क्षेत्रीय आयुर्विज्ञान संस्थान, इंफाल: मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
(An Autonomous Institute under the Ministry of Health & Family Welfare, Govt. of India

Phone : 0385- 2414720
0385-2414750
e-mail : rims@rims.edu.in
website : www.rims.edu.in

CIRCULAR

Imphal, the 21st January, 2026

No. 17/RIMS-MRU/2026: It is to notify that, the **9th Research Masterclasses 2026**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, **on 30th January, 2026 (Friday)**.

2. All the faculties (RIMS, Dental College, and College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and residents are invited to attend the session at **Banting Hall, RIMS, Imphal**.

Date: 30.01.2026 (Friday)
Time: 3:00 PM onwards
Venue: Banting Hall, RIMS, Imphal (DESIGNATED SITE FOR PARTICIPATION FOR RIMS)
Event name: Research Masterclass under DHR-ICMR Research Grand Rounds
Speaker Name: Dr. Rajiv Bahl, Secretary, DHR & Director General, ICMR, New Delhi

3. The **research paper** to be discussed during the Masterclass will be uploaded on the **RIMS website** and circulated to the concerned Departments/Colleges through official email.

4. As per the directives issued by the DHR, **maximum participation** from our institute is highly encouraged. MRU is submitting the attendance sheet to the DHR after the session concludes.

21-01-2026

Prof. T. Jeetenkumar Singh,
Nodal Officer,
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS, for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH, for kind information
3. The Dean (Academic), RIMS, for kind information & permission to utilize the facilities at Banting Hall.
4. The Principal, Dental College, RIMS
5. The Principal, College of Nursing, RIMS — with a request for ensuring maximum participation.
6. The Head of Department, RIMS, Imphal
7. The Chairperson/Co-Chairperson/Member, LRAC, MRU, RIMS
8. The Member, EC, MRU, RIMS, Imphal
9. The Principal Investigator, RIMS
10. The IT Cell, RIMS – with a request for uploading the notice in the website & technical support on **30.01.26**
11. Asst. Engineer (Elect. /Civil), RIMS - with a request for ensuring uninterrupted power supply & optimum AC functioning.
12. The Care Taker, Banting Hall, RIMS, Imphal- for proper upkeep of the venue & the accompanying facilities.
13. Guard file.

No. R.11016/03/2025-HR
Government of India
Ministry of Health & Family Welfare
Department of Health Research

IRCS Building, 2nd Floor,
Red Cross Road
New Delhi – 110 001
20.01.2026

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses for MRU network– reg.

Sir/Madam

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' proposed around the last Friday of each month. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The next Research Masterclass is scheduled for **30.01.2026 (Friday)** at **3:00 PM**. The invited speaker is **Dr. Rajiv Bahl, Secretary, Department of Health Research & Director General, ICMR, New Delhi**. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Your institute is requested to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 27.01.2026. These questions will be discussed with the speaker during masterclass.

Yours faithfully

(Dharkat R. Luikang)
Deputy Secretary to the Govt. of India

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

ORIGINAL ARTICLE

Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries

The WHO ACTION Trials Collaborators

ABSTRACT

BACKGROUND

The safety and efficacy of antenatal glucocorticoids in women in low-resource countries who are at risk for preterm birth are uncertain.

METHODS

We conducted a multicountry, randomized trial involving pregnant women between 26 weeks 0 days and 33 weeks 6 days of gestation who were at risk for preterm birth. The participants were assigned to intramuscular dexamethasone or identical placebo. The primary outcomes were neonatal death alone, stillbirth or neonatal death, and possible maternal bacterial infection; neonatal death alone and stillbirth or neonatal death were evaluated with superiority analyses, and possible maternal bacterial infection was evaluated with a noninferiority analysis with the use of a prespecified margin of 1.25 on the relative scale.

RESULTS

A total of 2852 women (and their 3070 fetuses) from 29 secondary- and tertiary-level hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan underwent randomization. The trial was stopped for benefit at the second interim analysis. Neonatal death occurred in 278 of 1417 infants (19.6%) in the dexamethasone group and in 331 of 1406 infants (23.5%) in the placebo group (relative risk, 0.84; 95% confidence interval [CI], 0.72 to 0.97; P=0.03). Stillbirth or neonatal death occurred in 393 of 1532 fetuses and infants (25.7%) and in 444 of 1519 fetuses and infants (29.2%), respectively (relative risk, 0.88; 95% CI, 0.78 to 0.99; P=0.04); the incidence of possible maternal bacterial infection was 4.8% and 6.3%, respectively (relative risk, 0.76; 95% CI, 0.56 to 1.03). There was no significant between-group difference in the incidence of adverse events.

CONCLUSIONS

Among women in low-resource countries who were at risk for early preterm birth, the use of dexamethasone resulted in significantly lower risks of neonatal death alone and stillbirth or neonatal death than the use of placebo, without an increase in the incidence of possible maternal bacterial infection. (Funded by the Bill and Melinda Gates Foundation and the World Health Organization; Australian and New Zealand Clinical Trials Registry number, ACTRN12617000476336; Clinical Trials Registry–India number, CTRI/2017/04/008326.)

The members of the writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Oladapo at the United Nations Development Program–United Nations Population Fund–United Nations Children's Fund–World Health Organization–World Bank Special Program of Research, Development, and Research Training in Human Reproduction, Department of Sexual and Reproductive Health and Research, World Health Organization, 20 Ave. Appia, Geneva, Switzerland, or at oladapoo@who.int; or to Dr. Bahl at the Department of Maternal, Newborn, Child, Adolescent Health and Ageing, World Health Organization, 20 Ave. Appia, Geneva, Switzerland, or at bahlr@who.int.

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PRETERM BIRTH IS A LEADING CAUSE OF death in infants and children younger than 5 years of age globally.[1] Infants born preterm are also at increased risk for a wide range of short-term and long-term respiratory, infectious, metabolic, and neurologic conditions, with higher risks among those born during the early preterm period.[2,3]

On the basis of trials conducted largely in high-resource countries, antenatal glucocorticoids have long been promoted as the key intervention for reducing preterm infant mortality and morbidity.[4,5] However, the generalizability of this evidence to low-resource settings was called into question in 2015, when a large population-based trial conducted in six low-resource countries showed that efforts to scale up the use of antenatal glucocorticoids could lead to harm.[6] In that trial, scaling up of glucocorticoids did not reduce mortality among infants who were below the fifth percentile for birth weight (a proxy for preterm birth) and unexpectedly was associated with an increase in the incidence of neonatal death, stillbirth, and suspected maternal infection in the population overall. These findings reopened the debate about the safety and efficacy of antenatal glucocorticoids in low-resource countries.[7,8]

Because of these considerations, in 2015 the World Health Organization (WHO) recommended that antenatal glucocorticoids should be used only under certain conditions, including the accurate assessment of gestational age, imminent preterm birth, the absence of maternal infection, and adequate care for childbirth and preterm newborns.[9] The guideline panel and an expert panel that was subsequently convened by the WHO identified the conduct of efficacy trials in hospitals in low-resource countries as a research priority in order to resolve this controversy and guide clinicians and policymakers on the use of antenatal glucocorticoids.[7,8] We conducted the WHO ACTION-I (Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns) trial, a randomized trial to assess the safety and efficacy of dexamethasone in women in hospitals in low-resource countries who were at risk for early preterm birth.

METHODS

TRIAL DESIGN AND OVERSIGHT

We designed a multicountry, multicenter, parallel-group, double-blind, individually randomized, placebo-controlled trial to compare intramuscular dexamethasone with identical placebo in women at risk for imminent preterm birth. We conducted the trial at 29 secondary- and tertiary-level hospitals across six trial sites in Bangladesh, India, Kenya, Nigeria, and Pakistan. The trial protocol, which has been published previously,[10] is available with the full text of this article at NEJM.org. It was approved by the relevant ethics committees and regulatory agencies in each country and by the WHO Ethics Review Committee. WHO was the trial sponsor. A steering group comprising a trial coordinating unit, principal investigators, and technical advisors provided trial oversight.

Fresenius Kabi–Labesfal (Portugal) produced dexamethasone sodium phosphate and identical placebo, which were packaged and shipped to the trial sites by Ivers–Lee Clinical Supplies Management (Switzerland). Fresenius Kabi–Labesfal had no role in the trial design, the collection, analysis, and interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. The first, second, third, and seventh members of the writing committee vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL SETTING

The trial hospitals were selected through a standardized assessment of maternal and newborn health care services (Table S1 in the Supplementary Appendix, available at NEJM.org) to ensure that the WHO criteria for antenatal glucocorticoid treatment could be reasonably met.[8,9] To make the trial procedures consistent and to ensure that the trial participants received at least the minimum quality of care, ultrasonographic systems (Philips HD5, the Netherlands), continuous positive airway pressure (CPAP) machines (DiaMedica UK, United Kingdom), pulse oximeters (Masimo International, Switzerland), and glucometers were procured for all the hospitals. Standardized training was provided to all research and clinical staff.

SCREENING AND RECRUITMENT

Pregnant women who had confirmed live fetuses between 26 weeks 0 days and 33 weeks 6 days of gestation and who were at risk for preterm birth were eligible for inclusion. The inclusion criteria were planned or expected birth in the next 48 hours (either provider-initiated preterm birth or

after preterm, prelabor rupture of membranes or spontaneous labor). Gestational age was determined by the earliest ultrasonographic examination or an ultrasonographic examination performed at admission. Women were excluded if they had clinical signs of severe infection, major congenital fetal anomalies, concurrent or recent (within the previous 2 weeks) use of systemic glucocorticoids, or a contraindication to glucocorticoids or if they were participating in another trial. Written informed consent was obtained from all the participants before randomization.

RANDOMIZATION AND TRIAL REGIMENS

The participants were randomly assigned in a 1:1 ratio to a course of intramuscular injections of either 6 mg of dexamethasone or identical placebo administered every 12 hours, for a maximum of four doses, or until hospital discharge or birth. The women were eligible for a repeat course if they had not given birth after 7 completed days but still met the inclusion criteria. The repeat course was identical to the first course and the same as the initial assignment.

Site-stratified individual randomization with balanced permuted blocks of 10 were used. The computer-generated randomization sequence was prepared centrally at the WHO. All the sites received serially numbered identical packs containing ampules of 4 mg per milliliter of dexamethasone or placebo for two full courses. The trial participants, care providers, and investigators were unaware of the trial-group assignments.

The participants received either dexamethasone or placebo immediately after randomization. Clinical care was provided according to local guidelines. Follow-up of the fetuses was conducted until 28 days after birth or until death (stillbirth or neonatal death), whichever came first, and follow-up of the women was conducted until 28 days after they gave birth or until death, whichever came first. Trained research staff collected data during the hospital admission or admissions and during community-level visits.

TRIAL OUTCOMES

The three primary outcomes were neonatal death (death of a live-born infant within 28 completed days of life), stillbirth or neonatal death, and a composite of possible maternal bacterial infection, defined as maternal fever (temperature ≥38°C) or clinically suspected or confirmed infection for which therapeutic antibiotics were used. The secondary outcomes were maternal and newborn mortality and morbidity as well as process-of-care outcomes (a list and definitions of these outcomes are provided in the Statistical Methods section in the Supplementary Appendix).

All trial-related information was stored securely at the trial sites. Data were double-entered into a Web-based data-management platform and centrally managed by Centro Rosarino de Estudios Perinatales (Argentina).

STATISTICAL ANALYSIS

We estimated that 6018 women would have to be recruited to detect a decrease in the risk of neonatal death of 15.00% or more, from 25.00% to 21.25%, in a two-sided 5% significance test with 90% power and 10% loss to follow-up. The estimated sample size would provide more than 80% power at the 2.5% significance level to detect whether dexamethasone is noninferior to placebo for maternal infection, within a noninferiority margin of 1.25 on the relative scale. The noninferiority margin was based on the consideration that a maximum increase of 25% over a 10% baseline incidence of maternal bacterial infection could be accepted for a fetal or infant mortality benefit.

For the primary outcomes, intention-to-treat analyses were to be performed. We hypothesized that the use of dexamethasone would result in a decrease in the risk of neonatal death and stillbirth or neonatal death without increasing the risk of maternal infection. Therefore, we applied a superiority hypothesis to neonatal death and stillbirth or neonatal death, and we applied a noninferiority hypothesis to maternal infection. Analyses were first performed on all available data, and sensitivity analyses were then performed with the use of multiple imputation[11] to judge the effect of missing data. Analyses of primary outcomes were corrected for multiplicity with the false-discovery-rate approach.[12] The dexamethasone group was compared with the placebo group for the primary outcomes with the use of relative risks with 95% confidence intervals, according to a logistic model with a binomial distribution and a log link to obtain relative risks. The stratifying variable — trial site

— was included in the model, as well as a clustering feature for multiple births for neonatal outcomes. For continuous variables, means and standard deviations or medians and interquartile ranges according to group were reported. The trial groups were compared with mean or median differences and 95% confidence intervals according to a general linear model that included trial site as the stratifying variable. Separate models were fitted for each of the primary and secondary outcomes.

The primary outcomes were analyzed in prespecified subgroups (see the Statistical Methods section in the Supplementary Appendix). The results for all secondary outcomes and subgroup analyses are presented as point estimates and 95% confidence intervals. No correction was made for multiplicity, and the width of the confidence intervals should not be used to infer treatment effects. All the models were fitted with the use of SAS software, version 9.4 (SAS Institute).

Three interim analyses by the data and safety monitoring board were planned. The board members were to inform the steering group chair if, in their view, there was proof beyond a doubt that dexamethasone was indicated or contraindicated on the basis of statistical considerations (using the Haybittle–Peto stopping rule[13] for the primary outcomes for fetuses and infants) or clinical considerations, practical issues, or new external information. After the second interim analysis involving 2304 women and 2536 fetuses and infants, with complete follow-up of primary outcomes, the data and safety monitoring board decided to unblind the trial and recommended that the trial be stopped for fetus and infant mortality benefits and strong evidence of a graded dose–response effect, in the context of existing evidence of benefits of antenatal glucocorticoids.[4] Recruitment was stopped across all sites on November 21, 2019, and all ethics committees and regulatory authorities were informed. The funders had no role in the decision to stop the trial.

RESULTS

PARTICIPANT CHARACTERISTICS

From December 2017 through November 2019, of the 7008 women who were screened for eligibility, 2852 underwent randomization (1429 to the dexamethasone group and 1423 to the placebo group) (Fig. 1). The most common reason for ineligibility was that birth was not planned or expected in the next 48 hours. A total of 90.0% of the infants in the dexamethasone group and 90.8% of those in the placebo group were born before 37 weeks. More than 99.0% of the women who underwent randomization and their infants completed follow-up. The characteristics of the dexamethasone and placebo groups were similar at trial entry (Table 1 and Table S2).

ADHERENCE TO ASSIGNED TRIAL REGIMEN

All the women except 1 received at least one dose of dexamethasone or placebo (Fig. 1). A total of 815 of 1429 women (57.0%) in the dexamethasone group and 756 of 1423 women (53.1%) in the placebo group received all four doses in the first course. The repeat course was administered to 61 women in the dexamethasone group and 74 women in the placebo group, of whom 46 and 47 women, respectively, received four doses. The most common reason that a scheduled dose was not administered was the occurrence of birth between the administration of doses.

