

Early corticosteroid use in infants with a clinical diagnosis of *Pneumocystis jiroveci* pneumonia in Malawi: a double blind randomised clinical trial

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**Background:** *Pneumocystis jiroveci* pneumonia (PJP) is the most common opportunistic infection in infants with vertically acquired HIV infection and the most common cause of death in HIV-infected infants.

**Objectives:** To determine whether early administration of adjuvant corticosteroids in addition to standard treatment reduces mortality in infants with vertically acquired HIV and clinically diagnosed PJP when co-infection with cytomegalovirus and other pathogens cannot be excluded.

**Methods:** A double-blind placebo-controlled trial of adjuvant prednisolone treatment in HIV-exposed infants aged 2–6 months admitted to Queen Elizabeth Central Hospital, Blantyre who were diagnosed clinically with PJP was performed. All recruited infants were HIV-exposed, and the HIV status of the infant was confirmed by DNA-PCR. HIV-exposed and infected infants as well as HIV-exposed but non-infected infants were included in the study. The protocol provided for the addition of prednisolone to the treatment at 48 hours if there was clinical deterioration or an independent indication for corticosteroid therapy in any patient not receiving it. Oral trimethoprim-sulfamethoxazole (TMP/SMX) therapy and full supportive treatment were provided according to established guidelines. Primary outcomes for all patients included survival to hospital discharge and 6-month post-discharge survival.

**Results:** It was planned to enroll 200 patients but the trial was stopped early because of recruitment difficulties and a statistically significant result on interim analysis. Seventy-eight infants were enrolled between April 2012 and August 2014; 36 infants (46%) were randomised to receive corticosteroids plus standard treatment with TMP/SMX, and 42 infants (54%) received the standard treatment plus placebo. In an intention-to-treat analysis, the risk ratio of in-hospital mortality in the steroid group compared with the standard treatment plus placebo group was 0.53 [95% CI 0.29–0.97,  $P=0.038$ ]. The risk ratio of mortality at 6 months was 0.63 (95% CI 0.41–0.95,  $P=0.029$ ). Two children who received steroids developed bloody stools while in hospital.

**Conclusion:** In infants with a clinical diagnosis of PJP, early use of steroids in addition to conventional TMP/SMX therapy significantly reduced mortality in hospital and 6 months after discharge.

**Keywords:** HIV, *Pneumocystis jiroveci* pneumonia, Infant

## **Introduction**

*Pneumocystis jiroveci* pneumonia (PJP) is a eukaryotic organism with features resembling a protozoa and fungi; phylogenetic analysis has demonstrated it to be a fungus. Exposure and colonisation occur during the first few months of life and invasive disease may occur during this initial infection, especially in infants with severe T-cell defects.<sup>1</sup> It is the most common opportunistic infection in infants with vertically acquired HIV. It occurs in infants with low CD4 counts<sup>2</sup> and is the most common cause of death in HIV-infected infants under 6 months of age,<sup>3</sup> accounting for one third to a half of all HIV-related deaths in African infants.<sup>4</sup> Clinical features include severe respiratory distress and severe hypoxaemia, with a relatively clear chest or diffuse signs on auscultation, and a low-grade fever.<sup>5</sup> In the absence of diagnostic tests in most parts of sub-Saharan Africa, many clinicians commence treatment with trimethoprim-sulfamethoxazole (TMP/SMX) and often adjunctive corticosteroids on the basis of clinical suspicion only.<sup>6</sup> The rationale for steroids is that inflammation often worsens after treatment with high-dose TMP/SMX has commenced and the patient may deteriorate. A systematic review suggested a beneficial effect of adjunctive steroids for PJP-infected adults with hypoxaemia, with a reduced risk of death and a reduced risk of requiring mechanical ventilation (RR 0.38).<sup>7</sup> Only one study in infants was included and it demonstrated the relative risk of death in hospital to be 0.81 but with wide confidence intervals.<sup>8</sup> Therefore infants were not included in the authors' recommendations for steroids as adjunctive treatment owing to insufficient evidence.<sup>7</sup>

One hundred infants with an average age of 3 months who had been exposed to HIV but had not been confirmed as infected and had been diagnosed clinically with PJP were randomised to receive prednisolone after 48 hours if there was clinical deterioration. Patients in the prednisolone group had a 43% better chance of survival but this was not statistically significant.<sup>8</sup>

