Antenatal dexamethasone for improving preterm newborn outcomes in low-resource countries: a cost-effectiveness analysis of the WHO ACTION-I trial

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Summary

Background After considerable debate, there is now unequivocal evidence that use of antenatal corticosteroids improves outcomes in preterm neonates when used in women at risk of early preterm birth in reasonably equipped hospitals in low-resource countries. We aimed to evaluate the cost-effectiveness of dexamethasone administration in the management of preterm birth in a cohort of pregnant women from five low-resource countries.

Methods We performed a cost-effectiveness analysis using data from 2828 women (and 3051 babies) who participated in the WHO ACTION-I trial, a multicentre, randomised, placebo-controlled trial that assessed the safety and efficacy of dexamethasone in pregnant women at risk of early preterm birth in 29 hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan. We used a decision tree model to assess the cost-effectiveness of dexamethasone treatment compared with no intervention from a health-care sector perspective. Outcome data were taken from the primary results of the trial and primary data on cost were collected in 28 hospitals. The primary cost-effectiveness outcome was cost per neonatal death or the cost per disability-adjusted life-years (DALYs) averted, or costs saved per 1000 woman–baby units if the intervention was found to be cost-saving.

Findings Administration of dexamethasone averted 38 neonatal deaths per 1000 woman–baby units and 1132 DALYs per 1000 woman–baby units. Compared with no intervention, use of antenatal corticosteroids was cost-saving in all five countries, ranging from a saving of US$1778 per 1000 woman–baby units (95% uncertainty interval [UI] –13 878 to 9483) in Nigeria, to $20 531 per 1000 woman–baby units (–46 387 to 4897) in Pakistan, to $36 870 per 1000 woman–baby units (–61 569 to –15 672) in Bangladesh, to $38 303 per 1000 woman–baby units (–64 183 to –10 753) in India, and to $53 681 per 1000 woman–baby units (–113 822 to 2394) in Kenya. Findings remained consistent following sensitivity analyses. In all five countries, dexamethasone was more effective and cost less compared with no treatment.

Interpretation Antenatal dexamethasone for early preterm birth was cost-saving when used in hospitals in low-resource countries. Decision makers in low-resource settings can be confident that use of antenatal dexamethasone for early preterm birth is cost-effective, and often cost-saving when used in reasonably equipped hospitals in low-resource countries.

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Introduction

In 2014, an estimated 14·8 million babies (11% of all livebirths) were born preterm.[1] Preterm birth is the leading cause of neonatal mortality, accounting for approximately 35% of all deaths in the first 28 days of life worldwide.[2] Antenatal corticosteroids administered to women at risk of imminent preterm birth can cross the placenta and accelerate fetal lung maturation. Trials have shown that use of this intervention before 34 weeks of gestation can significantly reduce neonatal mortality associated with preterm birth, respiratory distress syndrome, and intraventricular haemorrhage.[3]

Countries cannot add interventions to health benefits packages on the basis of efficacy evidence alone. Health budgets are finite, meaning that including or expanding access to antenatal corticosteroids in a country's health benefits package might require the exclusion of another health intervention. Therefore, policy makers can face difficult decisions over whether diverting scarce resources to improving availability and use of antenatal corticosteroids is likely to lead to better health outcomes in neonates than the status quo. Available evidence on the cost-effectiveness of antenatal corticosteroids for early preterm birth currently comes from high-income and

Research in context

Evidence before this study

The WHO ACTION-I trial, a multicentre, randomised, placebo-controlled trial in five low-resource countries, showed that antenatal corticosteroids were safe for use in women at risk of early preterm birth and reduced the risk of neonatal mortality when used in hospitals that could provide a reasonable level of maternal and preterm newborn care. To ensure that resources are appropriately allocated, decision makers in low-resource countries need additional data on economic evaluations of antenatal corticosteroid use. There are few previous economic evaluations of antenatal corticosteroids for preterm birth, particularly in low-resource settings. We searched MEDLINE and Embase on Dec 14, 2021, using search terms relating to preterm birth, antenatal corticosteroids, and cost-effectiveness, without language or date restrictions, to identify previous studies that analysed the costs and outcomes associated with use of antenatal corticosteroids compared with no use for early preterm birth. We found five previous studies from Brazil, the Netherlands, the UK, and the USA (two studies) that analysed the cost-effectiveness of antenatal corticosteroid use for early preterm birth in hospital settings. With the exception of one study, all remaining studies found that use of antenatal corticosteroids was more effective and cost less than did no use. The study in the Netherlands in 1992 found that use of antenatal corticosteroids was cost-effective, although not cost-saving. Only one of these studies was based on data from a randomised trial; the remainder used observational data or published effect estimates. Two additional studies assessed the costs and benefits of increasing nationwide coverage of antenatal corticosteroids for preterm birth by 20% in Ethiopia and to full coverage in South Africa. These studies used the Lives Saved Tool model and found that use of antenatal corticosteroids was highly cost-effective. We did not find any studies assessing the cost-effectiveness of antenatal corticosteroids for early preterm birth in low-income or lower-middle-income countries.

Added value of this study

The WHO ACTION-I trial conducted in Bangladesh, India, Kenya, Nigeria, and Pakistan showed that use of antenatal corticosteroids (ie, dexamethasone) for early preterm birth was safe and efficacious. This economic evaluation builds on the efficacy findings of the trial to establish evidence for the cost-effectiveness of antenatal corticosteroid use for reducing neonatal mortality in secondary and tertiary health facilities in these five countries. We found that use of antenatal corticosteroids in the management of early preterm birth in these countries was cost-saving and, therefore, has the potential to provide substantial economic and health benefits. This study addresses a considerable gap in the existing economic evidence base for antenatal corticosteroid use in low-income settings, where scale up of effective interventions for preterm birth is urgently needed. We also developed a calculator to estimate cost-effectiveness in other low-income and middle-income countries. This evidence on cost-effectiveness and affordability can support efforts to scale up use of antenatal corticosteroids more widely in similar settings.

