WORKING PAPER

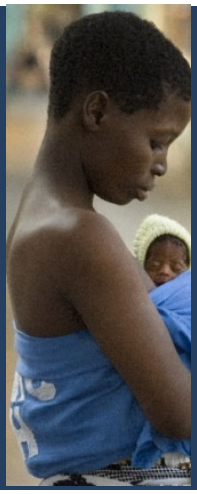
Prepared for the United Nations Commission on Life-Saving Commodities for Women and Children

March 2012

Case Study

Antenatal Corticosteroids

for the reduction of deaths in preterm babies



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Authors

Joy Lawn[1], Joel Segrè[2], Pierre Buekens[3], Fernando Althabe[4], José M Belizán[4,5], Alan Jobe[6], Steve Brooke[7], Steve Hodgins[8], Joseph de Graft Johnson[1,8]

[1] Saving Newborn Lives, Save the Children, South Africa
[2] Consultant to the Bill & Melinda Gates Foundation
[3] School of Public Health and Tropical Medicine, Tulane University, Louisiana, United States
[4] Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina
[5] Board member for The Partnership for Maternal Newborn and Child Health
[6] Cincinnati Children's Hospital, Ohio, USA
[7] Program for Appropriate Technology in Health (PATH), Seattle, USA
[8] Maternal and Child Health Integrated Program (MCHIP), Washington DC, USA

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Acronyms

ANCS	Antenatal Corticosteroids
Beta-Ac	Betamethasone acetate
Beta-PO4	Betamethasone sodium phosphate
Beta-	Betamethasone
Dexa-	Dexamethasone
NMR	Neonatal mortality rate
RCT	Randomized controlled trial
RDS	Respiratory Distress Syndrome

Photo credits: Save the Children

Table of Contents

Executive Summary

Problem of preterm birth:
Each year more than one in ten babies are born preterm[i] and over one million die due to complications of preterm birth[ii], most commonly respiratory complications due to lung immaturity often called Respiratory Distress Syndrome (RDS). This makes preterm birth the second most common cause of child deaths after pneumonia as of 2010, yet global attention and action is lacking. In addition to the mortality effects, millions of surviving preterm babies have long-term disability and higher risk of adult chronic disease. Hence preterm birth is one of the highest burden conditions highlighted in the Global Burden of Disease, and a major drain on families and economic potential globally. The large survival gap for preterm babies born in high income compared to low income countries is due to lack of even simple newborn care let alone intensive care.[iii]

Antenatal corticosteroid (ANCS) injection for women at risk of preterm delivery is the most effective intervention to reduce the risk of RDS for preterm babies.[iv] Fluorinated glucocorticoid hormones cross the placenta most efficiently and trigger a range of effects including the production of surfactant in the fetal lung. Surfactant enables babies to establish regular breathing without ventilator support or with reduced intensity of ventilation. Since its discovery in 1969,[v] more than twenty convincing randomized controlled trials (RCTs) have helped to make ANCS a standard of care for women with threatened preterm birth.[vi]

Potential lives saved with antenatal corticosteroids:
According to a meta-analysis of 18 RCTs in a Cochrane review, ANCS injection for women with preterm labor reduces neonatal mortality (NMR) by 31% and moderate/severe RDS by 45%. A meta-analysis of the only 4 RCTs from middle income countries found a higher effect of 53% reduction of NMR (RR 0.47, 95%CI 0.35 to 0.64).[vii] The effect is greatest between 31 weeks and 36 weeks gestation, but may still be effective down to 28 weeks although at these lower gestational ages ventilatory support may also be required. However only 5% of preterm births are lower than 28 weeks gestation, so the majority of preterm babies can survive without intensive care.

All these trials compared the additional impact of ANCS to local standard care for babies (including ventilation and in some cases also pulmonary surfactant). There are no published trials where the babies received simple care or no care at all, yet this is the norm at the community level and at most health facilities in the highest burden countries. An ongoing large cluster RCT in six low and middle income countries is designed to quantify the mortality effect of ANCS without special neonatal care. [viii] The beneficial effects of ANCS are based on a consistent biological

process, so all preterm babies should benefit, but the precise impact of ANCS for babies where there is no intensive care remains unknown.

If the beneficial effects are similar, and the intervention reached high coverage in the poorest countries where most of the births occur and where most preterm babies die, according to a Lives Saved Tool (LiST) analysis detailed in this report almost 400,000 lives may be saved each year with ANCS. The cost-effectiveness of ANC for use in Africa and Asia has been estimated at just under US$300 per death averted, which is highly cost effective and would give added gains in reduced morbidity in addition to the deaths averted included in the analysis.[ix]

Product definition:
Both betamethasone (beta-) and dexamethasone (dexa-) are administered as intramuscular injections. The effect is higher if there is 24 hours between the first dose of ANCS and the time of birth. Both drugs have a long history of wide use, strong efficacy and safe administration. Fourteen RCTs have used betamethasone, and 6 used dexamethasone. There is no definitive evidence to recommend one of these two options over the other. According to one Cochrane review, betamethasone resulted in a greater reduction in RDS (RR 0.56, 95%CI 0.48 to 0.65, 14 studies, 2563 infants) than dexamethasone treatment (RR 0.80, 95% CI 0.68 to 0.93, 6 studies, 1457 infants).[x] However, another Cochrane review in the same year suggested that dexamethasone is even more effective in reducing intraventricular hemorrhage than betamethasone (RR 0.44, 95% CI 0.21 to 0.92, 4 studies, 549 babies) but also that increased risk of puerperal sepsis may be associated with dexamethasone use.[xi] A very large trial or series of trials would be required in order to make definitive recommendations on choice of steroid and confidently measure risk of rarer outcomes, but it is clear that current evidence supports the use of either product to save lives safely. An advantage for betamethasone is that it requires only two injections compared to four dexamethasone injections. This might be an important consideration especially at the lower levels of the health system. However, dexamethasone is currently far less expensive and far more widely available than betamethasone.

