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Synopsis

Azithromycin therapy for prevention of chronic lung disease of prematurity (AZTEC): a randomised placebo-controlled trial

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Abstract

Background: Systematic reviews have reported conflicting evidence to confirm if macrolides reduce rates of chronic lung disease of prematurity in at-risk preterm-born infants, including in those colonised with pulmonary *Ureaplasma* spp. Since an adequately powered trial has been lacking, we conducted a double-blind, randomised, placebo-controlled trial to assess if the macrolide azithromycin improved survival without the development of physiologically defined moderate or severe chronic lung disease of prematurity in infants born at < 30 weeks' gestation.

Methods: Infants recruited from 30 neonatal units (median gestational age 27.0 weeks, interquartile range 25.3–28.6) requiring respiratory support within 72 hours of birth were randomised to intravenous azithromycin 20 mg/kg/day for 3 days followed by 10 mg/kg for 7 days or to placebo. Primary outcome was survival without development of physiologically defined moderate/severe chronic lung disease of prematurity at 36 weeks' postmenstrual age. A total of 796 infants were required to detect 12% improvement in survival without development of moderate or severe chronic lung disease of prematurity, including 10% dropout, with two-sided α-level of 5% and 90% power. The primary outcome was analysed using three-level logistic regression to account for clustering of multiple births and participants within centres and was adjusted for gestational age as a fixed effect. Secondary outcomes included death, chronic lung disease of prematurity severity, treatment interaction with *Ureaplasma* spp. colonisation, days of invasive and days of non-invasive respiratory support, treatment for nosocomial infections, treated patent ductus arteriosus, severe intraventricular haemorrhage, necrotising enterocolitis, treated retinopathy of prematurity and emergence of azithromycin resistance in stool and respiratory samples. Quantitative polymerase chain reaction identified respiratory *Ureaplasma* spp. and antibiotic resistance genes. Safety was also monitored.

Findings: After three withdrawals, 796 randomised infants were included in the final analyses. Survivors without physiologically defined moderate/severe chronic lung disease of prematurity were: 166/394 (42.1%) and 179/402 (44.5%) in the intervention and placebo groups, respectively (adjusted odds ratio 0.84; 95% confidence interval

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0.55 to 1.29; p = 0.43). Secondary outcomes were not significantly different between the treatment groups, except for treated retinopathy of prematurity in survivors (3.5% vs. 7.4%, azithromycin vs. placebo; odds ratio: 0.42, 95% confidence interval 0.18 to 0.98). *Ureaplasma* spp. colonisation did not influence treatment effect. No significant serious adverse effects were reported. From 1108 (n = 541 azithromycin, n = 567 placebo) respiratory aspirates and 709 stool samples from 348 infants, *erm*(C) and *msr*(A) were the most prevalent macrolide-resistance genes, but *erm*(C) increased with azithromycin treatment in both sample types (11% at baseline, 16% at day 14 in respiratory samples; 0% at baseline, 69% at day 14 in stool samples).

Interpretation: Prophylactic use of azithromycin did not improve survival without development of physiologically defined chronic lung disease of prematurity regardless of *Ureaplasma* spp. colonisation. Thus, it cannot be recommended in clinical practice. Since preterm-born infants are exposed to a range of antibiotics, in addition to the trial azithromycin, judicious use of antibiotics is required, given the emergence of multiresistant bacteria in this vulnerable group of infants.

Future work: Follow-up at ages 1 and 2 years will assess the medium-term effects. Investigating whether treatment modulated proinflammatory cytokine concentrations, including whether this was more prevalent in the *Ureaplasma* spp. colonised or non-colonised group, will be crucial to providing further assurances to the clinical community.

Limitations: Limitations include the (limited) missed oxygen reduction tests, inadequate collection of respiratory support data and lower-than-anticipated baseline sampling.

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Introduction

Rationale for research and background

The neonatal lung disease chronic lung disease of prematurity (CLD), often also called as bronchopulmonary dysplasia, is associated with significant mortality and lifelong morbidity, including potential premature development of chronic obstructive pulmonary disease (COPD).[1,2] Its severity in the neonatal period is most commonly defined by supplemental oxygen requirement, with or without ongoing respiratory support, at 36 weeks' postmenstrual age (PMA).[3] Despite advances in neonatal care, rates of CLD have remained largely unchanged, being confined mainly to those born at < 30 weeks' gestation.[4] The pathogenesis of CLD is multifactorial[5] with a number of risk factors identified for its development, including antenatal factors, such as chorioamnionitis, and postnatal ones, such as oxygen therapy and invasive mechanical ventilation. The role of pulmonary colonisation by the mollicute *Ureaplasma* spp. in the development of CLD has caused controversy despite several systematic reviews showing a significant association between pulmonary colonisation with *Ureaplasma* spp. at birth and subsequent development of CLD.[6] A common pathway for the risk factors, including in those colonised with pulmonary *Ureaplasma* spp., leading to the development of CLD is polymorphonuclear neutrophil-driven pulmonary inflammation, which results in injury to the lung parenchyma with the subsequent tissue remodelling, leading to dysregulated future lung growth and development. Trials of corticosteroids targeting pulmonary inflammation are extensive, but given their safety profile, including concerns of long-term neurodevelopmental outcomes, these are often reserved for ventilator-dependent infants, where potential benefits may outweigh the risks.[7] Thus, there has been a search for new therapies, especially to target pulmonary inflammation to ameliorate rates of CLD.

