Endotracheal surfactant for infants with life-threatening bronchiolitis (BESS): a randomised, blinded, sham-controlled, phase 2 trial

*Malcolm G Semple, Chloe Donohue, Laura Price, Rachael Cooper, Carly Vaughan, Tracy Moitt, Lynsey Finnetty, Paul C Ritson, Blessing Osaghae, Evette Allen, Clare Fowler, Rachel S Agbeko, Edgar Brincat, Jane V Cassidy, Patrick E Davies, Peter J Davis, Elisabeth Day, Constantinos Kanaris, Simona Lampariello, Richard Levin, Tsz-Yan Milly Lo, Kevin P Morris, Ahmed Osman, Stephen D Playfor, Julie Richardson, Gerri Sefton, Santosh Sundararajan, James Weitz, Annmarie Wherton-Whitehurst, Elizabeth Deja, Kerry Woolfall, Jens Madsen, Anthony D Postle, Catrin Barker, Carrol Gamble, Howard W Clark, John Pappachan, Kentigern Thorburn, Matthew Peak, Paul S McNamara, Mark A Turner, Ashley P Jones, on behalf of the BESS Investigators**

Lancet Respir Med 2026; 14: 432–42

Published Online March 21, 2026 https://doi.org/10.1016/S2213-2600(26)00008-1

See Comment page 380

*BESS Investigators listed at the end of the Article and in the appendix (p 193)

Health Protection Research Unit in Emerging and Zoonotic Infections, Department of Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary, and Ecological Sciences, University of Liverpool, Liverpool, UK (Prof M G Semple PhD, B Osaghar PhD); **Department of Respiratory Medicine, Liverpool Institute of Child Health and Wellbeing, Alder Hey Children's NHS Foundation Trust, Liverpool, UK** (Prof M G Semple, Prof P S McNamara PhD); **Liverpool Clinical Trials Centre, University of Liverpool, Liverpool, UK** (C Donohue BSc, L Price BSc, R Cooper MSc, C Vaughan BSc, T Moitt, L Finnetty, Prof C Gamble PhD, A P Jones PhD); **Physiotherapy Department, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, UK** (P C Ritson MSc); **Parent Lay Representative and Edge Hill University, Ormskirk, UK** (E Allen PhD); **Parent Lay Representative and Countess of Chester Hospital NHS Foundation Trust, Chester, UK** (C Fowler HNC); **Paediatric Critical Care Unit, Great North Children's Hospital, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK** (R S Agbeko PhD, E Day MBBS); **Translational and Clinical Research Institute,**

Summary

Background Bronchiolitis is a common viral respiratory disease of infants, with severity ranging from mild symptoms, such as coryza and feeding difficulties, to fulminant respiratory failure. Endotracheal administration of exogenous surfactant has been shown in small studies to improve gas exchange in critically ill infants with bronchiolitis. We aimed to investigate the safety and efficacy of endotracheal poractant alfa for treating critical bronchiolitis compared with a sham procedure.

Methods BESS was a multicentre, blinded, randomised, sham-controlled, parallel-group, phase 2, superiority trial with exploratory mechanism evaluation studies. The trial was done in 15 paediatric intensive care units in the devolved National Health Service (NHS) of England, Scotland, and Northern Ireland. Preterm and term-born infants younger than 26 weeks of gestationally corrected age admitted to hospitals with bronchiolitis requiring invasive mechanical ventilation (IMV) were randomly assigned (1:1) to receive up to three doses of endotracheal poractant alfa (Curosurf) or sham intervention, allocated through web-based randomisation. Randomisation was stratified by duration of IMV before randomisation (<24 h and ≥24 h) and by site. The infants and their families, clinical care staff, Liverpool Clinical Trial Centre staff, and members of the site research teams were masked to treatment allocations. Endotracheal poractant alfa was given initially at 200 mg/kg, followed by 100 mg/kg at 12 h intervals. The primary endpoint was the duration of IMV from randomisation to final successful extubation. All infants who were successfully extubated were included in the intention-to-treat analysis. Safety outcomes were analysed in infants who had received at least one trial intervention. This trial was registered prospectively with ISRCTN (ISRCTN11746266) and EudraCT (2018–001169–18), and is completed.

Findings The trial was completed after six recruitment seasons. Between Dec 18, 2018, to March 31, 2024, 1009 infants were assessed for eligibility, 232 of whom were randomly assigned to receive either endotracheal poractant alfa (n=115) or a sham intervention (n=117). 130 (56%) of 232 infants were male and 102 (44%) were female. Three infants were withdrawn from the study. None were lost to follow-up. The median duration of IMV was 64·9 h (IQR 43·2–92·1) in the endotracheal poractant alfa group and 62·0 h (39·3–95·1) in the sham intervention group. The geometric mean ratio was 1·02 (95% CI 0·84–1·24; *t*-test p=0·86). No clinically significant safety issues were associated with endotracheal poractant alfa and there were no deaths.

Interpretation Poractant alfa, administered endotracheally to infants with early critical bronchiolitis, although safe, did not reduce the duration of IMV compared with the sham intervention. Therefore, our findings suggest that it should not be used for this indication at this dose and administration method.

Funding UK National Institute for Health and Care Research, UK Research and Innovation Medical Research Council, Chief Scientist Office Scotland, Health and Social Care Research and Development Division Northern Ireland, and Chiesi Farmaceutici, Italy.

Introduction

Bronchiolitis is a common acute viral respiratory tract disease of infants, ranging in severity from coryza with feeding difficulties to fulminant respiratory failure. The youngest infants and those born prematurely are most often and most severely affected.[1] Bronchiolitis is the most common cause of hospital admission among infants in high-income countries and a leading cause of

Research in context

Evidence before this study

We searched ISRCTN.com and ClinicalTrials.gov from database inception to Jan 1, 2026, without language restrictions, using the search terms "bronchiolitis" as the condition AND "surfactant" OR "Poractant alfa" as the intervention. We found no other relevant trials were registered on either database at the time of our study's inception, and none are reported as active or complete as of Jan 1, 2026. Endotracheal administration of exogenous surfactant is an established and licensed treatment for neonates with respiratory distress syndrome. Infants with severe bronchiolitis have reduced quality of endogenous surfactant. A Cochrane systematic review with meta-analysis, published in 2012 and updated in 2015, of three small, randomised controlled trials of exogenous surfactant administered endotracheally to infants requiring invasive mechanical ventilation (IMV) for life-threatening bronchiolitis, favoured surfactant. Their pooled analyses showed improvements in both gas exchange and a reduction in the duration of IMV (–29 h [95% CI –40 to –18]), with no adverse effects. The Cochrane review recommended larger trials with adequate statistical power. The UK National Institute for Health and Care Research prioritisation process commissioned this topic-specific research. Before this study, approximately 1000 infants per year required IMV for around 5 days. There remains no disease-specific therapy for infants with bronchiolitis.

Added value of this study

Our large, randomised, sham-controlled, blinded, superiority, phase 2 trial of poractant alfa, administered early in critical bronchiolitis in infants, was sufficiently powered (85%) to detect a minimal clinically meaningful reduction of 18 h in IMV duration. We found that endotracheal poractant alfa had a similar safety profile to the sham procedure but did not significantly decrease IMV duration or improve any physiologically derived parameters.

Implications of all the available evidence

Although safe, based on these findings, routine early endotracheal surfactant administration in this population at this dose cannot be recommended. Further research is necessary to explore targeted use and identify which infants, if any, might benefit from this intervention.

infant death in low-income and middle-income countries.