In the absence of conclusive evidence from a randomised controlled trial, there are a number of concerns about extrapolating to infants the benefits of steroids in adults. This includes concern about the immunosuppressive effects of steroids in infants who have an immature immune system as well as HIV-related immunosuppression. HIV-exposed infants with respiratory distress are often co-infected with viruses, particularly cytomegalovirus (CMV) whose role in the pathological process is unclear, and steroids may further immunosuppress this group of infants and contribute to the development of CMV pneumonia. CMV viraemia peaks at around 3–4 months of age and is higher in HIV-infected than in HIV-exposed infants.<sup>9</sup> One study described 85 HIV- and PJP-infected infants in the pre-ART era, 48% of whom were co-infected with CMV.<sup>10</sup> PJP/CMV co-infected infants were more likely to require mechanical ventilation, and there was a trend towards poorer survival. Adjunctive steroids did not improve survival but it raised the question of whether this was because of the high rate of co-infection with CMV. Thus there are concerns that steroids may negatively affect the clinical course in an infant co-infected with CMV, which might outweigh the potential benefit of steroids in PJP-infected infants in a setting where CMV can be neither tested nor treated.

The aim of this study was to determine whether the early administration of adjuvant steroids with high-dose oral TMP/SMX reduces mortality in infants with

vertically acquired HIV and clinically diagnosed PJP when co-infection with CMV and other pathogens cannot be excluded.

## **Methods**

### *Study design*

This was a randomised, double-blind, placebo-controlled trial in HIV-exposed infants aged 2–6 months admitted to hospital with severe respiratory distress who were diagnosed clinically with PJP.

The study was undertaken in the paediatric department of Queen Elizabeth Central Hospital (QECH), Blantyre. QECH has 300 paediatric beds and admits 25,000 children a year, and there are about 80,000 emergency and outpatient attendances per annum. QECH is an 1100-bed tertiary, government hospital that serves the southern half of Malawi. It is the main teaching hospital of the medical school and the district hospital for the Blantyre region. All treatment is free. In 2011, Malawi introduced integrated anti-retroviral/ prevention of mother-to-child transmission (ART/PMTCT) guidelines which integrated PMTCT services into maternal and child health services. The guidelines include lifelong ART for all pregnant women, regardless of WHO stage or CD4 count.<sup>11</sup>

### *Study participants*

Infants aged 2–6 months with vertically acquired HIV or HIV exposure and with clinical features of PJP were enrolled after guardians had been fully informed about the study in Chichewa or English and had given written consent. PJP was defined by meeting all the following clinical criteria: vertically acquired HIV or HIV exposure, an oxygen

requirement (saturation on air <90%) and severe respiratory distress and cough. Severe respiratory distress was defined as an infant with tachypnoea (respiratory rate >60 breaths/min), tachycardia (heart rate >140 beats/min), subcostal and intercostal recessions and flaring of the alae nasi. Although not a requirement for a clinical diagnosis, a history of low-grade fever, clear chest or absence of focal signs such as crackles on auscultation were considered to support a clinical diagnosis of PJP.

Patients were excluded if they had a previously known allergy, hypersensitivity or other contra-indication for steroids or TMP/SMX. Infants were also excluded if they had been treated previously for suspected PJP or if there had been a delay of more than 24 hours in commencing steroids after starting high-dose TMP/SMX. Infants with clear clinical features of bronchiolitis and those whose guardians did not consent were excluded.

#### *Randomisation and masking*

Infants were randomised to one of two groups: standard care plus placebo or the intervention group. Computer-generated randomisation was completed by an independent statistician before the study commenced. Infants were allocated to receive oral prednisolone or placebo, TMP/SMX and supportive treatment. Allocation was concealed by using numbered, sealed, opaque envelopes in sequence which were opened by the enrolling clinician after obtaining consent. No stratification methods were used. The placebo and study drug were identical when in white powder form and reconstituted in water. The placebo was calcium carbonate. Parents, guardians, enrolling clinician, nurses reconstituting and administering the study drug, those assessing outcomes and those

analysing the data were masked to the group assignment. The masking was assessed by an independent paediatrician.

### *Procedures*

Treatment with TMP/SMX was commenced upon diagnosis of PJP. Recruitment to the study (i.e. addition of either steroids or placebo) was undertaken within 24 hours of diagnosis. The study medicine identified in the envelope was given according to the child's body weight. The steroid regimen consisted of once daily oral prednisolone, 2 mg/kg for 7 days, then 1 mg/kg for 7 days, then 0.5 mg/kg for 7 days for a total of 21 days.

