Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial

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Summary

Background **One in eight schoolchildren have an episode of acute infective conjunctivitis every year. Standard clinical practice is to prescribe a topical antibiotic, although the evidence to support this practice is scarce. We undertook a randomised double-blind trial to compare the effectiveness of chloramphenicol eye drops with placebo in children with infective conjunctivitis in primary care.**

Methods **Our study included 326 children aged 6 months to 12 years with a clinical diagnosis of conjunctivitis who were recruited from 12 general medical practices in the UK. We assigned 163 children to receive chloramphenicol eye drops and 163 to receive placebo eye drops. Eye swabs were taken for bacterial and viral analysis. The primary outcome was clinical cure at day 7, which was assessed from diaries completed by parents. All children were followed up for 6 weeks to identify relapse. Survival statistics were used for comparison, and analysis was by intention to treat.**

Findings **Nine children were lost to follow-up (one in chloramphenicol group; eight in placebo group). Clinical cure by day 7 occurred in 128 (83%) of 155 children with placebo compared with 140 (86%) of 162 with chloramphenicol (risk difference 3·8%, 95% CI –4·1% to 11·8%). Seven (4%) children with chloramphenicol and five (3%) with placebo had further conjunctivitis episodes within 6 weeks (1·2%, –2·9% to 5·3%). Adverse events were rare and evenly distributed between each group.**

Interpretation **Most children presenting with acute infective conjunctivitis in primary care will get better by themselves and do not need treatment with an antibiotic.**

Lancet 2005; 366: 37–43

Published online June 22, 2005
DOI:10.1016/S0140-6736(05)66709-8

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Introduction

Acute infective conjunctivitis has a substantial effect on the health-service workload despite its low morbidity. The disease accounts for up to 1% of consultations in primary care.[1,2] One in eight children have an episode of conjunctivitis every year,[3] with more than 1 million episodes in the UK and more than 5 million in the USA. Although a diagnosis of acute conjunctivitis is usually straightforward, most family doctors recognise the difficulty of differentiating a viral cause from a bacterial cause. Standard clinical practice is the prescription of topical antibiotics,[4] which reinforces the need for consultation, and the scale of ocular antibiotic prescriptions is large—in England, 2·3 million are issued every year in primary care to individuals of all ages.[5]

Antibiotic resistance is a growing global problem. With research showing little benefit from antibiotics in children with sore throat and otitis media,[6,7] there has been a reduction in antibiotic prescribing in the UK for common childhood respiratory viral infections. Acute conjunctivitis often has a bacterial cause and therefore prescription of antibiotics seems rational. Moreover, social factors and public-health policy often dictate that children receive treatment before returning to nursery or school (Rose PW, Ziebland S, Harnden A, et al, unpublished). A Cochrane systematic review of treatment showed that topical antibiotics resulted in significantly greater clinical and microbiological remission than placebo, but also showed a high rate of resolution with placebo.[8] However, the included trials were all based on secondary-care populations, with exclusively bacterial infection and in which disease severity was probably increased. Most patients present in primary care with mild disease, so extrapolation of the Cochrane results to this setting would be difficult. We designed a randomised trial to investigate the effectiveness of topical chloramphenicol for children presenting with acute infective conjunctivitis presenting in primary care.

Methods

Participants

The study was a placebo-controlled, double-blind, randomised controlled trial consisting of 326 children with a clinical diagnosis of conjunctivitis. Children were randomly assigned to receive chloramphenicol (n=163) or placebo eye drops (n=163). Chloramphenicol was chosen because it is the most common preparation used by family doctors[4] and has a low rate of resistance in common organisms.[9,10] Previous fears about the drug's safety[11] have not been proven.[12] The study was approved by the Oxfordshire clinical research ethics committee (C01·204).

12 practices in Oxfordshire, UK, were recruited to participate in the Oxford Childhood Infection Study (OXCIS). Family doctors in these practices recruited

children aged between 6 months and 12 years who presented during office hours with a working diagnosis of acute infective conjunctivitis. Children were excluded if they were known to be allergic to chloramphenicol, were taking any antibiotic currently or within the previous 48 h, were immunocompromised, or had evidence of severe infection (eg, periorbital cellulitis). Some children were prepared to be assessed and were followed up but were not prepared to undergo random assignment, usually because their parents specifically wanted an antibiotic. These children followed the protocol without undergoing randomisation—to allow comparison of baseline characteristics with those who were included—but were excluded from the main trial analysis.