The most common causal pathogens of bronchiolitis are the human respiratory syncytial virus and the human rhinovirus. However, the aetiology is complex because up to a third of patients have viral co-infection, which can affect the severity of the disease, and many other respiratory viruses also cause bronchiolitis.[2–4] Regardless of the causal pathogen, infants with bronchiolitis are treated as having the same disease; therefore, virological investigation is not recommended in the national guidance that directs care across the UK.[5,6] Bronchiolitis prevalence peaks sharply during the winter in temperate regions but has smaller biennial peaks in Nordic countries and even less seasonality in tropical zones.[7,8] At the time that the protocol for this study was first developed in 2013, there was no disease-specific treatment for bronchiolitis, nor respiratory syncytial virus or rhinovirus infection. Management of bronchiolitis remains supportive, with a focus on hydration and oxygenation.[5]

Infants with respiratory failure require invasive mechanical ventilation (IMV). A systematic review and meta-analysis of three small trials (n=79) found that endotracheal administration of exogenous surfactant (various types) to ventilated infants with bronchiolitis favoured surfactant treatment.[9–12] However, these data were insufficient to establish effectiveness, and there have been no relevant clinical trials in children with bronchiolitis since 2002. However, in 2019, a feasibility study of endotracheal poractant alfa in children younger than 2 years (n=69) with paediatric acute respiratory distress syndrome reported improved gas exchange without adverse effects.[13]

Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Emilia-Romagna, Italy) is a biophysically active natural surfactant prepared from porcine (domesticated pig) lungs, containing almost exclusively lipids, in particular phosphatidylcholine (about 70% of the total phospholipid content), and about 1% of specific low molecular weight hydrophobic proteins (surfactant proteins B and C).[14]

We aimed to investigate the safety and efficacy of endotracheal poractant alfa in reducing the duration of IMV for infants with respiratory failure requiring intubation and mechanical ventilation in paediatric intensive care units due to clinically diagnosed bronchiolitis.

Methods

Study design and participants

The Bronchiolitis Endotracheal Surfactant Study (BESS) was a multicentre, blinded, randomised, sham-controlled, parallel-group, phase 2, superiority trial with exploratory mechanism evaluation studies assessing the efficacy of endotracheally administered poractant alfa. The trial was offered to 23 paediatric intensive care units in the devolved National Health Service (NHS) of England, Scotland, Wales, and Northern Ireland that had a historic case load of more than ten cases per year of bronchiolitis.

This study was conducted in 15 centres. Infants born at term who were younger than 26 weeks (or if born prematurely, younger than 26 weeks when their chronological age was gestationally corrected for

Newcastle University, Newcastle, UK (R S Agbeko); **Paediatric Critical Care Unit, Royal Hospital for Children, NHS Greater Glasgow and Clyde, Glasgow, UK** (E Brincat MD, R Levin MBChB); **College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK** (E Brincat, R Levin); **Paediatric Intensive Care Unit, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK** (J V Cassidy MBBS, K P Morris MD); **Paediatric Critical Care, Nottingham Children's Hospital, Nottingham, UK** (P E Davies BMBS); **Paediatric Intensive Care Unit, Bristol Royal Hospital for Children, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK** (P J Davis MBChB); **Paediatric Intensive Care Unit, Staffordshire Children's Hospital, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK** (C Kanaris PhD, A Wherton-Whitehurst MSc); **Cambridge University NHS Foundation Trust, Cambridge, UK** (C Kanaris); **Paediatric Critical Care Unit, The Royal London Children's Hospital, Barts Health NHS Trust, London, UK** (S Lampariello MD); **Paediatric Critical Care Unit, Royal Hospital for Children and Young People, NHS Lothian, Edinburgh, UK** (T-Y M Lo PhD); **Usher Institute, University of Edinburgh, Edinburgh, UK** (T-Y M Lo); **Institute of Applied Health Research, University of Birmingham, Birmingham, UK** (K P Morris); **Paediatric Intensive Care Unit, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, Southampton, UK** (A Osman MBChB, J Pappachan MBBChir); **Paediatric Intensive Care Unit, Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester, UK** (S D Playfor DM); **Royal Belfast Hospital for Sick Children, Belfast Health and Social Care Trust, Belfast, UK** (J Richardson MBChB); **Paediatric Intensive Care Unit,**

Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, UK (G Sefton PhD, K Thorburn MD); **Children's Critical Care Unit, Leeds Children's Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK** (S Sundararajan MD); **Paediatric Intensive Care Unit, Oxford Children's Hospital, Oxford University NHS Foundation Trust, Oxford, UK** (J Weitz MBBS); **Department of Paediatrics, University of Oxford, Oxford, UK** (J Weitz); **Institute of Population Health, University of Liverpool, Liverpool, UK** (E Deja PhD, Prof K Woolfall PhD); **Department of Neonatology, Elizabeth Garrett Anderson Institute for Women's Health, University College London, London, UK** (J Madsen PhD, Prof H W Clark PhD); **Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK** (Prof A D Postle PhD, J Pappachan); **National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK** (Prof A D Postle, J Pappachan); **Pharmacy, Alder Hey Children's NHS Foundation Trust, Liverpool, UK** (C Barker MSc); **Research Directorate, Alder Hey Children's NHS Foundation Trust, Liverpool, UK** (Prof M Peak PhD); **Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK** (Prof P S McNamara, Prof M A Turner PhD)

Correspondence to: Prof Malcolm G Semple, Department of Clinical Infection, Microbiology, and Immunology, Institute of Infection, Veterinary, and Ecological Sciences, University of Liverpool, Liverpool L69 7BE, UK
m.g.semple@liverpool.ac.uk

See **Online** for appendix

For the **protocol** see https://doi.org/10.1186/ISRCTN11746266

For the **Liverpool Clinical Trial Centre** see https://lctc.org.uk/

premature birth), had a clinical diagnosis of bronchiolitis per National Institute for Health and Care Excellence Guideline 9,[1] required IMV with tracheal intubation, and had parental written informed consent for enrolment within 48 h of intubation were included. Gestational correction of infant age for premature birth is a well established method for adjusting the assessment of premature infants who are anatomically, physiologically, immunologically, and neurodevelopmentally immature for their chronological age. Exclusion criteria were major congenital anomalies, pre-existing neuromuscular disease, intubation for more than 48 h before randomisation, previous use of extracorporeal membrane oxygenation, intratracheal surfactant administration during the current bronchiolitis episode, or primary apnoea being the sole reason for IMV.

Ethnicity data were retrospectively collected from participants' NHS hospital records if parents had declared it, or, if asked, using the 2011 Ethnicity Harmonised Standard mandated by all UK NHS providers. Sex data were collected as sex assigned at birth. Details of patient and public involvement and engagement are provided in the appendix (p 2).

Parents face specific challenges when deciding whether to consent to their children's participation in research during emergencies.[15] Due to the limited timeframe for seeking informed consent, we used a proportionate approach, allowing a 48 h window from intubation to obtain consent and conduct randomisation.[16] The acceptability of administering medicines derived from pigs to infants from families of the Jewish and Islamic faiths was discussed with a representative from the Kashrus and Medicines Information Service for the Ashkenazi Beth Din of the United Synagogue and the Union of Orthodox Hebrew Congregations, and a member of the Research and Documentation Committee of the Muslim Council of Britain. Both authorities confirmed that medicines derived from pigs, which can be given to children for severe, life-threatening conditions, are exempt from religious proscription.

The study received approval from the UK Health Research Authority and the South Central Berkshire Research Ethics Committee (Integrated Research Application System ID 220853). This trial was registered prospectively with ISRCTN (ISRCTN11746266) and EudraCT (2018–001169–18), and is completed. The protocol is available online.

Randomisation and masking

Eligible infants were randomly assigned (1:1) to receive either endotracheal poractant alfa or a sham procedure using air as a placebo intervention. Randomisation was performed using a web-based system (WebEZ, Almac Clinical Services, UK) with computer-generated permuted blocks (block size four), stratified by the duration of IMV before randomisation (<24 h or ≥24 h) and by each site.