Implications of all the available evidence

Antenatal dexamethasone for women at risk of early preterm birth in reasonably equipped hospitals in low-resource countries could improve outcomes in preterm neonates and is estimated to be cost-saving, compared with no intervention. Direct costs of the intervention were relatively small, and were offset by costs averted from the reduced need for interventions to address complications in preterm neonates. This study shows how findings from previous studies suggesting that use of antenatal corticosteroids is cost-effective in high-resource settings also applies in low-resource settings, where the mortality and morbidity burden of preterm birth is greatest. Scale up of antenatal corticosteroid use in Bangladesh, India, Kenya, Nigeria, and Pakistan is likely to reduce costs.

upper-middle-income countries.[4–8] However, economic evidence from high-resource settings cannot be assumed to apply to low-resource settings with different staffing, equipment, and drug costs, as well as dissimilar health systems and hospital financial arrangements.[5] Thus, direct evidence is needed on the affordability and cost-effectiveness of antenatal corticosteroids to guide policy decision making for maternal and newborn health in low-resource countries.

The WHO ACTION-I trial[9] was a multicentre, randomised, placebo-controlled trial conducted in Bangladesh, India, Kenya, Nigeria, and Pakistan, which investigated use of antenatal corticosteroids in women at risk of preterm birth from 26 to 34 weeks of gestation. The trial was conducted to address the knowledge gap regarding the efficacy of antenatal corticosteroid use (in

this case, dexamethasone) in hospitals with at least a minimal set of resources in low-resource countries. The findings of the study showed that, compared with matching placebo, a regimen of intramuscular dexamethasone reduced neonatal mortality associated with preterm birth, with no evidence of increased harm to maternal or newborn health. In light of these results, we conducted an economic evaluation to inform decision making on adopting antenatal corticosteroids into health benefits packages in low-resource countries. We aimed to evaluate the cost-effectiveness of antenatal dexamethasone in the five low-resource countries that participated in the WHO ACTION-I trial. Additionally, we aimed to develop a tool to estimate the cost-effectiveness of antenatal dexamethasone in other low-income and middle-income countries (LMICs).

Methods

Study design

This cost-effectiveness study was based on the WHO ACTION-I trial, a multicountry, parallel-group, double-blind, individually randomised, placebo-controlled trial that randomly assigned between Dec 24, 2017, and Nov 21, 2019.[9] Women and neonates were recruited from 29 secondary-level and tertiary-level hospitals: six in Bangladesh, four in India, four in Kenya, 13 in Nigeria, and two in Pakistan.[10] Hospitals were eligible to participate if they could reasonably meet the WHO criteria for antenatal dexamethasone administration.[9] The full protocol has been published with main findings separately.[9,10] Briefly, pregnant women at risk of imminent preterm birth with confirmed live fetuses from 26 weeks and 0 days (26^{+0} weeks) of gestation to 33^{+6} weeks of gestation were eligible. Women allocated to the intervention group were offered a regimen of 6 mg intramuscular dexamethasone every 12 h, to a maximum of four 6 mg doses, or until hospital discharge or birth. Women were also eligible for a repeat course if they had not given birth after 7 completed days and were still at risk of preterm birth before 34 weeks of gestation (the allocation for the repeat course was identical to the first course). The control group in this study was the same regimen of a matching placebo (ie, no dexamethasone). The WHO ACTION-I trial protocol[9] was approved by the WHO Ethics Review Committee and by the relevant ethics committees and regulatory agencies in each country.

For this economic evaluation, the study population and settings were the same as those used in the WHO ACTION-I trial, using the 2828 women and 3051 newborn babies for whom data on the primary outcome were available. The trial database was used for data on participant characteristics and efficacy estimates for process of care and health outcomes. A cost-effectiveness study protocol was approved by the Alfred Hospital Ethics Committee (Burnet Institute, Melbourne, VIC, Australia; protocol identification number 787/20) on Feb 2, 2021, and by relevant ethics committees between March 4 and July 7, 2021, in participating countries. Principal investigators obtained formal agreement to collect data for the study from hospitals before participation. Hospital staff who were interviewed completed a written informed consent form.

Outcomes

The primary outcomes of the WHO ACTION-I trial were neonatal death; any baby death (ie, stillbirth or neonatal death); and possible maternal bacterial infection, a composite outcome defined as maternal fever (≥38°C) or clinically suspected or confirmed infection for which therapeutic antibiotics were used. The trial also reported various secondary maternal, newborn, and process-of-care outcomes. The trial showed a significant reduction in neonatal death (relative risk 0·84 [95% CI 0·72–0·97])

and any baby death (0·88 [0·78–0·99]) in the intervention group, and no difference between the two groups in possible maternal bacterial infection.

Hence, cost per neonatal death averted was the primary cost-effectiveness outcome in this study. If the intervention was found to be cost-saving (ie, the intervention was dominant), then the costs saved per 1000 woman–baby units would be reported. Neonatal deaths were also converted into disability-adjusted life-years (DALYs) by multiplying the number of neonatal deaths by years of life lost, using a life expectancy of 72·6 years (based on Bangladesh, which has the highest life expectancy among countries in this study)[11] and an annual discount rate of 3·0%,[12] to estimate the cost per DALY. The same life expectancy was assumed for each country to avoid implicitly valuing lives differently across settings. DALYs are a measure of life lost due to premature mortality and time lived in states of less than full health, and represent the loss of an equivalent 1 year in full health. Life expectancy and discount rates were varied in sensitivity analyses.