Procedures

Recruitment occurred between October and April in 2001–02, 2002–03, and 2003–04, because more infective events rather than allergic conjunctivitis (the main clinical differential diagnosis in children) arise during these months. The recruiting family doctors gave parents a standard information sheet, with written information designed for children. Usually within 4 h of recruitment, children were seen by a research nurse, either in the family doctor's surgery or at home. The study was explained to parents and children, and those agreeing to participate signed a consent form.

We undertook an audit of the medical records of all children consulting a family doctor in the recruiting practices. The audit period was for 1 week every month during recruitment. The audit recorded all children in the age group who had presented with acute infective conjunctivitis, including those presenting out of working hours, to estimate the proportion of all children who were recruited in our study.

For baseline assessments, a research nurse assessed clinical severity, including the degree of redness of the eye, by comparison with validated photographs.[13] Two conjunctival swabs were taken from the worst-affected eye by use of a cotton swab for bacterial culture and a Dacron swab (Technical Services Ltd, Heywood, UK) for viral PCR assays. The Dacron swab was immediately placed into stabilising buffer (NucliSens lysis buffer, bioMerieux UK, Basingstoke, UK). All research nurses were trained in proper conjunctival sampling techniques by a nurse specialist from the Oxford Eye Hospital, Oxford, UK.

Identical bottles were prepared containing either 0·5% chloramphenicol (Preservative Free Eye Drops BP) or distilled water with the excipients boric acid (1·5%) and borax (0·3%). The active and placebo drops were prepared externally and labelled A and B by the supplier; one person locally knew the code but did not participate in the trial. The bottles were randomised centrally by use of random number tables in blocks of ten.

Parents were given a bottle of eye drops by the recruiting nurse with instructions to put one drop in each of their child's affected eye every 2 h for the first 24 h when their child was awake and then four times daily until 48 h after the infection had resolved. Parents were asked to complete a symptom sheet about their child's condition every time drops were given and also record when they regarded the disease as cured.

At 7 days' follow-up, the child was seen again by a research nurse after recruitment when a clinical assessment was made and two swabs were taken from the same eye as the first swab. Parents were telephoned 6 weeks to identify any further eye problems since the end of the trial. Any additional reported contact with the family doctor or hospital in this time was confirmed with reference to medical records of the children.

The primary outcome measure was the clinical cure rate at 7 days, as stated by parents. The length of time from recruitment to cure was determined from the diary; the time of cure was the first recorded time in the diary after which none of three symptoms (pain, redness, or discharge) was recorded. Any discrepancy between the recorded time of cure and the continuous entries in the diary was resolved by discussion among the researchers. In one case with diary information missing, the outcome at 7 days was assessed from the research nurse's records.

For microbiological outcome measures, conjunctival swabs were taken to the laboratory immediately after sampling and processed on arrival. Blood agar and chocolate agar plates were inoculated with cotton swabs and the tubes of stabilising buffer were stored at –80°C until molecular testing was completed. Agar plates were incubated at 37°C in 5% CO_2 for at least 48 h, and all morphologically different bacterial types were identified by standard clinical microbiological techniques. We used molecular assays to detect the presence or absence of adenovirus, picornavirus, herpes simplex virus, and *Chlamydia trachomatis* (Brueggemann AB, Rose PW, Perera R, et al, unpublished).