An ideal treatment would target both the infective and pulmonary inflammatory pathways that contribute to the development of CLD.[8] Macrolides, such as azithromycin, have potent anti-infective and anti-inflammatory activities, hence these are frequently used in several respiratory conditions, including COPD[9] and cystic fibrosis.[10] Mechanistically, besides its antibiotic properties, azithromycin has several anti-inflammatory activities, especially against neutrophil-driven inflammation, including decreased proinflammatory cytokine production, decreasing neutrophil chemotaxis and recruitment into the alveolar spaces while also enhancing bacterial clearance and limiting biofilm formation.[11] Importantly, azithromycin has potent activity in the lungs as it is concentrated in resident pulmonary cells, whereby its concentration in the lungs is 100 times greater than in plasma.[12] Azithromycin has thus emerged as a potential attractive treatment for preterm-born infants at risk of developing CLD due to its activity against *Ureaplasma* spp.[13] and due to its potent anti-inflammatory properties, especially against neutrophil activity in the lung.[11]

Azithromycin treatment started early in life in preterm-born infants who are at risk of developing CLD has

the potential to target both pulmonary *Ureaplasma* spp. colonisation and neutrophil-driven pulmonary inflammation, peaking consistently at 7–10 days of age in infants who subsequently develop CLD.[14,15] However, the widespread use of azithromycin, particularly in neonates, raises concerns regarding development of antimicrobial resistance.[16] Antimicrobial resistance not only compromises the therapeutic effectiveness of azithromycin but also poses wider threats via development of multiantibiotic resistant bacteria.[17] Moreover, global concerns about emerging antibiotic resistance and the association of increased antibiotic use in preterm-born infants with significantly increased morbidity and mortality are important considerations.[18–20]

Systematic reviews of previous trials of early macrolide treatment have been conflicting, citing the lack of an adequately powered study to confirm the place of macrolides in the treatment of CLD in preterm-born infants.[21,22] A dosing regimen has been defined following extensive pharmacokinetic studies.[23] We, therefore, conducted the adequately powered azithromycin therapy for chronic lung disease (AZTEC) trial, which assessed if early treatment with 10 days of intravenous azithromycin, targeting pulmonary inflammation, improved rates of survival without development of physiologically defined moderate or severe CLD in preterm infants born at < 30 weeks' gestation. We also assessed the impact of any respiratory *Ureaplasma* spp. colonisation on survival without development of CLD and the impact of azithromycin therapy on macrolide resistance in respiratory samples.

Objectives

The primary objective of the AZTEC trial was to assess the effectiveness of a 10-day course of azithromycin on improving survival without physiologically defined CLD in infants born at < 30 weeks' gestational age. The secondary objectives were to determine the effect of azithromycin on CLD severity and mortality rate (at 36 weeks' PMA); to determine the effectiveness of azithromycin in reducing the duration of positive pressure respiratory support; to determine the safety and tolerability of azithromycin; to determine if azithromycin alters resistance to macrolides among microbes isolated from respiratory and stool samples and to investigate if colonisation with *Ureaplasma* spp. prior to randomisation modifies the treatment effect of azithromycin compared to placebo.

Methods for data collection and analysis

The full details of the trial methods, data collection and statistical analysis were presented in the published protocol[24] and were published as a statistical analysis plan.[25]

Briefly, AZTEC was a double-blind, randomised, placebo-controlled trial conducted in 28 tertiary neonatal intensive care units in the UK. Infants were eligible if they were born at < 30 weeks' gestation and had received at least 2 hours of either non-invasive (continuous positive airway pressure or humidified high flow nasal cannula therapy) or invasive respiratory support (via endotracheal tube) within 72 hours of birth. Eligible infants also required: a high probability of an indwelling intravenous line for drug administration for 10 days of study treatment while being an inpatient at the recruiting centre; follow-up to primary outcome to be feasible; and their parent or guardian being able to provide written informed consent for their infant to take part in the study.[8] Infants were excluded if a serious congenital anomaly was known at birth, if they had previous exposure to a macrolide antibiotic (not maternal) or if the local investigator's opinion was that survival beyond 72 hour was unlikely. Treatment was randomly allocated in a 1 : 1 ratio, stratified by centre and gestational age at birth (< 28 weeks vs. ≥ 28 weeks). Each infant from multiple births was randomised separately. Parents, clinical and research teams were masked to the intervention.

Active therapy was 10 days of intravenous azithromycin, given once daily at 20 mg/kg for the first 3 days, which was followed by 10 mg/kg for a further 7 days by intravenous infusion. Placebo therapy consisted of sterile water for injection. An endotracheal aspirate (ETA) (if receiving endotracheally intubated mechanical ventilation) or a nasopharyngeal aspirate (NPA) sample (if not endotracheally intubated) was collected to assess baseline pulmonary *Ureaplasma* spp. colonisation before administration of the first investigational medicinal product (IMP) dose. To assess antimicrobial resistance, further respiratory samples were obtained at approximately 5 and 10 days, with a final sample taken between 14 and 21 days post-treatment initiation. Stool samples were collected opportunistically following the same time points. A timeline of data collection is illustrated in *Figure 1*.

The approach to analysing the respiratory samples utilised a published multiplex real-time quantitative polymerase chain reaction (qPCR) to identify the presence of *Ureaplasma* spp., and the method is detailed in the supplementary appendix to the main trial's published results.[8] The methodology for analysis of antimicrobial resistance in both respiratory and stool samples was established and published.[26] Macrolide-resistance genes in deoxyribonucleic acid extracted from clinical samples were detected using a multiplex qPCR assay. Six commonly reported macrolide-resistance genes were detected: four erythromycin ribosomal methyltransferase genes, *erm*(A),