***Panel*: Events in the cost-effectiveness model of antenatal dexamethasone for early preterm birth in Bangladesh, India, Kenya, Nigeria, and Pakistan**

Intervention
- Administration of intramuscular dexamethasone in women at risk of imminent preterm birth

Cointerventions for management of preterm birth
- Obstetric ultrasonography for estimating gestational age
- Use of tocolysis for women in spontaneous preterm labour
- Use of magnesium sulphate for fetal neuroprotection

Neonatal morbidity outcomes
- Major neonatal resuscitation at birth
- Neonatal hypoglycaemia
- Oxygen therapy for neonates with severe respiratory distress
- Use of continuous positive airway pressure
- Use of mechanical ventilation
- Use of surfactant treatment
- Neonatal sepsis
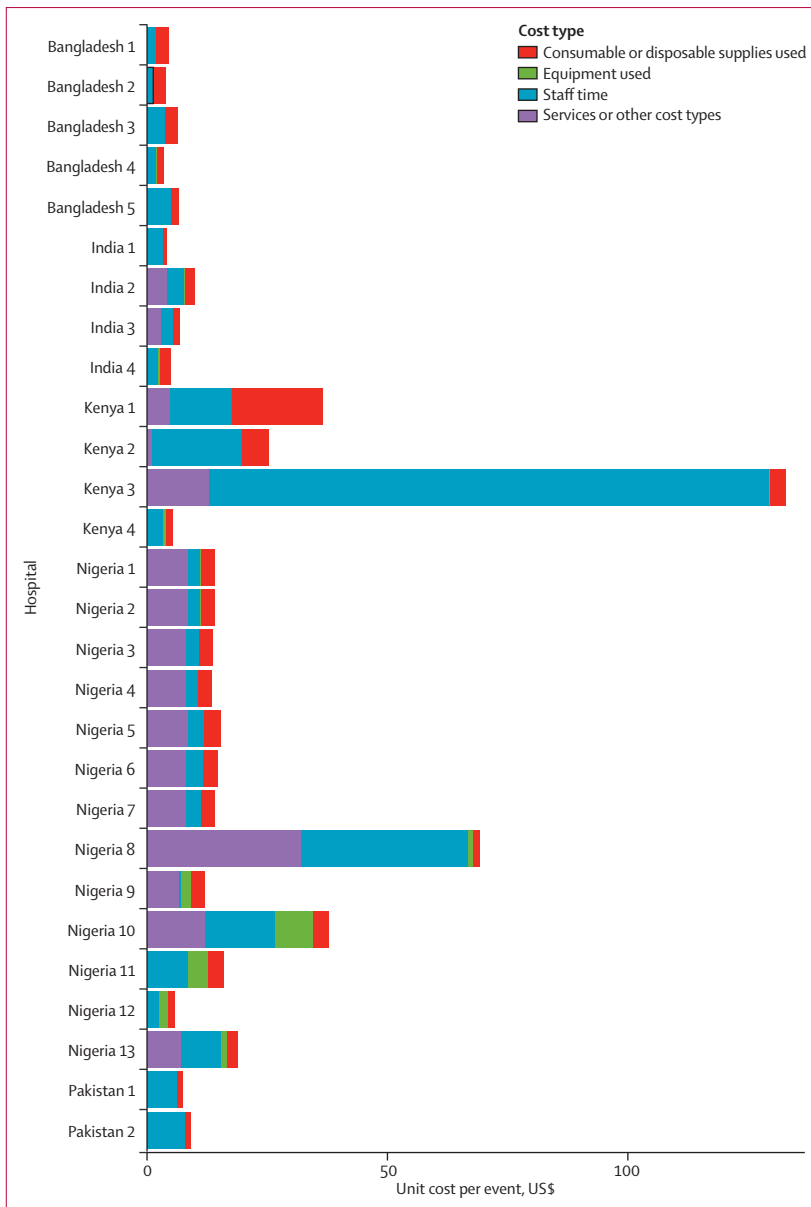- Severe intraventricular haemorrhage

Maternal morbidity outcomes
- Maternal fever
- Chorioamnionitis
- Post-partum endometritis
- Wound infection

Mortality outcomes
- Maternal death
- Stillbirth
- Neonatal death

Comprehensive definitions for these 19 events are provided in appendix 1 (pp 5–7).

See **Online** for appendix 1

***Figure 1:* Costs of administering one course of antenatal intramuscular dexamethasone for women at risk of early preterm birth in five countries, by hospital**
One course involved a maximum of four doses of 6 mg intramuscular dexamethasone every 12 h. Data are provided for 28 hospitals: five in Bangladesh, four in India, four in Kenya, 13 in Nigeria, and two in Pakistan. For each hospital, total cost included consumables, human resources, use of equipment, and investigations.

Cost inputs

Cost inputs were those incurred during hospital admission from randomisation until 28 days postnatal (ie, the trial's period of interest for ascertainment of the primary outcome). An ingredients-based approach was used to estimate costs for 19 predefined events corresponding to the intervention, key cointerventions, and health-care activities associated with outcomes in the WHO ACTION-I trial (panel). This approach allowed the estimated cost of care to be compared between the intervention group and the control group in each of the five countries. Costs for each event were collected between May 17 and Oct 21, 2021, from 28 (97%) of 29 hospitals (one hospital in Bangladesh was unable to participate due to staffing changes). Consistent with a health-care sector perspective, all costs of care were collected whether paid for by the care recipient, government, private companies, or donors. Costs were collected using prices during 2020–21 in local currency and converted to 2021 US\$, and no discounting or inflation were applied as they only pertain to 1 year. Further detail on the costing approach is provided in appendix 1 (p 4).

Statistical analysis

We compared costs and health outcomes for all women and neonates in both the intervention group and the control group. However, because 267 (9·4%) of 2852 women in the trial had a multiple birth, and the intervention was targeted to women while the benefits were incurred by neonates, cost-effectiveness outcomes related to average outcomes per woman–baby unit, which incorporated adjustment for incidence of multiple births (appendix 1 p 9). In other words, 1000 woman–baby units represented 1000 women in both groups and 1082 babies in the intervention group or 1076 babies in the control group.

Data on effectiveness and cost were used as inputs for a decision tree model (implemented in R statistical software) to evaluate cost-effectiveness. For each country, the total cost per randomised woman–baby unit was calculated for both the intervention group and the control group by multiplying the proportion of women and babies experiencing each event (based on point estimates from the primary findings of the WHO ACTION-I trial) by the country-specific cost of each event (average cost across all facilities that provided cost data for a given country). For every woman–baby unit in the intervention group, the costs associated with dexamethasone administration were included, adjusted to reflect the total number of doses (up to four per course) and courses (up to two) received by each woman in the trial. Facility costs per event were estimated using the day costs of beds and data on both length of inpatient stay for women and babies, and length of neonatal intensive care unit stay recorded in the trial (appendix 1 pp 4, 7, 8). Costs of oxygen therapy and continuous positive airway pressure (CPAP) were adjusted for length of therapy recorded in the trial (appendix 1 pp 7, 11). Therefore, the difference in costs between the intervention group and the control group was a consequence of the different proportions of women and babies experiencing the event in both groups (figure 1).