The protocol provided for the addition of prednisolone to the treatment of infants not receiving steroids at 48 hours if there was clinical deterioration or an independent indication for steroid therapy. The infant would then receive no more study solution and the prednisolone regimen in the treatment group would be commenced: 2 mg/kg for 7 days, then 1 mg/kg for 7 days, then 0.5 mg/kg for 7 days for a total of 21 days. The patients in the placebo and treatment groups who received prednisolone after randomisation were disregarded in a treatment-only analysis.

Infants in both arms were commenced on trimethoprim, 8 mg/kg/dose, plus sulphamethoxazole, 60 mg/kg/dose (TMP/SMX) twice daily for 21 days as per WHO Guidelines.<sup>12</sup> Given the suspected high rate of co-infection and to cover the main differential diagnosis of bacterial pneumonia, Patients were also commenced on parenteral benzylpenicillin (50,000 IU/kg/dose four times a day) and gentamicin (7.5 mg/kg once a day) for at least 5 days. Additional oral zinc sulphate, 10 mg daily for 7

days, was given because of growing evidence that zinc sulphate reduces fatality in HIV-exposed infants with pneumonia.<sup>13</sup> Nasal prong oxygen was provided if oxygen saturations were <90% in air. Oxygen was escalated according to the Malawi National Guidelines on the Care of the Infant and Neonate<sup>14</sup> and infants who required bubble continuous positive airway pressure (bCPAP Pumani, 3rd Stone Design, San Rafael, CA) received it, depending on availability.

On recruitment, the following medical and clinical history was obtained by study staff using standardised forms: details about the present illness; demographic details; past medical history (including pre-existing conditions); birth history; HIV status; previous hospitalisations; exposure to tuberculosis and visits to the local health centre.

Temperature, pulse rate, respiratory rate (over 1 minute) and weight were recorded. The infant's arterial oxygen saturation was measured with an appropriately sized sensor and a Nellcor pulse oximeter (Welch Allyn Spot Vital Signs Devices, Skaneateles Falls, NY, USA) placed on a toe or finger, while the patient breathed room air. Measurements were recorded after stabilisation for at least 3 minutes.

An ELISA and PCR for HIV was undertaken in all HIV-exposed infants according to the National HIV guidelines for early infant diagnosis of HIV.<sup>11</sup> As they met the criteria for 'presumed severe HIV disease', exposed infants who were clinically diagnosed with PJP were commenced on anti-retroviral treatment during hospital admission. The reason for commencing it before confirmation of HIV status was a delay in receiving DNA PCR results of 6–8 weeks.

In all infants, a thick blood film was tested for malarial parasites and packed cell volume estimated as standard care. Before antibiotics were commenced, 1–2 mls of

venous blood was taken for culture from all infants. The patients were re-evaluated twice daily until discharge from high dependency and daily until discharge from hospital.

#### *Follow-up post discharge*

After hospital discharge, infants were followed up by the study clinicians at 1, 3 and 6 months to assess survival and monitor adverse events.

#### *Outcomes*

The primary outcomes for all patients were survival to hospital discharge and 6-month post-hospital discharge survival. Adverse events related to the antibiotics or steroids were documented and graded as mild, moderate and severe: mild if the event was transient and did not interfere with the child's activity; moderate if the event caused sufficient discomfort to interfere with activity; and severe if the event was incapacitating and prevented normal activity or resulted in death. If the severity changed over time, the maximum severity was recorded.

#### *Sample size and statistical analysis*

Hospital mortality in the sub-Saharan African region for HIV-exposed, PJP-infected infants ranges from 20% to 63%.<sup>15</sup> The most recently published estimate of mortality from PJP in HIV-exposed Malawian infants is 63%.<sup>5</sup> The study was published in 2000, before bCPAP was introduced and before antiretroviral treatment was widely available, and it included only a small number of infants (16) with confirmed PJP. A 2002 study from a tertiary care centre in South Africa reported a mortality rate of 27%.<sup>16</sup> For the

present study, the conservative figure of 45% was chosen for the purposes of sample size calculation. It was estimated that steroids could reduce mortality by 20%, as the study by Terblanche and colleagues<sup>8</sup> demonstrated a relative risk of mortality of 0.81 in those treated with steroids compared with those not given steroids. With a two-sided  $\alpha$  level of 0.05, it was necessary to enrol 200 patients in order to attain a power of 80% to detect a relative reduction of 20% in mortality in the steroid group.