There is still debate about exactly which bacteria, other than *Haemophilus influenzae* and *Streptococcus pneumoniae*, are pathogenic in childhood conjunctivitis. Because we needed to define our microbiological outcome measures with respect to bacterial cause, we undertook a meta-analysis to compare the bacteria cultured from the conjunctivae of 518 children with conjunctivitis and 283 healthy control children, aggregating data from two previous studies[14,15] with our unpublished data (figure 1). The most common organisms in conjunctivitis samples compared with controls were *H influenzae*, *S pneumoniae*, and *Moraxella catarrhalis*. Evidence showed substantial heterogeneity in the study-specific risk ratios for coagulase-negative *Staphylococcus* spp. This result was probably due to the large group of different staphylococci, and therefore every study probably had varying isolation rates of individual *Staphylococcus* species. A species-specific analysis was not possible, and therefore the pooled risk ratio estimate for coagulase-negative *Staphylococcus* species should be interpreted with caution. Thus, we assessed microbiological outcomes by

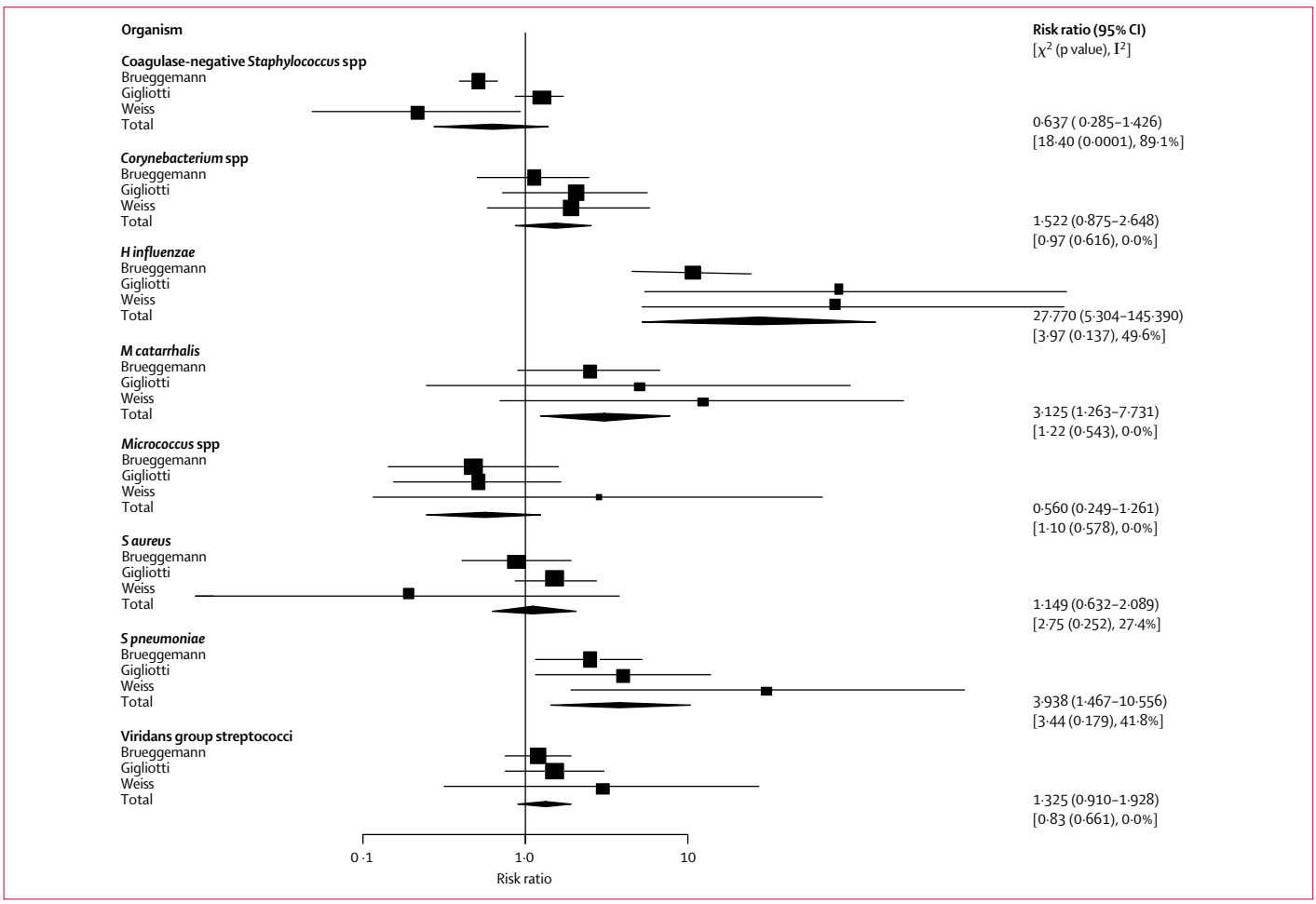

Figure 1: **Meta-analysis of three datasets reporting presence of bacterial organisms recovered from the conjunctivae of children with conjunctivitis and healthy controls**

comparing the number of colony-forming units at recruitment and at day 7 for these three organisms.