Policy and regulation:
The WHO lists antenatal corticosteroids for prevention of RDS as a priority intervention in management of preterm labor (PMNCH, 2011)[xii] and both dexa- and betamethasone are listed on the WHO Priority medicines list as a key commodity to reduce mortality in preterm babies. Dexamethasone is on the WHO essential medicines list, although for indications other than preterm labor (eg, allergies). Despite the extensive, high quality evidence, only Argentina, Australia and New Zealand have registration of ANCS for the indication of fetal lung maturation. Use for fetal lung maturation in other countries is technically off-label, although considered as a standard of care by ministries of health and obstetric societies. In high income countries, if ANCS were not given in accordance with standards of care that have been well established for almost 20 years the doctor would be liable for malpractice.

Cost, manufacturing and supply chain:
Injectable dexamethasone is widely available and low cost from many producers of generic drugs. The average price across more than 10 Indian suppliers is US $0.51 per course of treatment.[xiii] The same course would wholesales for about US $5 in the USA.

Injectable betamethasone is less commonly available and more costly. For this indication, most caregivers in developed countries prefer a suspension of betamethasone phosphate and betamethasone acetate, known by its brand name Celestone Soluspan™. The wholesale price is around US $40 for a full course in developed countries. However it has faced supply shortages in recent years and retails for around US $7. There are few known generics of Celestone Soluspan™ and the drug is difficult to find in the developing world. Production costs and its generics remain unknown.

Challenges to scale up:
In high income countries, ANCS are used in around 90% of cases of women in preterm labor, but in 75 high burden countries coverage rates are estimated at 10%. Barriers to uptake include lack of product availability (for betamethasone), lack of provider awareness, or restricted prescribing for certain providers or levels of care, and misdiagnosis of preterm labor. Side effects are not a major concern, so caregivers should be encouraged to err in favor of administration, especially since even a few hours between ANCS and birth has an effect on RDS which has high fatality rates especially if neonatal intensive care is unavailable.

Priority actions to be considered by the Commission:
The following recommendations have the potential to help save almost half a million lives in a relatively short time period:

1. ***Prioritize immediate scale up of dexamethasone for use to reduce deaths for preterm babies:*** Betamethasone is simpler to administer in only two injections, and may have some advantage in efficacy (not statistically established), yet its lower availability and much higher cost are serious challenges. Dexamethasone is far less expensive, and already more widely available than betamethasone including in low income countries. If an affordable betamethasone were to be produced, and the clinical data established a definite advantage over dexamthasone, then betamethasone could replace dexamethasone at a future date but in the meantime many lives could be saved with rapid scale up of dexamethasone.

2. ***Add fetal lung maturation to the indications for dexamethasone on the WHO Essential Medicines list:*** Although few national regulatory bodies have approved ANCS for fetal lung maturation, there are decades of evidence to show its safety and efficacy, such that failure to prescribe ANCS for preterm labor in a high income country could result in litigation. Corticosteroids are already on the Priority Medicines list for this indication of reducing the

risk of deaths due to preterm birth but the Essential Medicines List is closely linked to policy change in many countries. Further analysis is required to determine if national registration for fetal use is important to pursue given the widespread precedent of off-label usage for fetal lung maturation in the wealthy world.

3. ***Increase policy awareness and provider support to correctly administer ANCS:*** Strong policy promotion and provider education was crucial to the adoption of ANCS in the wealthy world, and is a key opportunity now for rapid adoption in the rest of the world as well. Currently it has received little focus or attention from global policy leaders including the relevant UN organizations. Empowering midwives to provide ANCS for women in preterm labor would immediately increase access.

4. ***Invest in rigorous implementation research:*** Scaling up this cost-effective intervention will require investment in understanding context-specific, local barriers, in designing innovative strategies capable of overcoming those barriers, and in conducting rigorous research to measure effectiveness and cost of ANCS at all levels of the healthcare system, in varying contexts, through various providers and linked to other cost-effective care options to reduce deaths among preterm babies such as Kangaroo Mother Care. In addition research is required to improve the coverage and process data tracking to promote accountability for provision of this high impact intervention.

1. Global need for Antenatal Corticosteroids

1.1. Preterm birth and long term effects

Each year more than one million children die directly due to complications of preterm birth,[xiv]most commonly respiratory complications due to lung immaturity often called Respiratory Distress Syndrome (RDS). More than one in ten of the world's 135 million births are preterm and many millions of babies born who survive have long-term disability and also a higher risk of adult chronic disease.[xv] Preterm birth is one of the single largest conditions highlighted in the global burden of disease and a major drain on economic potential in low and middle income countries as well as in high income settings. New analysis shows that in every country with reliable time trend data, the rates of preterm birth have increased over the last two decades.