PRIMARY OUTCOMES

There were 278 neonatal deaths among 1417 live-born infants in the dexamethasone group (19.6%) and 331 neonatal deaths among 1406 live-born infants in the placebo group (23.5%) (relative risk, 0.84; 95% confidence interval [CI], 0.72 to 0.97; P=0.03) (Table 2). We determined that 25 women would need to be treated with dexamethasone to prevent 1 neonatal death (95% CI, 14 to 110). The incidence of stillbirth or neonatal death was also significantly lower in the dexamethasone group than in the placebo group (25.7% vs. 29.2%; relative risk, 0.88; 95% CI, 0.78 to 0.99; P=0.04).

Possible maternal bacterial infection occurred in 68 of 1416 women (4.8%) in the dexamethasone group and in 89 of 1412 women (6.3%) in the placebo group (relative risk, 0.76; 95% CI, 0.56 to 1.03; P=0.002 for noninferiority); this result was consistent with noninferiority at the prespecified margin of 1.25 (Table 2). In the per-protocol population, possible maternal bacterial infection occurred in 63 of 1393 women (4.5%) in the dexamethasone group and in 89 of 1385

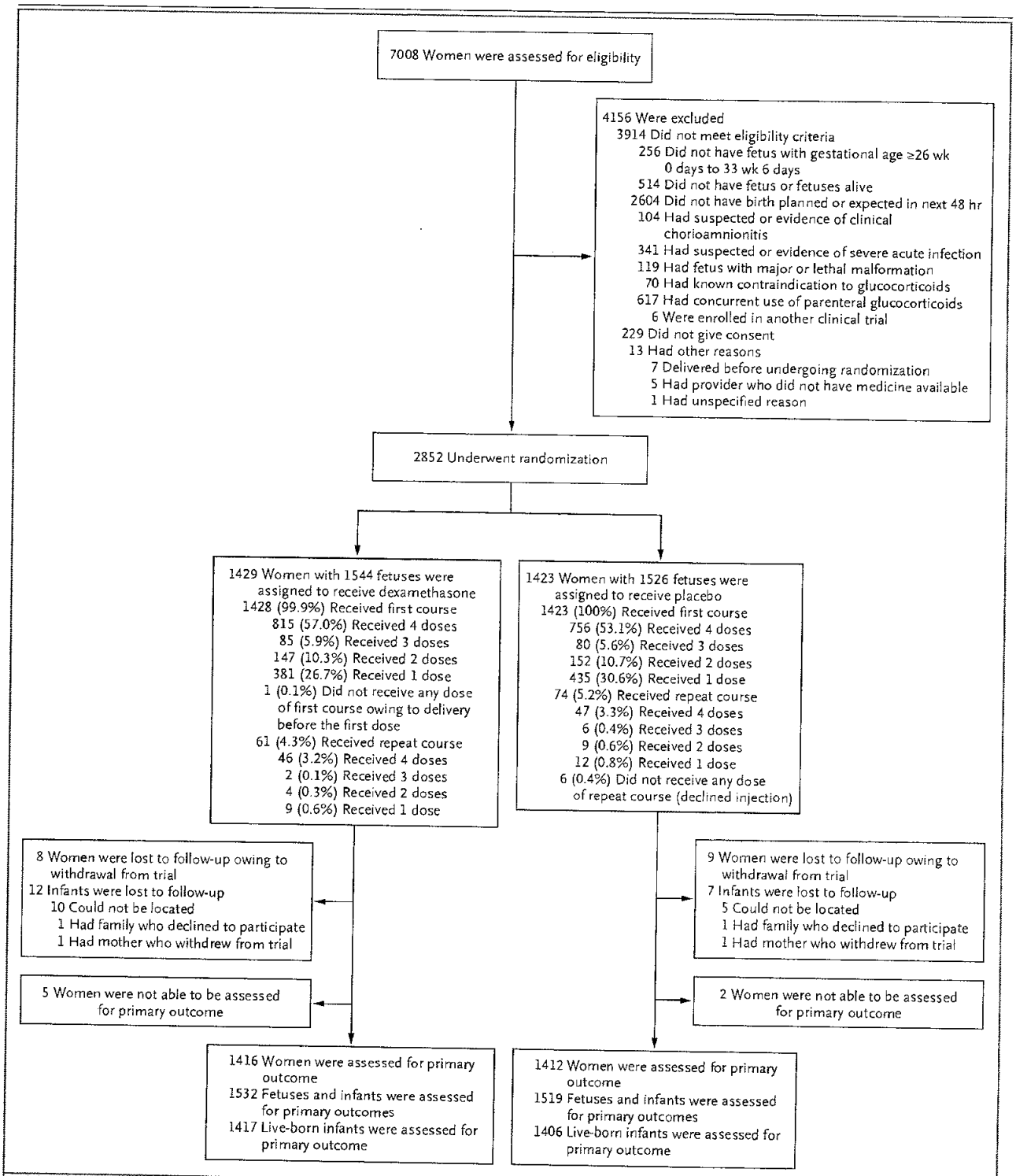

Figure 1. Screening, Enrollment, Randomization, and Follow-up.

Women could have more than one reason for not meeting eligibility criteria.

Table 1. Characteristics of the Participants at Trial Entry.*

Characteristic	Dexamethasone (N=1429)	Placebo (N=1423)
Clinical assessment of imminent preterm birth at trial entry — no. (%)		
Spontaneously initiated preterm birth	874 (61.2)	858 (60.3)
Preterm prelabor rupture of membranes	455 (31.8)	388 (27.3)
Spontaneous preterm labor	419 (29.3)	470 (33.0)
Provider-initiated preterm birth	555 (38.8)	565 (39.7)
Gestational age at trial entry — wk	30.8±2.0	30.7±2.0
Maternal age — yr	27.5±5.8	27.5±5.9
Fetuses in the current pregnancy — no. (%)		
Single	1295 (90.6)	1290 (90.7)
Twin	125 (8.7)	129 (9.1)
Higher-order multiples	9 (0.6)	4 (0.3)
Nulliparous women — no. (%)	529 (37.0)	549 (38.6)
History of preterm birth — no. (%)†	177 (12.4)	188 (13.2)
Obstetrical condition present — no. (%)‡		
Gestational diabetes	22 (1.5)	15 (1.1)
Preeclampsia or eclampsia	275 (19.2)	326 (22.9)
Gestational hypertension§	75 (5.2)	68 (4.8)
Known or suspected oligohydramnios	336 (23.5)	310 (21.8)
Known or suspected polyhydramnios	19 (1.3)	30 (2.1)
Known or suspected intrauterine growth restriction	94 (6.6)	95 (6.7)
Abruptio placentae	49 (3.4)	40 (2.8)
Placenta previa	115 (8.0)	110 (7.7)
Other obstetrical hemorrhage	66 (4.6)	42 (3.0)
No obstetrical condition	616 (43.1)	592 (41.6)
Medication administered before randomization — no. (%)		
Tocolytic agent	251 (17.6)	267 (18.8)
Magnesium sulfate for neuroprotection	141 (9.9)	179 (12.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† This category was assessed only in women with a previous pregnancy.
‡ Women may have had more than one condition.
§ This category excludes preeclampsia and eclampsia.

women (6.4%) in the placebo group (relative risk, 0.70; 95% CI, 0.51 to 0.96); this result was also consistent with noninferiority. Multiple imputation for missing values[11] yielded identical results for all the primary outcomes (Table S3).

The results according to the prespecified subgroups are shown in Figure 2 and Figure S1. Analyses of neonatal death, according to the time from the first dose of dexamethasone or placebo to birth, stratified according to gestational age, suggest greater benefit with increasing time from the first dose to birth and increasing gestational age at the first dose (from 26 to 32 weeks) (Fig. S2). In a post hoc analysis of the causes of neonatal death, the frequency of neonatal death caused by respiratory distress syndrome was lower in the dexamethasone group than in the placebo group (Table S4).

Table 2. Primary Outcomes.

Outcome	Dexamethasone	Placebo	Relative Risk (95% CI)*	P Value†
	no./total no. (%)			
Neonatal death	278/1417 (19.6)	331/1406 (23.5)	0.84 (0.72–0.97)	0.03
Stillbirth or neonatal death	393/1532 (25.7)	444/1519 (29.2)	0.88 (0.78–0.99)	0.04
Possible maternal bacterial infection‡	68/1416 (4.8)	89/1412 (6.3)	0.76 (0.56–1.03)	0.002§

* Relative risks and 95% confidence intervals, calculated from modeling, were adjusted for trial sites and accounted for clustering due to multiple births.
† P values were adjusted for multiplicity for the three primary outcomes with the use of the false-discovery-rate approach.
‡ Possible maternal bacterial infection was defined as the occurrence of fever (temperature ≥38°C) or clinically suspected or confirmed infection for which therapeutic antibiotics were used. Suspected or confirmed infection included obstetrical infection (chorioamnionitis, postpartum endometritis, or wound infection) or nonobstetrical infection (respiratory tract infection [pneumonia, pharyngitis, sinusitis, or a similar infection], urinary tract infection [excluding pyelonephritis], pyelonephritis, acute cholecystitis, or other system infection) captured during hospital admission or admissions only.
§ This P value was calculated for noninferiority.

SECONDARY NEONATAL OUTCOMES

The results with respect to early neonatal death, severe respiratory distress at 24 hours after birth, neonatal hypoglycemia at 6 hours after birth, major resuscitation at birth, the use of CPAP, and the duration of oxygen therapy provide support for the primary findings. Other secondary and process-of-care outcomes were similar in the dexamethasone and placebo groups (Table 3 and Table S5).

SECONDARY MATERNAL OUTCOMES

The secondary maternal outcomes were similar in the dexamethasone and placebo groups (Table 3). Five women died in the dexamethasone group, and four women died in the placebo group.

ADVERSE EVENTS

Prespecified maternal and neonatal outcomes were excluded from the reporting of serious adverse events. There was no significant between-group difference in the incidence of serious adverse events, which occurred in 1.1% of the women in both groups (Table S6). No serious adverse events were reported in the neonates.

DISCUSSION

In this hospital-based randomized trial conducted in low-resource countries, we found that the administration of dexamethasone to women who were at risk for early preterm birth reduced the incidences of neonatal death and stillbirth or neonatal death without increasing the incidence of maternal bacterial infection. Dexamethasone had no effect on stillbirth, but the findings for several secondary outcomes, including early neonatal death, severe respiratory distress, and the use of major neonatal resuscitation and CPAP were consistent with the overall results for neonatal deaths by 28 days. These clinical benefits were observed even though 45% of the participants received fewer than four doses of their assigned medication.

Our findings are generally consistent with the results of a meta-analysis of 22 trials that were mostly conducted in high-resource settings. That meta-analysis showed a substantial decrease in the incidence of neonatal death among infants of women who received glucocorticoids.[4] Previous efforts to increase the low use of antenatal glucocorticoids in women at risk for preterm birth in low-resource countries[14] were challenged by the results of the Antenatal Corticosteroids Trial (ACT).[6,15] ACT was a cluster-randomized trial of an implementation strategy that included provider training and tools to identify women who were eligible to receive dexamethasone at all levels of care, including primary health care and care at the community level.

In contrast to ACT, which selected women for treatment on the basis of their last menstrual period or measurement of uterine height and included clinical settings where resources for neonatal care were inadequate, the hospitals in our trial selected patients for whom treatment

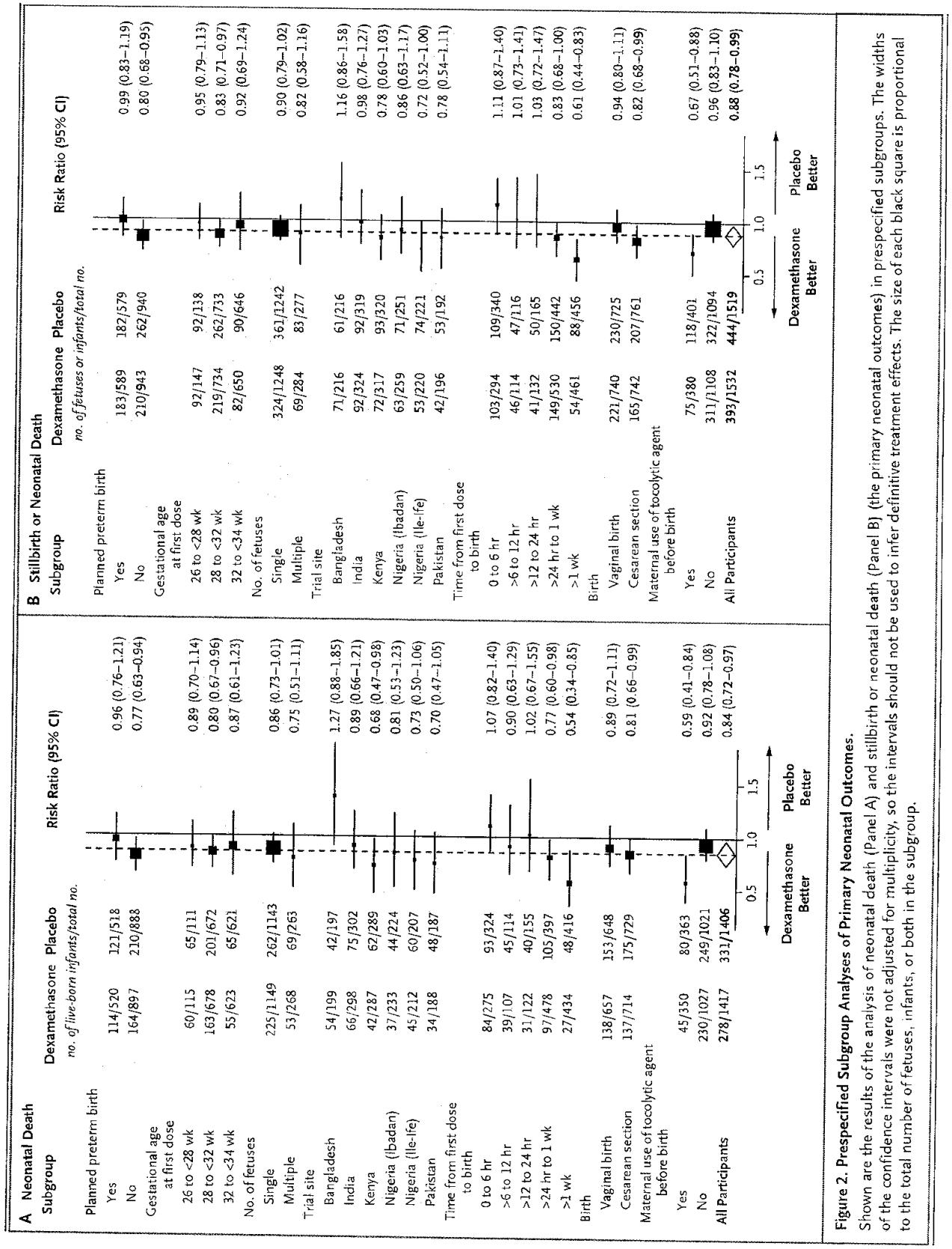

Figure 2. Prespecified Subgroup Analyses of Primary Neonatal Outcomes.

