive blood culture (9% vs 30%), RDS (25% vs 44%), necrotizing enterocolitis (3% vs 11%) and intra-ventricular haemorrhage (7% vs 12%) were all lower in babies born to mothers who had received antibiotics. Twenty neonatal deaths are reported but it is not clear how these were distributed between mothers who did or did not receive antibiotics.

Discussion

There is high-quality evidence that antibiotics for pPROM reduce the risk of complications due to prematurity and risk of neonatal infection in high-income settings. The evidence for a reduction in neonatal mortality is less strong. Our meta-analysis of 14 trials estimates a 10% reduction in all-cause neonatal mortality but with a wide CI that included no effect. However, there is a dearth of data from low-income countries, where newborns have less access to other forms of care including antenatal steroids, surfactant therapy, ventilation and even antibiotic treatment for infection. In the absence of these other interventions, the use of antibiotics for pPROM will certainly prevent neonatal deaths by preventing RDS, which is the most common cause of death due to complications of prematurity. Similarly, in settings in which newborns do not have easy access to antibiotic therapy for neonatal infections, the prevention of sepsis cases through the use of antibiotics for pPROM will certainly prevent infection deaths. We did not observe strong evidence that oral antibiotics were less effective than IVl antibiotics though our power to detect any such difference is limited by the small number of studies using oral antibiotics only. Clearly, in low-income settings, oral-only regimens will be easier to deliver than regimens involving intravenous administration of the antibiotics.

There is evidence ($P = 0.01$) of a reduction in the incidence of RDS (estimated reduction 12%, 95% CI 3–20%) with larger reductions in intra-ventricular haemorrhage (33%, 95% CI 8–51%, $P = 0.01$) and necrotizing enterocolitis (24%, 95% CI 5–44%, $P = 0.09$) although the evidence for an effect on necrotizing enterocolitis is relatively weak. Given that RDS is the most common complication and has the smallest effect estimate, we propose assuming that antibiotics for pPROM can reduce deaths due to complications of prematurity by 12% (uncertainty range 3–20%) among newborns born following pPROM. About one-third of pre-term deliveries are associated with pPROM,[2] so we propose an affected fraction of 33% of all pre-term deaths. Thus, we estimate that increasing coverage with antibiotics for pPROM from 0% to 100% might prevent 4% of all pre-term deaths.

Our analysis suggests a 39% reduction in incidence of neonatal sepsis (95% CI 23–52%, $P < 0.001$) with antibiotic therapy for pPROM among newborns born following pPROM. In order to estimate by how much this intervention might reduce sepsis deaths as a whole, we need to take into account how many sepsis deaths occur in pre-term babies and the proportion of pre-term births with pPROM (assumed to be one-third, see above). If 60% of neonatal sepsis deaths

occur in pre-term babies,[30] one-third of which occur after pPROM, then this implies that 20% of sepsis deaths occur in pPROM babies. Thus, antibiotics for pPROM might reduce sepsis deaths by about 8% overall (i.e. 39% reduction among 20% of deaths).

Potential benefits of empiric antibiotic therapy following pPROM must be weighed against possible adverse consequences related to antibiotic administration. Most data have been reassuring, with no increased adverse sequelae following empiric antibiotic therapy for pPROM.[2,9,31] The ORACLE I trial, the single largest reported, of nearly 5000 women with pPROM randomized to either placebo or one of several antibiotic regimens found neither increases in immediate neonatal adverse sequelae related to antibiotics nor differences in neurodevelopmental outcome at 7 years of age.[9,31] However, in a related concurrent trial, empiric antibiotic therapy for pre-term labour, without rupture of membranes, was associated with an increased risk of neonatal necrotizing enterocolitis (associated with co-amoxiclav) and of subsequent neurodevelopmental functional impairment (associated with erythromycin) without any significant prolongation in pregnancy or improvement in other neonatal comorbidities.[32,33] The reasons for increases in neonatal morbidity following antibiotic therapy in pre-term labour remain speculative but

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Box 1 Cause-specific mortality effect and quality grade of the estimate for antibiotics given to women with pPROM.

Causes of mortality to act on:
Direct complications of prematurity and infections.

Cause-specific effect and range:
Twelve percent reduction in incidence of RDS (95% CI 3–20%).
Thirty-nine percent reduction in incidence of neonatal sepsis (95% CI 22–52%)
We assume that these reductions in incidence of severe morbidity translate into similar reductions in mortality amongst babies born to mothers with pPROM.
We assume that one-third of pre-term births are related to pPROM and that ∼60% of infection deaths are related to prematurity.
Thus, we estimate that giving antibiotics to mothers with pPROM could reduce neonatal deaths due to the direct complications of pre-term birth by 4% and neonatal deaths due to sepsis by 8%.

Quality of input evidence:
Moderate
18 RCTs, but mainly from high-income settings. Evidence strong for an effect on severe morbidity but less strong for an effect on mortality. The few data available from low/middle-income countries are consistent with an effect on mortality.

Proximity of the data to cause specific mortality effect:
Moderate (severe morbidity)

Limitations:
The control groups in most or all of these studies will have had access to a high level of routine care whereas the group of interest for programmes in low-income countries are newborns currently receiving little or no medical care.

Possible adverse effects:
Co-amoxiclav is not recommended as it has been associated with an increased risk of necrotizing enterocolitis.

may relate to disruptions in the microbial colonization of the neonatal gut by low- virulence microflora that has recently been demonstrated to begin *in utero*, even with intact fetal membranes, allowing subsequent colonization by more virulent micro-organisms following birth.[34] In contrast, antibiotic therapy following pPROM may prevent the ascending colonization of amniotic fluid by more virulent strains arising from the maternal lower genital tract, thereby reducing neonatal infections.

Empiric antibiotic therapy following pPROM reduces risk of neonatal respiratory distress, intra-ventricular haemorrhage and confirmed neonatal sepsis. Whereas most of the data supporting this conclusion derive from studies performed in high-income countries, the limited data from low and middle-income countries suggest similar reductions in neonatal morbidity. Empiric antibiotic therapy following pPROM represents an efficacious and low cost intervention to improve neonatal outcomes. Studies to assess translational feasibility of this intervention and to track its coverage in low and middle-income countries are urgently needed.

Conclusion

Although there are many trials and the results of these trials are quite consistent, we have graded the overall evidence quality as moderate because of the limited evidence from low and middle-income settings, and the fact that the strong evidence of effectiveness is for severe morbidity rather than mortality. In order to estimate mortality effects, we have had to make certain assumptions and in doing so we have tried to be conservative. In low-income settings where infections in pregnancy are more prevalent, yet the available care for mothers and for babies is much more limited, the impact of antibiotic therapy may be greater than in high-income settings. Nevertheless, we propose that, amongst births complicated by pPROM, empiric antibiotic therapy could reduce deaths due to complications of prematurity by 12% and deaths due to sepsis by 39%. Taking account of the proportion of births affected by pPROM and the proportion of sepsis deaths that may occur in pre-term babies in low-income settings, these effects translate into a 4% reduction in all deaths due to complications of prematurity and an 8% reduction in all deaths due to neonatal sepsis.

Supplementary data

Supplementary data are available at *IJE* online.

Funding

Acknowledgements

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