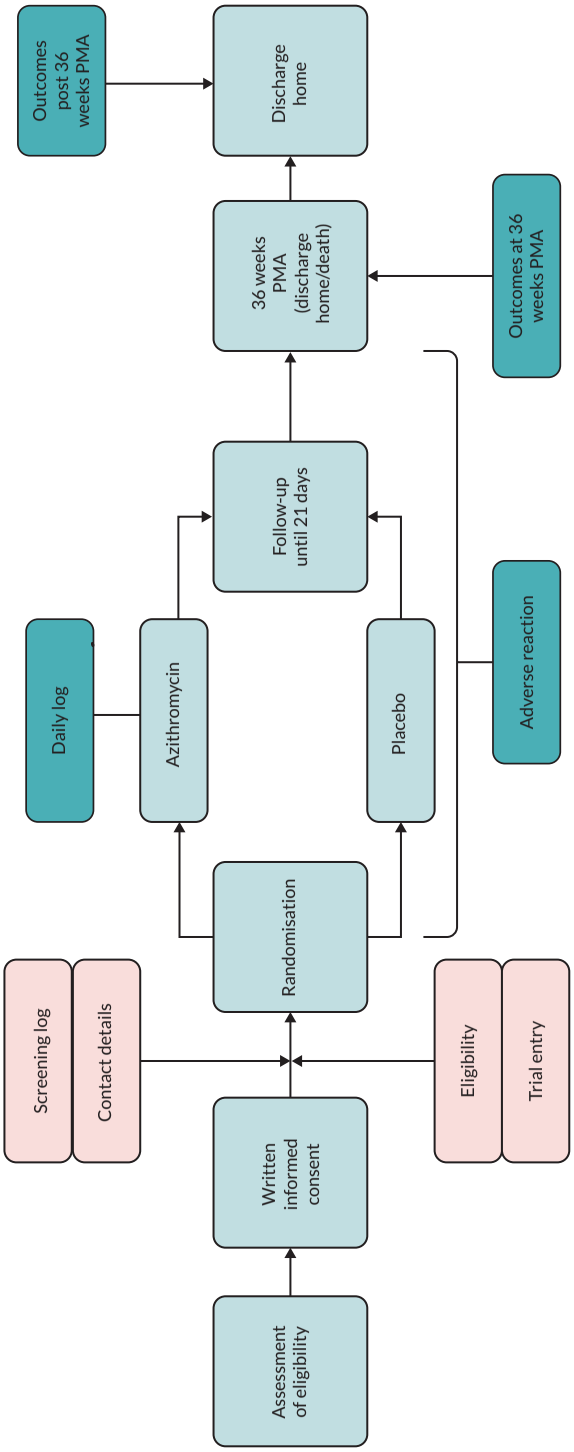

FIGURE 1 Schematic of AZTEC trial. Blue boxes represent patient flow through the study. Red boxes represent recruitment processes, and green boxes represent major data collection points.

erm(B), *erm*(C) and *erm*(F), and two efflux pump genes, *mef*(A/E) and *msr*(A).

Based on prevailing data at the time of trial design, we estimated our sample size on observing an improvement of 12% in survival without development of physiologically defined moderate or severe CLD from 50% to 62%, including an estimated 25% mortality rate. With a two-sided α-level of 5% and 90% power, 716 infants were estimated to be required to be studied. Including an estimated 10% dropout rate, it was estimated that 796 infants would be required.

Outcomes were analysed on an intention-to-treat basis. The composite primary outcome was survival without the development of physiologically defined moderate/severe CLD at 36 weeks' PMA. The analysis used three-level logistic regression to account for clustering of multiple births and participants within recruitment centres and adjusted for gestational age as a fixed effect. Results were reported as unadjusted and two-level (gestational age and recruitment centre) and three-level (addition of multiple births) adjusted odds ratios (aORs) as 95% confidence intervals (CIs) and *p*-values. Only the three-level models are reported here. Infants who missed their oxygen reduction test when eligible were assumed to have moderate CLD.

Sensitivity analyses of the primary analyses were conducted by imputing missed oxygen reduction tests and removing these infants for complete case analysis. Impact of baseline *Ureaplasma* spp. colonisation was reported by extending the primary analysis to include a *Ureaplasma* spp. colonisation by treatment group interaction term. Differential treatment effects were also explored by gestational age, recruitment centres and whether born at (inborn) or transferred to the recruiting centre (outborn). Complier-average causal effect analysis was used to investigate the effect of time to initiation of the IMP and the proportion of IMP taken.

Secondary outcomes at 36 weeks' PMA included CLD severity, mortality and effect of baseline *Ureaplasma* spp. colonisation, together with selected clinical events between birth and 36 weeks' PMA, including number of days of respiratory support/oxygen dependency, treatment for patent ductus arteriosus (PDA), number of nosocomial infections (blood or cerebrospinal fluid culture-positive), worst extent of severe intraventricular haemorrhage (IVH) (grade III/IV, IVH), necrotising enterocolitis (NEC) (Bell stage II and above, NEC), treatment for retinopathy of prematurity (ROP), highest liver and renal function and serious adverse events/reactions. Secondary outcomes were not adjusted for multiple comparisons.

Secondary outcomes were analysed using logistic regression, and if dichotomous, using the three-level modelling approach described previously in survivors only and in a composite analysis incorporating death. Days each infant required supplemental oxygen and respiratory support were analysed as counts, with the in-survivors' analysis, including count data up until the point of death (if death occurred) and the composite-incorporating-death analysis defined as days alive without respiratory support between random allocation and the 36 weeks' PMA time point. These outcomes were modelled using a multilevel Poisson regression with robust standard errors to account for any heteroscedasticity (e.g. minor deviations from the underlying assumption in the Poisson model that the mean equals the variance). Multilevel linear regression models with Box-Cox transformations were used for obtaining maximum liver and renal function values (including in those dying).

Regarding data emerging from the sample analysis for antimicrobial resistance, continuous data were compared using independent *t*-tests or analysis of variance with Bonferroni correction, or by Chi-square for categorical data.

Results summary

The AZTEC trial results have been published in *The Lancet Respiratory Medicine*.[8] The recruitment period ran between May 2019 and March 2022. Due to the COVID pandemic, all sites were suspended between March 2020 and June 2020. In total, 1739 infants were screened at 28 level III neonatal units, with 1505 being eligible for inclusion in the study. A total of 799 infants were recruited and randomised; 3 infants were fully withdrawn from the trial, and 1 infant was inadvertently randomised twice (the initial allocation being implemented), leaving 796 infants included in the analysis (394 allocated to azithromycin and 402 allocated to placebo) (*Figure 2*). No discernible differences were noted between treatment groups at baseline besides greater antenatal antibiotic use in the placebo group (42.1% vs. 36.2%). Overall, the median gestational age was 27 weeks [interquartile range (IQR) 25.3–28.6], birthweight 895 g (IQR: 703–1130); 442 (55.5%) infants were male, and 467 (58.7%) infants were born by caesarean section.