Preventing preterm birth has had limited success to date and is a globally recognized research priority. The dramatic reductions in deaths due to preterm birth in high income countries have been primarily through neonatal care, although the later addition of antenatal corticosteroids (ANCS) was still associated with major, additional mortality and morbidity reduction. Full neonatal intensive care is expensive and complex. There are a number of simpler, high-impact interventions that are not commodity-dependent such as Kangaroo Mother Care, which are starting to be scaled up but are currently at very low coverage. The equity gap for survival of preterm babies is over 20-fold between the richest and poorest countries, and has increased over the last decade. While babies born at 25 weeks gestation in Europe or the North America have a 50% chance of survival, babies even in hospitals in the poorest countries may have less than 50% survival at 32 weeks gestation. Preterm birth affects families all over the world, and parent groups in high income settings have been a key part of advocating for improved care, yet the most preventable deaths due to preterm birth occur in low and middle income settings and have received little attention. Seven low and middle income countries have halved deaths due to preterm birth in the last decade, showing that this is achievable. [xvi]

1.2. Evidence for antenatal corticosteroids effect and effect size

Profile of evidence and effectiveness for antenatal corticosteroids

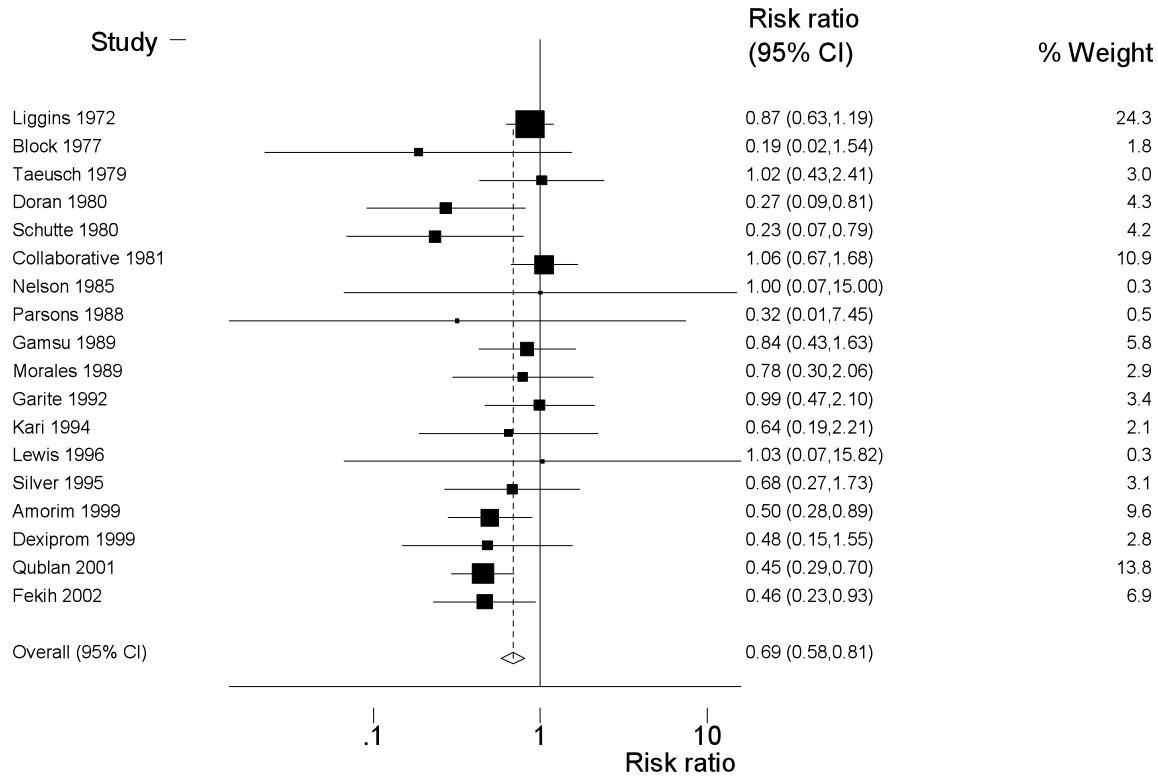
Antenatal steroid treatment for women at risk of preterm delivery is considered to be the most effective intervention for the prevention of RDS, reducing early neonatal mortality and morbidity. Fluorinated glucocorticoid hormones cross the placenta and trigger the maturational process that leads to the production and release of surfactant into the alveoli of the fetal lung. In 1969 Liggins made the discovery amongst preterm lambs in New Zealand.[xvii] Around 25 years and 18 convincing RCTs later, the National Institutes of Health (NIH) consensus statement made ANCS a standard of care in 1994.[xviii]

Evidence for mortality effect of antenatal corticosteroids

The Cochrane review by Robert & Dalziel included 21 RCTs of ANCS. According to a meta-analysis of the 18 RCTs that measured mortality, ANCS reduce neonatal mortality by 31% and moderate/severe RDS by 45%. A meta-analysis of the only 4 RCTs from middle-income countries found a higher effect of 53% reduction of NMR.[xix] It is crucial to emphasize that all

these trials compared the addition of ANCS to standard care including ventilation and in some cases also surfactant although surfactants were only FDA approved in the US in 1990. As yet there are no trials where the comparison group is newborns who receive simple care or no care at all. In such cases, the mortality effects may be expected to be higher, although still uncertain.