Data were expressed as means and standard deviations. The Mann–Whitney test was used for continuous variables and the  $\chi^2$  test for categorical variables. A two-sided  $P$ -value of  $<0.05$  was considered to indicate statistical significance. Intention-to-treat analysis was used as well as a treatment-only per protocol analysis (PPA). Within the PPA, patients in the placebo and treatment groups who received prednisolone after randomisation were disregarded. The Kaplan–Meier method was employed to estimate time-to-event distributions, which were compared using the log-rank test and a cox-proportional hazard ratio. Analyses were performed with STATA, version 12.0.

### *Ethics approval*

Approval was granted by the College of Medicine Research and Ethics Committee.<sup>17</sup> The study was registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02149433. An independent safety-data monitoring committee (DSMB) reviewed the data on safety and efficacy at pre-determined intervals: after 50 patients had been recruited and every 6 months thereafter.

## **Results**

Infants were enrolled from 5 April 2012 to 28 August 2014. It proved impossible to recruit the sample size over this period of time, perhaps because of falling numbers of new HIV infections in neonates and to the routine use of preventive TMP/SMX for HIV-exposed infants, which is very effective in preventing PJP. After 2.5 years of the study, only 78 eligible infants had been enrolled with informed consent. Because of difficulties in continuing the study and the fact that it would take at least one more year to recruit even 100 participants, it was decided to provide the DSMB with an interim analysis of outcome data. Given the slower than expected recruitment to the study and that the interim analysis reported a statistically significant difference in mortality between the two groups of more than 20%, it was agreed to halt the study in May 2015.

Study enrolment, randomisation and follow-up are shown in the trial profile in Figure 1. Altogether, 116 infants were screened for eligibility: consent was refused for eight and 30 were ineligible for enrollment, and therefore 78 eligible infants were enrolled and randomly assigned to one of the two study groups. Thirty-six infants (46%) were randomised to receive steroids, TMP/SMX and supportive treatment, and 42 infants (54%) received the TMP/SMX and supportive treatment alone (placebo group). Two infants in the standard treatment group and three infants in the steroid group were given steroids because of clinical deterioration, per the protocol provision. When this occurred, the study solution was withheld and the infant was commenced on the prednisolone regimen as in the treatment group: 2 mg/kg for 7 days, then 1 mg/kg for 7 days, then 0.5mg/kg for 7 days for a total of 21 days. The two infants in the standard group who received steroids died while in hospital. Two of the three children in the steroid group who were taken off the study solution and given known steroids survived to hospital

discharge and one died. Of the two infants who survived; one was lost to follow-up and the other survived to 6 months.

All infants were followed up to discharge from hospital or in-hospital demise. After discharge from hospital, five infants (6%) were lost to follow-up at 6 months: three infants in the steroid arm and two in the standard treatment arm.

### **[f]FIG. 1[/f]**

#### *Demographic and clinical characteristics*

The base-line characteristics of the two treatment groups were similar (Table 1). The mean standard (SD) age was 3.5 (1.1) months, and 42% were male. Clinical signs and symptoms were consistent with published series of patients with a clinical diagnosis of PJP including hypoxia, tachypnoea and clear lungs. Twenty-seven mothers of recruited infants (34.6%) knew that they were HIV-positive during pregnancy. Sixteen mothers (20.5%) gave their infants daily nevirapine prophylaxis during the first 6 weeks of life and nine infants (11.5%) received daily prophylactic TMP 4 mg/kg/day plus SMX 30 mg/kg/day after 6 weeks of life according to the national HIV guidelines.<sup>11</sup> None of the recruited infants presented to hospital with a DNA-PCR result and none was on anti-retroviral medication on admission.

All infants were HIV-exposed; 47 (60.2%) were tested for HIV by DNA-PCR during admission. The other infants were not tested for HIV with DNA-PCR because they died before they could be tested. Thirty-seven infants (47.4%) tested positive for HIV by DNA-PCR and ten (12.8%) tested negative. These ten HIV-exposed but DNA-

PCR-negative infants were included in the analysis. Forty-one infants (52.6%) survived and qualified to commence antiretroviral treatment.

Of all recruited infants, bCPAP was commenced in 31 (40.8%). The most common reason for not providing a child with bCPAP was lack of available equipment. There was no statistical difference between the groups in the numbers managed by bCPAP.