Colony counts were grouped as follows: 100 or more colonies=3, 11–99=2, 1–10=1, and no growth=0. The outcome was the difference between colony count classifications on the recruitment and swabs at day 7 for *H influenzae*, *S pneumoniae*, and *M catarrhalis* identified in every case. Zero colony counts on the second swab were labelled as cured, reduced colony counts labelled as improved, same colony counts labelled as unchanged, and increased colony counts labelled as worse. If *H influenzae*, *S pneumoniae*, or *M catarrhalis* were detected concomitantly, the final outcome was taken as the worst outcome among the multiple bacteria. To assess the effect of the intervention, children who were cured or improved were compared with those that were unchanged or worse in the two groups.

Statistical analysis

For all dichotomous outcomes, the risk difference between the chloramphenicol and placebo groups with 95% CIs was calculated. For the clinical cure outcome at day 7, an estimate of the number of children needed to treat (NNT=1/risk difference) was obtained. A Mann-Whitney test was used to compare time to clinical cure (continuous), since this was highly skewed. Clinical cure rates in the two groups were compared with the log-rank test and Kaplan-Meier survival statistics. Individuals lost to follow-up were treated as still not cured by the end of day 7 (ie, intention-to-treat analysis). We preplanned a subgroup analysis with respect to microbiological cause. Data were double entered into Microsoft Access and analysed with SPSS version 12.0 for Windows. The main analysis was undertaken before the randomisation code was broken. Meta-analyses of random-effects models were used to define which bacterial organisms were greatly associated with conjunctivitis, with relative risk as the summary statistic, whereas heterogeneity was assessed by use of χ^2 and I^2 statistics.[16]

A 19% difference in cure rate at 7 days had been previously reported[17] and was judged by all investigators to be a clinically important difference.