A total of 767 out of 796 (96.4%) infants received the first dose of IMP within 72 hours of age, being similar between the intervention [median 49.4 hours (IQR 36.2–63.8)] and

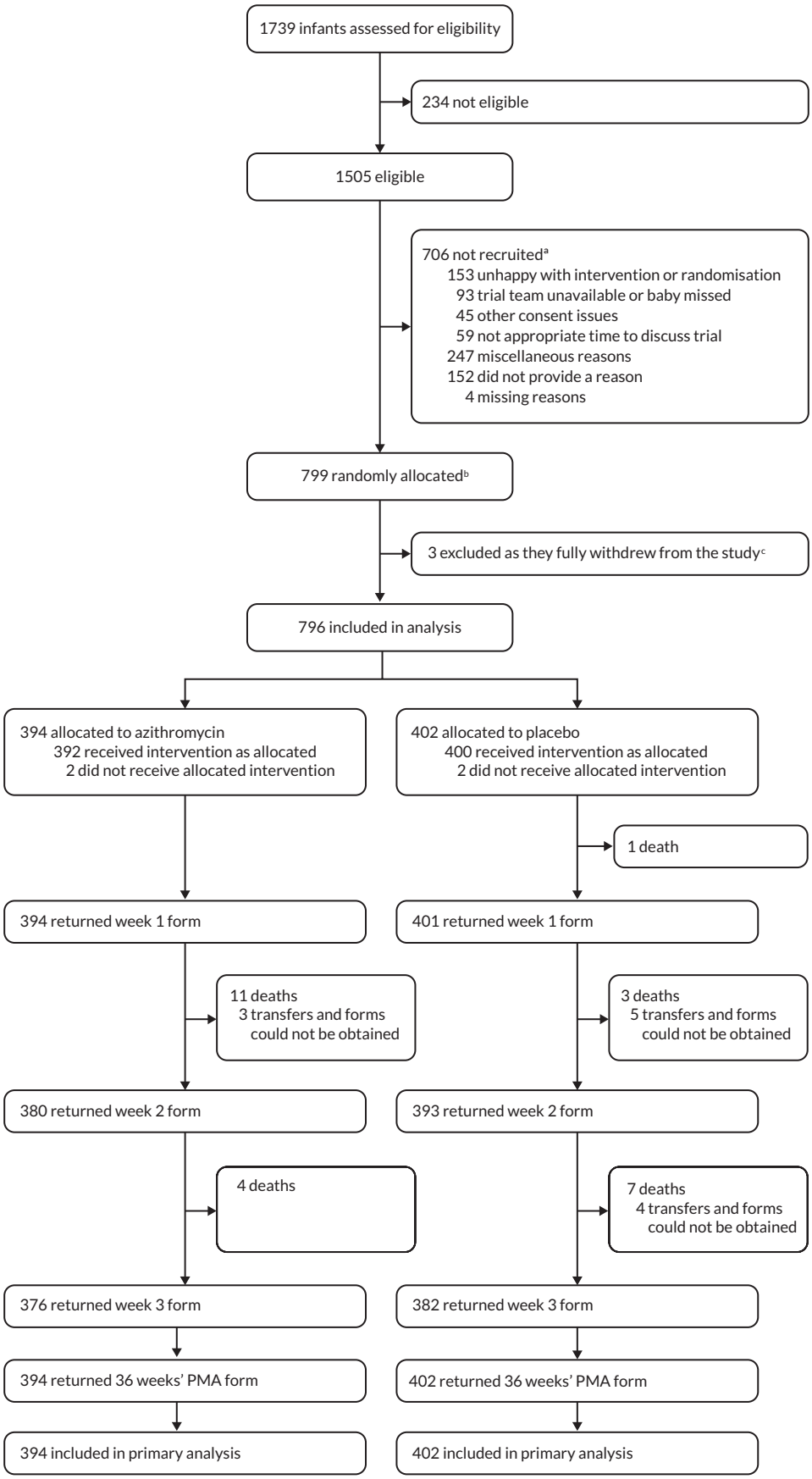

FIGURE 2 Consolidated Standards of Reporting Trials diagram for AZTEC trial. a, Some parents gave multiple reasons. b, One eligible infant was screened once during enrolment but was inadvertently randomly allocated twice. c, Three infants were fully withdrawn from the study, including the use of any data collected previously. This figure is reproduced with permission from Lowe *et al.*[8] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

placebo groups [51 hours (IQR 36.9–63.3)]. Four infants did not receive IMP: three died shortly after randomisation, and one due to local clinical decision; 567 (71.6%), 636 (80.3%) and 687 (85.6%) of 796 infants received 10, 9 and 8 doses, respectively.

Physiological assessment of CLD and CLD severity was performed as per international guidelines[3] and other recent studies.[27] For the primary outcome, 741 out of 796 (93.1%) infants had the CLD outcome physiologically assessed. The remaining 55 (6.9%) infants in low-flow oxygen at 36 weeks' PMA did not undergo an oxygen reduction test, so they were classified as having moderate CLD following the primary outcome definitions [34/394 (8.6%) and 21/402 (5.2%) in the azithromycin and placebo groups, respectively]. Survival without moderate or severe CLD occurred in 166/394 (42.1%) and 179/402 (44.5%) infants in the azithromycin and placebo groups, respectively (three-level aOR 0.84, 95% CI 0.55 to 1.29; $p = 0.43$). This finding remained unchanged after all sensitivity analyses. No subgroup treatment effect was noted on the primary outcome by any *Ureaplasma* spp. colonisation (interaction aOR 0.59, 95% CI 0.19 to 1.84; $p = 0.36$) nor by the other predefined subgroups of < 28 weeks' gestation (interaction aOR 0.70, 95% CI 0.34 to 1.41; $p = 0.31$), inborn infants (interaction aOR 0.78, 95% CI 0.48 to 1.25; $p = 0.29$) or recruitment centres (chi-square value = 2.63 with p-value 0.105). There were seven serious adverse events in the azithromycin group and six in the placebo group that met the per-protocol reporting requirements.