Shown are the results of the analysis of neonatal death (Panel A) and stillbirth or neonatal death (Panel B) (the primary neonatal outcomes) in prespecified subgroups. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. The size of each black square is proportional to the total number of fetuses, infants, or both in the subgroup.

Table 3. Secondary Maternal and Neonatal Outcomes.*

Outcome	Dexamethasone	Placebo	Relative Risk (95% CI)†
	no./total no. (%)		
Neonatal outcome			
Stillbirth	115/1544 (7.4)	113/1526 (7.4)	1.00 (0.78–1.30)
Early death: ≤7 days after birth	218/1417 (15.4)	268/1406 (19.1)	0.81 (0.68–0.96)
Severe respiratory distress‡	116/1245 (9.3)	141/1223 (11.5)	0.81 (0.64–1.03)
At 24 hr after birth	34/1122 (3.0)	58/1065 (5.4)	0.56 (0.37–0.85)
Sepsis	183/1284 (14.3)	197/1264 (15.6)	0.92 (0.76–1.11)
Hypoglycemia‡	301/1242 (24.2)	328/1217 (27.0)	0.91 (0.80–1.04)
At 6 hr after birth	92/1224 (7.5)	123/1194 (10.3)	0.73 (0.56–0.95)
At 36 hr after birth	54/1035 (5.2)	62/999 (6.2)	0.85 (0.60–1.21)
Severe intraventricular hemorrhage	6/810 (0.7)	3/720 (0.4)	1.85 (0.46–7.42)
Apgar score <7 at 5 min after birth	276/1359 (20.3)	293/1368 (21.4)	0.95 (0.82–1.10)
Major resuscitation at birth	101/1382 (7.3)	144/1383 (10.4)	0.70 (0.55–0.88)
Use of oxygen therapy‡	726/1429 (50.8)	756/1413 (53.5)	0.95 (0.88–1.02)
Use of CPAP‡	265/1429 (18.5)	337/1413 (23.9)	0.78 (0.67–0.90)
Use of mechanical ventilation‡	83/1284 (6.5)	103/1264 (8.1)	0.79 (0.59–1.05)
Use of parenteral therapeutic antibiotics for ≥5 days§	527/1245 (42.3)	494/1175 (42.0)	1.00 (0.91–1.10)
Use of surfactant‡	9/1284 (0.7)	18/1264 (1.4)	0.49 (0.22–1.08)
Admission to a special care unit	905/1287 (70.3)	897/1268 (70.7)	0.99 (0.94–1.04)
Readmission	39/1429 (2.7)	48/1413 (3.4)	0.81 (0.53–1.25)
Maternal outcome			
Death	5/1429 (0.4)	4/1423 (0.3)	1.23 (0.33–4.57)
Fever	78/1417 (5.5)	70/1406 (5.0)	1.10 (0.80–1.50)
Chorioamnionitis	17/1429 (1.2)	18/1423 (1.3)	0.93 (0.48–1.80)
Endometritis	5/1429 (0.4)	3/1423 (0.2)	1.65 (0.39–6.92)
Wound infection	8/1429 (0.6)	15/1423 (1.1)	0.53 (0.22–1.25)
Nonobstetrical infection	34/1429 (2.4)	42/1423 (3.0)	0.81 (0.52–1.26)
Use of therapeutic antibiotics	68/1427 (4.8)	89/1422 (6.3)	0.76 (0.56–1.03)
Any antibiotic use	1205/1353 (89.1)	1216/1355 (89.7)	1.00 (0.97–1.02)
Postpartum readmission	14/1429 (1.0)	13/1423 (0.9)	1.07 (0.50–2.26)

* CPAP denotes continuous positive airway pressure.
† The 95% confidence intervals are not adjusted for multiplicity and should not be used to infer definitive treatment effects.
‡ This outcome was measured from the initial postnatal hospitalization until death, discharge, or completed day 7 (whichever came first).
§ This category includes the use of parenteral therapeutic antibiotics in neonates for 5 days or more, even if interrupted, except for the use in those who died before 5 completed days. Referral of live-born infants for treatment was not included because of very few events.

was warranted (through assessment by obstetrical physicians and verification of gestational age by ultrasonographic examination) and provided minimum standards of neonatal care, including access to oxygen and CPAP. In the current trial, 90% of the infants who were exposed to dexamethasone were born preterm, whereas only 16% of the infants exposed to dexamethasone in the

ACT intervention clusters had a birth weight below the fifth percentile. The low incidence of apparent preterm birth among infants exposed to dexamethasone in ACT indicates substantial overtreatment, which may explain at least in part the lack of mortality benefit and overall harm observed. Appropriate selection of participants and the provision of a minimum standard of care appear to be critical in achieving benefits and preventing potential harms from glucocorticoids and should be incorporated into future implementation strategies.

The results of our trial provide reassurance regarding the beneficial effects of glucocorticoids with respect to reducing neonatal mortality in low-resource settings, and they expand the scarce body of evidence from low- and middle-income countries.[16-20] Although smaller trials conducted in low- and middle-income countries have suggested benefits, most of them were not placebo-controlled trials.[17,19,20]

The use of dexamethasone in our trial did not increase the risk of maternal or neonatal infection; this finding is consistent with those of previous trials conducted in low- and middle-income countries,[16-20] where the baseline risks of such infections are high.[21-23] The lack of effect on the overall incidence of neonatal hypoglycemia and the suggestion of a reduced risk of early hypoglycemia with the use of dexamethasone, however, were unexpected. Studies in animals and pharmacokinetic studies have indicated that neonatal hypoglycemia is a potential complication of the use of standard doses of dexamethasone.[24] Moreover, in the Antenatal Late Preterm Steroids trial, the administration of betamethasone to women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation who were at risk for preterm birth increased the incidence of neonatal hypoglycemia by 60%.[25] The effects of maternal glucocorticoid administration on preterm infants have been inconsistent across studies[26,27] and may differ in infants with early preterm birth and those with late preterm birth.

The current trial is larger than previous placebo-controlled trials assessing the efficacy and safety of antenatal glucocorticoids in low-resource countries, and we used broad eligibility criteria. We assessed neonatal death according to the standard definition (which was largely unspecified or restricted to in-hospital deaths in previous trials[7]), and we carefully selected hospitals that could reasonably meet minimum preconditions for glucocorticoid use. The loss to follow-up of trial participants and the percentage of participants with missing primary outcome data were very low despite the need for follow-up in the community. The trial was limited by the challenges in standardizing maternal and neonatal care across trial sites and the use of ultrasonographic examination to assess gestational age for a substantial percentage of the participants in the third trimester.

Further study is warranted to determine the most appropriate dosing regimen[28,29] and the safety and efficacy of administering glucocorticoids in late preterm pregnancy,[30] particularly in low-resource countries. The observed benefits with respect to neonatal mortality appeared to increase with tocolysis and with the duration of fetal exposure to dexamethasone; the role of tocolytic agents in safely delaying early preterm birth in women who are eligible for the use of antenatal glucocorticoids also merits further investigation.

The use of antenatal dexamethasone that was targeted to women at risk for imminent preterm birth in hospitals with minimum resources for maternal and preterm newborn care resulted in significantly lower risks of neonatal death and stillbirth or neonatal death than did the use of placebo, without any evidence of harm to women or newborns.

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Olukemi Tongo, Olubunmi O. Busari, Michael A. Okunlola, Olatunji Lawal, Collins Kalu, Francisca N. Ali, Kenneth Nwachukwu, Fatima A. Sallau, Lilian O. Ekwem, Anastasia E. Ajuwan, Folarin B. Jimoh, Felix F. Akindeju, Olugbenga Runsewe, Abimbola O. Oladeji, Olumide Alao, and Madise-wobo Akpoembele; in Nigeria [Ile-Ife], Adebanjo B. Adeyemi, Olusola C. Famurewa, Nosakhare O. Enaruna, Olufunmilayo V. Adebara, Aboyeji A. Peter, and Mokuolu Olugbenga; and in Pakistan, Mubarak Ali, Saleem Laghari, Jamal Anwar, Shazia Memon, Nida Najmi, Shazia Rani, Farrukh Raza, Masawar Hussain, Amjad Hussain, and Imran Ahmed); the members of the data and safety monitoring board (Betty Kirkwood [chair], Jon Deeks [independent statistician], Siddarth Ramji, Elizabeth Bukusi, and Robert Pattinson [who served from 2015–2019], and G. Justus Hofmeyr [who began to serve in 2019]) for their role in monitoring the overall conduct and quality of the trial; Cynthia Pileggi-Castro for trial protocol development; Liana Campodonico and Gabriela Camacho Garcia for data management; Vania A. Nilsson and Luciana Abreu for statistical programming and analysis; Lynn Coppola, Sandhya Maranna, and Devasenathipathy Kandasamy for obstetrical and neonatal ultrasonography training and quality assurance; Adam Devall for preparing the subgroup analysis figures; and Janna Patterson, Jerker Liljestrand, and Hilary Gammill for their technical input and support as program managers for the WHO ACTION Trials Collaboration at the Bill and Melinda Gates Foundation.

APPENDIX

The members of the writing committee are as follows: Olufemi T. Oladapo, M.D., M.P.H., Joshua P. Vogel, M.B., B.S., Ph.D., Gilda Piaggio, Ph.D., My-Huong Nguyen, M.D., Ph.D., Fernando Althabe, M.D., A. Metin Gülmezoglu, M.D., Ph.D., Rajiv Bahl, M.D., Ph.D., Suman P.N. Rao, M.B., B.S., M.D., D.M., Aycsha De Costa, M.D., Ph.D., Shuchita Gupta, M.B., B.S., M.D., M.P.H., Ph.D., Abdullah H. Baqui, M.B., B.S., M.P.H., Dr.P.H., Rasheda Khanam, M.B., B.S., M.P.H., Ph.D., Mohammod Shahidullah, M.B., B.S., Saleha B. Chowdhury, M.B., B.S., Salahuddin Ahmed, M.B., B.S., Nazma Begum, M.A., Dip.Comp.Sc., Arunangshu D. Roy, M.B., B.S., M.A. Shahed, M.B., B.S., Iffat A. Jaben, M.B., B.S., M.P.H., Farida Yasmin, M.B., B.S., M. Mozibur Rahman, M.B., B.S., Anjuman Ara, M.B., B.S., Soofia Khatoon, M.B., B.S., M.H.P.Ed., Gulshan Ara, M.B., B.S., Shaheen Akter, M.B., B.S., M.D., Nasreen Akhter, M.B., B.S., Probhat R. Dey, M.B., B.S., M.D., M. Abdus Sabur, M.B., B.S., Mohammad T. Azad, M.B., B.S., M.D., Shahana P. Choudhury, M.B., B.S., M.A. Matin, M.B., B.S., Shivaprasad S. Goudar, M.D., Sangappa M. Dhaded, M.D., Mrityunjay C. Metgud, M.D., Yeshita V. Pujar, M.D., Manjunath S. Somannavar, M.D., Sunil S. Vernekar, M.D., Veena R. Herekar, M.D., Shailaja R. Bidri, M.D., Sangamesh S. Mathapati, M.D., Preeti G. Patil, D.N.B., Mallanagouda M. Patil, M.D., Muttappa R. Gudadinni, M.D., Hidayatullah R. Bijapure, M.D., Ashalata A. Mallapur, M.D., Geetanjali M. Katageri, M.S., Sumangala B. Chikkamath, M.D., Bhuvaneshwari C. Yelamali, M.D., Ramesh R. Pol, M.D., Sujata S. Misra, M.D., Leena Das, M.D., Saumya Nanda, M.D., Rashmita B. Nayak, M.D., Bipsa Singh, M.D., Zahida Qureshi, M.B., B.S., Fredrick Were, M.B., Ch.B., Ph.D., Alfred Osoti, M.B., Ch.B., M.P.H., Ph.D., George Gwako, M.B., Ch.B., Ahmed Laving, M.B., Ch.B., John Kiruthia, M.B., Ch.B., M.P.H., Hafsa Mohamed, M.B., Ch.B., Nawal Aliyan, M.B., Ch.B., Adelaide Barassa, M.B., Ch.B., Elizabeth Kibaru, M.B., Ch.B., Margaret Mbuga, M.B., Ch.B., Lydia Thuranira, M.B., Ch.B., Njoroge J. Githua, M.B., Ch.B., Bernadine Lusweti, M.B., Ch.B., Adejumoke I. Ayede, M.B., B.S., Adegoke G. Falade, M.B., B.S., M.D., Olubukola A. Adesina, M.B., B.S., Atinuke M. Agunloye, M.B., B.S., Oluwatosin O. Iyiola, M.B., Ch.B., Wilfred Sanni, B.M., B.Ch., Ifeyinwa K. Ejinkeonye, M.B., B.S., Hadiza A. Idris, M.B., B.S., M.R.H., Chinyere V. Okoli, M.B., B.S., M.P.H., Theresa A. Irinyenikan, M.B., B.S., M.P.H., Omolayo A. Olubosede, M.B., B.S., M.P.H., Olaseinde Bello, M.B., Ch.B., Olufemi M. Omololu, M.B., B.S., Olanike A. Olutekunbi, M.B., B.S., Adesina L. Akintan, M.B., B.S., Olorunfemi O. Owa, M.B., B.S., M.P.A., Rosena O. Oluwafemi, M.B., Ch.B., M.P.H., Ireti P. Eniowo, M.B., B.S., Adetokunbo O. Fabamwo, M.B., B.S., Elizabeth A. Disu, M.B., B.Ch., Joy O. Agbara, M.B., B.S., Ebunoluwa A. Adejuyigbe, M.B., Ch.B., Oluwafemi Kuti, M.B., B.S., Henry C. Anyabolu, M.B., B.S., Ibraheem O. Awowole, M.B., Ch.B., Akintunde O. Fehintola, M.B., B.S., M.P.H., Bankole P. Kuti, M.B., Ch.B., Anthony D. Isah, M.B., B.S., Eyinade K. Olateju, M.B., B.S., Olusanya Abiodun, M.B., Ch.B., Olabisi F. Dedeke, M.B., B.S., M.P.H., Francis B. Akinkunmi, M.B., Ch.B., Lawal Oyeneyin, M.B., B.S., Omotayo Adesiyun, M.B., B.S., Hadijat O. Raji, M.B., B.S., Adedapo B.A. Ande, M.B., Ch.B., M.P.H., Ikechukwu Okonkwo, M.B., B.S., Shabina Ariff, M.B., B.S., Sajid B. Soofi, M.B., B.S., Lumaan Sheikh, M.B., B.S., Saima Zulfiqar, M.B., B.S., Sadia Omer, M.B., B.S., Raheel Sikandar, M.B., B.S., Salma Sheikh, M.B., B.S., Daniel Giordano, B.Sc., Hugo Gamerro, B.Sc., Guillermo Carroli, M.D., Jose Carvalho, B.Sc., M.Sc., Ph.D., James Neilson, M.D., Elizabeth Molyneux, M.B., B.S., Khalid Yunis, M.D., Kidza Mugerwa, M.B., Ch.B., and Harish K. Chellani, M.D.