The infants and their families, clinical care staff, Liverpool Clinical Trial Centre staff (excluding appropriate statistical team members), and all members of the site research teams (excluding agreed staff dedicated to randomly assigning participants and administering interventions) were blinded to treatment allocations. Participating sites identified staff who would be aware of allocation in advance of randomisation (unblinded staff). The staff responsible for randomisation also administered the interventions, so they were, by necessity, aware of the intervention allocations. The dosage witnesses were also aware of the intervention allocations, meaning they were not blinded. Appropriate Liverpool Clinical Trial Centre statistical staff were unblinded to specific allocations, but only after events requiring safety assessments. Unblinded staff were not responsible for the care of infants and did not engage in decisions related to readiness for extubation and the timing of extubation.

The intervention was prepared by unblinded staff in the privacy of a drug preparation room. The allocated intervention (poractant alfa or air) was drawn into a syringe, and an occlusive label was applied to mask the contents. The intervention syringe was placed on a tray and covered before being taken to the bedside by the unblinded staff. To maintain blinding at the bedside, the usual clinical staff and parents were asked to leave, curtains were drawn, or the room was closed, leaving only the unblinded staff with the infant to conduct the study procedures.

Procedures

After tracheal toilet and bronchoalveolar lavage, infants received up to three doses of endotracheal poractant alfa, initially 200 mg/kg, followed by 100 mg/kg at 12 h intervals or up to three sham interventions. The sham intervention mimicked the administration process for endotracheal poractant alfa, but instead of surfactant, the equivalent volume of air was used.

Sedation and neuromuscular blocking drugs were used at the clinician's discretion and not directed by protocol. Infants were weaned and extubated according to a standardised protocol, and readiness for extubation was assessed using predefined physiological and clinical criteria.[17]

Study procedures (tracheal toilet and bronchoalveolar lavage, followed by the allocated intervention) were not performed once the criteria for readiness for extubation had been met. On Jan 30, 2023, bronchoalveolar lavage sampling was removed from the protocol, as sufficient samples had been obtained for the exploratory mechanism evaluation studies. These studies will be reported elsewhere.

Details of participant timeline, procedures, interventions, assessments, and parent-reported quality of life questionnaire (Liverpool Respiratory Symptom Questionnaire [LRSQ][18]) are described in sections 8 and 9 of the protocol (appendix pp 39–55).

Routine respiratory tract virology results reported by discharge were collected as a prespecified baseline characteristic.

Outcomes

The primary outcome was the duration of IMV from randomisation to final extubation, including any periods off IMV following unsuccessful extubation attempts that resulted in re-intubation. An attempt to extubate was considered to have failed if the infant was re-intubated within 48 h of the most recent extubation. This outcome was not centrally assessed.

Secondary outcomes were the scored value of the parent-reported outcome measure of respiratory symptoms in the LRSQ[18] at 6 months and 12 months after randomisation; time to meet readiness criteria for a spontaneous breathing trial; the number of trial interventions administered; changes over time from baseline in ventilation index, oxygenation index, and oxygen saturation index while mechanically ventilated; ratio of peripheral O_2 saturation to fraction of inspired O_2 (SpO_2:FiO_2) at 6, 12, 24, 36, and 48 h; duration of requirement for supplemental oxygen after extubation; use of steroids to assist extubation; duration of post-extubation non-invasive respiratory support; and duration of stay in the paediatric intensive care unit and hospital.

To assess the safety of the intervention for infants with life-threatening bronchiolitis, the following outcomes were included: failure to administer the intervention due to adverse events during the study procedures (tracheal toilet or bronchoalveolar lavage); failure to complete administration of the intervention due to any adverse event during the administration of the intervention; any need to replace the endotracheal tube between random assignment and successful extubation; any incidents of air leak (pneumothorax, pneumomediastinum, or both) occurring between random assignment and discharge from the paediatric intensive care unit; death during paediatric intensive care unit admission and all-cause mortality at 90 days after randomisation. Regardless of causality, all adverse events were reported from random assignment until 24 h after the infant's last intervention administration. Parent-reported infant hospital readmissions up to 90 days after random assignment were noted. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 21.0).

Statistical analysis

The sample size calculation was based on data from an audit of 60 eligible infants admitted to the paediatric intensive care unit at Alder Hey Children's Hospital (Liverpool, UK) during the winter respiratory viral seasons 2012–13 and 2013–14. This showed a mean duration of ventilation of 4·83 days (SD 2·50; Paediatric Intensive Care Audit Network for the UK and Ireland data, 2012–14). We estimated that 284 infants would provide at least 90% power, and 206 participants would confer at least 80% power to detect a difference of 18 h (0·75 days) between the two groups at a two-sided significance level of 0·05, allowing for a potential drop-out rate of 5%.[19] We aimed to recruit participants over successive seasons to reach a sample size of at least 80% power.

We published our full statistical analysis plan on April 25, 2024, before conducting any comparative analysis of the treatment groups. Study-specific data required for the statistical analysis plan were prospectively collected by site staff using a paper case report form and adhered to the principle of data minimisation.

For the **statistical analysis plan** see https://doi.org/10.1186/ISRCTN11746266

The efficacy analyses used the full analysis set, comprising all randomly assigned infants. The safety analysis set included all randomly assigned infants who received at least one intervention. Analyses were by intention-to-treat, without adjustment for multiplicity.

For baseline and demographic data, categorical data were summarised by frequencies and percentages and continuous data were summarised by mean (SD) or median (IQR) and range. We did not test differences between baseline data by intervention allocation. Age corrected for gestation was calculated post hoc from chronological age with a correction for premature birth. The UK adheres to the WHO definition of preterm birth as one that occurs before 37 completed weeks of pregnancy. A full-term pregnancy typically lasts between 37 and 41 weeks. Babies who were not born prematurely did not require a correction to their age and were assumed to have been born at 40 weeks of gestation, as is standard reporting practice in the UK and much of the world.

For the primary outcome, group means for infants in the endotracheal poractant alfa group and infants in the sham procedure group were compared using a two-sample *t*-test on the natural logarithm-transformed data. The difference between groups in the natural logarithm-transformed data was back-transformed by exponentiation to provide the geometric mean ratio, with a corresponding 95% CI.

A linear mixed effects model was also fitted to the natural logarithm-transformed data, using analysis of covariance to test for differences between groups while adjusting for the stratification factor of time on IMV before random assignment (<24 h and ≥24 h), sex, and adjusted age at enrolment as fixed effects, with sites included as a random effect (random intercept only). A prespecified subgroup analysis, which was stratified by gestation at birth (preterm-born and term-born) was requested by the trial steering committee before the database being locked and while the trial steering committee were still blinded to treatment allocations. A post-hoc subgroup analysis stratified by gestational age was conducted.

The primary outcome analysis was a complete case analysis that included only those infants for whom the primary outcome had been observed. If any infants had

not undergone a successful extubation by the time they were last followed up (eg, consent for follow-up was withdrawn), a prespecified sensitivity analysis was conducted to include these participants and assess the robustness of the primary outcome analysis.

For the secondary outcomes, longitudinal data for ventilation index, oxygenation index, oxygen saturation index, and SpO_2:FiO_2 were analysed using joint modelling. LRSQ data were modelled longitudinally, and comparisons were made between groups. Continuous secondary outcomes were compared using a two-sample *t*-test on the natural logarithm-transformed data. The difference between groups in the natural logarithm-transformed data was back-transformed by exponentiation to provide the geometric mean ratio, with a corresponding 95% CI. Binary data were reported in terms of relative risk (RR) with 95% CIs. Ordered categorical data were analysed using the χ^2 test for trend or Fisher's exact test as appropriate. Analyses were performed using SAS (version 9.4 or later).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The funders provided financial and material resources to enable the study, including the intervention endotracheal poractant alfa and independent randomisation software linked to poractant distribution to sites by an independent distributor. The funders were allowed to review the manuscript and provide comments only on the funding description and the provision of the intervention.