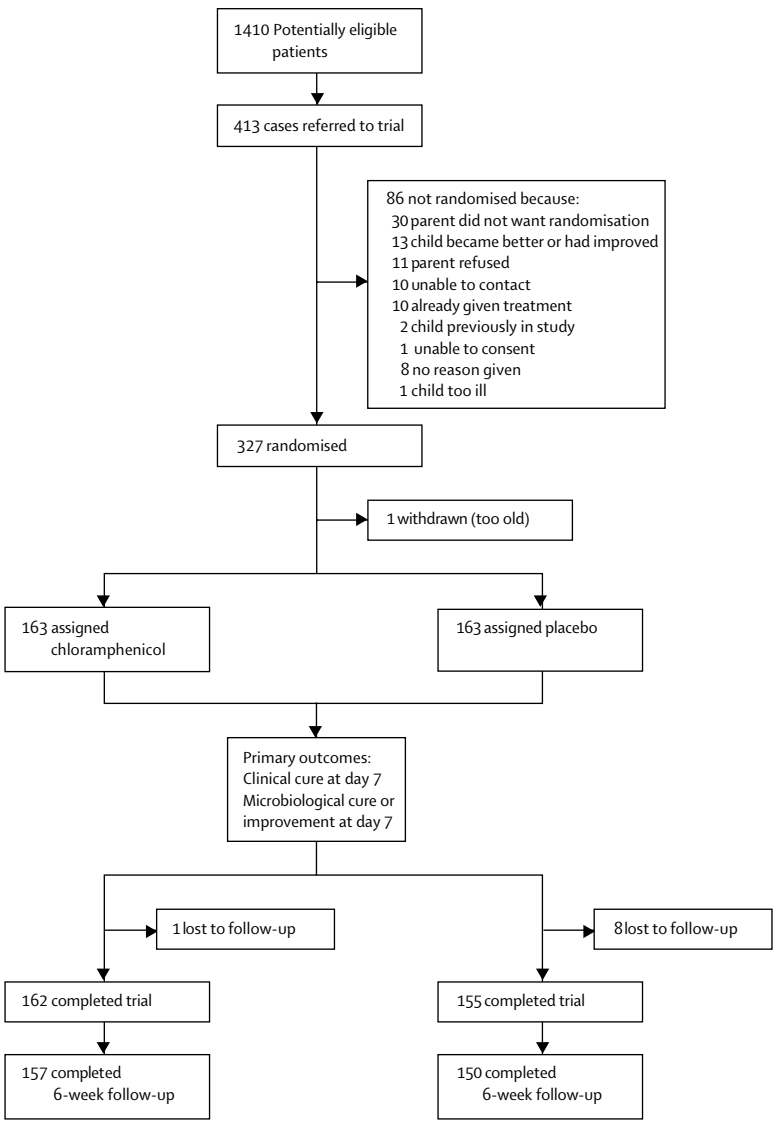

Figure 2: **Trial profile**

	Chloramphenicol (n=163)	Placebo (n=163)	Non-randomised children (n=30)
Age (years)			
Mean (SD)	3·3 (2·8)	3·3 (2·6)	3·7 (2·9)
Median (IQR)	2·4 (1·2–4·3)	2·6 (1·3–4·3)	2·9 (1·4–4·9)
Sex			
Number of male individuals	83 (51%)	87 (53%)	19 (63%)
Clinical features			
Moderate or severe redness	36/153 (24%)	39/152 (26%)	10 (33%)
Purulent discharge	135/162 (83%)	130/161 (81%)	28 (93%)
Pain or soreness	81/163 (50%)	77/162 (48%)	22 (73%)
Unilateral	58 (36%)	50 (31%)	11 (37%)
Social class*			
Professional or managerial	90/161 (56%)	77/157 (49%)	16 (53%)

*Taken as the mother's social class; if data were missing the mother's partner's social class was used.

Table 1: **Baseline characteristics of eligible children**

The initial planned sample size (n=500) cited in the original protocol was sufficient to detect this difference with a power of 80%, α=0·05 using a two-tailed test based on a placebo cure rate of 72%, and a prevalence of bacterial events of 60% (with the assumption that viral events would be unaffected by the antibiotic). However, the sample size was recalculated (without breaking the randomisation code) when these later assumptions clearly did not hold—almost 80% of events were bacterial and the overall 7-day cure rate was more than 80%. After the third recruitment winter, we re-estimated that we had already achieved 80% power to detect a 12–14% difference and if we continued to recruit to the original sample size, this power would not increase substantially; the trial was therefore stopped.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the trial profile. From the audit, an estimated 29% of all children presenting in the study period were recruited. No clinical differences were seen between the baseline characteristics of the children in both the chloramphenicol and placebo groups (table 1). More children complained of pain or soreness in the non-randomised group (n=30, p=0·01), but no other difference was recorded between the baseline characteristics of the randomised and non-randomised groups.

Table 2 shows no significant difference between the chloramphenicol and placebo groups in the types and prevalence of bacteria and viruses detected. Pathogenic bacteria were cultured from about 250 children: about 60% were *H influenzae*, about 20% *S pneumoniae*, and about 10% *M catarrhalis*. Adenovirus or picornavirus (or both) were detected from more than 10% of

	Chloramphenicol (n=162)	Placebo (n=163)	Total (n=325)
Bacteria			
Total*	126 (78%)	126 (77%)	252 (78%)
H influenzae	99 (61%)	98 (60%)	197 (61%)
S pneumoniae	32 (20%)	32 (20%)	64 (20%)
M catarrhalis	20 (12%)	16 (10%)	36 (11%)
Virus			
Total	24 (15%)	19 (12%)	43 (13%)
Adenovirus	11 (7%)	8 (5%)	19 (6%)
Picornavirus	13 (8%)	11 (7%)	24 (7%)

Data are number (%). *Some samples from children grew more than one type of pathogen.