The affiliations of the members of the writing committee are as follows: World Health Organization, Geneva (O.T.O., J.P.V., G.P., M.-H.N., F.A., A.M.G., R.B., S.P.N.R., A.D.C., S.G.); Johns Hopkins Bloomberg School of Public Health, Baltimore (A.H.B., R.K.); Bangabandhu Sheikh Mujib Medical University (M.S., S.B. Chowdhury), Projahnmo Research Foundation (S. Ahmed, N.B., A.D.R., M.A. Shahed, I.A.J.), Institute of Child and Mother Health (F.Y., M.M.R.), Center for Woman and Child Health (A.A., S.K.), and Enam Medical College and Hospital (G.A., S. Akter), Dhaka, and Sylhet Muhammad Ataul Gani Osmani Medical College Hospital (N. Akhter, P.R.D.), Jalalabad Ragib–Rabeya Medical College Hospital (M.A. Sabur, M.T.A.), and Sylhet Women's Medical College Hospital (S.F.C., M.A.M.), Sylhet — both in Bangladesh; KLE Academy of Higher Education and Research, Jawaharlal Nehru Medical College, Belagavi (S.S.G., S.M.D., M.C.M., Y.V.P., M.S.S., S.S.V., V.R.H.), Shri B.M. Patil Medical College, Vijayapura (S.R.B., S.S. Mathapati, P.G.P., M.M.P., M.R.G., H.R.B.), S. Nijalingappa Medical College, Bagalkot (A.A.M., G.M.K., S.B. Chikkamath, B.C.Y., R.R.P.), Srirama Chandra Bhanja Medical College, Cuttack (S.S. Misra, L.D., S.N., R.B.N., B.S.), and Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi (H.K.C.) — all in India; University of Nairobi (Z.Q., F.W., A. Osoti, G.G., A.L.) and Kenyatta National Hospital (J.K.), Nairobi, Coast Provincial General Hospital, Mombasa (H.M., N. Aliyan), Nakuru Level 5 Hospital, Nakuru (A.B., E.K.), Kiambu Level 5 Hospital, Kiambu (M.M., L.T.), and Thika Level 5 Hospital, Thika (N.J.G., B.L.) — all in Kenya; the College of Medicine, University of Ibadan, and University College Hospital, Ibadan (A.I.A., A.G.F., O.A.A., A.M.A., O.O.I.), Kubwa General Hospital, Kubwa (W.S., I.K.E.), Nyanya General Hospital, Nyanya (H.A.I., C.V.O.), State Specialist Hospital (T.A.I., O.A. Olubosede, O.B.) and Mother and Child Hospital (A.L.A., O.O.O., R.O.O., I.P.E.), Akure, Lagos Island Maternity Hospital (O.M.O., O.A. Olutekunbi), and Lagos State University Teaching Hospital (A.O. Fabamwo, E.A.D., J.O.A.), Lagos, Obafemi Awolowo University, Ile-Ife (E.A.A., O.K., H.C.A., I.O.A., A.O. Fehintola, B.P.K.), University of Abuja, Abuja (A.D.I., E.K.O.), Sacred Heart Hospital, Abeokuta (O. Abiodun, O.F.D.), Mother and Child Hospital, Ondo (F.B.A., L.O.), University of Ilorin, Ilorin (O. Adesiyun, H.O.R.), and University of Benin, Benin City (A.B.A.A., I.O.) — all in Nigeria; Aga Khan University, Karachi (S. Ariff, S.B.S., L.S.), Sheikh Zayed Medical College and Hospital, Rahim Yar Khan (S.Z., S.O.), and Liaquat University Hospital, Hyderabad (R.S., S.S.) — all in Pakistan; Centro Rosarino de Estudios Perinatales, Rosario, Argentina (D.G., H.G., G.C.); Statistika Consultoria, Campinas, Brazil (J.C.); University of Liverpool, Liverpool, United Kingdom (J.N.); College of Medicine, University of Malawi, Blantyre (E.M.); American University of Beirut, Beirut, Lebanon (K.Y.); and the Makerere University College of Health Sciences, Kampala, Uganda (K.M.).

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The WHO ACTION Trials Collaborators. Antenatal dexamethasone for early preterm birth in low-resource countries. N Engl J Med 2020;383:2514-25. DOI: 10.1056/NEJMoa2022398

Table of Contents

The WHO ACTION Trials Collaborators

- **Trial Co-ordinating Unit**
  - **UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland:** Olufemi T. Oladapo MD, MPH, FWACS, Joshua P. Vogel BMedSci, MBBS, PhD, Gilda Piaggio MSc., PhD (Statistician), My Huong Nguyen MD, PhD (Data Manager), Fernando Althabe MD, MSc. (from 2019), A. Metin Gülmezoglu MD, PhD (2015-2019)
  - **Department of Maternal, Newborn, Child, Adolescent Health, and Ageing, World Health Organization, Geneva, Switzerland:** Rajiv Bahl MD, PhD, Suman P.N. Rao MBBS, MD, DM (from 2019), Ayesha De Costa MD, PhD (from 2019), Shuchita Gupta MBBS, MD, MPH, PhD (from 2019)
- **Bangladesh site:**
  - **Johns Hopkins Bloomberg School of Public Health, Baltimore, USA:** Abdullah H. Baqui MBBS, MPH, DrPH, (Principal Investigator), Rasheda Khanam MBBS, MPH, PhD
  - **Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh:** Mohammod Shahidullah MBBS, FCPS (Principal Investigator), Saleha Begum Chowdhury MBBS, FCPS (Principal Investigator)
  - **Projahnmo Research foundation, Banani, Dhaka, Bangladesh:** Salahuddin Ahmed MBBS, Nazma Begum MA, Dip. Comp. Sc., Arunangshu Dutta Roy MBBS (from 2018), M.A. Shahed MBBS (from 2018), Iffat Ara Jaben MBBS, MPH (from 2018)
  - **Centre for Woman and Child Health, Ashulia, Savar, Dhaka, Bangladesh:** Soofia Khatoon MBBS, FCPS, MHPEd, Anjuman Ara MBBS, FCPS (from 2018)
  - **Sylhet M. A. G. Osmani Medical College Hospital, Sylhet, Bangladesh:** Probhat Ranjan Dey MBBS, FCPS, MD, Nasreen Akhter MBBS, DGO, FCPS (from 2019)
  - **Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet, Bangladesh:** Md. Abdus Sabur MBBS, FCPS (2017-2019), Mohammad Tarek Azad MBBS, DCH, MCPS, MD
  - **Enam Medical College and Hospital, Savar, Dhaka, Bangladesh:** Gulshan Ara MBBS, FCPS (2017-2019), Shaheen Akter MBBS, MD, FCPS (2017-2019)
  - **Institute of Child and Mother Health, Matuail, Dhaka, Bangladesh:** Md Mozibur Rahman MBBS, DCH, FCPS, Farida Yasmin MBBS, DGO, MCPS, FCPS
  - **Sylhet Women's Medical College Hospital, Sylhet, Bangladesh:** M.A. Matin MBBS, DCH, Shahana Ferdous Choudhury MBBS, FCPS

- **India site:**
    - **KLE Academy of Higher Education and Research, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India:** Shivaprasad S. Goudar MD, MHPE (Principal Investigator), Sangappa M. Dhaded MD (Principal Investigator), Mrityunjay C. Metgud MD, Yeshita V. Pujar MD, Manjunath S. Somannavar MD, Sunil S. Vernekar MD, Veena R. Herekar MD
    - **S Nijalingappa Medical College, Bagalkot, Karnataka, India:** Ashalata A. Mallapur MD (Principal Investigator), Geetanjali M. Katageri MS, Sumangala B. Chikkamath MD, Bhuvaneshwari C. Yelamali MD, Ramesh R. Pol MD
    - **BLDE University's Shri B M Patil Medical College, Bijapur, Karnataka, India:** Shailaja R. Bidri MD (Principal Investigator), Sangamesh S. Mathapati MD, Preeti G. Patil DNB, Mallanagouda M. Patil MD, Muttappa R. Gudadinni MD, Hidaytullah R. Bijapure MD
    - **Srirama Chandra Bhanja Medical College, Cuttack, Odisha, India:** Sujata S. Misra MD (from 2018) (Principal Investigator), Leena Das MD (from 2018), Saumya Nanda MD (from 2018), Rashmita B. Nayak MD (from 2018), Bipsa Singh MD (from 2018)
- **Kenya site:**
    - **University of Nairobi, Nairobi, Kenya:** Zahida Qureshi MBBS, MMed (Principal Investigator), Fredrick Were MBChB, MMed, FNIC, PhD (Principal Investigator), Alfred Osoti MBChB, MMed, MPH, PhD, George Gwako MBChB, MMed, Ahmed Laving MBChB, MMed
    - **Kenyatta National Hospital, Nairobi, Kenya:** John Kinuthia MBChB, MMed, MPH (Principal Investigator)
    - **Coast Provincial General Hospital, Mombasa, Kenya:** Hafsa Mohamed MBChB, MMed (2018-2019), Nawal Aliyan MBChB, MMed (from 2019)
    - **Nakuru Level 5 Hospital, Nakuru, Kenya:** Adelaide Barassa MBChB, MMed, Elizabeth Kibaru MBChB, MMed (2018-2019)
    - **Kiambu level 5 Hospital, Kiambu, Kenya:** Margaret Mbuga MBChB, MMed, Lydia Thuranira MBChB, MMed (from 2019)
    - **Thika level 5 Hospital, Thika, Kenya:** Njoroge John Githua MBChB, MMed, Bernadine Lusweti MBChB, MMed, ESPE Fellow
- **Nigeria (Ibadan) site:**
    - **College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria:** Adejumoke Idowu Ayede MBBS, MSc., FMCPead, FRCPE (Principal Investigator), Olubukola Adeponle Adesina MBBS, FWACS, MSc. (from 2019) (Principal Investigator),

Adegoke Gbadegesin Falade MBBS, MD, FMCPead, FRCPE, Atinuke Monsurat Agunloye MBBS, FMCR, FWACS, Oluwatosin Olaniyi Iyiola MBChB, MWACS

- **Kubwa General Hospital, Abuja, Nigeria:** Wilfred Sanni BMBCh, FWACS, Ifeyinwa Kate Ejinkeonye MBBS, FWACP
- **Nyanya General Hospital, Abuja, Nigeria:** Hadiza Abdulaziz Idris MBBS, FMCOG, MRH, Chinyere Viola Okoli MBBS, FMCPead, MPH
- **State Specialist Hospital, Akure, Nigeria:** Theresa Azonima Irinyenikan MBBS, MPH, FMCOG, FWACS, Omolayo Adebukola Olubosede MBBS, MPH, FMCPaed, Olaseinde Bello MBChB, FWACP
- **Lagos Island Maternity Hospital, Lagos, Nigeria:** Olufemi Motunolani Omololu MBBS, FWACS, Olanike Abosede Olutekunbi MBBS, FWACP (from 2018)
- **Mother and Child Hospital, Akure, Nigeria:** Adesina Lawrence Akintan MBBS, FWACS, Olorunfemi Oludele Owa MBBS, MPA, FWACS (from 2018), Rosena Olubanke Oluwafemi MBChB, MPH, FWACP, Ireti Patricia Eniowo MBBS, FMCPaed (from 2018)
- **Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria:** Adetokunbo Olusegun Fabamwo MBBS, MSc., FMCOG, FWACS, Elizabeth Aruma Disu MBBCh, MSc., FWACPaed, Joy Onyinyechi Agbara MBBS, MSc., FMCOG, FWACS

- **Nigeria (Ile-Ife) site:**
  - **Obafemi Awolowo University, Ile-Ife, Nigeria:** Oluwafemi Kuti MBBS, FWACS, FMCOG, FRCOG (Principal Investigator), Ebunoluwa Aderonke Adejuyigbe BSc., MBChB, FMCPaed (Principal Investigator), Henry Chineme Anyabolu MBBS, FWACP, Ibraheem Olayemi Awowole MBChB, FWACS, FMCOG, MRCOG, Akintunde Olusegun Fehintola MBBS, FMCOG, MPH, Bankole Peter Kuti MBChB, FWACP, FMCPaed
  - **University of Benin, Benin City, Nigeria:** Adedapo Babatunde Anibaba Ande BSc., MBChB, FWACS, MPH, Ikechukwu Okonkwo MBBS, FWACP
  - **University of Ilorin, Ilorin, Nigeria:** Omotayo Adesiyun MBBS, FMCPaed, Hadijat Olaide Raji MBBS, MSc., FWACS (from 2019)
  - **University of Abuja, Gwagwalada, Federal Capital Territory, Nigeria:** Anthony Dennis Isah MBBS, FWACS, Eyinade Kudirat Olateju MBBS, FMCPaed
  - **Sacred Heart Hospital, Lantoro, Abeokuta, Nigeria:** Olusanya Abiodun MBChB, FWACS, Olabisi Florence Dedeke MBBS, FWACPaed, MPH
  - **Mother & Child Hospital, Ondo, Nigeria**: Lawal Oyeneyin MBBS, FWACS, FMCOG, FICS, mni, Francis Bola Akinkunmi MBChB, FWACPaed

- **Pakistan site:**
    - **Aga Khan University, Karachi, Pakistan:** Shabina Ariff MBBS, FCPS, FCPS (Principal Investigator), Sajid Bashir Soofi MBBS, FCPS (Principal Investigator), Lumaan Sheikh MBBS, FCPS, MRCOG, FRCOG (Principal Investigator)
    - **Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan:** Saima Zulfiqar MBBS, MCPS, FCPS, Sadia Omer MBBS, FCPS
    - **Liaquat University Hospital, Hyderabad, Pakistan:** Raheel Sikandar MBBS, FCPS, Salma Sheikh MBBS, DCH, MRCPCH, FRCPCH, PGPN
- **Data Management Team:**
    - **Centro Rosarino de Estudios Perinatales, Rosario, Argentina:** Daniel Giordano BSc., Hugo Gamerro BSc., Guillermo Carroli MD
- **Statistical Programming:**
    - **Statistika Consultoria, São Paulo, Brazil:** Jose Carvalho BSc., MSc., PhD
- **Technical Advisory Group:**
    - **University of Liverpool, Liverpool, United Kingdom**: James Neilson MD, FRCOG (Trial Steering Group chair)
    - **College of Medicine, University of Malawi, Blantyre, Malawi**: Elizabeth Molyneux MBBS, FRCPCH, FRCEM, DSC h.c
    - **American University of Beirut, Beirut, Lebanon**: Khalid Yunis MD, FAAP
    - **Makerere University College of Health Sciences, Kampala, Uganda:** Kidza Mugerwa MBChB, MMed
    - **Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi**: Harish Kumar Chellani MD, DCH

Statistical methods

Sample size

We estimated the sample size on the basis of the primary outcome neonatal mortality at 28 completed days with a two-sided 5% significance level test and a power of 90%. A total of about 5,416 women are needed to detect a reduction of 15.0% or more from a 25.0% deaths to 21.3%, among neonates of women who were administered ACS at <34 weeks. With 10% loss to follow-up, we estimated that about 6,018 women had to be recruited.

For the composite possible maternal bacterial infection outcome, a non-inferiority hypothesis was used. A total sample size of 5,024 women are needed (including 10% loss to follow up) to demonstrate non-inferiority within that margin of 2.5% for the increase in the maternal infection outcome, assuming equal prevalence of 10% in the two arms, with a power of 80% and a significance level of 2.5%.