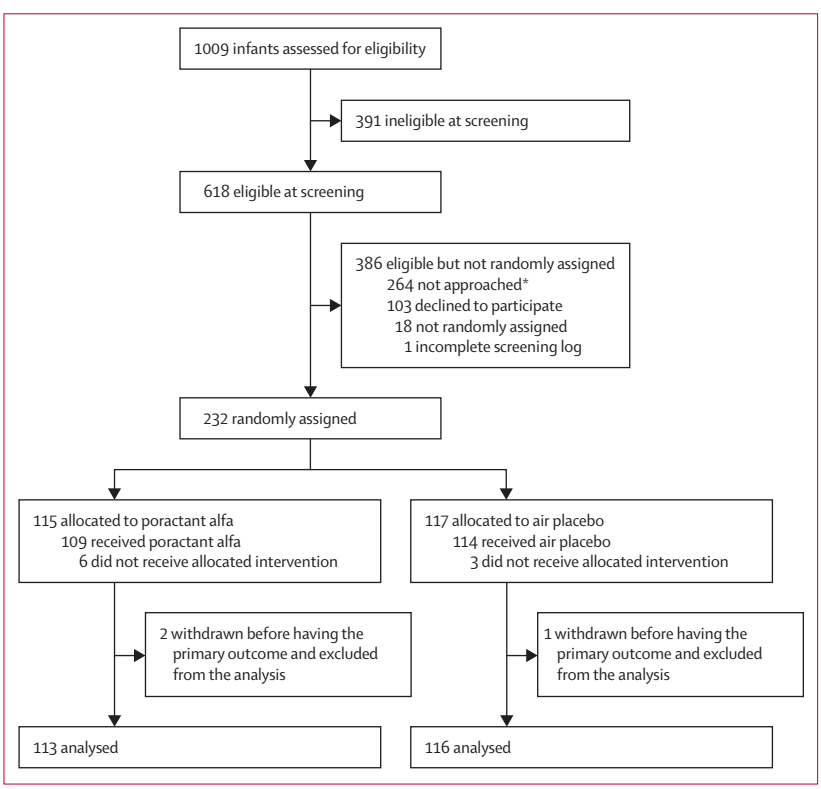

Figure: **Trial profile**
*Reasons not approached are in the appendix (p 139).

Results

From Dec 18, 2018, to March 31, 2024, 1009 infants with bronchiolitis requiring mechanical ventilation were assessed for eligibility across 15 paediatric intensive care units in England, Scotland, and Northern Ireland. Of these, 618 met the inclusion criteria and, following informed consent, 232 were randomly assigned to receive either endotracheal poractant alfa (n=115) or a sham intervention (n=117; figure). The first infant was enrolled on Jan 2, 2019, and the last on March 19, 2024.

Enrolment was reduced during the winter seasons of 2020–21 and 2021–22 by effective public health measures aimed at mitigating the severe impact of the COVID-19 pandemic on UK society, which also substantially reduced admission for bronchiolitis. Seasonal respiratory disease remained attenuated in 2022–23, which, combined with the impact of COVID-19 on paediatric intensive care unit research staff capacity, hindered recruitment in winter 2022–23. By winter 2023–24, the seasonality of bronchiolitis had returned, and research capacity had been replenished at sufficient centres to enable the study to exceed the minimum enrolment target and be completed in its sixth season.

16 (14%) of 115 infants in the endotracheal poractant alfa group and 14 (12%) of 117 in the sham intervention group had at least one major protocol deviation. A full breakdown of both minor and major protocol deviations is in the appendix (p 146). In the endotracheal poractant alfa group, two infants were withdrawn by their parents without explanation. One infant was withdrawn from the sham intervention group by a doctor who reported that parents were too upset by the clinical status of their infant to be able to continue making informed decisions about the trial. Three infants, two in the endotrachael poractant alfa group and one in the sham intervention group, were withdrawn after random assignment but before their allocated interventions were administered. The other infant was withdrawn after receiving endotracheal poractant alfa but before spontaneous breathing trial criteria were met. These three withdrawn infants are excluded from the primary outcome analysis, as per the protocol and statistical analysis plan, which only included completed cases. No infants were lost to follow-up. Trial data entry privileges were revoked, and the database was locked on Dec 13, 2024.

130 (56%) of 232 infants were male and 102 (44%) were female (table 1). The proportion of preterm-born infants was slightly higher in the endotracheal poractant alfa group (66 [57%] of 115 infants) than in the sham intervention group (61 [52%] of 117 infants). Anonymised ethnicity data were collected at the end of the trial and

cannot therefore be presented split by treatment group. Where ethnicity was declared by parents (n=173), 151 (87%) infants were White, and 22 (13%) were of another ethnicity. Ethnicity data are described further in the appendix (p 188).

The number of infants who completed their first intervention was 107 (94%) of 114 who were expected to receive this dose in the endotracheal poractant alfa group (six infants did not start their first intervention [one of whom withdrew before receipt and so was not included in the number expected to receive the dose] and two infants started but did not complete their first intervention) and 114 (97%) of the 117 in the sham intervention group (three infants did not start their first intervention), 89 (79%) of 113 and 104 (89%) of 117 completed their second intervention, and 80 (76%) of 106 and 82 (78%) of 105 completed their third intervention. Infants did not receive any intervention once readiness for extubation criteria were met. Otherwise, the reasons why an expected dose was not administered are listed in the appendix (p 147). No significant difference was observed in the total number of trial interventions administered between the two groups (appendix p 168).

Six participants had their treatment allocation unblinded while on treatment (four in the endotracheal poractant alfa group and two in the sham intervention group), this was accidental in one infant in both treatment groups. Reasons included the sharing of verbal or written information between the blinded and non-blinded teams (three in the endotracheal poractant alfa group and one in the sham intervention group), clinical need for ongoing care (one in the endotracheal poractant alfa group), and other reasons (two in the endotracheal poractant alfa group and one in the sham intervention group); more than one reason could have been included for each infant.

The duration of IMV was not significantly different between the two intervention groups. The median IMV duration was 64·9 h (IQR 43·2–92·1) in the endotracheal poractant alfa group and 62·0 h (39·3–95·1) in the sham intervention group. The geometric mean ratio of the endotracheal poractant alfa group compared with the sham intervention group was 1·02 (95% CI 0·84 to 1·24; p=0·86; table 2). The results from the mixed effects model for the sensitivity analysis, which included the three infants with no known outcome due to their withdrawal from the study, confirmed the results from the primary analysis (appendix p 164). The prespecified subgroup analysis, stratified by gestation at birth (preterm-born and term-born), did not show any significant differences between the two treatment groups (appendix p 166). The post-hoc subgroup analysis stratified by gestational age did not show any significant treatment differences within the gestational age subgroups (appendix pp 189–190).

No significant differences were seen between the groups in ventilation index, oxygenation index, oxygen saturation index, or SpO_2:FiO_2 ratio (appendix pp 174–175). There was no significant difference between the groups in the median time from randomisation to readiness for a