Figure 1: A meta-analysis (fixed effects) of 18 RCTs comparing administration of antenatal steroids for preterm labor with placebo and showing effect on neonatal mortality outcome after preterm labor

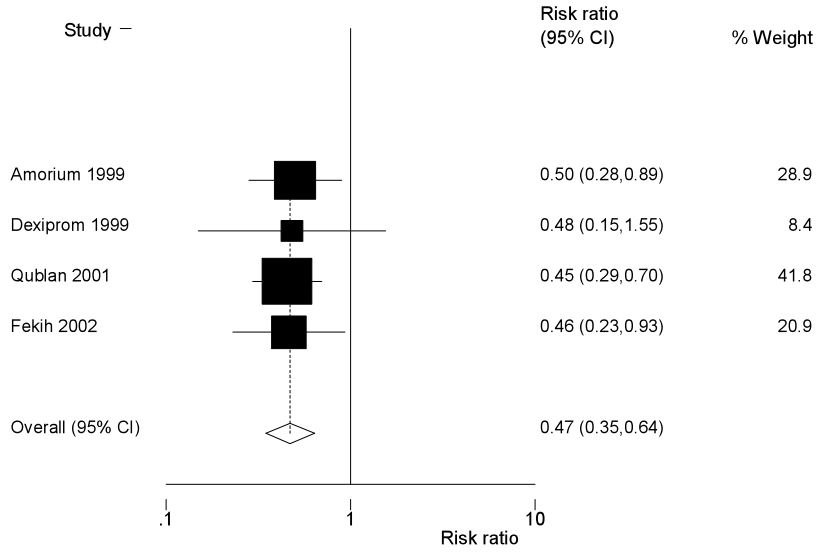


Total events = 491 neonatal deaths
Heterogeneity chi-squared = 21.54 (d.f. = 17) p = 0.203
Test of RR=1 : z= 4.50 p = 0.000
Fixed effect meta-analysis
Source: 18 RCTs from the Robert's & Dalziel's Cochrane review but meta-analysis revised to order by date of study instead of author alphabetical order showing a tendency to higher effect size for ANCS before surfactant was routinely in use (around 1990).[xx]

Figure 1 shows that in the majority of the trials the risk ratios for neonatal deaths is lower than 1.0, which is in favor of ANCS. The overall risk ratio is 0.69, with a confidence interval not overlapping 1, which suggests that this 31% reduction of mortality risk is not due to chance.

Figure 2 shows that the all trials have risk ratios lower than 1, which is in favor of ANCS reducing neonatal deaths. The overall risk ratio is 0.47, with a confidence interval not overlapping 1.0, which makes it unlikely that this 53% reduction of risk is due to chance. Compared to Figure 1, this suggests that the impact in middle income countries may be still higher than that observed in the wealthy world.

Figure 2 A meta-analysis (fixed effects) of 4 RCTs from middle-income countries comparing administration of antenatal steroids for preterm labor with placebo and showing effect on neonatal mortality outcome after preterm labor



Total events = **142**
Heterogeneity chi-squared = 0.08 (d.f. = 3) p = 0.994
Test of RR=1 : z= 4.87 p = 0.000
Fixed effect meta-analysis
Source: Mwansa J et al IJE 2010

1.3. Lives saved and cost effectiveness analysis

If the beneficial effects are similar in low income settings, and the intervention reached 95% coverage in the 75 Countdown priority countries where most of the births occur and where most preterm babies die, the according to a Lives Saved Tool (LiST) analysis almost 400,000 lives may be saved each year with ANCS.[xxi]

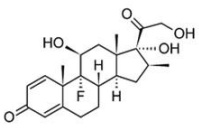
The cost-effectiveness of ANC for use in Africa and Asia has been estimated at just under US$300 per death averted, which is highly cost effective and would give added gains in reduced morbidity in addition to the deaths averted included in the analysis.[xxii]

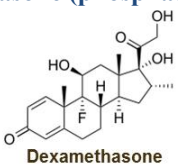
2. Antenatal steroid preparations

2.1. Choice of antenatal corticosteroids drug formulation

Dexamethasone sodium phosphate and a combination of betamethasone sodium phosphate with betamethasone acetate (in a single preparation) are the most popular antenatal corticosteroids for fetal lung maturation. Only injectable forms of these drugs are used for fetal indications. Both beta- and dexa- are administered as intramuscular injections. Both drugs have a long history of wide use, strong efficacy data and several decades of safe administration in high income settings.

Figure 3 Comparison of dexamethasone and betamethasone (phosphate + acetate)





Drug	Betamethasone (Phosphate+Acetate)	Dexamethasone
Dose / Injection	12 mg	6 mg
# Injections	2	4
Interval btwn injections	24hrs	12hrs
Total Amount	24 mg	24 mg
Avg Price/ 24mg (India)	No Known Indian Supplier	$0.51 (10 brands)
Injectable form on WHO Essential Medicines List?	No	Yes

The majority of work with betamethasone has been with a specific formulation combining both fast acting betamethasone phosphate (Beta-PO4) and long acting betamethasone acetate (Beta-Ac), commercially available for at least the past 40 years under the brand name Celestone Soluspan ™. In most cases in the literature, reference to "betamethasone" is actually this specific formulation of beta-PO4 + Beta-Ac. We will adopt this convention through this paper. We are aware of only one study using Beta-PO4 (without Beta-Ac)for fetal lung maturation[xxiii]. We are unaware of an injectable suspension of Beta-Ac (without Beta-PO4), and have not encountered any studies of Beta-Ac for human fetal lung maturation.