Statistical analysis

For primary outcomes, intention-to-treat (ITT) analyses were to be performed. Analyses were first performed on all available data and sensitivity analyses were then performed using multiple imputation to judge the effect of missing data. Analyses of primary outcomes were corrected for multiplicity using the False-Discovery-Rate approach. For the primary outcomes, fetal or neonatal mortality and maternal severe infection outcomes pertain to the enrolled population, whereas neonatal mortality pertains to liveborn neonates only.

We also conducted a secondary "per-protocol" analysis for the maternal primary outcome, as recommended for non-inferiority analyses, excluding women with protocol violations that might affect the primary outcome.

Baseline characteristics were compared between groups to detect imbalances in prognostic variables that could bias the results. Most study outcomes are binary variables. For this type of variables, the number of participants, number of missing values and percentages by group were reported. The intervention arm was compared against the control arm for the three primary outcomes using risk ratios with 95% confidence intervals. The statistical technique used to conduct tests and obtain confidence intervals was a logistic model with a binomial distribution and the log link to obtain relative risks. The stratifying variable study site, a design variable, was included in the model, as well as a clustering feature for multiple births for neonatal outcomes. Separate models were fitted for each of the primary and secondary outcomes.

For continuous variables, the number of participants, the number of missing values, means and standard deviations or medians, quartiles and interquartile range (IQR) by group were reported. The intervention arm was compared against the control arm using mean or median differences and 95% confidence intervals. The statistical technique used to conduct tests and obtain confidence intervals for this type of variables was a general linear model including study site in the model as stratifying variable, as well as a clustering feature for multiple births for neonatal outcomes.

All models were fitted using SAS Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Prespecified subgroup analyses

We conducted the following prespecified subgroup analyses of the primary outcomes neonatal death, stillbirth or neonatal death, and possible maternal bacterial infection:

1. Planned preterm birth: yes vs. no
2. Gestational age at first dose: 26 to <28 weeks vs. 28 to <32 weeks vs. 32 to <34 weeks
3. Number of fetus: single vs. multiple
4. Study site: Bangladesh vs. India vs. Kenya vs. Nigeria (Ibadan) vs. Nigeria (Ile-Ife) vs. Pakistan
5. Time from first dose to birth: 0 to 6h vs. >6 to 12h vs. >12 to 24h vs. >24h to 1 week vs. over 1 week
6. Mode of birth: vaginal birth vs. cesarean section
7. Any use of tocolytics: yes vs. no

We further analysed the effect of time of first dose to birth on treatment effect using a logistic model, including gestational age (GA) at first dose and number of doses in the model.

Assessing confounders and effect modifiers of neonatal primary outcomes

The effect of treatment, gestational age, time from first dose to birth and number of doses on the probability of stillbirth or neonatal death and neonatal death was assessed using a logistic model.

Variables:

- Response: stillbirth or neonatal death, or neonatal death
- Treatment (randomized): dexamethasone and placebo
- Site: (randomization was done within sites)

- Covariates: gestational age (weeks), time from first dose to birth (hours), number of doses.

Model

$$y = \log\left(\frac{p}{1-p}\right) = \mu + treat + site + exposure \cdot (treat) + exposure^2(treat) + ndoses(treat) + ga(treat)$$

where

A(B) means A within B,

p=proportion of events for binary neonatal outcome,

$$p = \frac{1}{1+e^{-y}}$$

y=logit for binary neonatal outcome (stillbirth or neonatal death, or neonatal death)

treat=treatment

exposure= time from first dose to birth (hours)

ndoses=number of doses

ga=gestational age at first injection (weeks)

site=study site

Gestational age at first injection was used instead of gestational age at birth because the latter is confounded with time from first dose to birth. The time interval between trial entry and birth is thus split in two non-overlapping time intervals (gestational age at first injection and time from first dose to birth).

Models were considered including terms for interactions, and the final model was selected excluding interaction terms that were not significant at 5%. Significance is assessed by p-values, in raw format and also expressed as logWorth, a logarithmic transformation of the P-value:

$$logWorth = -\log_{10}(p) = \log_{10}(1/p)$$

Goodness of fit of the model was assessed by the difference between the log-likelihood of the saturated model and that of the fitted model.

The effect of treatment was calculated in terms of relative risk (RR) from the model and plotted against time from first dose to birth by categories of gestational age at first injection.

Results

Neonatal death

The following table shows, for **the neonatal death outcome**, the significance for the different terms in the model described above. The most important effect by far is gestational age at first injection. Time from first dose to birth, study site, number of doses and treatment are significant at 1% level. The effects of gestational age, time from first dose to birth and number of doses are significantly different for each treatment.

Source	LogWorth	p-value
ga(treat)	97.784	0.00000
exposure(treat)	7.795	0.00000
site	4.187	0.00006
ndoses(treat)	3.042	0.00091
treat	1.873	0.01339
exposure*exposure(treat)	0.816	0.15267

The following table shows statistics of goodness of fit. The P-value for goodness of fit is 1, suggesting that the model fits the data well.

Source	**DF**	**-LogLikelihood**	**p-value**
Saturated model	2803	5.5452	
Fitted model	14	1141.4016	
Lack of fit	2789	1135.8564	1.0000

Stillbirth or neonatal death

The following table shows, for **the stillbirth or neonatal death outcome**, the significance for the different terms in the model described above. The effects are very similar to those described for the neonatal death outcome.

Source	LogWorth	p-value
ga(treat)	116.999	0.00000
exposure(treat)	8.226	0.00000
site	3.438	0.00036
ndoses(treat)	2.632	0.00233
treat	1.073	0.08459
exposure*exposure(treat)	0.326	0.47224

The following table shows statistics of goodness of fit. The P-value for goodness of fit is 0.9785, suggesting that the model fits the data well.

Source	DF	-LogLikelihood	p-value
Saturated model	3028	6.9315	
Fitted model	14	1436.3927	
Lack of fit	3014	1429.4613	0.9785

Data safety monitoring

A Data Safety Monitoring Board (D5MB) was appointed to monitor accruing trial data, in strict confidence, and three interim analysis were planned. The DSMB terms of reference were that they should inform the steering group chair if, in their view, there was proof beyond doubt that treatment with dexamethasone is indicated or contraindicated based on statistical considerations, practical issues, clinical considerations or new external information. The DSMB considered the Haybittle-Peto stopping rule on the primary infant mortality outcomes, as the statistical guidance for their recommendation. Using this rule, a two-sided test of hypothesis to assess superiority of one of the groups (intervention or placebo) was conducted. If the result was significant at α=0.001, the DSMB would consider recommending stopping the trial for superiority of one of the groups.

Two interim analyses were conducted by both the trial statistician (blinded) and the DSMB statistician (unblinded on request) and results were presented at DSMB meetings. The DSMB could be unblinded to the study groups if and when needed. The first interim analysis was conducted when 874 women and 972 infants (including 894 liveborn neonates) had been recruited and their complete data entered in the database. At their meeting on 19-20 November 2019, after review of 2304 women and 2536 infants (including 2337 liveborn neonates) with complete follow-up of primary outcomes, the DSMB decided to unblind the trial and recommended the trial to be stopped for mortality benefits, supported by evidence of a graded dose-response effect. Recruitment was stopped across all sites on 21 November 2019 and all ethics committees and regulatory authorities were informed of the decision to stop.

DSMB rationale for stopping the trial

The DSMB decided to recommend that the trial be stopped because they decided after a lengthy debate that the evidence of benefit was so strong that they judged it unethical to continue.

They recognized that this was a deviation from the stopping rule. However, it was in line with Section 3.4.4 of the trial protocol, which specified that the DSMB decision to stop the trial following an interim analysis was to be guided not only by statistical considerations, but also by practical issues (adverse events, ease of treatments administration, unanticipated costs), as well as clinical considerations or new external information. Likewise, in Section 8.2 of the DSMB charter for the trial (**The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules**), it is stated that: "The statistical stopping rules should not be taken as the only criterion for a recommendation to stop the trial. Safety results from the trial as well as external information should be considered. A recommendation to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians, including those supporting the trial/s and the general clinical community."

The decision to stop the trial was driven by:

1) New external information from sheep studies became available during the conduct of the trial about strong effect of duration of fetal exposure to glucocorticoids on fetal lung maturation[1,2]
These studies concluded that the duration of materno-fetal glucocorticoid exposure, not total dose or peak drug exposure, is a key determinant for a sustained fetal lung maturation and antenatal glucocorticoid efficacy. Evidence of fetal lung maturation was observed with at least 24 hours of glucocorticoid exposure, with exposure of 48 hours providing more sustained effect.

On account of this external information, the DSMB decided to carry out a planned pre-specified sensitivity analysis excluding women giving birth less than 24 hours during their second interim analysis and to include the findings in their decision making. This decision was made blinded to treatment allocation.

On completion of the second interim analysis of 2304 women and 2536 infants using the database closed in November 2019, the DSMB noted a clear evidence of reduction in both neonatal mortality and in stillbirth or neonatal death, the two primary outcomes, in the dexamethasone intervention arm compared to the control (placebo) arm. At that time, the overall result was a relative reduction of 18% (95% CI: 5% to 29%; p=0.008) in neonatal death with dexamethasone, and a relative reduction of 13% (95% CI: 2% to 23%; p=0.02) in stillbirth or neonatal death in the dexamethasone arm, compared to placebo. However, the results of the planned pre-specified sensitivity analysis on account of external new information described above, excluding women who delivered within 24

hours of the first injection of trial medication (whose babies would not be expected to benefit because of a short exposure to glucocorticoid) showed a 30% reduction in neonatal death (P=0.0017) and a 24% reduction in stillbirth or neonatal death (P=0.0015). This analysis further showed that dexamethasone effects strengthened for both neonatal primary outcomes as women with varying degrees of shorter intervals between first injection and birth were excluded, reaching the z=3 level after those who could only have received one dose (i.e. up to 12 hours) are removed. These findings were indicative of graded dose-response relationship and efficacy of dexamethasone.

2) Considering the evidence from the trial in the context of the existing evidence of the benefits of antenatal glucocortioids (from the Cochrane review meta-analysis), well beyond the stopping boundary

While acknowledging the fact that the P-values from these analyses were very close to but did not strictly attain the 0.001 specified by the Haybittle Peto rule, the DSMB noted that these findings were consistent with the results of the Cochrane review (involving 7774 women and 8158 infants) that largely included studies from high-income countries, which showed overall reduction of 31% in neonatal death, and concluded that it would be unethical to further expose more women (and babies) to placebo given the existing body of knowledge from high-income setting. The DSMB was not only sensitive to these individual ethics but also considered the findings of these analyses convincing to influence policy and clinical practice (collective ethics), according to the DSMB charter.

Based on these considerations, the DSMB recommended that all recruitment be stopped, and this recommendation was unanimously accepted by the Technical Advisory Group, ACTION Trial Investigators, and WHO. The funder had no role in the deliberations and in the decision to stop the trial.

Primary and secondary outcome definitions

PRIMARY OUTCOMES	OPERATIONAL DEFINITION AND MEASUREMENT
1. Neonatal death	Death of a live birth within 28 completed days of life.
2. Stillbirth or neonatal death	Any death of a fetus (post randomization) or death of a live birth within 28 completed days of life.
3. Possible maternal bacterial infection	Occurrence of maternal fever or clinically suspected or confirmed infection, for which therapeutic antibiotics were used. *Suspected or confirmed infection could be an obstetric infection (chorioamnionitis, postpartum endometritis, or wound infection) or non-obstetric infection, as defined below. Captured during hospital admission/s only*
SECONDARY OUTCOMES	
A. For the neonate	
A1. Mortality outcomes	
1. Stillbirth	Any death of a fetus (post randomization).
2. Early neonatal death	Death of a live birth within 7 completed days of life.
A2. Morbidity outcomes	
3. Severe respiratory distress*‡	Clinical features are the presence of fast breathing (respiratory rate ≥ 70 breaths per minute) AND at least one of the following clinical signs: 1. Marked nasal flaring during inspiration, 2. Expiratory grunting audible with naked ear 3. Severe chest in drawing. AND SpO2 less than 90%, or use of supplemental oxygen.
4. Neonatal sepsis*	Defined as the presence of at least two (or more) of the following signs: • Stopped feeding well • Severe chest in-drawing • Fever (body temperature of 38 °C or greater) • Hypothermia (body temperature less than 35.5 °C) • Movement only when stimulated or no movement at all • Convulsions
5. Severe Intraventricular haemorrhage (sIVH)	Defined as a Papile's intraventricular hemorrhage classification grade 3 or 4, as per transcranial ultrasound assessment. Liveborn neonates <34 weeks at birth will be routinely screened with transcranial ultrasound. Liveborn neonates ≥ 34 weeks at birth will receive transcranial ultrasound if indicated. Transcranial ultrasound assessment will be performed at day 7 postnatal or discharge (if discharge occurs before 7 days after birth).
6. Neonatal hypoglycaemia*§	Neonatal hypoglycemia is defined as blood glucose measure less than 45 mg/dl (2.6mmol/l). All liveborn newborns in hospital will have glucose levels recorded at 6 and 36 hours (before feeding or IV fluids). Any documented hypoglycaemia will also be recorded.