The point estimate cost per neonatal death averted was calculated by dividing the difference in total costs per 1000 woman–baby units in each country by the difference in the number of neonatal deaths per

1000 woman–baby units between the intervention group and the control group in the overall trial outcomes. The point estimate cost per DALY averted was calculated similarly.

A probabilistic multivariate uncertainty analysis was used to generate 95% uncertainty intervals [UIs] for outcomes in each country, combining uncertainty in both effectiveness and cost estimates. Sensitivity analyses were used to test the effect of all model parameters on outcomes as they varied across their maximum ranges from collected data or literature, including: if the relative difference in the proportion of women and babies experiencing each event was at the lower or upper bound reported in the trial rather than the point estimate; if the costs of all events in each country was the minimum or maximum estimated from facilities in the country; if the life expectancy for DALY calculations was the lowest current estimate across all five countries (55 years in Nigeria[11]); and discount rates of 1% or 5%. We also explored the difference in costs between private and public hospitals for those countries where two or more public and private hospitals participated (ie, Bangladesh and Nigeria). We explored the effects on cost-effectiveness if gestational age was unknown for a proportion of women (50% and 100%) and who would, therefore, require ultrasonography for estimating gestational age on admission, which would impose additional intervention-related costs. We also assessed the effect of varying the proportion of using two cointerventions (tocolysis for delaying the time of birth and magnesium sulphate for fetal neuroprotection) in the intervention group. All statistical analysis was done in R (version 3.6.3).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
The WHO ACTION-I trial randomly assigned 1429 women and 1544 babies to the intervention group and 1423 women and 1526 babies to the control group. The WHO ACTION-I trial reported 196 neonatal deaths per 1000 woman–baby units in the intervention group and 234 per 1000 woman–baby units in the control group (table); therefore, administration of dexamethasone averted 38 neonatal deaths, reducing neonatal mortality by 16% (95% CI 3–28; p=0·03). Dexamethasone averted 1132 DALYs per 1000 woman–baby units in all five countries (table). We also assessed the effect of varying the proportion of using two cointerventions (tocolysis for delaying the time of birth and magnesium sulphate for fetal neuroprotection) in the intervention group, which were assumed to be equal across groups for the main analysis because they did not differ significantly in the WHO ACTION-I trial.

The cost-effectiveness dataset of 28 hospitals comprised 11819 items for the 19 events. We observed variability between facilities in the total costs of each event both across and within countries. For example, the total cost of administering one course (four doses) of intramuscular dexamethasone varied from US$5·48 in Bangladesh to $53·05 in Kenya (figure 2). Analysis of cost data ingredients and follow-up discussions with hospital staff indicated that variation in costs between facilities reflected actual differences in standard practice and cost

	Bangladesh	India	Kenya	Nigeria	Pakistan
Total cost per 1000 woman–baby units, US$					
No dexamethasone use	370 485 (369 157 to 402 129)	412 514 (388 120 to 426 518)	972 001 (937 166 to 1 022 597)	220 181 (215 244 to 231 130)	340 423 (323 137 to 358 178)
Dexamethasone use	333 615 (331 140 to 362 589)	374 211 (352 533 to 386 321)	918 320 (881 224 to 963 116)	218 403 (213 060 to 229 182)	319 892 (302 397 to 337 004)
Additional cost	–36 870 (–61 569 to –15 672)	–38 303 (–64 183 to –10 753)	–53 681 (–113 822 to 2394)	–1778 (–13 878 to 9483)	–20 531 (–46 387 to 4897)
Total number of neonatal deaths per 1000 woman–baby units					
No dexamethasone use	234 (210 to 256)	234 (212 to 257)	234 (213 to 257)	234 (212 to 254)	234 (212 to 256)
Dexamethasone use	196 (175 to 219)	196 (177 to 217)	196 (175 to 218)	196 (177 to 217)	196 (176 to 218)
Number of deaths averted	38 (7 to 65)	38 (10 to 68)	38 (7 to 68)	38 (8 to 68)	38 (10 to 69)
Total number of DALYs per 1000 woman–baby units					
No dexamethasone use	6968 (6253 to 7621)	6968 (6316 to 7642)	6968 (6336 to 7642)	6968 (6316 to 7558)	6968 (6316 to 7621)
Dexamethasone use	5836 (5206 to 6508)	5836 (5248 to 6445)	5836 (5206 to 6487)	5836 (5248 to 6445)	5836 (5227 to 6466)
Number of DALYs averted	1132 (207 to 1932)	1132 (312 to 2017)	1132 (208 to 2036)	1132 (247 to 2036)	1132 (290 to 2057)
Cost-effectiveness, US$					
Additional cost per neonatal death averted	–968 (–5123 to –310)	–1006 (–3500 to –206)	–1409 (–7471 to 246)	–47 (–623 to 390)	–539 (–2217 to 144)
Additional cost per DALY averted	–33 (–172 to –10)	–34 (–118 to –7)	–47 (–251 to 8)	–2 (–21 to 13)	–18 (–75 to 5)

Data are point estimate (95% UI). Consistent point estimates for neonatal deaths and DALYs per 1000 woman–baby units reflect that the effectiveness estimates were based on point estimates from overall primary findings of the WHO ACTION-I trial, while variability in the 95% UI between countries reflects the probabilistic multivariate uncertainty analysis in this study. DALY=disability-adjusted life-year. UI=uncertainty interval.