Table 2: **Microbiological causes at baseline**

children. Overall a pathogen was identified in 261 (80%) children, of whom 217 (67%) grew one or more bacterial pathogens, nine (3%) showed a virus alone, and 34 (10%) were positive for both a virus and bacteria. *C trachomatis* and herpes simplex virus were not detected in any of the children.

At day 7, 86% of children were clinically cured in the antibiotic group compared with 79% in the placebo group (table 3). This intention-to-treat analysis included children lost to follow-up as treatment failures—if children lost to follow-up were excluded, 86% of children were clinically cured in the antibiotic group compared with 83% of those in the placebo group (table 3). The NNT to achieve one more clinical cure by day 7 was therefore estimated as 14–25.

No significant differences were seen in clinical cure rate, microbiological improvement or cure, or median time to cure at day 7. Even in the subgroup of children who grew a bacterial pathogen only, the clinical cure rate did not differ significantly between antibiotic (85%) and placebo (80%) groups—an estimated NNT of 22. However, the numbers of children treated with chloramphenicol who showed bacterial eradication (40%) differed significantly to those treated with placebo (23%, NNT 6; table 3).

Figure 3 shows the proportion of children reported as cured on every day of the trial. The curves diverge at day 2 (26% cured in chloramphenicol group and 16% in the placebo group) and remain separated until day 7 (log-rank test p=0·025). The mean difference in the time to cure was 0·3 days, which does not change greatly from days 2 to 7. Nine children failed to complete the trial (because they did not respond to telephone attempts to make an appointment); eight of these were in the placebo group. Some children were prescribed antibiotic eye drops by their family practitioner during the trial because of parental concern about lack of resolution; however, the numbers were small (12 events) and equal in each group.

6-week audit data were available for 307 (94%) children. Adverse events were rare and evenly distributed between each group. Only one event could have been possibly attributed to chloramphenicol: a child with swollen eyelids and face. Relapses or new episodes of conjunctivitis were rare (<5%) in the 5 weeks after the trial and were evenly distributed between the groups (table 3). In addition to consultations for conjunctivitis, 19 (6%) children in the antibiotic group and 19 (6%) in the placebo group consulted their family doctor for other minor problems between day 8 and 6 weeks after the trial.

Discussion

We have shown that symptoms resolve without antibiotics in most children with acute infective conjunctivitis. In our intention-to-treat analysis, we recorded a

	Chloramphenicol (n=163)*	Placebo (n=163)*	Difference (95% CI)
Time to cure (days)			
Median (IQR)	5 (3 to 6)	5 (4 to 7)	0
Mean (SD)†	5·0 (1·9)	5·4 (1·9)	−0·33 (−0·75 to 0·09)
Clinical cure at day 3			
Intention-to-treat comparison	64 (39%)	54 (33%)	6·2% (−4·3% to 16·5%)
Clinical cure at day 7‡			
Intention-to-treat comparison	140 (86%)	128 (79%)	7·4% (−0·9% to 15·6%)
Exclusion of children lost to follow-up	140/162 (86%)	128/155 (83%)	3·8% (−4·1% to 11·8%)
Children with bacterial pathogen only	101/119 (85%)	94/117 (80%)	4·6% (−5·1% to 14·2%)
Microbiological cure at day 7			
Microbiological cure	50/125 (40%)	29/125 (23%)	16·8% (5·5% to 28·1%)
Microbiological improvement	31/125 (25%)	40/125 (32%)	−7·2% (−18·3% to 3·9%)
Microbiological cure or improvement	81/125 (65%)	69/125 (55%)	9·6% (−2·5% to 21·7%)
Relapse rate			
Further episode of conjunctivitis within 6 weeks	7 (4%)	5 (3%)	1·2% (−2·9% to 5·3%)
Adverse clinical events			
Day 1–7§	3 (2%)	3 (2%)	0% (−2·9% to 2·9%)

Data are number (%) unless stated otherwise. *Percentages rounded to nearest whole number. †Censored from day 8. ‡Includes one child whose diary was incomplete but nurse reported clinical cure. §Chloramphenicol group: one child developed eyelid and facial oedema, one admitted with bronchiolitis, and one subsequently diagnosed with Thygeson's keratitis. Placebo group: two children developed a generalised rash and one developed otitis media.