Six of the RCTs in the Cochrane review that mentioned the type of corticosteroid used, used dexamethasone, and 14 used betamethasone (8 using a combination of Beta-PO4 + Beta-Ac, 1 using Beta-PO4 alone, and 5 unspecified). There is no definitive evidence to recommend beta- over dexa- or vice versa. According to one Cochrane review, betamethasone resulted in a greater reduction in RDS (RR 0.56, 95%CI 0.48 to 0.65, 14 studies, 2563 infants) than dexamethasone treatment (RR 0.80, 95% CI 0.68 to 0.93, 6 studies, 1457 infants) (Roberts & Dalziel, 2006).[xxiv] However, another Cochrane review in the same year suggested that dexamethasone is even more effective in reducing intraventricular hemorrhage than betamethasone (RR 0.44, 95% CI 0.21 to 0.92, 4 studies, 549 babies) but also that increased risk of puerperal sepsis may be associated with dexamethasone use (Brownfoot, et al., 2008).[xxv] An advantage for betamethasone is that it is simpler to administer since it requires only two injections over 24 hours compared to four dexamethasone injections. This might be an important consideration especially at the lower levels of the health system. However, dexamethasone is a widely available for many other medical purposes and at a much lower cost than betamethasone. A very large trial or a series of trials would be required in order to make definitive recommendations for superiority between these two steroids and confidently measure risk of rarer outcomes. Current evidence supports the use of either product to save lives safely.

2.2 Timing of administration

Timing of Doses: The effect of ANCS appears greatest when birth occurs between 24 to 48 hours after treatment. When birth occurs more than seven days after treatment no benefit of treatment is apparent (RR 1.45 (0.75, 2.8, 561 babies)). This may also reflect the increasing maturity of such babies.

Number of doses: In the 18 mortality outcome RCTS examined here, 8 included a repeated course of treatment each week until birth. In their study comparing repeated steroid doses to women at risk of preterm labor, Crowther and colleagues found that babies born to women who had received repeat corticosteroids were less likely to have respiratory problems after birth than those treated with a single course.[xxvi] In addition, babies that did develop respiratory problems had less severe episodes and lower requirement for ventilation. However, these studies did not show that repeated doses had any benefit on neonatal mortality and long-term follow-up of these children is not yet available. Hence repeated doses of ANCS are not formally recommended at this point. The standard recommendation is for one course of ANCS for all women in preterm labor, or at high risk of it. If the woman does not give birth after a week, a second course could be considered.

2.3 Possible risks considered concerning ANCS

Risks to the baby

There are no known adverse effects of ANCS on newborns. There are 21 published trials that include women at high risk of preterm birth; four that reported preterm birth rates between 67% and 85%.[xxvii] These rates are consistent with the 70% reported in a systematic review of tocolytics in preterm labor trials.[xxviii] Thus, the evaluation of potential adverse events also includes up to 30% of babies born at term. There is no evidence of short-term adverse effects for these infants. In the sub-population of preterm rupture of membranes (PPROM) infants, there is no evidence of an increased risk of infection (RR 1.05, CI95% 0.66-1.68) (Harding et al., 2001). Long-term follow-up studies with participants in three trials at 3, 6, 12, 20, 30 and 31 years have been published,[xxix] to evaluate the effects on neurodevelopment, physical and psychosocial development, cognitive function, blood pressure, health-related quality of life and cardiovascular risk factors. All studies except for one have shown that antenatal corticosteroids are not associated with long-term adverse events. In a study by Dalziel et al (2005a), long-term follow-up of subjects in the corticosteroid group revealed that they had slightly higher insulin resistance rates compared to those in the placebo group; however, the prevalence of diabetes or cardiovascular disease was similar. Whether this finding will lead to a later increase in the rates of cardiovascular disease in those exposed is not yet known.

Risks to the Woman

There is also no evidence of a significant risk of adverse events in mothers taking ANCS (NIH, 1994). The risk of maternal infection was a concern, specifically in women with prolonged rupture of the membranes, but Harding's systematic review combined evidence of 15 trials with more than 1,400 women with PPROM and showed that there is no increased risk of infection (RR

0.86, 95%CI 0.61-1.20).[xxx] Maternal pulmonary edema can occur when antenatal corticosteroids are used in combination with tocolytic agents. This complication is more commonly associated with maternal infection, fluid overload and multiple gestations. Pulmonary edema has not been reported when antenatal corticosteroids are used alone. In July 2006, the FDA issued a MedWatch with safety labeling changes that included the statement that corticosteroids should not be used patients with cerebral malaria (FDA, 2006). There are no published reports of contraindications to the administration of antenatal corticosteroids in pregnant women with HIV infection.

These trials have been conducted in hospital settings. Further assessment is required of the use corticosteroids at lower levels in the health system, for example with a pre-referral dose at a primary care clinic.

3. Global and National Regulatory Policy

3.1 Guidelines for the use of ANCS

The WHO,[xxxi] Royal College of Obstetrics and Gynecology (RCOG), American College of Obstetrics and Gynecology (ACOG), United States National Institutes of Health (NIH), and World Association of Perinatal Medicine (WAPM) all recommend the use of antenatal corticosteroids.

3.2. WHO Model List of Essential Medicines

Injectable dexamethasone is listed on the 2011 WHO Essential Medicines List under the following indications:

- Anti-allergy & medicines use in anaphylaxis
- Anti-emetics
- Palliative care

There is no mention of fetal lung maturation as an indication for dexamethasone. Injectable betamethasone is not listed at all.