Table: Total cost of antenatal dexamethasone administration per woman–baby unit, number of neonatal deaths, and DALYs per 1000 woman–baby units in five countries
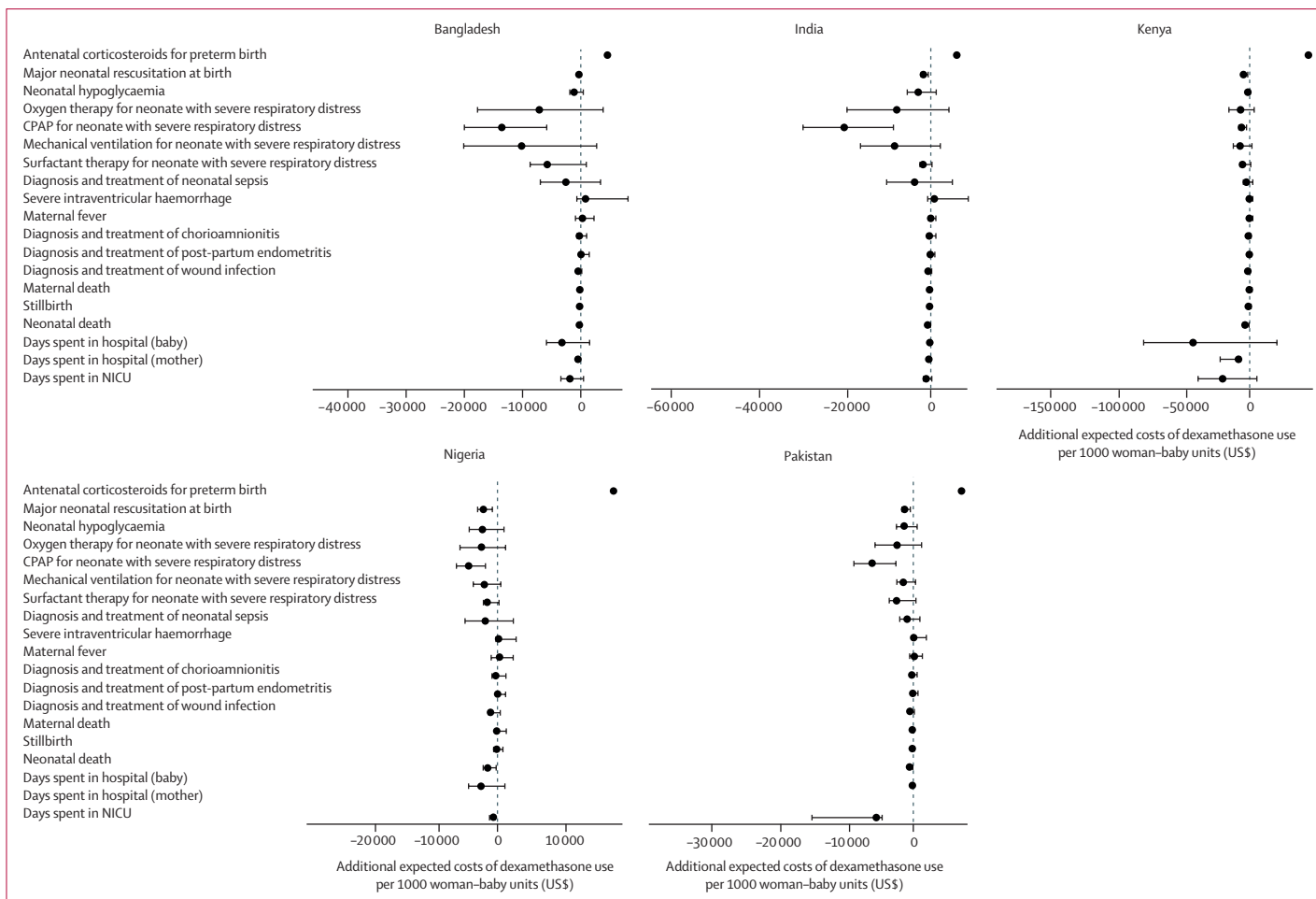
***Figure 2*: Additional expected costs of antenatal intramuscular dexamethasone use for women at risk of early preterm birth, per 1000 woman–baby units**
Point estimates of the difference in costs are provided for each event, based on differential requirements between the intervention group and the control group. Error bars represent the uncertainty arising from each event's risk ratio 95% CI. CPAP=continuous positive airway pressure. NICU=neonatal intensive care unit.

inputs, including the investigations conducted alongside administration of dexamethasone, the staff time required to administer dexamethasone and provide associated clinical care, and salary levels at different facilities. The costs of other events were similarly observed to vary both within and between countries (appendix 1 p 9).

The difference in costs between the intervention group and the control group was predominantly driven by the additional costs of dexamethasone administration and the reduced use of CPAP, oxygen therapy, mechanical ventilation for neonates, and days in hospital (figure 2); however, there were variations between countries in the unit costs of each event.

The administration of dexamethasone reduced costs (or was cost-saving) in all five countries (figure 3), ranging from a cost difference of US$–53 681 (95% UI –113 822 to 2394) per 1000 woman–baby units in Kenya to $–1778 (–13 878 to 9483) per 1000 woman–baby units in Nigeria (table). In the probabilistic uncertainty analysis, the intervention was cost-saving for 100·0% of

simulations in Bangladesh, 99·5% in India, 96·8% in Kenya, 64·3% in Nigeria, and 94·2% in Pakistan (appendix 1 p 12). Across all five countries, the highest upper bound of the 95% UI for cost per DALY averted was $13 in Nigeria (table).