7. Apgar score at 5 minutes	Assessment of neonatal vitality at 5 minutes after birth. Reported as Apgar score, and proportion of babies with Apgar <7.
B. For the Woman	
B1. Mortality outcomes	
8. Maternal death	Any maternal death in a trial participant, from time of randomization to 28 completed days postpartum.
B2. Morbidity outcomes	
9. Maternal fever	Maternal fever ≥38.0 C since randomization (on any one occasion, during hospital admission/s only).
10. Chorioamnionitis	Chorioamnionitis (suspected or confirmed) based on clinical assessment by obstetric care physician. Clinical or laboratory features may include: • Maternal fever ≥38.0 C • Maternal and/or fetal tachycardia • Purulent or foul smelling vaginal discharge • Uterine tenderness • Maternal leukocytosis • Bacterial culture indicative of infection measured during hospital admission only (from randomization until birth)
11. Postpartum endometritis	Postpartum endometritis (suspected or confirmed) based on clinical assessment by obstetric care physician. Clinical or laboratory features may include: • Maternal fever ≥38.0 C • Maternal and/or fetal tachycardia • Purulent or foul smelling vaginal discharge • Uterine tenderness • Maternal leukocytosis • Bacterial culture indicative of infection measured during hospital admission/s only
12. Wound infection	Infection of a wound or incision site (including perineal tear, episiotomy incision or cesarean section abdominal incision), suspected or confirmed by obstetric care physician Measured during hospital admission/s only
13. Non-obstetric infection	Acute non-obstetric infection (suspected or confirmed) based on clinical assessment by obstetric care physician. This includes: • respiratory tract infection (including pneumonia, pharyngitis, sinusitis or similar) • Urinary tract infection (excluding pyelonephritis) • Pyelonephritis • Acute cholecystitis • Other systemic infection *Malaria is specifically excluded from this outcome* Measured during hospital admission/s only

C. Process of care outcomes	
C1. Measures of care given to neonate	
14. Major neonatal resuscitation at birth	The use of positive pressure ventilation for more than one minute
15. Timing of breast milk feeding initiation*	Timing of initiation of breast milk feeding in hours after birth (breastfeeding, cup or tube feeding).
16. Time to full enteral feeding*	Timing to full enteral feeding (in days)
17. Use of oxygen therapy*	Defined as any use of oxygen therapy, using any method
18. Length of oxygen therapy*	This is defined as the total number of days of oxygen use during hospital stay. The total number of days will be counted, even if use was intermittent.
19. Use of continuous positive airway pressure (CPAP) ventilation*	Defined as any use of CPAP during admission to neonatal special care unit/ward
20. Length of use of continuous positive airway pressure (CPAP) ventilation*	Total number of days used will be counted, even if use is interrupted for hours or days.
21. Use of mechanical ventilation (MV)*	Any use of MV during admission
22. Length of use of mechanical ventilation (MV)*	Total number of days used will be counted, even if use is interrupted or intermittent
23. Any use of parenteral therapeutic antibiotic therapy for 5 or more days *	Any use of therapeutic antibiotics (intravenous or intramuscular) for 5 or more days, even if interrupted, excluding neonates who died before 5 completed days
24. Length of use of parenteral therapeutic antibiotic therapy*	Total number of days of use of parenteral antibiotic therapy
25. Use of surfactant treatment*	Any use of surfactant
26. Number of doses of surfactant treatment*	Total number of doses of surfactant treatment
C2. Health service utilization (newborn)	
27. Length of hospital stay after birth	Length of stay in hospital after birth in complete days (initial postnatal hospitalization only)
28. Admission to a special care unit (SCU)	Admission to special neonatal care unit or neonatal intensive care unit after birth (initial postnatal hospitalization only)
29. Length of admission to	Length of admission to special neonatal care unit or neonatal intensive care unit in days

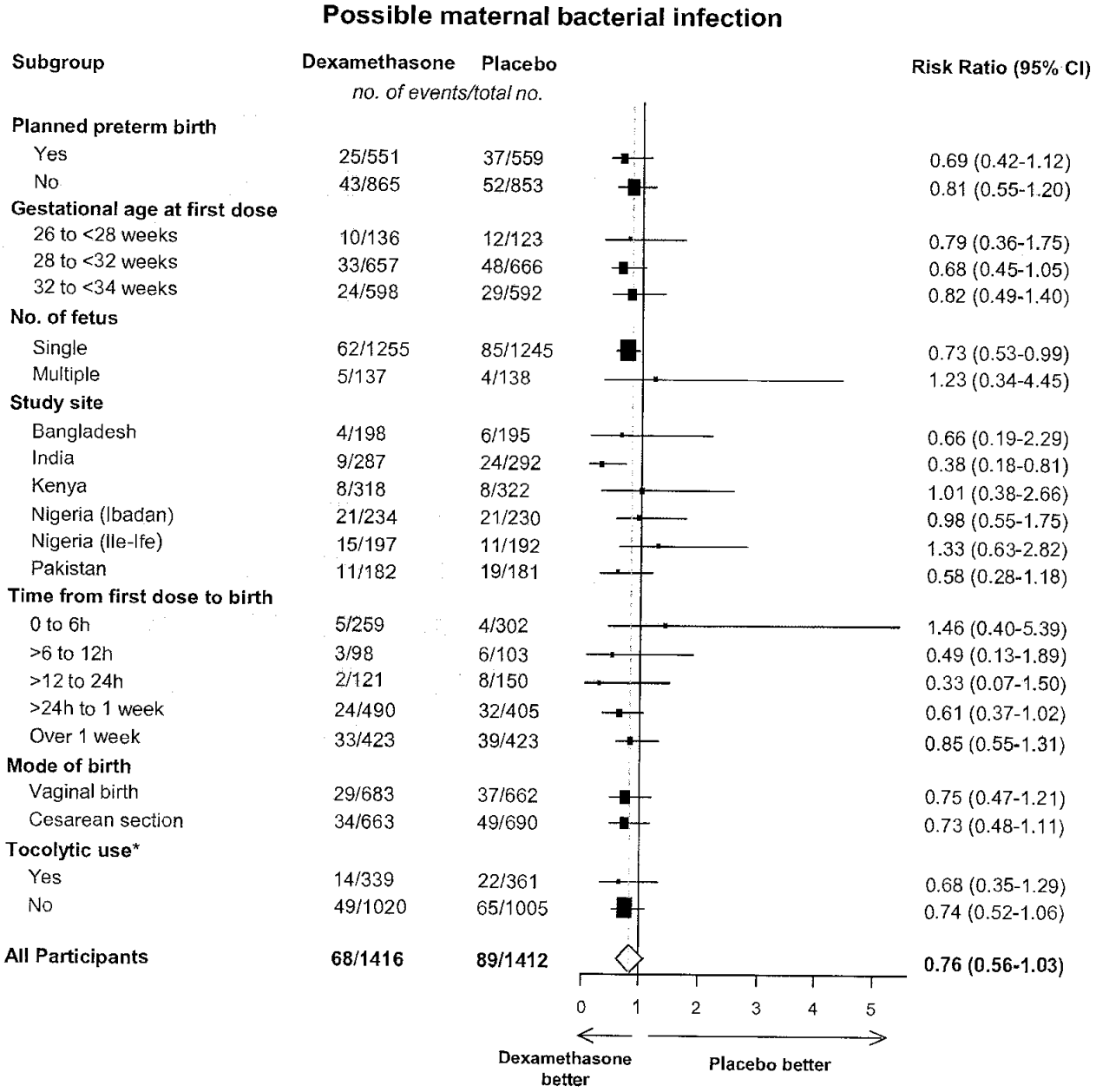
special care unit (days)	
30. Newborn readmission for health care at facility	Any readmission to a health care at facility, for any reason.
31. Length of stay for newborn readmission	Length of readmission stay in facility in days
32. Number of newborn readmission for health care at facility	Number of readmissions for health care at facility, for any reason.
33. Cause of neonatal readmission for health care at facility	All causes of neonatal readmission to health care at facilities will be recorded as per clinical diagnosis
C3. Measures of care given to woman	
34. Therapeutic antibiotics	Therapeutic antibiotics for suspected or confirmed infection (obstetric or non-obstetric). *Use of antibiotics for prophylaxis is not included in this outcome.* Measured during hospital admission/s only
35. Number of days of therapeutic antibiotic use	Number of days of use of therapeutic antibiotics for suspected or confirmed infection (obstetric or non-obstetric). Use of antibiotics for prophylaxis is not included in this outcome. Measured during hospital admission/s only
36. Any antibiotic use	Any use of antibiotics in a randomized participant (maternal) while in facility (prophylactic or therapeutic) Measured during hospital admission/s only
C3. Health service utilization (woman)	
37. Length of total maternal hospitalization for birth (days)	number of days which women are hospitalized for birth (i.e. the admission in which birth occurs). Measured from day of admission to day of official discharge from facility, in days
38. Any postpartum maternal readmission to facility	Any postpartum readmission of the woman to hospital for any reason up to 28 completed days postpartum
39. Length of stay for postpartum maternal readmission	Length of readmission stay in facility in days
40. Number of maternal readmissions to facility	Number of postpartum readmissions of the woman to hospital for any reason up to 28 completed days postpartum
41. Cause of maternal readmission to facility	All causes of maternal readmission to hospital will be recorded as per clinical diagnosis

42. Any referral of woman to another facility for treatment of complications	Any referral of woman to another hospital for treatment of complications
Measures of compliance	
43. Compliance with study allocation	Defined as the proportion of women who complete the entire course, as per the allocation
44. Use of repeat course	Total number and proportion of women who received a repeat course of dexamethasone or placebo
45. Total number of treatment doses received	Total number of treatment (dexamethasone or placebo) doses received (initial and repeat)
46. Time from initiation of first dose until birth	Defined as the time from initiation of first dose (dexamethasone or placebo) to birth, measured in hours

** Measured during initial postnatal hospitalization only, until death, discharge or completed day 7 (whichever comes first); ‡overall, and at 24 hours; § overall, and at 6 and 36 hours*

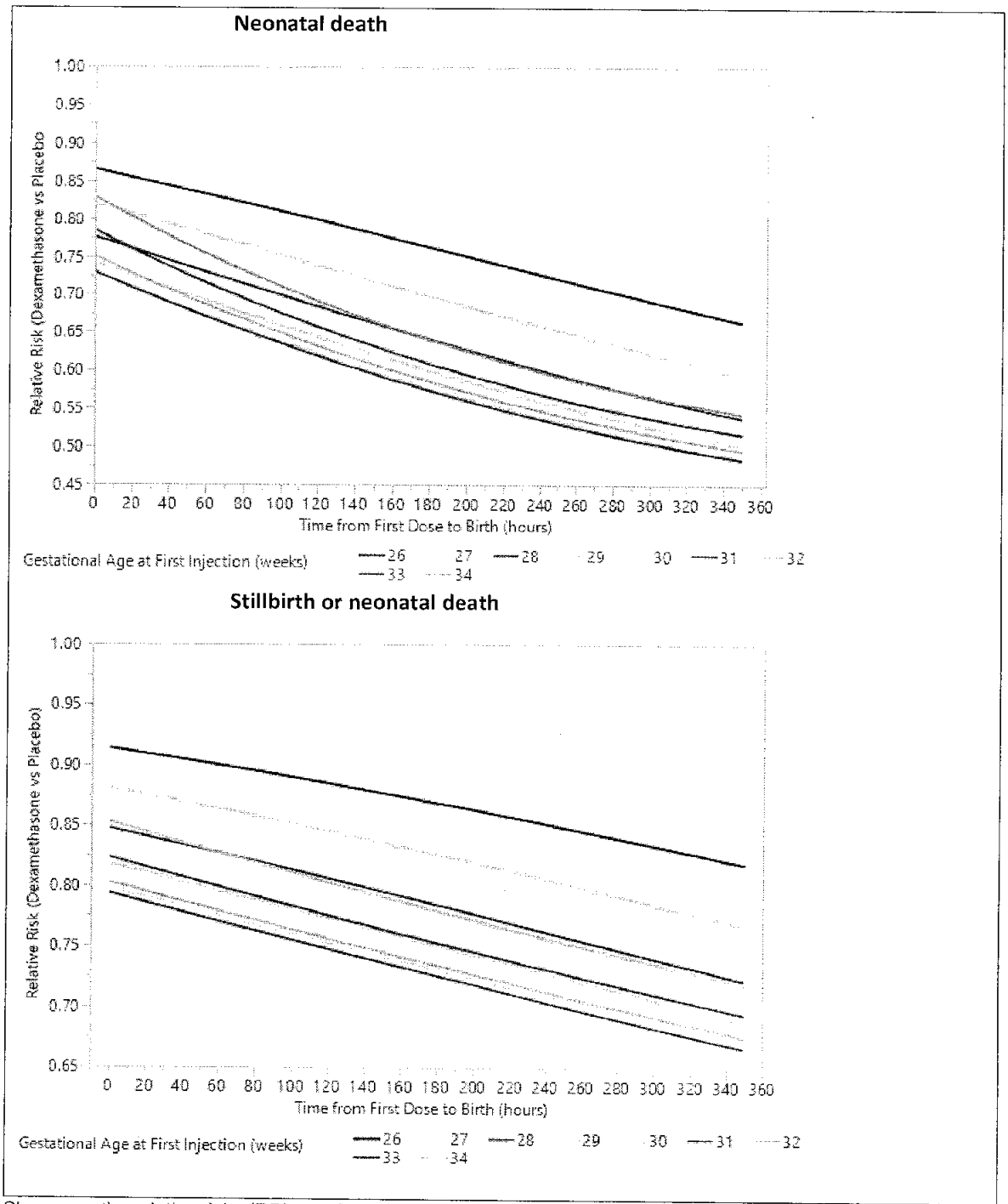
Supplementary figures and tables

Figure S1: Prespecified subgroup analyses of possible maternal bacterial infection



*Maternal use of tocolytic agent before birth. Shown are the results of the analysis of possible maternal bacterial infection (maternal primary outcome) in prespecified subgroups. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. The size of each black square is proportional to the total number of women in the subgroup.

Figure S2. Relative risks of dexamethasone vs. placebo according to time from first dose to birth and gestational age at first dose



Shown are the relative risks (RR) as a function of the time from first dose to birth in hours, for different gestational ages at first injection for the two neonatal primary outcomes. There is a significant trend for the relative risk to decrease with time from first dose to birth, suggesting that dexamethasone is more protective as time of fetal exposure increases. It appears that the effect of dexamethasone is more protective as the gestational age at first injection increases from 26 until 32 weeks. However, this trend is not sustained as gestational age at first injection increases above 32 weeks. There might be confounding of time from first dose to birth with gestational age at birth that might mask or modify the effect of the intervention.

Table S1. Characteristics of ACTION-I trial hospitals

SITE	BANGLADESH					
FACILITY	**Facility 1**	**Facility 2**	**Facility 3**	**Facility 4**	**Facility 5**	**Facility 6**
Hospital location	Peri-urban	Peri-urban	Peri-urban	Peri-urban	Urban	Urban
Hospital level	Secondary	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary
Number of births in 2016	1197	3000	5640	3624	3360	9180
Usual lower limit of gestational age for viability (i.e. active measures)	28 weeks 0 days	29 weeks 0 days	28 weeks 0 days	28 weeks 0 days	28 weeks 0 days	28 weeks 0 days
OBSTETRIC CARE						
All comprehensive obstetric care signal functions available	Yes	Yes	Yes	Yes	Yes	Yes
Number consultant obstetricians	9	7	14	24	7	12
Availability	Available during day time only	Available 24x7	Available during day time only	Available 24x7	Available 24x7	Available 24x7
What % of obstetricians are trained to perform ultrasound?	80%	100%	100%	80%	60%	5%
Number of beds:						
Admission area/s	55	46	100	180	47	42
Labor ward/s	5	2	4	30	27	42
Delivery ward/s	2	16	35	4	3	5
Postnatal ward/s	7	8	6	30	16	0
Maternal ICU	0	5	0	0	0	0

Maternal Special Care Unit	0	6	4	6	0	0
Post-operative ward/s	7	6	6	10	0	16
How soon after birth are women (without complications) routinely discharged?	24 hours	24 hours	8 hours	24 hours	24 hours	24 hours
NEONATAL CARE						
NICU available	No	Yes	Yes	Yes	Yes	No
If yes, how many beds:	-	20	50	6	12	-
Neonatal Special Care Unit available	No	No	Yes	Yes	No	No
If yes, how many beds:	-	-	85	4	0	-
Thermal control in newborn ward:						
N° of functioning incubators available:	1	10	5	3	3	4
N° of functioning radiant warmers available:	1	2	0	2	2	8
N° of functioning cradles available:	4	10	0	0	0	4
Shared use of the thermal control device	No	No	No	No	No	Yes
Antibiotics administration						
Intramuscular	No	No	No	Yes	Yes	Yes
Intravenous	Yes	Yes	Yes	Yes	Yes	Yes
Per oral	Yes	Yes	Yes	Yes	Yes	Yes

Exogenous surfactant	Not available	Always available when indicated	Not available	Always available when indicated	Not available	Not available
Respiratory support						
N° of functioning CPAP available:	1	3	4	3	3	0
N° of functioning Mechanical ventilators available:	0	2	0	6	2	0
Number Consultant Neonatologists	3	4	2	6	1	2
Availability	Available during day time only (after 8pm they are available over phone)	Available during day time only (after 8pm they are available over phone)	Available 24x7	Available 24x7	Available 24x7	Available during day time only (after 8pm they are available over phone)
Number Consultant Paediatricians	11		7	1	6	5 6
Availability	Available during day time only (after 8pm they are available over phone)		Available during day time only (after 8pm they are available over phone)	Available 24x7	Available 24x7	Available during day time only (after 8pm they are available over phone) Available 24x7
Diagnostic equipment						
X-ray	Routinely available		Routinely available	Routinely available	Routinely available	Routinely available Routinely available
Ultrasound for IVH	Not available		Routinely available	Routinely available	Routinely available	Routinely available Available upon request