	Endotracheal poractant alfa group (n=115)	Sham intervention group (n=117)
Sex		
Male	63 (55%)	67 (57%)
Female	52 (45%)	50 (43%)
Premature birth		
Yes	66 (57%)	61 (52%)
No	49 (43%)	56 (48%)
Gestational age		
Extremely preterm (<28 weeks)	5 (4%)	5 (4%)
Very preterm (28–31 weeks)	7 (6%)	13 (11%)
Moderate preterm (32–33 weeks)	11 (10%)	12 (10%)
Late preterm (34–39 weeks)	39 (34%)	27 (23%)
Term (≥40 weeks)	49 (43%)	56 (48%)
Not known	4 (3%)	4 (3%)
Gestational age, weeks*		
Mean	36·7 (3·9)	36·5 (4·4)
Median	38·0 (34·0 to 40·0)	39·0 (33·0 to 40·0)
Range	26·0 to 40·0	24·0 to 40·0
Age corrected for gestation at randomisation, all infants, weeks		
Mean	5·0 (6·5)	4·8 (5·9)
Median	4·0 (0·0 to 8·0)	3·0 (1·0 to 7·0)
Range	–5·0 to 25·0	–4·0 to 23·0
Median age of premature born infants at randomisation, corrected for gestation, weeks	n=66; 1·0 (–1·0 to 5·0)	n=61; 2·0 (–1·0 to 4·0)
Median age of term-born infants at randomisation, weeks†	n=49; 6·0 (4·0 to 11·0)	n=56; 6·0 (3·0 to 10·0)
Weight, all infants, kg		
Mean	4·2 (1·5)	4·2 (1·5)
Median	4·0 (3·0 to 5·0)	4·0 (3·1 to 5·0)
Range	2·0 to 8·9	2·0 to 8·8
Intubated on arrival to the PICU		
Yes	90 (78%)	97 (83%)
No	25 (22%)	20 (17%)
Median time on mechanical ventilator before arrival at PICU, h	30·1 (22·7 to 37·0)	29·9 (21·3 to 37·1)
Data unobtainable	4 (3%)	1 (1%)
Bacterial infection identified		
Yes	29 (25%)	31 (26%)
No	79 (69%)	82 (70%)
No sample taken	4 (3%)	2 (2%)
Data unobtainable	3 (3%)	2 (2%)
Viral infection identified		
Yes	101 (88%)	111 (95%)
No	8 (7%)	5 (4%)
No sample taken	4 (3%)	0
Data unobtainable	2 (2%)	1 (1%)

Data are n (%), mean (SD), median (IQR), range, or n; median (IQR). Data are complete unless specified as unobtainable. PICU=paediatric intensive care unit. *Data on gestational age were only collected for those infants who were deemed to be preterm. †Negative value indicates a negative corrected age.

Table 1: **Baseline demographic and clinical characteristics at randomisation**

	Endotracheal poractant alfa group* (n=115)	Sham intervention group* (n=117)	Geometric mean ratio (95% CI)	p value
Total duration of mechanical ventilation, h	64·9 (43·2–92·1)	62·0 (39·3–95·1)	1·02 (0·84 to 1·24)	0·86
Time to readiness for spontaneous breathing trial, h	57·3 (32·4–75·6)	37·2 (25·6–81·4)	0·99 (0·75–1·31)	0·94
Duration of oxygen supplementation, h	40·9 (17·0–90·0)	34·0 (16·0–81·4)	2·42 (1·03–5·68)	0·043
Duration of post-extubation respiratory support, h	0·0 (0·0–15·7)	0·0 (0·0–0·0)	1·68 (0·48–5·80)	0·41
Duration of stay at PICU, h	104·4 (67·9–153·1)	93·4 (66·6–144·8)	1·01 (0·86–1·18)	0·95
Duration of total stay in hospital, h	165·3 (111·3–231·2)	142·2 (96·6–221·9)	1·13 (0·96–1·33)	0·13

PICU=paediatric intensive care unit. *Data are median (IQR) of the raw data with no transformations in hours.

Table 2: **Primary and secondary continuous outcome results**

spontaneous breathing trial (table 2). The median duration of oxygen supplementation was greater in the endotracheal poractant alfa group than in the sham intervention group (table 2). The median duration of post-extubation non-invasive respiratory support in the endotracheal poractant alfa group was not significantly different between the two groups (table 2). To assist in extubation from IMV, 51 (44%) of the 115 infants in the endotracheal poractant alfa group and 49 (42%) of the 117 infants in the sham intervention group required steroids. The difference between the two groups was not statistically significant (RR 1·06 [95% CI 0·79–1·42]; p=0·70).

The duration of stay in the paediatric intensive care unit and duration of stay in the hospital were not significantly different between the two groups (table 2). The LRSQ completion rates at 6 and 12 months were such that the planned statistical testing was not possible. Summary data for this outcome are in the appendix (p 181).

Virology and bacteriology results at the point of discharge are reported in the appendix (pp 186–187).

Adverse events leading to failure to administer the intervention (either during the preparatory process or the administration) occurred in three (3%) of 115 infants in the endotracheal poractant alfa group and none of the 117 infants in the sham intervention group. This difference was not statistically significant. Air leak (pneumothorax and pneumomediastinum) occurred before discharge from the paediatric intensive care unit in one (1%) infant in the endotracheal poractant alfa group and one (1%) in the sham group. 18 (16%) infants in the endotracheal poractant alfa group and 21 (18%) in the sham intervention group required replacement of the endotracheal tube (RR 0·87 [95% CI 0·49–1·55]; p=0·64).

There were no deaths in either treatment group during admission to the paediatric intensive care group or up to 90 days after randomisation. Of the 232 randomly assigned patients, 54 (23%) completed the patient-reported readmission to hospital survey: 26 (23%) were in the endotracheal poractant alfa group and 28 (24%) were in the sham intervention group. Patient-reported hospital readmissions (up to 90 days after randomisation) occurred in 11 (42%) of 26 infants in the endotracheal poractant alfa group (six infants had one readmission, one infant had two readmissions, and four infants had three admissions) and five (18%) of 28 infants in the sham group (five infants had one readmission), with no significant difference observed between the two groups.

The incidence of serious adverse events and non-serious adverse events was similar between the treatment groups. Seven serious adverse events were reported from six infants in the endotracheal poractant alfa group, and six serious adverse events were reported from six infants in the sham intervention group (appendix p 157). There were no suspected unexpected serious adverse reactions in the endotracheal poractant alfa group and two (one of pneumonia and one pneumothorax) in two infants in the sham intervention group. Summary data for all serious adverse events, including severity and causality and stratification by the use of muscle relaxants, are in the appendix (pp 157–159).

26 non-serious adverse events were reported by 22 (10%) of the 223 participants in the safety population, including 17 non-serious events in 14 infants in the endotracheal poractant alfa group and nine non-serious adverse events in eight infants in the sham intervention group (table 3). One non-serious adverse event in the endotracheal poractant alfa group was classified as severe (bradycardia) and was considered related to the use of endotracheal poractant alfa. Summary data for all non-serious adverse events, including severity and causality and stratification by the use of muscle relaxants, are in the appendix (pp 152–156).

Discussion

In this randomised, sham-controlled trial, we evaluated the efficacy and safety of endotracheal poractant alfa in critically ill infants with bronchiolitis requiring IMV. We found that early endotracheal administration of poractant alfa had a similar safety profile to the sham procedure but did not significantly reduce the duration of IMV compared with the sham intervention, nor did it substantially beneficially affect other secondary outcomes, including ventilation indices, time to readiness for a spontaneous breathing trial, duration of post-extubation respiratory support, or durations of stay in the paediatric intensive care unit or hospital. Endotracheal administration of poractant alfa was associated with a clinically small but statistically significant increases in the duration

of supplemental oxygenation following extubation. Considering the number of secondary analyses conducted without correction for the false discovery rate, this isolated statistical finding should be regarded as noise and is unlikely to hold any true statistical or clinical significance.

Surfactant therapy has been an established part of neonatal practice since regulatory approval by the US Food and Drug Administration in 1989.[20] Endotracheal poractant alfa has been licensed for use in the UK since 1994.[11] Exogenous endotracheal surfactant reduces mortality, decreases the incidence of pulmonary air leak (pneumothoraxes and pulmonary interstitial emphysema), and lowers the risk of chronic lung disease or death at 28 days of age in intubated newborn infants with surfactant-deficient lung disease.[21] The pathophysiology of respiratory failure in bronchiolitis of infants is complex and includes reduced lung compliance and surfactant deficiency.[22,23] Surfactant is used off-label in many centres as rescue therapy for infants and children with paediatric acute respiratory distress syndrome due to various causes, who do not meet oxygenation or gas exchange goals using conventional IMV. This unlicensed application is used to buy time to establish or avoid the use of extracorporeal membrane oxygenation.[24] Early and prophylactic use of surfactant is superior to its late and selective use in newborn infants with surfactant-deficient lung disease.[21,25] Similarities between surfactant-deficient acute respiratory failure in neonates and paediatric acute respiratory distress syndrome in infants with bronchiolitis prompted us, and others, to investigate whether early exogenous surfactant is useful in critically ill infants with bronchiolitis.[10–12] A Cochrane systematic review of the three previous small randomised controlled trials (pooled n=79) concluded that surfactants reduced the duration of mechanical ventilation and stay in the intensive care unit and improved oxygenation and CO_2 elimination.[9] However, as these studies were small, available evidence has, before this study, been insufficient to establish the effectiveness of surfactant therapy for bronchiolitis in critically ill infants who require IMV. The existing evidence justified the need for larger blinded trials with adequate power.