The parameters with the greatest effect on the cost per neonatal death averted are shown in a tornado plot (figure 4; appendix 1 pp 15–16). With the exception of Nigeria, all simulations remained cost-saving in all sensitivity analyses. The biggest driver of cost-effectiveness (measured by cost per neonatal death averted) for most countries was the intervention's effect on use of neonatal interventions, such as oxygen therapy and CPAP. The cost sampling method had a larger effect on cost-effectiveness in countries with more variation in the cost data; for example, in Nigeria, outcomes ranged from a cost saving of $195 per death averted when minimum event costs were used to $448 per death averted when maximum event costs were used. The model was also run for private and public facilities
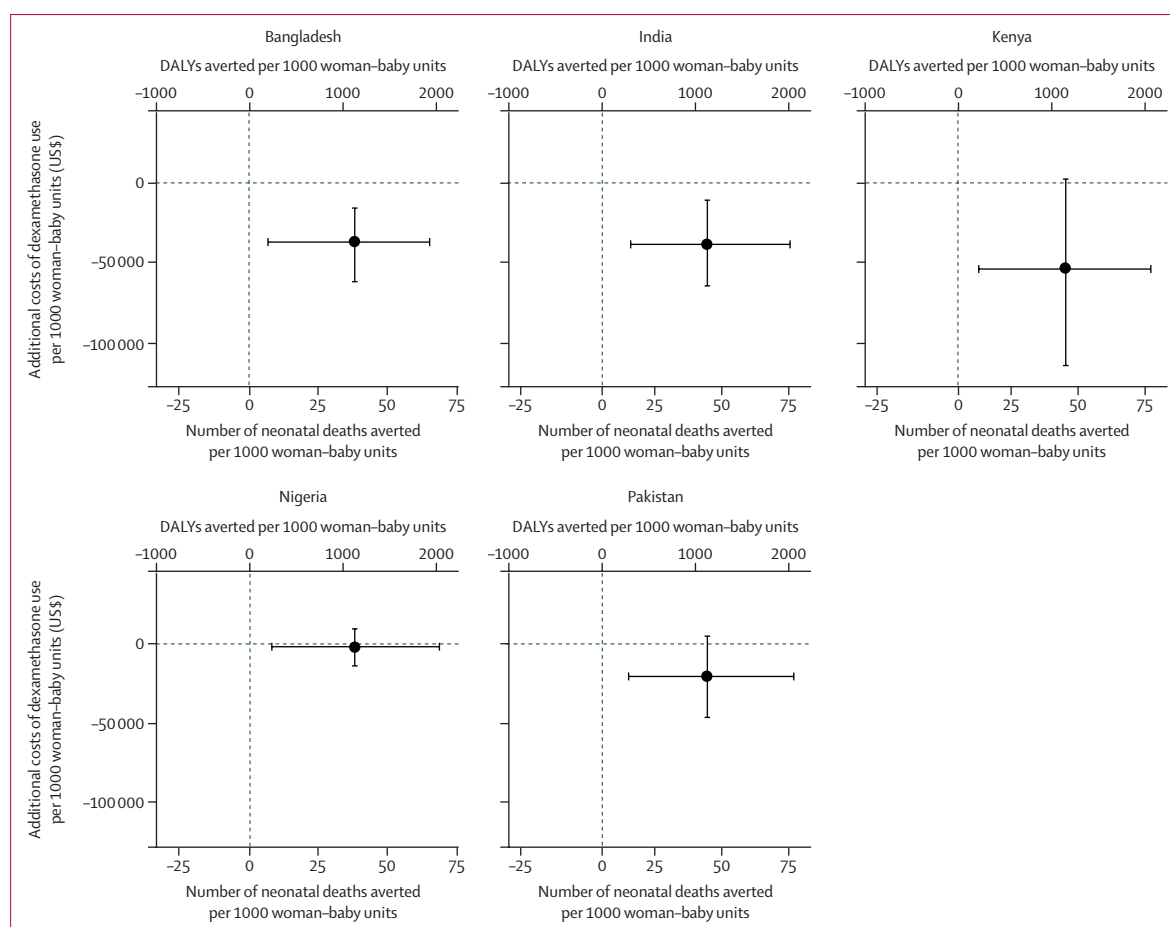
Figure 3: Cost-effectiveness plane of antenatal intramuscular dexamethasone for women at risk of early preterm birth compared with no intervention in five countries

The central point represents the median; error bars for each country represent 95% UIs from the multivariate probabilistic uncertainty analysis. The intervention averted 1132 DALYs per 1000 woman–baby units using a discount rate of 3·0% and life expectancy of 72·6 years. Consistent point estimates for neonatal deaths averted per 1000 woman–baby units reflect that the effectiveness estimates were based on point estimates from overall primary findings in the WHO ACTION-I trial, while variability in the 95% UIs between countries reflects the probabilistic multivariate uncertainty analysis in this study. DALY=disability-adjusted life-year. UI=uncertainty interval.

separately in Bangladesh and Nigeria. In Nigeria, public facilities averted more costs with dexamethasone administration, whereas private facilities averted more costs in Bangladesh (appendix 1 p 17). When lowering life expectancy and varying discounting rate assumptions in the DALY calculations, the intervention remained cost-saving (appendix 1 pp 17–18).

Discussion

This multicountry economic evaluation found that, compared with no intervention, a regimen of intramuscular dexamethasone administered to women in hospital at risk of early preterm birth was either cost-saving or cost-neutral in five low-resource countries, while averting neonatal death and reducing DALYs arising from early preterm birth. Direct intervention costs were relatively small and likely to be offset by the reduced need for more costly newborn interventions, such as oxygen therapy, CPAP, and hospital admission.

Findings from the sensitivity analyses were robust and the largest source of uncertainty was the estimated effect of dexamethasone on the use of neonatal interventions. Additional costs were incurred when women required ultrasonography for estimating gestational age before dexamethasone administration; however, the sensitivity analysis indicated that dexamethasone was either cost-saving (in Bangladesh, India, Kenya, and Pakistan) or highly cost-effective (in Nigeria), even when 100% of women require ultrasonography before administration. Given that dexamethasone was found to be cost-saving, it would probably be affordable to include in health benefit packages, although the extent of savings might vary.