Secondary analyses of the trial were undertaken, and the results were stratified by gestational age and were clustered within multiple births and recruitment centres. The components of the primary outcome death and severity CLD were similar across both trial groups [death: 34/394 (8.6%) and 31/402 (7.7%), severity of CLD: 194/360 (53.9%) and 192/371 (51.2%) in the azithromycin and placebo groups, respectively]. No between-group differences were noted for postnatal corticosteroid use (43% vs. 43%), treated PDA (37% vs. 40%), late-onset infection (65% vs. 623%), severe IVH (14% vs. 13%), and NEC (14% vs. 15%). Compared with the placebo group, the azithromycin group was associated with a lower rate of treated ROP [12/40 (3.5%) of survivors vs. 26/350 (7.4%) of survivors; three-level aOR 0.42, 95% CI 0.18 to 0.98; $p = 0.04$]. Recruiting centres prioritised the measurement of different liver enzymes. However, serum creatinine, alkaline phosphate and liver enzymes were similar between the groups, except for marginally lower aspartate aminotransferase in the azithromycin group [median 43, IQR 23–65; vs. median 43, IQR 27–80 units/l, Box-Cox transformed coefficient: −0.12, 95% CI −0.22 to −0.01; $p = 0.03$, data available for 39.2% of randomised participants (312/796)]. The quality of data collection for daily supplemental oxygen amount and invasive or non-invasive respiratory support was insufficient for reliable analysis. Therefore, daily records of participating infants receiving invasive or non-invasive respiratory support were obtained from the National Neonatal Data Analysis Unit (www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data-analysis-unit/), which collates neonatal data submitted by almost all UK neonatal units. No differences were noted between the intervention and placebo groups in terms of duration of respiratory support.

From the aim to include the first 350 recruited infants in the antimicrobial resistance work, 348 were included since this coincided with the pause in recruitment due to the severe acute respiratory syndrome coronavirus 2 pandemic. A total of 1108 respiratory samples (ETA 490 and NPA 618) were analysed (323 taken at baseline, 278 at day 5, 264 at day 10 and 243 between days 14 and 21), comprising 567 (51.2%) and 541 (48.8%) from the placebo and azithromycin groups, respectively. In the placebo group, macrolide-resistance genes were detected in 361/567 (63.7%) respiratory samples. The abundance of all macrolide-resistance genes was low at baseline day 1, but the abundance of *erm*(A), *erm*(B), *erm*(C) and *msr*(A) increased over the first 2 weeks of life (*Figure 3*); *erm*(F) and *mef*(A/E) remained low over this time period.

From the 541 samples from the azithromycin group, a similar proportion of 346 (63.9%) were positive for macrolide resistance genes as to the placebo group 361 (63.7%). Similar to the placebo group, increases of *erm*(A), *erm*(B), *erm*(C) and *msr*(A) over the first 2 weeks, but not *erm*(F) and *mef*(A/E), were also noted in the azithromycin group (see *Figure 3*). No differences were noted between the azithromycin and placebo groups for any of the genes except for *erm*(C). In both groups, *erm*(C) increased over time, but *erm*(C) was greater at days 5 (47% vs. 33%), 10 (60% vs. 36%) and 14 (62% vs. 30%), but not at baseline, in the azithromycin group when compared with the placebo group.

A total of 709 stool samples were analysed (43 obtained at baseline, 261 at day 5, 137 at day 10, 268 at day 14), comprising 338 in the azithromycin group and 371 in the placebo group. Similar to the respiratory samples, abundance of all macrolide-resistance genes was low at baseline, but abundance of *erm*(B), *erm*(C) *erm*(F) and *msr*(A) increased over the first 2 weeks of life; *erm*(A), and *mef*(A/E) remained low over this time period (*Figure 4*). No differences

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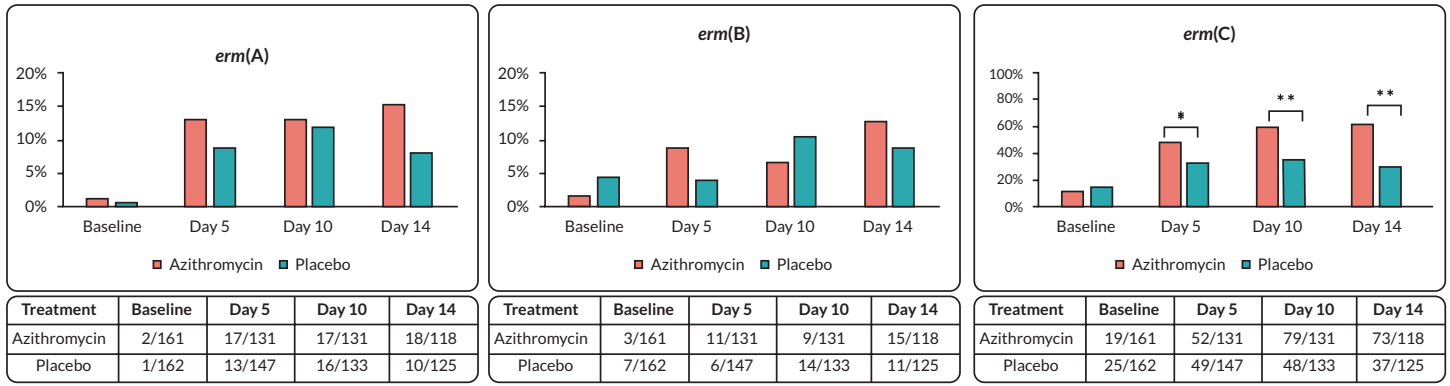


Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	2/161	17/131	17/131	18/118
Placebo	1/162	13/147	16/133	10/125

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	3/161	11/131	9/131	15/118
Placebo	7/162	6/147	14/133	11/125