Our findings contrast with the three previous smaller studies and their meta-analysis, which reported positive effects of surfactant administration on IMV duration, oxygenation, and CO_2 elimination in infants with bronchiolitis. To our knowledge, our study is the largest randomised controlled trial to evaluate this intervention. We have taken great care to ensure the blinding of clinical staff and investigators, thus providing a robust assessment of efficacy in a critically ill population across numerous centres in three health-care devolved nations of the UK.

Our finding of no observed benefit of endotracheal poractant alfa might be attributed to several factors. First, the timing of surfactant administration might play a crucial role in its efficacy. Second, variations in aetiology, disease progression, and individual responses to the intervention might have influenced outcomes. Furthermore, improvements in supportive care and non-invasive ventilation methods since previous studies might have diminished the potential effect of surfactant therapy on the duration of IMV. The short-term effects on respiratory physiology observed by others might not translate into clinical benefits due to other pathophysiological mechanisms of bronchiolitis. However, we did not observe any beneficial effects on respiratory physiology.

A major strength of our study was its rigorous design, which included a multicentre setting, randomisation, blinding, and a sham control intervention to minimise bias, as well as a standardised protocol for assessing readiness for extubation. We enrolled a representative patient sample over six seasons, before, during, and

	Endotracheal poractant alfa group		Sham intervention group	
	Events	Patients (n=109)	Events	Patients (n=114)
Total	17	14 (13%)	9	8 (7%)
Cardiac disorders: bradycardia	4	4 (4%)	0	0
Ear and labyrinth disorders: otorrhoea	0	0	1	1 (1%)
General disorders and administration site conditions				
Perforation	0	0	1	1 (1%)
Pyrexia	0	0	1	1 (1%)
Total	0	0	2	2 (2%)
Infections and infestations				
Bronchiolitis*	0	0	1	1 (1%)
Pneumonia	1	1 (1%)	0	0
Total	1	1 (1%)	1	1 (1%)
Injury, poisoning, and procedural complications				
Endotracheal intubation complication	1	1 (1%)	1	1 (1%)
Sedation complication	1	1 (1%)	0	0
Total	2	2 (2%)	1	1 (1%)
Investigations: oxygen saturation decreased	5	4 (4%)	0	0
Metabolism and nutrition disorders				
Hypokalaemia	1	1 (1%)	0	0
Total	1	1 (1%)	0	0
Nervous system disorders: epilepsy	0	0	1	1 (1%)
Reproductive system and breast disorders: genital discharge	1	1 (1%)	0	0
Respiratory, thoracic and mediastinal disorders				
Atelectasis	0	0	1	1 (1%)
Hypoxia	0	0	1	1 (1%)
Respiratory depth decreased	1	1 (1%)	0	0
Total	1	1 (1%)	2	2 (2%)
Extubation	2	2 (2%)	1	1 (1%)

*Subsequent admission after discharge and recovery, for further episode of bronchiolitis during the safety reporting period.

Table 3: **Non-serious adverse events**

after the COVID-19 pandemic, in 15 paediatric intensive care units across three countries with devolved national health services. Our sample size was adequate to detect a clinically meaningful difference in IMV duration, and adherence to the standardised extubation protocol across sites enhanced the internal validity of our findings. The sham control intervention also addressed potential placebo effects, which are particularly relevant in trials with subjective endpoints such as readiness for extubation. The study was completed before passive immunisation against human respiratory syncytial virus was routinely offered to preterm-born infants in the UK.

The study has some limitations. As a phase 2 trial, our study was designed to assess the efficacy and safety of the licensed dose regimen of endotracheal poractant alfa, which might not have been optimal for infants with bronchiolitis. However, there was a strong rationale for using the licensed dose regimen, which has been shown to be effective in surfactant-deficient lung disease in premature infants. The proportion of preterm-born infants was slightly higher in the endotracheal poractant alfa group (66 [57%]) than in the sham intervention group (61 [52%]), but the median and IQRs for gestational age at birth and corrected gestational age at randomisation were similar between groups. It is unlikely that the small chance difference in the proportion of premature infants between treatment groups has influenced the trial outcome. Data on bronchopulmonary disease status and concomitant passive immunisation against respiratory syncytial virus, and whether discharged home on oxygen, were not collected. Ongoing studies are exploring mechanistic outcomes in subgroups defined by age, gestational status, and disease severity.

Our findings do not support the routine use of endotracheal poractant alfa in critically ill infants with bronchiolitis requiring IMV. However, because surfactant administration did not increase adverse events, it remains a potential rescue therapy in specific clinical scenarios, such as proven severe surfactant deficiency or when conventional ventilation is failing to meet oxygenation or gas exchange targets. The role of surfactant therapy in different patient subgroups, including those with comorbidities or who have undergone prolonged ventilation, warrants further investigation in clinical trials.

Future research should identify biomarkers or clinical criteria to enhance the prediction of which infants are likely to benefit from surfactant therapy. Furthermore, studies investigating the timing of administration and potential synergies with other respiratory support strategies could offer additional insights into optimising treatment for severe bronchiolitis.

This large, multicentre, randomised, sham-controlled trial did not find a significant benefit of endotracheal poractant alfa in reducing IMV duration or improving secondary outcomes in critically ill infants with bronchiolitis. The use of surfactant in this population varies between centres, with polarised views on efficacy and no consensus. Although safe, based on our findings, routine surfactant administration in this population cannot be recommended. Further research is necessary to explore targeted use and identify which infants, if any, might benefit from this intervention.