Furthermore, we developed a calculator tool to estimate the cost-effectiveness of antenatal dexamethasone in other LMICs, where users could modify inputs for key model parameters to reflect their country or health-care setting (appendix 2 pp 1–3). In this tool, commodities and human resources commonly required to administer

See **Online** for appendix 2
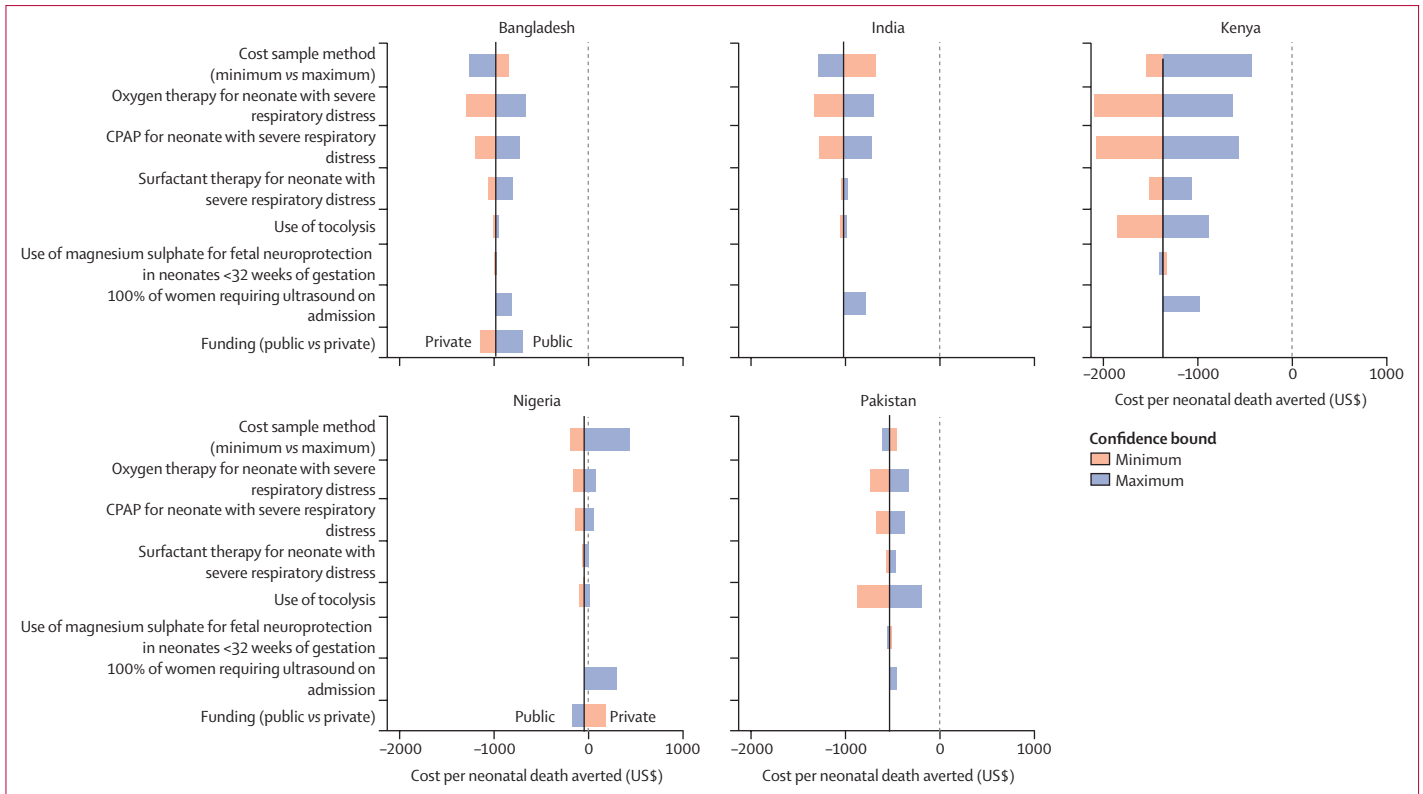
Figure 4: Effects of varying individual key parameters on the cost per neonatal death averted of antenatal dexamethasone use for early preterm birth in five countries
The sensitivity analysis showed that seven parameters had the largest effect on the incremental cost-effectiveness ratio (excluding the denominator variable) when varied within the upper and lower bounds shown. The centreline represents the point estimate for cost per neonatal death averted for each country, with bars showing the cost per neonatal death averted if the costs in each country were the minimum (orange) or maximum (blue) estimated from facilities in that country; if the probabilities of events occurring were set at the lower (orange) and upper (blue) bounds of parameters from the WHO ACTION-I trial; if the use of cointerventions (eg, magnesium sulphate for fetal neuroprotection or tocolysis) increased in the intervention group by 10% (blue) or reduced by 10% (orange); if all women required ultrasonography for gestational age dating on admission in the intervention group (and none in the control group; blue); and if only the costs of public (blue) or private (orange) facilities were reflected. CPAP=continuous positive airway pressure.

dexamethasone could be varied to test different scenarios.

Six previous studies analysed the cost-effectiveness of antenatal corticosteroid use in early preterm birth; four from high-income countries (the Netherlands, the UK, and the USA) and one from an upper-middle-income country (Brazil).[4–8,13] A modelling study in the Netherlands in 1992 used published cost and efficacy estimates and found that use of antenatal corticosteroids was cost-effective for neonatal survival.[7] The other four studies found that antenatal corticosteroids for early preterm birth was dominant (ie, cost-saving) compared with no intervention due to the reduced need for neonatal interventions, which is consistent with this current study. Only one of these studies, from the USA in 1986, was based on a randomised trial and found that use of antenatal corticosteroids reduced the incidence of respiratory distress syndrome in neonates and hospital costs compared with no use.[6] Two studies in the UK and the USA were based on cohort data or published effectiveness estimates, and also reported that use of antenatal corticosteroids was cost-saving.[5,8] More recently, a study in Brazil in 2016 assessed use of antenatal

corticosteroids compared with no treatment to establish the effect on costs and neonatal morbidity (neonatal mortality was excluded).[4] Data were obtained from a retrospective cohort study of premature infants at one hospital, and authors reported that use of antenatal corticosteroids significantly reduced several outcomes related to neonatal morbidity and hospitalisation costs, and was cost-saving. The magnitude of cost savings in this current study were smaller than in some previous studies (eg, US$2–54 per woman–baby unit *vs* $3172 per patient in 1995[5] and $3413 per patient in 2013[4]), possibly reflecting lower costs of health care compared with higher-income settings.

Strengths of this study included the use of a standardised data collector training package and in-person hospital visits to collect cost data directly from hospital staff and financial documentation. Study findings were robust under sensitivity analyses, in which varying cost parameters across a plausible range of values indicated that the intervention remained cost-saving.