3.3. National regulation and licensing

Dexamethasone (and to a lesser extent betamethasone) are registered for use in many developing countries for a broad range of indications, but very rarely registered for RDS prevention. In fact, the only three countries with registrations for this fetal indication are Argentina, Australia, and New Zealand. This means that administration of corticosteroids for lung maturation is an off-label use for which the clinician must carry full legal responsibility. Country registration for fetal use, therefore poses special challenges, as manufacturers are unlikely to be willing or able to produce registration dossiers with data relevant to antenatal use.

Country registration may be especially important for distribution of ANCS via public sector supply chains. In general, only medicines included in a country's national essential medicines list are included in public sector formularies, and in most cases, their labeled uses are most likely to be qualify for national procurement and cost-recovery schemes. If ANCS is not registered for fetal indications public sector procurement could be challenging, although this is less of an issue for dexathasone which is widely used for many other indications.

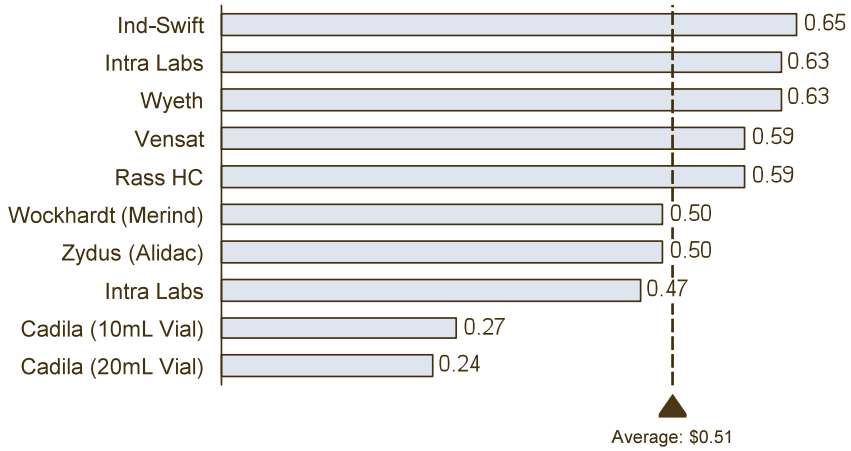
Another critical issue for national - policy is price controls. According to Merck, for example, Celestone Soluspan™ was discontinued in India due to regulation and enforcement of price controls on betamethasone which legally limited the price of the drug to be less than Merck's manufacturing costs. In this case, therefore, the Celestone Soluspan™ is registered for sale in the country, but not produced or sold. Incidentally, GSK has recently been fined more than US$14M for selling a range of drugs including other formulations of betamethasone, for more than their government-controlled prices. In this case, policy intended to decrease prices and presumably increase access has backfired to discontinue Celestone Soluspan™ in India all together.

4. Financing Antenatal Corticosteroids

4.1 Cost

Dexamethasone for injection is readily available from a variety of generics companies. In India, market prices range from about $0.65 to $0.24 per 24mg of active ingredient. American wholesale prices are around $5 for the same amount.

Figure 4: Indian price per 24 mg of injectable dexamethasone (USD)



While there are several manufacturers of betamethasone for injection, few besides Merck and American Regent appear to offer the combination of Beta-PO4 and Beta-Ac found in Celestone Soluspan™. In the United States, the wholesale price of Celestone is around US$40, with retail prices close to US$70 per 5ml (30mg betamethasone) vial.

4.2 Potential for public procurement

Dexamethasone's low cost and wide availability makes it an excellent option for public procurement. As policymakers begin to better understand the devastating effects of preterm birth, they are likely to recognize dexamethasone as perhaps the single most cost effective intervention to reduce preterm related mortality. The case for betamethasone is less clear. The relatively high cost and limited availability of beta-Ac + beta-PO4 may be less appealing to policymakers, and logistically more difficult given that there are very few suppliers globally.

4.3 Potential for private purchase

It is unclear whether or not off-label usage of ANCS inhibits public sector usage. In the event that it does, private sales may be an especially important channel for adoption of this drug. Again, the low cost and wide availability of injectable dexamethasone offer important advantages over betamethasone.

5. Manufacturing and Supply

5.1 Betamethasone

Betamethasone phosphate (Beta-PO4) is soluble in water, and therefore relatively simple to prepare as an injection. Betamethasone acetate (Beta-Ac), however, is not water-soluble and must be suspended for injection. Schering (Merck) has historically been the major player in the market for Beta-PO4 + Beta-Ac combination formulations with Celestone Soluspan™. In recent years, there have been efforts to create a generic, including one by American Regent. However, the specific particle size of Beta-Ac used in suspension could affect the pharmacokinetics of the product in important ways. In fact, some caregivers are reticent to use the generic version of Celestone Soluspan™ due to concerns around the milling process and particle size of the Beta-Ac component. Merck's specifications for the particle size as well as the distribution of particle sizes of the Beta-Ac /Beta-PO4 suspension remain trade secrets.

Both Merck and American Regent provide their product in 5ml multi-dose vials. Both companies state "Protect from Light" on the product label. American Regent labels their product "Store between 20 – 25 degrees C (68 - 77 degrees F), which Schering (Merck) states "Store at 25 degrees C (77 F), excursions permitted to 15 C to 30 C. The American Regent package insert further states that this product is sensitive to heat.