BESS Investigators

Helen Adamson, Rachel S Agbeko, Cara Alexander, John Alexander, Evette Allen, Laura Anderson, David Armstrong, Lydia Ashton, Judit Bak, Katherine Baptiste, Catrin Barker, Kirsten Beadon, Rebecca Beckley, Lynne Bell, Ashley Best, Amy Brammar, Edgar Brincat, Wendy Browne, Lara T Bunni, Lisa-Marie Butt, Hilary Callaghan, Lorena Caruana, Jane V Cassidy, Tania Castillo Hernandez, Susanne Cathcart, Hannah Child, Bessie Cipriano, Howard W Clark, Hannah Clarke, Stephanie Clarke, Rob Claydon, Sophie Coles, Vanessa Compton, Amber Cook, Rachael Cooper, Lindsay Crate, Tracey Curtis, Sarah Daggett, Patrick E Davies, Peter J Davis, Anne Dawson, Elisabeth Day, Elizabeth Deja, Laura Dodge, Chloe Donohue, Rachael Dore, Sarah-Jayne Eames, Nichola Etherington, Samantha Finn, Lynsey Finnetty, Clare Fowler, Sarah Fox, Crawford Fulton, Carrol Gamble, Simon Gates, Bernadette C Gavin, Annabel Giddings, Jessica Green, Michael Griksaitis, Paris-Lucia Harrison, Ellen Haskins, Nadine Heenan, Elizabeth Henderson, Rebecca Hill, Sarah Hopton, Claire F Jennings, Rebecca Jennings, Petr Jirasek, Ashley P Jones, Dawn Jones, Ebraheem Junaid, Constantinos Kanaris, Nosheen Khalid, Tahmina Khatun, Ramiya Kirupananthan, Craig Knott, Ramesh Kumar, Samantha La Roche, Stephanie Laidlaw, Benjamin Lakin, Christopher Lamb, Simona Lampariello, Richard Levin, Flora Lewis, Christina Linton, Vicki Linton, Tsz-Yan Milly Lo, Lisa Lucyk, Jeremy Lyons, Christine Mackerness, Jens Madsen, Dave Malabar, Michael Mander, Muhammed Pradhika Mapindra, Helen Marley, Ross Marscheider, Michael J Marsh, Rebecca Marshall, Lindy Martin, Shelley Mayor, Joseph McCann, Nicola McClelland, Laura McConaghy, Jenni McCorkell, Jackie McCormick, Liz McCullagh, Rachel McMinnis, Paul S McNamara, Samantha Mead, Christie Mellish, Natalie Milburn, Bethany Millman, Philip Milner, Holly Minchin, Amisha Mistry, Sarah Mogan, Tracy Moitt, Seana Molloy, Dave J Morgan, Kevin P Morris, Tara Murray, Manoj Kumar Muthusamy, Clara Nelson, Katie M Neville, Bethan Newell, Heather Nicholls, Olivia Nugent, Laura O'Malley, Udeme Ohia, Zoe Oliver, Blessing Osaghae, Ahmed Osman, Madhuri Panchal, John Pappachan, Helen Parker, Holly Parkin, Roger Parslow, Rekha Patel, Simone Paulson, Harriet Payne, Matthew Peak, Rachael Percival, Nicolene Plaatjies, Stephen D Playfor, Jenny Pond, Anthony D Postle, Catherine Postlethwaite, Jennifer Preston, Laura Price, Laura Rad, Raghu N Ramaiah, Pavanasam Ramesh, Maxine Ramsay, Samantha Reed, Kathryn Reeves, Julie Richardson, Emma K Riley, Laura Rimmer, Paul C Ritson, Ceri Robbins, Natasha Roberts, Christa Ronan, Tomasz Rygielski, Avishay Sarfatti, Rohit Saxena, Alvin Schadenberg, Emily Scriven, Gerri Sefton, Malcolm G Semple, Chidambaram Sethuraman, Chris Simons, Frances Sinfield, Anna Stancombe, John Stiven, Elizabeth Stoddart, Colin Summers, Santosh Sundararajan, Laura J Sutton, Kate Teeley, Mark Terris, Carla Thomas, Charlotte Thompson, Clare Thompson, Kentigern Thorburn, Natasha Thorn, Joanne Tomlinson, Patrick Tomlinson, Carly Tooke, Marie Turner, Mark A Turner, Clare van Miert, Carly Vaughan, Anand Wagh, Laura Wallis, Penny Walsh, Marie Ward, Sophia Ward, Jacqueline Waters, Jack Watson, James Weitz, Annmarie Wherton-Whitehurst, Grace Williamson, Helen Winmill, Andrea Wood, Laura Wooler, Kerry Woolfall.

Contributors

Conceptualisation: KTh and MGS. Data curation: LF. Analysis: APJ, MGS, and RCo. Funding acquisition: ADP, APJ, CB, CFo, CG, EA, HWC, JMa, JPa, JR, JWe, KPM, KTh, KW, MAT, MGS, MPe, PCR, PSM, RL, RSA, SDP, SLam, SS, TMo, and T-YML. Investigation: AO, AW-W, CKa, EB, EDa, GS, JPa, JR, JVC, JWe, KPM, KTh, PCR, PED, PJD, RL, RSA, SDP, SLam, SS, and T-YML. Methodology: ADP, APJ, CB, CFo, CG, EA, HWC, JMa, JPa, KPM, KTh, KW, MAT, MGS, MPe, PCR, PSM,

RSA, and TMo. Project administration: BO, CD, CV, LP, and TMo. Resources: AO, AW-W, CKa, EB, EDa, GS, JPa, JR, JVC, JWe, KPM, KTh, PED, PJD, RL, RSA, SDP, SLam, SS, and T-YML. Supervision: ADP, APJ, AO, AW-W, CB, CFo, CG, CKa, CV, EA, EB, EDa, GS, HWC, JMa, JPa, JR, JVC, JWe, KPM, KTh, KW, MAT, MGS, MPe, PCR, PED, PJD, PSM, RL, RSA, SDP, SLam, SS, TMo, and T-YML. Validation: APJ, and LF. Visualisation: APJ, MGS, and RCo. Writing original draft: APJ and MGS. Writing, review, and editing: ADP, APJ, AO, AW-W, BO, CB, CD, CFo, CG, CKa, CV, EA, EB, EDa, EDe, GS, HWC, JMa, JPa, JR, JVC, JWe, KPM, KTh, KW, LF, LP, MAT, MGS, MPe, PCR, PED, PJD, PSM, RCo, RL, RSA, SDP, SLam, SS, TMo, and T-YML. The following authors have access to the raw data of the trial: APJ, CG, LF, MGS, and RCo. All authors did not have access to the raw data as this is not practical in a large, multinational trial and would risk disclosure in a commercially sensitive study. APJ and RCo accessed and verified the underlying data. All authors had final responsibility for the decision to submit for publication. The BESS Investigators were responsible for: analysis (ABe); funding acquisition (AD, CSu, CvM, JA, JPr, MJM, RPar, and RS); investigation (ABr, AC, AM, ASa, ASc, ASt, AWa, AWo, BC, BCG, BL, BM, BN, CA, CThoma, CFu, ChThomp, CFJ, CKn, CLa, CLi, ClThomp, CMa, CMe, CN, CP, CRob, CRon, CSe, CSi, CTo, DA, DJ, DM, DJM, EHa, EHe, EJ, EKR, ESc, ESt, FL, FS, GW, HA, HPay, HCa, HCh, HCl, HParke, HMa, HMi, HParki, HW, JA, JMcCorm, JB, JMcCork, JG, JL, JMcCa, JPo, JS, JT, JWats, KBa, KBe, KR, KTe, LMcCo, LAn, LAs, LTB, LCa, LCr, LL, LO, LRa, LRi, LWa, LWo, MG, MKM, MM, MJM, MPM, MR, MTe, MTu, MW, NE, NH, NK, NMc, NMi, NP, NR, NT, ON, PJ, P-LH, PR, PT, PW, RCl, RD, RMarsh, RPat, RH, RJ, RKi, RKu, RMc, HN, RMarsc, RNR, RS, SMog, SCa, SCl, SCo, SD, SMol, SFi, SFo, SG, SH, S-JE, SLR, SMe, SMa, SP, SR, SW, TC, TCH, TK, TMu, UO, VC, VL, WB, and ZO); methodology (JPr and MJM); project administration (AD, CSu, LCa, LD, LMa, SLai, and TR); resources (ASa, ASc, AWa, BL, CThoma, CFu, CKn, CSe, DA, EHe, GW, JA, JG, JL, JWate, LMcCo, LB, LTB, LMcCu, L-MB, MG, MKM, MTe, NT, PJ, PM, PR, PT, RKi, RKu, RPe, RNR, SMol, SP, and UO); software (LJS); supervision (AG, ASa, ASc, DA, GW, JA, JL, KMN, LTB, MG, MTe, PJ, PR, RB, RKu, RNR, RS, SMol, and SP); and validation (KMN).