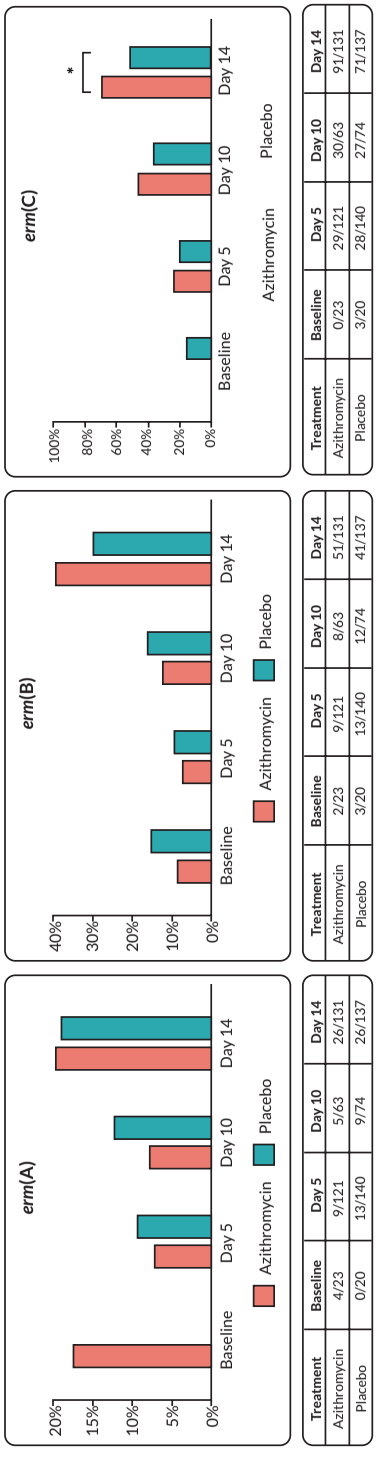
Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	19/161	52/131	79/131	73/118
Placebo	25/162	49/147	48/133	37/125

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	4/161	2/131	7/131	1/118
Placebo	6/162	4/147	2/133	5/125

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	6/161	3/131	3/131	5/118
Placebo	4/162	4/147	7/133	6/125

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	29/161	72/131	78/131	68/118
Placebo	39/162	89/147	93/133	81/125

FIGURE 3 Abundance of macrolide-resistance genes in respiratory samples from preterm-born infants before, during and after azithromycin or placebo treatment. *$p < 0.05$; **$p < 0.001$.



Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	4/23	9/121	5/63	26/131
Placebo	0/20	13/140	9/74	26/137

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	2/23	9/121	8/63	51/131
Placebo	3/20	13/140	12/74	41/137

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	0/23	29/121	30/63	91/131
Placebo	3/20	28/140	27/74	71/137

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	3/23	3/121	3/63	6/131
Placebo	0/20	2/140	4/74	9/137

Treatment	Baseline	Day-5	Day-10	Day-14
Azithromycin	2/23	52/121	39/63	113/131
Placebo	3/20	45/140	45/74	121/137

Treatment	Baseline	Day 5	Day 10	Day 14
Azithromycin	2/23	11/121	10/63	39/131
Placebo	1/20	12/140	12/74	35/137

FIGURE 4 Abundance of macrolide-resistance genes in stool samples from preterm-born infants before, during and after azithromycin or placebo treatment. *$p < 0.05$.

were noted between the azithromycin and placebo groups for any of the genes except for *erm*(C), which was higher in the azithromycin group compared to placebo by day 14 after commencement of treatment (69% vs. 51%).

Research papers synthesised in the synopsis

Lowe J, Gillespie D, Aboklaish A, Lau TMM, Consoli C, Babu M, *et al.* Azithromycin therapy for prevention of chronic lung disease of prematurity (AZTEC): a multicentre, double-blind, randomised, placebo-controlled trial [published online ahead of print April 25 2024]. *Lancet Respir Med* 2024. https://doi.org/10.1016/S2213-2600(24)00079-1.

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Lau TMM, Lowe J, Pickles T, Hood K, Kotecha S, Gillespie D. AZTEC-azithromycin therapy for prevention of chronic lung disease of prematurity: a statistical analysis plan for clinical outcomes. *Trials* 2022;**23**:704. https://doi.org/10.1186/s13063-022-06604-2.

Lowe J, Gillespie D, Hubbard M, Zhang L, Kirby N, Pickles T, *et al*. Study protocol: azithromycin therapy for chronic lung disease of prematurity (AZTEC) – a randomised, placebo-controlled trial of azithromycin for the prevention of chronic lung disease of prematurity in preterm infants. *BMJ Open* 2020;**10**:e041528. https://doi.org/10.1136/bmjopen-2020-041528.

Discussion

Principal findings and achievements

We conducted a high quality, robust and adequately powered trial, and to our knowledge, the largest single trial to date, which exceeded our power calculation due to lower-than-anticipated death rates and a very low dropout rate. We did not observe improved survival without the development of physiologically defined moderate or severe CLD with azithromycin treatment, nor did *Ureaplasma* spp. colonisation affect the primary outcome. Azithromycin treatment did not affect the important secondary outcomes, including rates of death, CLD, corticosteroid use, the need for invasive or non-invasive ventilation, treated nosocomial infection or treated PDA, NEC or IVH. Rates of treated ROP were lower in surviving infants in the intervention group, but not when death was included in the outcome. The safety profile of azithromycin was reassuring.

Regarding antimicrobial resistance, in the preterm-born infants receiving placebo, thus representing the 'usual' situation, macrolide-resistance genes increased during the first 2 weeks of life in both respiratory and stool samples. However, treatment with azithromycin increased only one of the six studied genes, namely *erm*(C), when compared to the placebo group. These increases were not related to the mode of delivery (increased staphylococcal colonisation is associated with caesarean section), or to other early life factors, including prelabour rupture of membranes, thus these are most likely to be related to antibiotics used during the first 2 weeks of life.

Contribution to existing knowledge

Azithromycin therapy for prevention of chronic lung disease of prematurity is the largest trial to address a key knowledge gap, which has existed for several decades, around the effectiveness of macrolides in preventing the development of CLD in preterm infants at high risk of developing CLD. By conducting a robust, adequately powered, double-blind, multicentre, randomised controlled trial, we have demonstrated that azithromycin does not improve survival without development of physiologically defined moderate or severe CLD. We did find a significant reduction in the rates of treated ROP in survivors, although not when death was included in the outcome. None of the other secondary outcomes were modified by azithromycin treatment either, but few adverse events were noted, which is reassuring.