SITE			INDIA	
FACILITY	**Facility 1**	**Facility 2**	**Facility 3**	**Facility 4**
Hospital location	Urban	Urban	Urban	Urban
Hospital level	Tertiary	Tertiary	Tertiary	Tertiary
Number of births in 2016	6,116	4,012	10,082	2,405
Usual lower limit of gestational age for viability (i.e. active measures)	28 weeks 0 days	28 weeks 0 days	28 Weeks 0 Days	27 weeks 0 days
OBSTETRIC CARE				
All comprehensive obstetric care signal functions available	Yes	Yes	Yes	Yes
Number consultant obstetricians	18	18	28	8
Availability	Available 24x7	Available 24x7	Available 24x7	All available during day time. One available 24x7, all can be called if needed
What % of obstetricians are trained to perform ultrasound?	80%	90%	100%	80%
Number of beds:				
Admission area/s	36	60	40	7
Labor ward/s	12	8	12	8
Delivery ward/s	8	6	13	10
Postnatal ward/s	76	20	100	0
Maternal ICU	3	3	5	0
Maternal Special Care Unit	14	1	20	0
Post-operative ward/s	6	15	10	10
How soon after birth are women (without complications) routinely discharged?	72 hours	48 hours	24-48 hours	72 hours
NEONATAL CARE				
NICU available	Yes	Yes	Yes	Yes
If yes, how many beds:	14	30	22	40

Neonatal Special Care Unit available	No	Yes	Yes	No
If yes, how many beds:		30	24	
Thermal control in newborn ward:				
N° of functioning incubators available:	0	30	0	3
N° of functioning radiant warmers available:	14	30	10	40
N° of functioning cradles available:	0	0	0	10
Shared use of the thermal control device	No	No	No	No
Antibiotics administration				
Intramuscular	Yes	Yes	Yes	Yes
Intravenous	Yes	Yes	Yes	Yes
per oral	Yes	Yes	Yes	Yes
Exogenous surfactant	Available if parents can afford	Always available when indicated	Always available when indicated	Always available when indicated
Respiratory support				
N° of functioning CPAP available:	2	2	2	2
N° of functioning Mechanical ventilators available:	0	4	0	12
Number Consultant Neonatologists	2	0	0	1
Availability	0	N/A	N/A	1
Number Consultant Paediatrician	2	12	8	10
Availability	Available during day time only	Available 24x7	Available during day time only	Available 24x7
Diagnostic equipment				
X-ray	Available upon request	Routinely available	Available upon request	Routinely available
Ultrasound for IVH	Available upon request	Routinely available	Available upon request	Routinely available

SITE	KENYA			
FACILITY	**Facility 1**	**Facility 2**	**Facility 3**	**Facility 4**
Hospital location	Urban	Urban	Urban	Urban
Hospital level	Tertiary	Secondary	Secondary	Secondary
Number of births in 2016	10094	10544	7941	10334
Usual lower limit of gestational age for viability (i.e. active measures)	28 weeks 0 days	30 weeks	28 weeks 0 days	28 weeks 0 days
OBSTETRIC CARE				
All comprehensive obstetric care signal functions available	Yes	Yes	Yes	Yes
Number consultant obstetricians	2	2	3	2
Availability	Available 24x7	Available 24x7	Available 24x7	Available 24x7
What % of obstetricians are trained to perform ultrasound?	100%	50%	0	0
Number of beds:				
Admission area/s	5	2	7	1
Labor ward/s	14	35	3	12
Delivery ward/s	0	3	3	6
Postnatal ward/s	60	20	16	18
Maternal ICU	0	0	0	0
Maternal Special Care Unit	0	0	0	6
Post-operative ward/s	0	10	16	24
How soon after birth are women (without complications) routinely discharged?	24 hours	24 hours	24 hours	24 hours
NEONATAL CARE				
NICU available	Yes	No	Yes	Yes
If yes, how many beds:	1	-	16	40

Neonatal Special Care Unit available	Yes	No	No	Yes
If yes, how many beds:	44 cots 10 incubators			12
Thermal control in newborn ward:				
N° of functioning incubators available:	10	6	6	14
N° of functioning radiant warmers available:	2	2	4	0
N° of functioning cradles available:	0	10	5	10
Shared use of the thermal control device	Yes	Yes	Yes	Yes
Antibiotics administration				
Intramuscular	No	No	No	No
Intravenous	Yes	Yes	Yes	Yes
Per oral	Yes	Yes	Yes	Yes
Exogenous surfactant	Not available	Not available	Not available	Not available
Respiratory support				
N° of functioning CPAP available:	0	0	0	0
N° of functioning Mechanical ventilators available:	1	0	0	0
Number Consultant Neonatologists	0	0	0	0
Availability	-	-	-	-
Number Consultant Paediatrician	2	2	2	2
Availability	Available 24x7	Available 24x7	Available 24x7	Available 24x7
Diagnostic equipment				
X-ray	Routinely available	Routinely available	Routinely available	Available upon request
Ultrasound for IVH	Routinely available	Not available	Routinely available	Available upon request

SITE	NIGERIA-IBADAN						
FACILITY	**Facility 1**	**Facility 2**	**Facility 3**	**Facility 4**	**Facility 5**	**Facility 6**	**Facility 7**
Hospital location	Urban	Urban	Urban	Urban	Urban	Peri-urban	Peri-urban
Hospital level	Secondary	Tertiary	Secondary	Secondary	Tertiary	Secondary	Secondary
Number of births in 2016	3000	3000	2750	2000	2580	3000	2653
Usual lower limit of gestational age for viability (i.e. active measures)	26 weeks 0 days	28 weeks 0 days	26 weeks 0 days	26 weeks 0 days	26 weeks 0 days	26 weeks 0 days	26 weeks 0 days
OBSTETRIC CARE							
All comprehensive obstetric care signal functions available	yes	yes	yes	yes	yes	yes	yes
Number consultant obstetricians	8	10	2	5	20	2	3
Availability	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7
What % of obstetricians are trained to perform ultrasound?	100%	0%	100	60%	25%	100%	67%
Number of beds:							
Admission area/s	36	30	10	0	44	35	0
Labor ward/s	17	15	4	8	5	3	8
Delivery ward/s	8	26	4	14	5	3	0
Postnatal ward/s	62	30	25	26	46	15	6
Maternal ICU	7	0	0	4	0	4	0

Maternal Special Care Unit	8	6	1	10	8	3	0
Post-operative ward/s	14	26	15	26	10	19	14
How soon after birth are women (without complications) routinely discharged?	24 hours	24 hours	8 hours	24 hours	2 days	24 hours	6 hours
NEONATAL CARE							
NICU available	Yes	Yes	Yes	No	Yes	No	No
If yes, how many beds:	6	12	6	-	12	-	-
Neonatal Special Care Unit available	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If yes, how many beds:	12	20	12	14	26	9	7
Thermal control in newborn ward:							
N° of functioning incubators available:	12	3	4	3	6	3	5
N° of functioning radiant warmers available:	3	3	3	4	3	2	3
N° of functioning cradles available:	10	1	15	14	16	4	4
Shared use of the thermal control device	No	No	No	Yes	Yes	Yes	No

Antibiotics administration							
Intramuscular	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intravenous	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Per oral	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Exogenous surfactant	Available for babies with severe illnesses	Not available	Not available	Not available	Not available	Not available	Not available
Respiratory support							
N° of functioning CPAP available:	3	3	2	2	3	1	2
N° of functioning Mechanical ventilators available:	0	0	0	0	0	0	0
Number Consultant Neonatologists	1	2	2	1	3	2	1
Availability	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7
Number Consultant Paediatricians	1	0	2	4	3	2	2
Availability	Available 24x7	-	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7
Diagnostic equipment							
X-ray	Routinely available	Routinely available	Routinely available	Routinely available	Not provided	Routinely available	Available upon request
Ultrasound for IVH	Routinely available	Routinely available	Routinely available	Routinely available	Not provided	Routinely available	Available upon request

SITE	NIGERIA- ILE IFE					
FACILITY	**Facility 1**	**Facility 2**	**Facility 3**	**Facility 4**	**Facility 5**	**Facility 6**
Hospital location	Urban	Peri-urban	Peri-urban	Urban	Urban	Urban
Hospital level	Tertiary	Tertiary	Secondary	Tertiary	Tertiary	Tertiary
Number of births in 2016	2256	1829	1590	2210	2056	1874
Usual lower limit of gestational age for viability (i.e. active measures)	27 weeks 0 days	26 weeks 0 days	27 weeks 0 days	26 weeks 0 days	26 weeks 0 days	24 weeks 0 days
OBSTETRIC CARE						
All comprehensive obstetric care signal functions available	yes	yes	yes	yes	yes	yes
Number consultant obstetricians	14	13	2	7	14	20
Availability	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7
What % of obstetricians are trained to perform ultrasound?	100%	65%	50%	80%	100%	50%
Number of beds:						
Admission area/s	1	4	3	4	16	18
Labor ward/s	10	14	6	5	10	12
Delivery ward/s	10	8	6	0	4	8
Postnatal ward/s	30	49	42	16	32	Included in admission area
Maternal ICU	4	7	0	2	4	Included in General ICU 6 beds

Maternal Special Care Unit	0	8	2	1	0	Included in admission area and labor ward
Post-operative ward/s	30	34	21	11	25	Included in admission area
How soon after birth are women (without complications) routinely discharged?	24-48 hours	36-48 hours	48 hours	24 hours	24 - 48 hours	24 - 48 hours
NEONATAL CARE						
NICU available	No	No	No	Yes	Yes	Yes
If yes, how many beds:	-	-	-	8	25	N/A
Neonatal Special Care Unit available	Yes	Yes	Yes	Yes	Yes	Yes
If yes, how many beds:	32	33 cots, 15 incubators	22	15	25	50
Thermal control in newborn ward:						
N° of functioning incubators available:	13	15	6	4	6	21
N° of functioning radiant warmers available:	3	2	3	5	6	10
N° of functioning cradles available:	18	33	none	4	30	50
Shared use of the thermal control device	yes	yes	yes	no	sometimes	no
Antibiotics administration						
Intramuscular	yes	yes	yes	no	yes	yes
Intravenous	yes	yes	yes	yes	yes	yes
Per oral	yes	yes	yes	yes	yes	yes

Exogenous surfactant	Not available	Not available (unless patient procures it)	Available for babies with severe illnesses	Not available	Not available	Always available when indicated
Respiratory support						
N° of functioning CPAP available:	1	1	3	2	1	15
N° of functioning Mechanical ventilators available:	0	1	0	0	1	6
Number Consultant Neonatologists	2	2	2	2	3	4
Availability	9	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7
Number Consultant Paediatricians	9	14	2	1	15	20
Availability	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7	Available 24x7
Diagnostic equipment						
X-ray	Routinely available	Available upon request	Routinely available	Routinely available	Routinely available	Routinely available
Ultrasound for IVH	Routinely available	Available upon request	Routinely available	Available upon request	Routinely available	Available upon request

SITE	PAKISTAN	
FACILITY	**Facility 1**	**Facility 2**
Hospital location	Urban	Urban
Hospital level	Tertiary	Tertiary
Number of births in 2016	16245	15000
usual lower limit of gestational age for viability (i.e. active measures)	26 weeks	28 weeks 0 days
OBSTETRIC CARE		
All comprehensive obstetric care signal functions available	yes	yes
Number consultant obstetricians	40	18
Availability	Available 24x7	Available 24x7
What % of obstetricians are trained to perform ultrasound?	15%	70%
Number of beds:		
Admission area/s	72	8
Labor ward/s	6	32
Delivery ward/s	0	32
Postnatal ward/s	62	80
Maternal ICU	0	4
Maternal Special Care Unit	2	4
Post-operative ward/s	62	80
How soon after birth are women (without complications) routinely discharged?	6 to 12 hours	12 to 24 hours
NEONATAL CARE		
NICU available	No	Yes
If yes, how many beds:	-	16

Neonatal Special Care Unit available	Yes	Yes
If yes, how many beds:	20	10
Thermal control in newborn ward:		
N° of functioning incubators available:	7	8
N° of functioning radiant warmers available:	8	10
N° of functioning cradles available:	8	30
Shared use of the thermal control device	Yes	Yes
Antibiotics administration		
Intramuscular	No	No
Intravenous	Yes	Yes
Per oral	Yes	Yes
Exogenous surfactant	Not available	Not available
Respiratory support		
N° of functioning CPAP available:	0	4
N° of functioning Mechanical ventilators available:	0	8
Number Consultant Neonatologists	no	7
Availability	On call rosters	Available 24x7
Number Consultant Paediatrician	8	9
Availability	Available 24x7	Available 24x7
Diagnostic equipment		
X-ray	Routinely available	Routinely available
Ultrasound for IVH	Not available	Not available

Table S2. Characteristics of women at trial entry

Characteristic	Dexamethasone (N=1429)	Placebo (N=1423)
Clinical assessment of imminent preterm birth at trial entry – no. (%)		
Spontaneously-initiated preterm birth	874 (61.2)	858 (60.3)
Preterm prelabor rupture of membranes	455 (31.8)	388 (27.3)
Spontaneous preterm labor	419 (29.3)	470 (33.0)
Provider-initiated preterm birth	555 (38.8)	565 (39.7)
Gestational age at trial entry – no. (%)		
26 weeks 0 days to 27 weeks 6 days	130 (9.1)	114 (8.0)
28 weeks 0 days to 31 weeks 6 days	654 (45.8)	679 (47.7)
32 weeks 0 days to 33 weeks 6 days	643 (45.0)	628 (44.1)
34 weeks 0 days to 36 weeks 0 days	2 (0.1)	2 (0.1)
Mean (± SD) gestational age at trial entry	30.8 (2.0)	30.7 (2.0)
Maternal age (yr) – mean (SD)	27.5 (5.8)	27.5 (5.9)
Missing – n (%)	1 (0.1)	0 (0.0)
Educational level completed – no. (%)		
No education	174 (12.2)	163 (11.5)
Primary education only	373 (26.1)	412 (29.0)
Secondary education only	549 (38.4)	501 (35.2)
Post-secondary/tertiary education	329 (23.0)	342 (24.0)
No answer	4 (0.3)	5 (0.4)
Marital status – no. (%)		
Married/Cohabiting	1380 (96.6)	1372 (96.4)
Single/Separated/Widowed/Divorced	49 (3.4)	51 (3.6)
Fetuses in the current pregnancy – no. (%)		
Single	1295 (90.6)	1290 (90.7)
Twin	125 (8.7)	129 (9.1)
Higher-order multiples	9 (0.6)	4 (0.3)
Parity – no. (%)		
0	529 (37.0)	549 (38.6)
1-2	646 (45.2)	630 (44.3)
3-4	217 (15.2)	195 (13.7)
5 or more	37 (2.6)	49 (3.4)
History of preterm birth – no. (%) *		
Yes	177 (12.4)	188 (13.2)
Unknown	28 (2.0)	21 (1.5)
Maternal weight (kg) – mean (SD)	65.4 (15.9)	64.2 (15.2)
Missing – n (%)	71 (5.0)	70 (4.9)