Beta-Ac + Beta PO4 is not listed in the UNICEF Supply Catalogue, and a search of the International Drug Price Indicator Guide (IDPIG) had no listing for any injectable form of betamethasone.

5.2 Dexamethasone

The most common form of dexamethasone used for human injection is dexamethasone sodium phosphate. Dexamethasone sodium phosphate injection, USP is a sterile solution of

dexamethasone sodium phosphate, and is supplied in both 4 mg/ mL and 10 mg /mL concentrations. There are at least nine pharmaceutical companies producing and distributing dexamethasone sodium phosphate for injection in the United States, and at least another ten in India as displayed in Figure 4 above. The 4mg/ml concentration is also available through the UNICEF Supply Catalogue; the IDPIG lists numerous suppliers including UNFPA and Mission Pharma, a major supplier of essential medicines to NGOs.

Dexamethasone sodium phosphate for injection is supplied in a variety of single and multi-dose vial sizes. Its labeled storage conditions are similar to those for betamethasone suspension, with some producers labeling dexamethasone for 20 C – 25 C storage while others allow a wider temperature storage range of 15 C to 30 C. Dexamethasone sodium phosphate for injection labeling typically also includes "Protect from light" and in addition clear statements of "Protect from freezing" and "Sensitive to heat".

5.3 Market Size

The annual global market for all injectable forms of betamethasone around US$100M with approximately US$70M accruing to combination Beta-Ac+Beta-PO4 drugs manufactured by Merck and American Regent. The annual global market for injectable dexamethasone is around US$282M. [xxxii] In both cases, the market is primarily driven by uses other than fetal lung maturation.

As an off-label use, there is no reliable data on the actual market size for antenatal use of these drugs. However, we can roughly approximate it as follows: if there are about 135M births annually and about 10% of them are premature, there are about 13.5M babies who could potentially benefit from ANCS. Currently, the drug is primarily limited to babies born in the wealthy world, which we'll roughly approximate at 10% of total births. This means that the current market size for ANCS may be around 135M x 10% x 10% or 1.35M births. The table below projects that if all of these babies were treated with betamethasone, the annual market size for betamethasone (at ~US$40 manufacturer's price per course) would be $54M. If all babies in this demographic were treated with dexamethasone (at a manufacturer's price of ~US$5 in the developed world), the total market size would be <$7M.

Table 1: Projected current market size for ANCS in wealthy countries

Source	Price/course (USD)	Market size based on current demand	Annual revenue based on current demand
Beta PO4 + Beta-Ac.	$40	1.35M	$54M
American Dexa- Vendors	$5	1.35M	<$7M

In each case, the antenatal application of these drugs is unlikely to catch the attention of major pharmaceutical companies. The revenues are just too small, especially given the perceived liabilities of producing a drug with fetal effects. Even if dexamethasone were to be used in 100% of all preterm births in the wealthy world, this would constitute only US$7M/US$282M= 2.3% of

global annual dexamethasone sales. If dexamethasone were rolled out globally to 95%+ coverage, Indian generics manufacturers would reduce the average selling price closer to US$0.50 per baby (their current prices) across the developing world customers, so the prospects of market growth would be modest—perhaps an additional US$6M in revenue over an additional 12M babies. In other words, expanding coverage to nearly every preterm baby in the world would only expand the market by US$6M/US$282M=2.1%. The good news is that applications outside antenatal health constitute a competitive marketplace for dexamethasone with multiple competing vendors around the world looking for growth opportunities. Supply of this drug does not appear to be in jeopardy.

The picture for betamethasone is not as clear. The US$70-100M market for all injectable indications combined is on the edge of being too small to retain the attention of large fully integrated biopharmaceutical companies. Technical barriers related to the suspension of Beta-Ac make entry of additional companies difficult. As of 2010, American Regent has rapidly gained market share from Merck, partly because Merck appears to have de-prioritized the product. Even at US$40/vial, betamethasone is may be a less attractive business proposition than other products in the Merck portfolio.

Given these modest opportunities to profit from the small antenatal market, manufacturers are unlikely to push for indication-specific regulatory approval of ANCS. Instead, they are more likely to focus on other indications for beta- and dexamethasone which represent much larger market opportunities. This means that package inserts are unlikely to have ANCS-specific dosing information. In addition, ANCS producers will likely have little incentive to push for more aggressive global and country-level policies given the relatively small potential profit in antenatal use of these products. As a result, the adoption of these drugs for antenatal applications will require global and country-level policymakers and others to 'pull' these products into their programs.

6. User-Centered Product Innovation: What Caregivers Want

More than supply issues for ANCS, low awareness by policy makers and frontline workers is hampering ANCS coverage.

6.1 Innovations to improve awareness

Lack of awareness of ANCS is a common problem in low income settings. Even women with previous neonatal deaths due to preterm birth and who are on bed rest in a hospital for threatened preterm labor may not be given an injection of ANCS. In high income countries, active dissemination of best practices has been shown to increase uptake of ANCS (see section 7). Similar efforts to actively increase awareness and understanding of preterm birth and ANCS will be an important part of saving lives. It is likely that the most important innovations to increase coverage of ANCS will be related to changing pre-service education and postgraduate training for obstetricians and also enabling midwives to prescribe ANCS. Wider recognition of the high impact and low coverage by key policy makers is also critical. For example the word “antenatal

corticosteroids" or any derivation of it does not occur on the website of UNICEF or UNFPA and these are the two UN agencies with implementation leadership for this technical area.