Strengths and weakness of the study/in relation to other studies

The key strengths of our trial are adequate power, robustly followed protocol and double-blinding, timely recruitment within our 2.5-year target despite pauses related to COVID-19, a very low dropout rate, a priori statistical analysis plan, the inclusion of a large representative UK population and timely early treatment. The trial had a high enrolment rate (53% of eligible infants were consented and randomly allocated). Moreover, this trial provides the largest group studied so far for antibiotic resistance in both the placebo group (to reflect the usual situation) and in the treated group.

Our results are concordant with the conclusions of the latest systematic review, including 484 infants,[22] which also did not suggest the efficacy of azithromycin in decreasing rates for the combined outcome of CLD and death. By only including infants requiring respiratory intervention at birth, we recruited a population that was at high risk for CLD and most likely to benefit from the intervention, borne out by the high rates of CLD and greater male prevalence in our cohort.

Important limitations include the missed oxygen reduction tests, inadequate collection of respiratory support data and lower-than-anticipated baseline respiratory sampling. The higher rates of infection than expected were due to using a broader definition of clinician-treated infection, positive cultures or a combination of both rather than identifying infection purely on grounds of positive culture results only. However, none of these would have affected the overall results, so we are confident the results are robust.

Reflections on the project

Once again, the UK neonatal community demonstrated their ability to recruit to this large IMP trial on target. The primary challenge to success of the trial was a requirement to suspend recruitment, considering the emerging COVID-19 pandemic at a juncture where recruitment was surpassing projections.

As a result of delays related to COVID-19, IMP date expired and remanufacture was required on both occasions to satisfy the demand on reopening the trial to recruitment. A recovery plan was proposed to National Institute for Health and Care Research (NIHR), including reprofiled recruitment projections based on pre-pandemic rates, with an expectation of achieving the required sample size by July 2022. However, following the project restart, we were able to complete enrolment in March 2022, substantially earlier than anticipated. This success was attributable to the enormous efforts of the recruiting centres, well exceeding our monthly recruiting targets.

As with many neonatal trials, the movement of infants from the recruiting centres (which are most often level III intensive care units) to other hospitals for continuation of their care was a consistent challenge. Although most hospitals participated in the study as a 'continuing care' site, one limitation was loss of data in instances where a local principal investigator (PI) could not be identified, or where the local research and development department would not permit trial activities to be undertaken. Loss of data was exacerbated by the COVID-19 pandemic since AZTEC was considered to be in the lowest tier of priority in respect of restarting, or being considered for processing of local permissions. Despite these issues, we were able to supplement our data with that collected by the National Neonatal Research Database , which provides a valuable resource to researchers.

Engagement with partners and stakeholders

We have received enormous support and engagement from the neonatal community and received continued expressions of interest to participate throughout the project. This commitment is demonstrated out by the ability to recruit to target ahead of time. The partners were delighted with the recruiting network setup by the AZTEC trial and the trial team was strongly encouraged to apply for another trial to utilise the network. A successful application for the "Bacterial mucosal immunotherapy for prevention of lower respiratory tract infections in preterm infants" (BALLOON) trial funded by NIHR/Efficacy and Mechanism Evaluation (EME) will utilise the excellent centres once again, continuing our journey to improve treatments for vulnerable preterm-born infants and their families.

Individual training and capacity-strengthening activities

Implementation of a Clinical Trial of an IMP and embedding the trial within the day-to-day practice of multidisciplinary teams nationwide across many neonatal units was a significant undertaking in its own right, and the efforts of all should be highly commended. In particular, the amount of trial-specific training delivered to the local nursing teams to ensure that each infant would be cared for by an individual with the competencies to prepare and administer IMP for 10 consecutive days was substantial. AZTEC was registered to, and supportive of the NIHR Associate PI scheme, although opportunities were limited due to the time frame of recruitment and the requirements of the scheme. Notwithstanding, the exceptional volume of good clinical practice and trial-specific training undertaken by sites will further support the conduct of future trials and continue to evolve the research culture within neonatal medicine.

Patient and public involvement

We included important aspects of patient and public involvement (PPI) throughout the course of the project, including prior to the grant application. This PPI continued throughout the trial period by inclusion of a parent representative who was involved in the generation of all participant-facing materials as well as implementation of the trial protocol. These documents were further reviewed by several parents attending the monthly Special Care Infant Parent Support Group based at the University Hospital of Wales in Cardiff alongside a presentation on key elements of the trial. Our PPI representatives also frequently attended the monthly Trial Management Group meetings. We ensured further PPI input was provided through appointment of a lay representative on the independent Trial Steering Committee. We intend to publish, in collaboration with our PPI representatives, a lay summary on the trial website and include a link to

This synopsis should be referenced as follows:
Lowe J, Gillespie D, Aboklaish A, Lau TMM, Consoli C, Babu M, *et al.* Azithromycin therapy for prevention of chronic lung disease of prematurity (AZTEC): a randomised placebo-controlled trial. *Health Technol Assess* 2026;**30**(12). https://doi.org/10.3310/GJSK0401

this synopsis. Additionally, all participants will receive a summary of the results and information on the treatment allocation assigned to their child.

Equality, diversity and inclusion

As an urgent intervention given in the postnatal period, azithromycin is available to all infants who might potentially benefit. Our inclusion and exclusion criteria were relatively few, and as such, there were few impediments to participation based on these factors. We had a wide geographic distribution of neonatal units, with an inclusive approach to recruitment and enrolment. We did not limit inclusion based on the ability to speak English, and indeed screening data obtained from participating centres did not indicate language barriers or obtaining informed consent to be a significant reason for otherwise eligible infants not being included. Data collected on sex and ethnic background indicated that participation was comparable to the UK population, with 18% from non-White ethnic minority groups. Thus, we anticipate the results to be highly generalisable among the population under study.

Impact and learning

The outcomes of the AZTEC project are immediately implementable into standard clinical practice and should be adopted into neonatal guidelines regarding the evidence base for the treatment of CLD.