#### [t]TABLE 1[/t]

#### *Outcomes*

The main outcome results for both the intention-to-treat analysis and per-protocol analysis are reported in Table 2. In the intention-to-treat analysis, 10 of 36 infants (27.8%) who received steroids died compared with 22 of 42 infants (52.4%) who received standard treatment only. Compared with the standard treatment group, the steroid group's risk ratio (RR) of in-hospital mortality was 0.53 (95% CI 0.29–0.97,  $P=0.038$ ). At 6 months post-hospital discharge, 15 of the 33 infants (45.5%) who received steroids had died compared with 29 of 40 infants (72.5%) who received the standard treatment alone (risk ratio 0.63, 95% CI 0.41–0.95,  $P=0.029$ ).

#### [t]TABLE 2[/t]

In the per-protocol analysis, nine of 36 infants (27.3%) who received steroids died compared with 20 of 40 infants (50.0%) who received standard treatment alone. Compared with the standard treatment group, the steroid group's RR of in-hospital mortality was 0.55 (95% CI 0.29–1.03,  $P=0.062$ ). By 6 months post-hospital discharge, 13 of 30 infants (43.3%) who received steroids had died compared with 27 of 38 (71.1%)

who received the standard treatment alone (RR 0.61, 95% CI 0.39–0.96,  $P=0.034$ ).

Figure 2 demonstrates that patients in the prednisolone group had a 53% better chance of survival at 6 months post-enrolment: According to the intention-to-treat analysis, the Cox proportional hazard ratio was 0.47 (95% CI 0.24–0.92,  $P=0.028$ ).

#### *Adverse events*

Two children who received steroids developed bloody stools while in hospital. This resolved within 2–3 days in one child who survived to 6 months post-discharge. The other child died from respiratory compromise while in hospital. No adverse events were noted in the standard treatment plus placebo group.

#### **Discussion**

In this double-blind, randomised trial, the early use of steroids in addition to conventional TMP/SMX and supportive treatment in HIV-exposed infants who are both HIV DNA-PCR-negative and HIV DNA-PCR-positive with a clinical diagnosis of PJP significantly reduced mortality compared with the placebo group. In a resource-poor setting in which accurate diagnostics may not be available, the findings suggest that it is safe and beneficial to give steroids to children with clinical findings which suggest PJP.

The Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities in resource-poor settings<sup>12</sup> now recommend empirical TMP/SMX for suspected PJP as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with chest indrawings or severe pneumonia. However, the guidelines do not mention whether adjunctive steroids should also be used. Our findings

suggest that empirical steroids should be included in these guidelines for HIV-infected and -exposed infants in whom there is clinical suspicion of PJP infection.

Infants infected with PJP may also be infected with CMV. In African children, CMV is usually acquired during the first year of life and HIV-infected infants are at increased risk of CMV pneumonia. The gold standard in terms of diagnosis is evidence of pathology on lung biopsy as identifying CMV in respiratory specimens may or may not be associated with pneumonia.<sup>9</sup> In a systematic review of nine paediatric autopsy studies, PJP was identified in 23% and CMV in 22% of autopsies on HIV-positive infants, with high rates of co-infection.<sup>18</sup> Another study examined lung tissue either by biopsy or using post-mortem tissue from 25 HIV-infected infants admitted to an intensive care unit with severe hypoxia: CMV was identified in 36% of patients, another 36% had dual infection and 24% had PJP alone.<sup>19</sup> Others found that 74% of HIV and PJP-infected infants (diagnosed molecularly) had CMV viraemia.<sup>15</sup> A study comparing levels of CMV viraemia between HIV-exposed and -infected infants with and without pneumonia reported that a level greater than 4.1 log copies/ml identified infants likely to have CMV infection.<sup>9</sup> Other researchers also used a cut-off of 4 log copies/ml to determine in which infants the empirical gancyclovir would be discontinued, a treatment they had commenced in all HIV-exposed infants who presented with acute respiratory failure.<sup>20</sup> It is therefore highly likely that infants in both arms of our study had CMV infection and pneumonia but, in the absence of the ability to diagnose or treat CMV, it appears that the addition of adjunctive steroids in HIV-positive and -exposed infants with a clinical diagnosis of PJP nonetheless reduced the mortality at discharge and at 6 months. Appropriate diagnosis and management of CMV in these patients would be optimal;

however, diagnosis and treatment of CMV with gancyclovir is not available in low-resource settings such as ours. This makes it difficult to determine whether steroids are also needed in these HIV-exposed infants when CMV is adequately managed.