Maternal height (cm) – mean (SD)	156.0 (7.7)	155.7 (7.6)
Missing – n (%)	102 (7.1)	90 (6.3)
Maternal midarm circumference (cm) – mean (SD)	28.3 (4.9)	28.1 (4.9)
Missing – n (%)	53 (3.7)	61 (4.3)
Medical conditions currently present – no. (%) **		
Chronic hypertension	64 (4.5)	71 (5.0)
Diabetes mellitus (non-gestational)	13 (0.9)	14 (1.0)
HIV or AIDS	33 (2.3)	32 (2.2)
Tuberculosis	1 (0.1)	2 (0.1)
Pyelonephritis	5 (0.3)	13 (0.9)
Anaemia (hematocrit ≤26% or haemoglobin ≤9g/dL)	100 (7.0)	128 (9.0)
Malaria	48 (3.4)	55 (3.9)
Obstetric conditions currently present – no. (%) **		
Gestational diabetes	22 (1.5)	15 (1.1)
Preeclampsia or eclampsia	275 (19.2)	326 (22.9)
Gestational hypertension***	75 (5.2)	68 (4.8)
Known or suspected oligohydramnios	336 (23.5)	310 (21.8)
Known or suspected polyhydramnios	19 (1.3)	30 (2.1)
Known or suspected intrauterine growth restriction	94 (6.6)	95 (6.7)
Abruptio placentae	49 (3.4)	40 (2.8)
Placenta previa	115 (8.0)	110 (7.7)
Other obstetric hemorrhage	66 (4.6)	42 (3.0)
No obstetric condition	616 (43.1)	592 (41.6)
First date of last menstrual period known – no. (%)		
Certain	844 (59.1)	826 (58.0)
Uncertain	173 (12.1)	166 (11.7)
Unknown	412 (28.8)	431 (30.3)
Trimester of pregnancy when ultrasound for gestational age estimate was performed – no. (%)		
1st trimester (up to 13 weeks 6 days)	156 (10.9)	147 (10.3)
2nd trimester (14 weeks 0 days to 27 weeks 6 days)	344 (24.1)	329 (23.1)
3rd trimester (28 weeks 0 days and beyond)	929 (65.0)	947 (66.5)
Medication administered prior to randomization – no. (%)		
Tocolytic agent	251 (17.6)	267 (18.8)
Magnesium sulfate for neuroprotection	141 (9.9)	179 (12.6)

**This category was assessed only among women with a previous pregnancy; **Women may have had more than one condition; ***This category excludes preeclampsia and eclampsia*

Table S3. Primary outcomes with multiple imputation of missing values*

Outcome	Relative risk (95% CI)	P-value§
Neonatal death	0.84 (0.72-0.97)	0.02
Stillbirth or neonatal death	0.88 (0.78 – 1.00)	0.04
Possible maternal bacterial infection	0.76 (0.56 – 1.03)	<0.001

**20 imputations; § P-value for superiority for neonatal death and stillbirth or neonatal death, and P-value for non-inferiority for possible maternal bacterial infection; adjustments for multiplicity resulted in P=0.03 for neonatal death, P=0.04 for stillbirth or neonatal death, and P=0.002 for possible maternal bacterial infection.*

Table S4. Cause-specific neonatal mortality

Final cause of death	Dexamethasone (N=1417)	Placebo (N=1406)	Relative risk (95% CI)
Perinatal asphyxia – no. (%)	61 (4.3)	78 (5.5)	0.78 (0.56-1.07)
Respiratory distress syndrome – no. (%)	113 (8.0)	156 (11.1)	0.72 (0.57-0.90)
Neonatal sepsis – no. (%)	77 (5.4)	74 (5.3)	1.03 (0.76-1.41)
Other specific causes – no. (%)	18 (1.3)	12 (0.9)	1.49 (0.73-3.16)
Indeterminate – no. (%)	9 (0.6)	11 (0.8)	0.81 (0.33-1.96)

95% CIs are not adjusted for multiplicity and should not be used to infer definitive treatment effects

Table S5. Other secondary maternal and neonatal outcomes

Neonatal outcome	Dexamethasone		Placebo		Mean or Median Difference (95% CI)[§]
	N	Mean (± SD) or Median (IQR)	N	Mean (± SD) or Median (IQR)	
Mean birth weight* – g	1495	1819 (623)	1482	1805 (624)	14.47 (-30.36 to 59.29)
Mean head circumference* – cm	1388	30 (3)	1378	30 (3)	0.10 (-0.12 to 0.32)
Mean body length* – cm	1387	42 (5)	1379	42 (5)	0.07 (-0.29 to 0.42)
Median gestational age at birth* – weeks	1544	33 (31-34)	1526	33 (31-34)	0.00 (-0.19 to 0.20)
Median duration of oxygen therapy – hours	726	36 (18-96)	756	48 (12-93)	-12.00 (-15.59 to -8.42)
Median duration of CPAP ventilation – hours	265	48 (24-96)	337	48 (24-84)	0.00 (-8.38 to 8.38)
Median duration of use of mechanical ventilation – hours	83	18 (12-48)	103	18 (12-60)	0.00 (-6.84 to 6.84)
Median duration of parenteral therapeutic antibiotic use – hours	864	144 (63-168)	894	132 (48-168)	11.85 (2.17 to 21.53)
Median length of hospital stay after birth – days	1320	8 (3-17)	1301	8 (3-17)	0.17 (-0.58 to 0.92)
Median duration of admission to special care unit – hours	905	168 (72-168)	897	162 (60-168)	6.00 (-4.99 to 16.99)
Median time until breast milk feeding initiation – hours	1126	24 (2-60)	1049	24 (2-60)	-0.14 (-4.02 to 3.73)

Median time to full enteral feeding – hours	667	12 (6-72)	628	12 (6-84)	0.00 (-0.20 to 0.20)
Median number of newborn readmission	39	1 (1-1)	48	1 (1-1)	-
Median length of stay during newborn readmission – days	37	5 (3-7)	37	4 (3-6)	1.00 (-1.13 to 3.13)
Maternal outcome					
Median number of days of therapeutic antibiotic use – days	64	4 (1-6.5)	81	5 (2-7)	-1.40 (-2.92 to 0.13)
Median length of total maternal hospitalization for birth – days	1323	8 (4-20)	1322	8 (4-19)	0.30 (-0.54 to 1.15)
Median length of maternal re-admission – days	13	5 (3-11)	13	4 (1-9)	0.00 (-8.60 to 8.60)

**All babies were assessed, outcome not prespecified; §Adjusted for study site; Median number of doses of surfactant not presented because few participants received surfactant; 95% CIs are not adjusted for multiplicity and should not be used to infer definitive treatment effects*

Table S6. Adverse events

Adverse event	Dexamethasone	Placebo	Total
Maternal adverse event			
Antepartum haemorrhage	0	2	2
Dyspnea	0	1	1
Gastrointestinal upset	1	0	1
Hyperglycemia	0	1	1
Leucocytosis	0	1	1
Migraine (unspecified)	1	1	2
Postpartum haemorrhage	3	3	6
Pyrexia (unspecified)	0	1	1
Seizure	2	0	2
Total	**7**	**10**	**17**
Maternal serious adverse event			
Antepartum haemorrhage	1	2	3
Cerebrovascular accident	1	0	1
Dyspnea	0	1	1
Intrapartum hemorrhage	1	0	1
Maternal death*	5	4	9
Pleural effusion	0	1	1
Postpartum haemorrhage	4	4	8
Seizure	2	2	4
Uterine rupture	2	0	2
Wound hematoma	0	2	2
Total	**16**	**16**	**32**
Neonatal adverse event*			
Birth asphyxia	1	1	2
Neonatal death	4	1	5
Neonatal sepsis	0	1	1
Total	**5**	**3**	**8**

**Also captured as part of secondary outcome measures*

Summary of the procedures to determine the final cause of neonatal death

An exercise was undertaken to determine the final single cause of neonatal death in the trial. Neonatal death is reported in the perinatal cause of death (PCD)form for all deaths that occurred in the facility and in the verbal autopsy form for deaths that occur outside the study facilities. The WHO Newborn Health team reviewed all 609 neonatal deaths based on the forms completed at each site. Each neonatal death was assigned one underlying cause of death based on the following processes:

- All causes of death were classified into one of the following main causes of death: respiratory distress syndrome, neonatal sepsis, perinatal asphyxia, other specific cause or indeterminate.
- Verbal autopsies were reviewed where PCD form was not available and a cause of death was assigned.
- ICD principles were followed in assigning the cause of death.
- Where no valid cause of death was available in the PCD form, all available forms for the infant were reviewed to assign a valid cause of death.
- The site-specific list of cause of death was reviewed by the neonatal Principal Investigators at the respective sites and compared with the source documents. The changes suggested by the PIs were made.

The list of final cause of death was shared with the statistical analysis team to determine cause specific mortality by study groups.

Procedures relating to ultrasound assessments

All participating hospitals were provided with the following ultrasound equipment:

- 1 x Philips HD5 ultrasound system
- 3 x probes – transabdominal, transcranial and intravaginal
- 1 x Uninterruptible Power Supply (UPS) device

This equipment was expressly for the purposes of facilitating assessment and recruitment of women to the ACTION trials and assessment of intraventricular haemorrhage in neonates (hereafter referred to as the ACTION Trial ultrasound systems). It was intended to augment existing ultrasound systems at participating hospitals, and (to the extent possible) minimize ultrasound access issues for trial participants.

Obstetric ultrasound for gestational age assessment

There are several considerations for performance of dating ultrasounds in low resource settings:

- Accurate estimated gestational age (EGA)/expected delivery date (EDD) assignment is limited by multiple factors:
    - Late initiation of antenatal care;
    - Uncertain last menstrual period;
    - No prior ultrasound evaluation (estimated gestational age has been assigned by a referring care provider based on fundal height only);
    - Third trimester fetal biometric variance (+/- 21 days at >28 weeks estimated gestational age);
    - Prior scans performed by sonographers outside of the hospital with varying/unknown levels of experience or expertise; and
    - Use of biometric nomograms derived from a different (often higher resource) populations.

Furthermore, many tertiary-level maternity facilities in low-resource countries do not always have routine or 24/7 access to obstetric ultrasound services.

In order to optimize the assessment of gestational age in routine care settings, the following procedures were developed and applied:

- For women to be eligible for the trial, the gestational age must be based on the earliest available obstetric ultrasound of reasonable quality. In the event an ultrasound was available from earlier in the pregnancy, the obstetric physician determined whether this ultrasound was of acceptable quality. If it was not available (or no ultrasound assessment was available), a dating ultrasound was performed at the participating hospital.
- The study Manual of Operations provided a gestational age estimation algorithm that was adapted from American College of Obstetrics and Gynaecology (ACOG) Committee Opinion on Method for Estimating Due Date (October 2014).[3] These procedures were reviewed by two independent experts from the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) (Dr Lynn Coppola and Dr Sandhya Maranna).
- Individuals at participating hospitals who were involved in performing obstetric ultrasound (varied by site, but generally involved ultrasonographers, radiologists and/or obstetricians)

underwent a standardized training provided by an ISUOG expert trainer (LC or SM). This training included use of ISUOG teaching modules as well as hands-on practice. Completion of 3 to 5 obstetric ultrasounds of acceptable quality was required to demonstrate proficiency.

The following measures were implemented for quality assurance:

- During the trial, the nominated Lead for obstetric ultrasound assessment at each hospital or study site conducted periodic internal peer-review of ultrasound scans performed, as well as any refresher training on an as-needed basis.
- For those women where the ACTION Trial ultrasound system was used to identify the gestational age, scans were digitally saved (using anonymized participant ID numbers) and logged in a standard logbook. The Manual of Operations pre-specified that approximately 5% of saved scans would be randomly sampled for quality assurance purposes.
- A random sample of scans for 175 participants (6.1% of the 2852 women randomized) were selected, reviewed and scored by an ISUOG expert. The scoresheet was pre-designed to assess whether the scan had been performed correctly from a technical standpoint, and was based on criteria of Salomon et al [4]. Based on available images and scores, scans were rated by the ISUOG expert as "acceptable" or "not acceptable" to be utilized by the sites for accurate estimation of gestational age.
- This sample was not evenly distributed across countries, as some hospitals (particularly those in India and Bangladesh) had a high proportion of women who had a dating ultrasound from the first trimester of pregnancy.
- Images of sufficient quality were available for 156 participants cases (5.5% of 2852 randomized women). Of these, 145 were rated "acceptable" (93%) and 11 were not acceptable.

Neonatal transcranial ultrasound intraventricular haemorrhage assessment

- **Equipment/Machine:** Philips HD5 scanner with a sector probe (5-8 MHz)
- **Protocol for obtaining neonatal CUS**: Transcranial ultrasound was performed routinely for newborns delivered at < 34 weeks by a trained provider at 7 days postnatal age or discharge, whichever occurred first. For babies born at ≥ 34 weeks, transcranial ultrasound was performed only when specifically requested by a clinician.
- **Presence and grading of intraventricular hemorrhage (IVH)**: The presence of IVH and its grading was evaluated as below:

- Any echogenicity at the level of caudothalamic groove (extending anterior to Foramen of Munro) is suggestive of IVH
- IVH was graded according to the grading proposed by *Papile* given below
    - Grade 1 – Sub-ependymal haemorrhage without ventricular extension
    - Grade 2 – Intraventricular Haemorrhage without ventricular dilatation
    - Grade 3 – Intraventricular Haemorrhage with ventricular dilatation
    - Grade 4 – Intraventricular haemorrhage with associated parenchymal involvement

- **Data/record maintenance:** The CUS scans at each site were digitally saved using anonymized participant ID numbers and logged in a standard logbook at each site.
- **Training and quality assurance:** The following measures were implemented for quality assurance:
    - Standard operating procedures were developed describing the CUS technique including the views required and other technical requirements, interpretation and grading of IVH.
    - Prior to trial initiation, all site sonologists were trained on standard operating procedures and interpretation and reporting by an expert. Around 70 staff were trained across all sites (including neonatologists, radiologists and sonologists, though staff cadre varied by site). The training involved a presentation on the basics of ultrasonography, hardware, CUS techniques and interpretation. The trainees were then trained on neonates under the supervision of the expert.
    - A sample of all positive scans (grade 1-4; as reported by sites) and a 5% random sample of all negative scans (grade 0; as reported by sites) were reviewed and graded independently by an external expert, blinded to the grading reported by sites. Any discrepancies in grading between the site sonologists and the external expert were reviewed and resolved by mutual discussion between the two.
    - Images were available for 108 of 137 (79%) positive scans and for 58 of 65 (89%) randomly selected negative scans:
        - Severe (grade 3-4), n=15 available of total 17 (88%): 5 graded same, 1 "downgraded" by expert but site maintained as "severe"
        - Non-severe (grade 1-2), n=93 available of total 120 (78%): 3 "upgraded" by expert (3%)
        - No IVH (grade 0), n= 65 available of total 65 (89%): all graded same by expert

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