A limitation of this study is that data on cost were collected during 2021, even though women were recruited onto the trial between December, 2017, and

November, 2019. It is possible that prices in 2021 were different to those during the trial period; however, we consider the effects of these differences to be small. Additionally, prices in 2021 might have been affected by the COVID-19 pandemic, given that the costs of equipment, medicines, and supplies (eg, oxygen) might have risen with the increased number of hospital admissions overall. However, feedback from some participating hospitals indicated that COVID-19 caused scarcity of oxygen and ventilators, rather than an increase in prices. In some hospitals in India and Bangladesh, we obtained prices that reflected costs before the pandemic to reduce the likelihood that oxygen costs were overstated in the analysis. Although the time window for costs was up to 28 days postnatal, trial data on use of neonatal interventions was focused on the first week of life. We also sought to obtain cost data for all prespecified events; however, in some instances, patient charges set by the hospital were used as a proxy, which might differ from actual costs of providing care. For example, in several hospitals, the costs of stays in neonatal intensive care units were subsidised by government; thus, collected cost data might understate full costs in both groups. We partially mitigated these differences by use of a multinational cost dataset, and by exploring different cost sampling methods and effect estimates in the sensitivity analysis. Due to practical constraints, we did not differentiate between costs incurred by women and families, and those paid for by governments or other providers.

Decisions to increase use of antenatal corticosteroids within national health benefits packages will be informed by its cost-effectiveness and affordability relative to other health-care interventions. Given the country-specific estimates of cost per DALY averted thresholds that reflect health opportunity costs and the relatively small intervention costs needed, the extra cost required for use of antenatal corticosteroids in each country should fall well within the opportunity costs of existing health packages.[14] Considering the totality of efficacy and economic evidence, it is evident that accelerated efforts to scale up safe and appropriate use of antenatal corticosteroids in many LMICs are warranted, and are likely to be highly cost-effective. For example, a 2019 study used the Lives Saved Tool model and published data to estimate the cost of scaling up 13 maternal and newborn health interventions in Ethiopia, including betamethasone for women in preterm labour.[15] A 20% nationwide increase in antenatal corticosteroid coverage was estimated to cost US$0·8 million and was highly cost-effective, at $98·0 per DALY averted. A similar study in South Africa found that scaling up antenatal corticosteroid coverage from baseline 20% to full coverage would cost $4·5 million, at $37 per neonatal life saved.[16] To support scale-up programmes, we developed a calculator tool in which users can input local cost and resourcing data to estimate cost-effectiveness for their setting, or identify

possible scenarios that would result in antenatal corticosteroids no longer being cost-saving (appendix 2 pp 1–3).

It should be noted that the WHO ACTION-I trial was conducted in secondary and tertiary hospitals, in which participants had access to the obstetric and preterm newborn care interventions that WHO has recommended as preconditions to safe use of antenatal corticosteroids.[9] However, WHO has acknowledged that these interventions might not be consistently available across low-resource settings.[17] It is not possible to reliably estimate what proportion of women at risk of preterm birth in these five countries would have access to these interventions outside of the strict conditions in a placebo-controlled trial. Furthermore, acknowledging that the cost-effectiveness of antenatal corticosteroids was driven by reduced use of newborn respiratory interventions, it is not yet clear whether these findings on cost-effectiveness can be generalised to lower-level facilities, where these interventions are less frequent or unavailable. Upfront and ongoing costs of implementing antenatal corticosteroids at scale might also vary, depending on how well equipped a health facility is, as well as the current funding and staffing arrangements in place. Answering these questions requires further research that can explore the economic implications of implementing antenatal corticosteroids at scale in a more diverse range of health-care facilities. To that end, WHO is planning a multicountry implementation research project in four low-resource countries (Bangladesh, Ethiopia, Nigeria, and Pakistan), which will develop and evaluate a care model that can achieve high population-level coverage of safe antenatal corticosteroid use. This project will include an evaluation of the care model's cost and cost-effectiveness.

The timeframe for primary outcomes in the WHO ACTION-I trial was 28 days postnatal; however, preterm neonates are known to have more health complications beyond the neonatal period.[18] The effects of longer-term health issues on overall cost-effectiveness in low-resource countries is not yet clear and warrants investigation, requiring long-term follow-up data. Therefore, this study was not able to capture the costs unrelated to health care that preterm birth can impose on communities and families (eg, lost employment), which also warrants further research. Nevertheless, in settings where families pay some or all of the costs of hospital care, they would probably benefit from the cost savings identified in this study.

Findings from this multicountry economic evaluation indicate that administration of intramuscular dexamethasone to women at risk of early preterm birth is cost-saving in five low-resource countries. These findings can inform efforts to scale up use of antenatal corticosteroids in similar settings, which could help to reduce neonatal mortality and morbidity associated with preterm birth, and health costs. The collection of economic

data in implementation research on safely increasing antenatal corticosteroid coverage in low-resource countries would be informative.

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Contributors

The idea for this economic evaluation was conceived by OTO, and the design was conceptualised by JPV, OTO, KEE, and NS. JPV, KEE, and NS coordinated the writing of the protocol, with input from the WHO ACTION-I trial country principal investigators and members of the WHO Trial Co-ordinating Unit. Data were collected by study teams at participating sites, with technical support provided by KEE, JPV, and NS. NS, KEE, TT, DF, and JPV performed the cost-effectiveness analysis. The country principal investigators, WHO Trial Co-ordinating Unit members, and the health economic analysis team reviewed and interpreted the final data at a meeting convened by WHO. The first draft of the manuscript was prepared by KEE, JPV, DF, NS, TT, and OTO, who also consolidated inputs from the country principal investigators and WHO Trial Co-ordinating Unit members, which was then reviewed and revised critically for intellectual content by all authors. All authors approved the final version and approved the manuscript for publication. The manuscript represents the views of the named authors only and does not reflect the views of UNDP–UN Population Fund–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction or WHO. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Requests for access to these data can be made to WHO through srhmph@who.int. Data sharing with any individual or organisation will be subject to WHO's data sharing policy.

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