Declaration of interests

In relation to this work, MGS declares a grant from the National Institute for Health and Care Research UK (NIHR) to his institutions, and a gift without encumbrance to his institutions of the clinical trial investigational medicinal product, with distribution to trial sites, from Chiesi Farmaceutici, Parma, Italy. Unrelated to this work, MGS declares other grants to his institutions from the NIHR, the Medical Research Council UK, and the Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool. Unrelated to this work, MGS's institution has received consultancy fees from GSK regarding respiratory syncytial virus vaccination policy, and fees from Pfizer as an independent, external, non-remunerated member of Pfizer's external data monitoring committee for Pfizer's mRNA vaccine programme. Unrelated to this work, MGS is a minority shareholder and was Chair of the Infectious Disease Scientific Advisory Board of Integrum Scientific, Greensboro, NC, USA, and a majority shareholder and Director of MedEx Solutions, UK. MGS has been seconded to the Scottish Government since Aug 5, 2025, as Chief Scientific Adviser for Scotland. In relation to this work, CG declares membership of the NIHR Efficacy and Mechanism Evaluation Programme Board 2015–19. Unrelated to this work, RC declares membership of the trial steering committees for other NIHR-funded trials. In relation to this work, PED declares that they are the Honorary Secretary of the Paediatric Critical Care Society, UK. In relation to this work, APJ, BO, CB, CD, CG, CV, EDe, GS, KT, KW, LF, LP, MAT, MP, PCR, PSM, RC, and TM declare a grant from the NIHR to their institutions and a gift without encumbrance to their institution of the clinical trial investigational medicinal product and distribution of the same to trial sites. In relation to this work, ADP, AO, AW-W, CK, EB, EDa, HWC, JM, JP, JR, JVC, JW, KPM, PED, PJD, RL, RSA, SDP, SL, SS, and T-YML declare a grant from the NIHR to their institutions. CF and EA declare no competing interests.

Data sharing

Data collected for BESS, including de-identified individual participant data, can be made available to researchers who provide a methodologically sound proposal to the Chief Investigator for BESS with a signed data access agreement that is approved by the University of Liverpool as sponsor (sponsor@liverpool.ac.uk).

Acknowledgments

The views expressed are those of the authors and not necessarily those of the sponsor, other participating organisations, Chiesi Farmaceutici, NIHR, UK Research and Innovation Medical Research Council, NHS, or the Department of Health and Social Care. The study was funded by the Efficacy and Mechanism Evaluation Programme (NIHR award 15/21/01), a partnership between the UKRI Medical Research Council and the NIHR, with additional contributions from the Chief Scientist Office in Scotland, the Health and Social Care Research and Development Division in Northern Ireland and Chiesi Farmaceutici. Parma, Italy. Chiesi Farmaceutici also supported the trial by providing the poractant alfa (Curosurf, 80 mg/mL, 3 mL vials), its storage at a central depot, and its distribution to the investigational sites as managed through an interactive randomisation response technology system (WebEZ, Almac Clinical Services, UK) as a gift without encumbrance. WebEZ was used for randomisation, including stratification and study treatment allocation and accountability at sites. Moreover, Chiesi Farmaceutici provided additional funds as a gift without encumbrance to the University of Liverpool to extend the recruitment period to include the sixth and final winter respiratory season (2023–24), which enabled us to achieve our enrolment target, and for this, we are truly thankful. The authors wish to acknowledge Prof Thomas Jaki and Prof Paula R Williamson for their helpful discussions regarding the design of the Bronchiolitis Endotracheal Surfactant Trial (BEST), an adaptive dose-ranging protocol with a sample size of 80. Although unsuccessful in its application to the NIHR, that protocol led to the development of BESS and its funding by the NIHR Efficacy and Mechanism Evaluation Programme. If BEST had been funded as submitted, then we would likely have saved time, money, and resources. The authors wish to celebrate the contributions of our dear friend and valued colleague, Afeda Mohamed Ali, Consultant in paediatric intensive care and BESS Principal Investigator at the paediatric intensive care unit, Birmingham Children's Hospital, who died in August, 2023 on service, during the conduct of this study.

References

1 Wang X, Li Y, Shi T, et al. Global disease burden of and risk factors for acute lower respiratory infections caused by respiratory syncytial virus in preterm infants and young children in 2019: a systematic review and meta-analysis of aggregated and individual participant data. *Lancet* 2024; **403:** 1241–53.

2 Semple MG, Cowell A, Dove W, et al. Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. *J Infect Dis* 2005; **191:** 382–86.

3 Meissner HC. Viral bronchiolitis in children. *N Engl J Med* 2016; **374:** 62–72.

4 Mansbach JM, Piedra PA, Teach SJ, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med* 2012; **166:** 700–06.

5 National Institute for Health and Care Excellence. Bronchiolitis in children: diagnosis and management. National Institute for Health and Care Excellence Guidance 9 (NG-9). https://www.nice.org.uk/guidance/ng9/chapter/Recommendations#assessment-and-diagnosis (accessed Nov 17, 2024).

6 Ralston SL, Lieberthal AS, Cody Meissner H, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014; **134:** e1474–502.

7 Vihikangas T, Palmu S, Koivisto AM, Heikkilä P. Changes in bronchiolitis incidence during the last two decades in Tampere, Finland: a retrospective study. *Pediatr Infect Dis J* 2022; **41:** 867–71.

8 Hogan AB, Anderssen RS, Davis S, et al. Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical Western Australia. *Epidemics* 2016; **16:** 49–55.

9 Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev* 2015; **2015:** CD009194.

10 Luchetti M, Casiraghi G, Valsecchi R, Galassini E, Marraro G. Porcine-derived surfactant treatment of severe bronchiolitis. *Acta Anaesthesiol Scand* 1998; **42:** 805–10.

11 Tibby SM, Hatherill M, Wright SM, Wilson P, Postle AD, Murdoch IA. Exogenous surfactant supplementation in infants with respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med* 2000; **162:** 1251–56.

12 Luchetti M, Ferrero F, Gallini C, et al. Multicenter, randomized, controlled study of porcine surfactant in severe respiratory syncytial virus-induced respiratory failure. *Pediatr Crit Care Med* 2002; **3:** 261–68.

13 Wolfler A, Piastra M, Amigoni A, et al. A shared protocol for porcine surfactant use in pediatric acute respiratory distress syndrome: a feasibility study. *BMC Pediatr* 2019; **19:** 203.

14 Electronic Medicines Compendium. Curosurf 240mg / vial endotracheopulmonary instillation suspension—summary of product characteristics. https://www.medicines.org.uk/emc/product/10955/smpc#about-medicine (accessed Dec 16, 2024).

15 Jansen-van der Weide MC, Caldwell PHY, Young B, et al. Clinical trial decisions in difficult circumstances: parental consent under time pressure. *Pediatrics* 2015; **136:** e983–92.

16 Deja E, Donohue C, Semple MG, Woolfall K. Stakeholders' perspectives on clinical trial acceptability and approach to consent within a limited timeframe: a mixed methods study. *BMJ Open* 2024; **14:** e077023.

17 Blackwood B, Tume LN, Morris KP, et al. Effect of a sedation and ventilator liberation protocol vs usual care on duration of invasive mechanical ventilation in pediatric intensive care units: a randomized clinical trial. *JAMA* 2021; **326:** 401–10.

18 Powell CVE, McNamara P, Solis A, Shaw NJ. A parent completed questionnaire to describe the patterns of wheezing and other respiratory symptoms in infants and preschool children. *Arch Dis Child* 2002; **87:** 376–79.

19 Wolfe R, Carlin JB. Sample-size calculation for a log-transformed outcome measure. *Control Clin Trials* 1999; **20:** 547–54.

20 US Food & Drug Administration. Orange Book: approved drug products with therapeutic equivalence evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020044#3598 (accessed Dec 16, 2024).

21 Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2012; **11:** CD001456.

22 Dargaville PA, South M, McDougall PN. Surfactant abnormalities in infants with severe viral bronchiolitis. *Arch Dis Child* 1996; **75:** 133–36.

23 Skelton R, Holland P, Darowski M, Chetcuti PA, Morgan LW, Harwood JL. Abnormal surfactant composition and activity in severe bronchiolitis. *Acta Paediatr* 1999; **88:** 942–46.

24 De Luca D, Cogo P, Kneyber MC, et al. Surfactant therapies for pediatric and neonatal ARDS: ESPNIC expert consensus opinion for future research steps. *Crit Care* 2021; **25:** 75.

25 Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2012; **2012:** CD000510.