***Table 3*: Main outcomes in children treated with chloramphenicol and placebo eye drops**

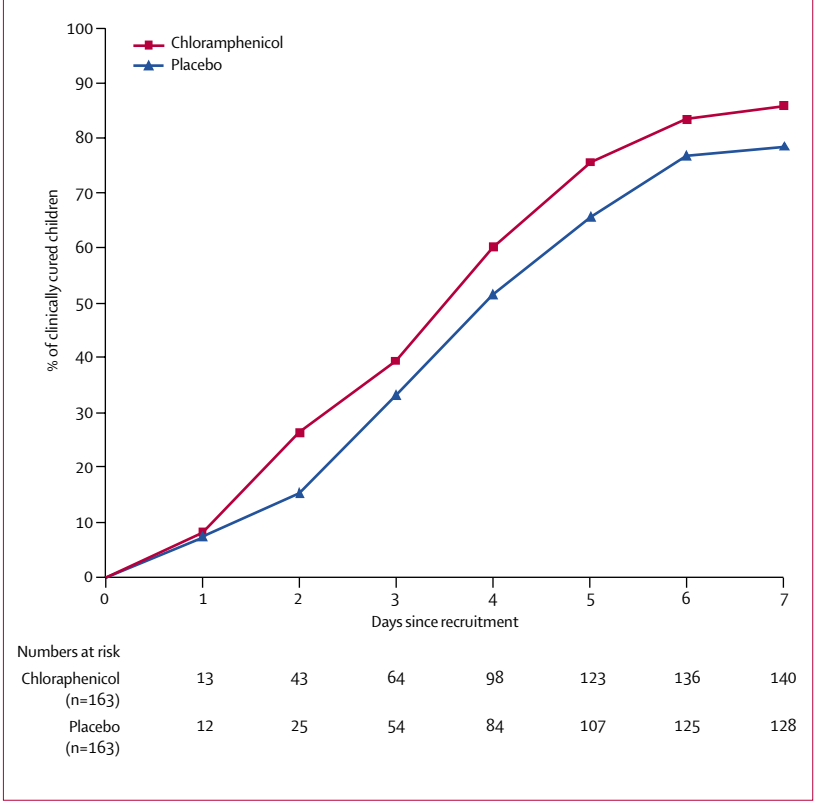

***Figure 3*: Cumulative proportion of children reported as cured during first week of treatment, according to parents' diaries**

Data are reported on intention-to-treat analysis and children lost to follow-up are included in the denominator in calculating percentages. Children clinically cured after 7 days were censored from the study. With exclusion of children lost to follow-up, the cumulative cure rate at 7 days was 86% in the chloramphenicol group and 83% in the placebo group. Day 0=day of recruitment.

modest improvement in symptom resolution at day 7 in the group receiving chloramphenicol. This improvement was further reduced if children lost to follow-up were excluded. We have no reason to believe that these excluded children would behave differently to those completing the trial. About half a day was gained in time to resolution between children treated with antibiotic and those with placebo, but this gain has to be weighed against the personal and health-care costs of a condition that improves without treatment. Our microbiology results confirm that chloramphenicol does reduce the number of pathogenic bacteria in the eye, but eradication is not essential for a clinical cure. Follow-up for 6 weeks after diagnosis showed that complications and relapse were uncommon, even without treatment.

Overall quality of the trial was good. The randomisation method was robust, and masking was maintained. The dropout rate was low—nearly 95% of children were followed up for 6 weeks after recruitment. The referral audit indicated that a third of all children presenting to the family practitioner with acute conjunctivitis during the recruitment period were referred into the trial. This proportion is acceptable for a trial of an acute disorder in primary care that had no recruitment out of working hours. However, although individuals who were not randomly assigned were similar to those in the trial, we cannot exclude selection bias completely: family doctors could have recruited patients with less severe symptoms to the trial, believing that those with more severe symptoms need antibiotics; and patients presenting out of working hours could have had more severe symptoms and a more abundant conjunctival flora of pathogens.