Our initial dissemination work has involved the primary publications cited in this report, and we plan to present the work at upcoming international meetings. We shall provide a link on the trial website on publication of this synopsis and will include a lay summary of the results. Since follow-up work is ongoing at the time of writing,[28] we are yet to communicate treatment allocations to parents and families; however, this task is scheduled to be done as soon as practicable. Additional funding has been secured to follow up the infants at 1 and 2 years of corrected ages to assess their respiratory status to identify if azithromycin has any longer-term benefits and neurodevelopment to establish longer-term safety.

The collaborative work undertaken by all participating institutions has been extremely fruitful and has led to the recent NIHR/EME funding of the BALLOON trial (NIHR156651: Bacterial mucosal immunotherapy for prevention of lower respiratory tract infections in preterm born infants), which will investigate whether a novel bacterial vaccine can improve respiratory outcomes after discharge from hospital in a similar population of infants recruited to AZTEC.

Research recommendations

Our work raises some important scientific questions on the mechanisms of action of azithromycin and methodological conundrums for future trials. Firstly, in the medium term, it will be important to assess the longer-term impact of azithromycin on respiratory and neurodevelopment, especially to assess longer-term effectiveness and safety. Secondly, the rationale for the trial was based around proof of concept in addressing pulmonary inflammation through azithromycin's impact on reducing neutrophil activity and proinflammatory cytokine production and through its ability to eradicate *Ureaplasma* species. Work is underway to investigate treatment-modulated proinflammatory cytokine concentrations, including whether this was more prevalent in the *Ureaplasma* spp. colonised or non-colonised group. This evidence will be crucial to contextualising the results of this trial and providing further assurances to the clinical community.

However, AZTEC joins the pantheon of recent trials of interventions attempting to reduce the rates of CLD, all of which have failed to impact on treating this multifactorial disease.[27,29] Taken together, these results suggest that a single intervention during the neonatal period may not be effective. Novel strategically combined multiple interventional strategies and trial designs are required to address this. As part of the dissemination activities, we plan to hold a stakeholder's meeting to address how best to address this challenge and set the direction for future research in this area.

Conclusions

The AZTEC trial has definitively shown that the use of early azithromycin in preterm-born infants at high risk of developing CLD does not improve survival without the development of physiologically defined moderate or severe CLD. Since the increased use of other antibiotics in preterm infants has been associated with increased morbidity (e.g. due to NEC), increased mortality and increased antibiotic microbial resistance, we do not currently recommend prophylactic use of azithromycin in this vulnerable population to prevent the development of CLD. Our choice of primary outcome was carefully considered, but later respiratory outcomes are also valued by parents and clinicians and may be of health economic importance, and evaluation of the AZTEC participants at 1 and 2 years of age is ongoing.

Additional information

CRediT contribution statement

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We thank all participating parents and infants and the site research nurses and doctors for their contributions to the trial.

Dedication

This publication is dedicated to Professor Nigel Klein, our expert collaborator, valued mentor, and very dear late friend. Professor Nigel Klein was a friend and collaborator for over thirty years, contributing with expert knowledge with grand humour. Nigel brought such a level-headed and measured scientific viewpoint to all the meetings we had. He was always able to distill down the salient and key aspects and provide a vision for how the work should progress and where we needed to focus our energies. His smile and intellect will be missed by all of us, and the clinical and scientific community is much the poorer for his passing.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The trial was approved by the Wales 2 Research Ethics Committee on 26 June 2018 (Ref 18/WA/0199).

Information governance statement

Cardiff University is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Cardiff University is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection. Data processors were the NHS organisations providing data for the trial.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJSK0401.

Primary conflicts of interest: Julian Marchesi reports payments or honoraria for lectures from Institut Biochimique SA, Cultech Ltd, EnteroBiotic Ltd, support for attending meetings from Fred Hutchinson Cancer Centre, and patents issued and pending.

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All other authors declare no competing interests.

Department of Health and Social Care disclaimer

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN11650227.

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Award publications

This synopsis provided an overview of the research award *AZithromycin ThErapy for Chronic lung disease (AZTEC): A randomised, placebo controlled trial of azithromycin for the prevention of chronic lung disease of prematurity in preterm infants*.

Other articles published as part of this thread are:

Lau TMM, Lowe J, Pickles T, Hood K, Kotecha S, Gillespie D. AZTEC—azithromycin therapy for prevention of chronic lung

disease of prematurity: a statistical analysis plan for clinical outcomes. *Trials* 2022;**23**:704. https://doi.org/10.1186/s13063-022-06604-2

Lowe J, Gillespie D, Aboklaish A, Lau TMM, Consoli C, Babu M, *et al*. Azithromycin therapy for prevention of chronic lung disease of prematurity (AZTEC): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Respir Med* 2024;**12**:608–18. https://doi.org/10.1016/S2213-2600(24)00079-1

Gallacher DJ, Zhang L, Aboklaish AF, Mitchell E, Wach R, Marchesi JR, Kotecha S. Baseline azithromycin resistance in the gut microbiota of preterm born infants. *Pediatr Res* 2024;**95**:205–12. https://doi.org/10.1038/s41390-023-02743-7

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/16/111/106).

Additional outputs

Lowe J, Gillespie D, Hubbard M, Zhang L, Kirby N, Pickles T, *et al*. Study protocol: azithromycin therapy for chronic lung disease of prematurity (AZTEC) – a randomised, placebo-controlled trial of azithromycin for the prevention of chronic lung disease of prematurity in preterm infants. *BMJ Open* 2020;**10**:e041528. https://doi.org/10.1136/bmjopen-2020-041528

About this synopsis

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List of abbreviations

AZTEC	azithromycin therapy for chronic lung disease
CLD	chronic lung disease of prematurity
COPD	chronic obstructive pulmonary disease
EME	Efficacy and Mechanism Evaluation
ETA	endotracheal aspirate
IMP	investigational medicinal product
IVH	intraventricular haemorrhage
NEC	necrotising enterocolitis
NIHR	National Institute for Health and Care Research
NPA	nasopharyngeal aspirate
PDA	patent ductus arteriosus
PI	principal investigator
PMA	postmenstrual age
PPI	patient and public involvement
qPCR	quantitative polymerase chain reaction
ROP	retinopathy of prematurity

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