It is more important to ensure that all pregnant women know their HIV status and that all infants are commenced on prophylactic TMP/SMX. In this cohort, only 35% of the mothers were aware of their HIV diagnosis and, of those who were aware, only 33% of their infants received prophylactic TMP/SMX. This is a biased sample as these infants presented with symptoms in keeping with PJP pneumonia. At a population level, in 2014, 79% of pregnant women in Malawi knew their HIV status, 93% of infants were commenced on nevirapine prophylaxis and 85% of infants were started on prophylactic TMP/SMX.<sup>21</sup>

Limitations of the study include not having a complete set of microbiologically confirmed diagnoses of PJP or CMV. Furthermore, chest radiograph findings as well as CD4 counts and viral loads would have been very useful in supporting the diagnosis of PJP. However, functioning radiographic equipment was not always available and infants were often too unstable to be transported safely to the radiology department. Similarly, in a resource-constrained environment, CD4 counts and viral loads are not routinely undertaken according to the National Guidelines on HIV-exposed infants with PJP.<sup>11</sup> Also, owing to recruitment difficulties, the study was halted early, resulting in less than robust results. Randomised controlled trials which are stopped early for the benefit of the patient often overestimate the effect of treatment on the outcome that precipitated early cessation of the study.<sup>22</sup>

The strength of the study is that it was undertaken in a pragmatic way which reflects a setting in which the vast majority of infants who are infected with HIV, PJP and CMV are managed.

Infants with a clinical diagnosis of PJP should be treated with adjunctive steroids even in the absence of information about coinfection with CMV. Current WHO guidelines should consider advising adjunctive steroids in addition to empiric TMP/SMX treatment for suspected PJP in infants in a resource poor setting. Every effort should be made to ensure all women know their HIV status in pregnancy and at delivery and to ensure all exposed babies receive prophylaxis to prevent PJP infection.

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**Table 1 Baseline characteristics**

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	Steroid group n=36 (%)	Placebo group n=42 (%)
Male	12 (33)	21 (50)
Age, mean (SD), mths	3.1 (2.7–3.9)	3.4 (2.9–4.4)
Weight, mean (SD), kg	5.1 (4.4–5.7)	4.7 (3.8–5.3)
Mother knew she was HIV-positive during pregnancy	11 (31)	16 (38)
Infant was given neviraprine prophylaxis	5 (14)	11 (26)
Infant was started on TMP/SMX	3 (8)	6 (14)
<i>Infant HIV status determined after admission</i>		
HIV-exposed, DNA-PCR-reactive	21 (58)	16 (38)
HIV-exposed, DNA-PCR-negative	4 (11)	6 (14)
HIV-exposed, DNA-PCR not done*	11 (31)	20 (48)
<i>Clinical characteristics at enrolment</i>		
Respiratory rate, mean (SD)	66 (60–78)	70 (62–80)
Oxygen saturation on room air, mean (SD)	68 (60–78)	70 (62–80)
Temperature, median, °C (range)	37.7 (36.0–40.0)	37.9 (36.3–40.5)
Chest findings:		
Clear lungs	24 (67)	30 (71)
Bilateral crackles	12 (33)	12 (29)
Packed cell volume, mean (SD), %	34 (32–39)	34 (29–36)
Placed on continuous positive airway pressure	16/35 (46)	15/41 (37)

\* DNA-PCR not undertaken owing to infant's demise

**Table 2 Primary study outcomes**

	Prednisolone group (%)	Placebo group (%)	RR	95% CI	P-value
<i>Intention-to-treat analysis</i>					
In-hospital mortality	10/36 (27.8)	22/42 (52.4)	0.53	(0.29–0.97)	0.038
6 mths post-discharge mortality	15/33 (45.5)	29/40 (72.5)	0.63	(0.41–0.95)	0.029
<i>Per-protocol analysis</i>					
In-hospital mortality	9/33 (27.3)	20/40 (50.0)	0.55	(0.29–1.03)	0.062
6 mths post-discharge mortality	13/30 (43.3)	27/38 (71.1)	0.61	(0.39–0.96)	0.034

RR, risk ratio; CI, confidence interval

**Figure 1 Trial profile**

**Figure 2 Kaplan–Meier survival plot**