The microbiological quality of the study also compares well with previous work. By use of a combination of culture and PCR, we could identify a microbiological cause in 80% of the children. The high yield of pathogens indicates that the training in the sampling technique was successful and the recruiting primary care physicians were good at identifying acute infective conjunctivitis and differentiating the disease from other causes of red eye. We recorded lower colony counts for *M catarrhalis* than for *H influenzae* and *S pneumoniae*, but exclusion of *M catarrhalis* as a pathogen in our analysis made no substantial difference to the results.

Oxfordshire has a social class structure that is less deprived than some other parts of the UK, but social class is more likely to affect transmission than microbiological causes of disease. We have no reason to believe that the children included in the trial were atypical in any other way. Thus, our results are probably generalisable to most primary care settings in developed countries.

The health economic argument against antibiotic prescription for acute conjunctivitis is compelling. The cost of 1 million general practice consultations and antibiotic prescriptions every year is substantial. However, parental concern and the current exclusion policy of many schools and nurseries for children with conjunctivitis could make implementation of a change in prescription policy difficult. An education programme and change in school policy to reflect national public-health advice might be needed before family doctors can realistically achieve a reduction in antibiotic prescriptions. Our study design could not assess the effect of non-prescriptions on transmission rates. Acute infective conjunctivitis is regarded as potentially transmissible, especially in children younger than 5 years. Despite our results, antibiotic treatment might still reduce the absolute number, and hence transmissibility of pathogens, and further research might be necessary if antibiotics cease to be prescribed for this disorder.

We recorded no evidence to suggest that microbiological investigation, for example near patient testing, to distinguish viral from bacterial causes with an immediate result, would be helpful. The small treatment benefit we saw arose even in children with proven bacterial infection. Bacterial eradication was unimportant—clinical cure was reported by parents even if bacteria could still be recovered at day 7. The relapse rate after antibiotic treatment stopped was low and irrespective of the randomisation group. We did not identify any children with *C trachomatis* infection in our cohort; substantial rates of infection with *C trachomatis* might be a reason for ongoing recommendations of antibiotic treatment in less economically developed countries.

We chose to assess the effectiveness of chloramphenicol because this drug is the most commonly used topical antibiotic for conjunctivitis in the UK, where antibiotic resistance to chloramphenicol is rare—no resistant isolates were detected in the study. No evidence suggested that another antibiotic would have been more effective. The other commonly used antibiotic in the UK is fusidic acid, and most trials comparing this compound with chloramphenicol have shown no difference in effectiveness.[18] Our trial cannot exclude the possibility of a lubricant hastening the resolution of symptoms. Therefore, parents should be encouraged to cleanse their children's eyes if an antibiotic is not prescribed.

We suggest that our results show that healthy children with acute conjunctivitis do not need an ocular antibiotic at first presentation to primary care. Parents should be encouraged to treat children themselves without medical consultation, unless their child develops unusual symptoms or the symptoms persist for more than a week.

Contributors

All authors participated in the conception and drafting of the study and commenting on drafts of the paper. P W Rose, as principal investigator, was responsible for overseeing the day-to-day running of the trial, statistical analysis, and report writing, A Harnden acted as principal investigator while P W Rose was on sabbatical leave for 6 months, A B Brueggemann was responsible for laboratory analysis of samples and A B Brueggemann and D Crook provided support on all microbiological aspects of the trial, R Perera was responsible for data cleaning and statistical analysis.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The research was funded by the Medical Research Council as part of a programme grant in childhood infection in primary care (G0000340). We thank the research nurses involved in this study: Susan Bates, Sarah Bryson, Sarah Burton, Susan Elsom, Fiona Goddard, Geraldine Jewell, Helen Lambourne, Diane McLeod, Angela Roome, Susan Rous, Judy White, and Wendy Willmore; David Griffiths for laboratory support; Susan Smith for administrative support; all the physicians and nurses in the OXCIS network of surgeries for recruiting the children into this study; and the participating children and parents.

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