6.2 Innovations to save time for providers

Researchers have explored and continue to explore several common methods of simplifying drug administration from other areas of maternal and neonatal health. For example, thoughtful investments in packaging could potentially increase uptake by bundling the correct number of pre-filled injectors together in a special pouch labeled especially for threatened preterm birth. Alternatively, product developers may wish to avoid the added costs of pre-filled injectors by bundling the correct number of vials and syringes together in a similar pouch. It should be noted that efforts to re-label the primary container of any ANCS in such a way that mentions fetal use would probably trigger considerable regulatory hurdles. Changes to secondary packaging, performed after a product has been imported, might reduce the regulatory burden.

6.3 Innovations to improve diagnosis of preterm labor

In other cases, providers may be aware of ANCS, but may be missing data on gestational age, fail to diagnose the onset of labor, or may not have the time to assemble the required doses.

Gestational Age: Pregnant women may not know or accurately report last menstrual period (LMP) data. Fundal height is widely used to complement LMP data but has a wide range of uncertainty (Table 3). First trimester ultrasound is often considered the 'gold standard" for determining gestational age, but is not widely used in low income settings and in any case the median week for first antenatal clinic visit in much of Africa and Asia is closer to the third trimester than the first. There may also be concerns with gender selective terminations given high first trimester ultrasound rates, especially if unregulated. There are lower cost ultrasound technologies and regulated deployment of these may help to improve a caregiver's capability to correctly use ANCS.

Table 2: Gestational age methods applicable before onset of labor showing accuracy and limitations

Method	Accuracy	Details	Availability/feasibility	Limitations
Early ultrasound scan	+/- 5days if first trimester +/- 7days after first trimester	Estimation of fetal crown-rump length +/- BPD/ femur length between gestational age 6 – 18 weeks	Ultrasound not always available in low income settings and rarely done in first trimester	May be less accurate if fetal malformation, severe growth restriction or maternal obesity.
Last Menstrual Period	~ +/- 14 days	Women's recall of the date of the first day of her last menstrual period	Most widely used	Lower accuracy in settings with low literacy. Affected by variation in ovulation and also by breastfeeding. Digit preference.
Fundal	~ +/- 3 weeks	Distance from	Feasible and low cost.	In some studies similar

Height		symphysis pubis to fundus measured with a tape measure		accuracy to LMP Potential use with other variables to estimate GA when no other information available
Best obstetric estimate	around +/- 10 days (Between ultrasound and newborn examination)	Uses an algorithm to estimate gestational age based on best information available	Commonly used in high income settings	Various algorithms in use, not standardised

Source: Blencowe et al. Chap 2 Born Too Soon: Global Action Plan for Preterm Birth

Diagnosis of Labor: Preterm labor may occur after an obvious risk factor such as multiple births or obstetric complications such as hypertension or in a woman with previous preterm birth. Caregivers and expecting mothers may not accurately predict the onset of labor, and could benefit from more advanced methods of cervical characterization to predict preterm birth, such as ultrasound. Assays of fetal fibronectin may also be used in some cases, but may not be feasible in low resource settings.

7. Scaling up coverage of Antenatal corticosteroids

7.1 Coverage of antenatal corticosteroids

In high income countries, ANCS are used in nearly 90% of cases of women in preterm labor. Middle income countries have variable coverage (e.g. an assessment in 9 countries of SE Asia suggested at 9-73%, and another survey of 22 hospitals in Mexico and 18 in NE Thailand suggested coverage less than 20%). In low income countries coverage rates are estimated at 10% for 75 high priority countries, but data is sparse.

In Uganda, a national sample of 132 facilities where births occur reveals that ANCS are available for less than half the hospitals and entirely absent from the lowest levels of care. Where ANCS are available, they are dexamethasone only.

Table 3: Health facility assessment data from 132 sites in Uganda during 2011

Health facility level	Availability in maternity units
Hospitals (N = 16)	44%
Health Centre IVs (N = 16)	18%
Health Centre IIIs (N =100)	0%

There are a number of possible explanations for low coverage of ANCS in developing countries including issues of drug supply, provider awareness, and which providers are licensed to give

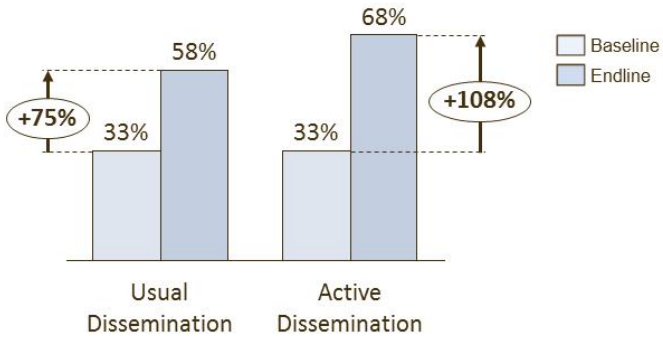
ANCS injections. In the Ugandan case, policies list injectable dexamethasone for anaphylactic emergencies (according to the revised Uganda MoH Essential Drug List, 2010). National norms and standards promote the use of dexamethasone for RDS preventions, but only by specialists at referral level facilities.

More broadly, issues of supply are discussed in section 6 (manufacturing and supply) and issues of provider awareness and capability are discussed in section 5 (user-centered product design). In all cases, barriers to coverage are likely context-specific and policy makers will need to conduct rapid assessments in geographies of interest in order to most efficiently increase coverage.

7.2 Cultivating demand from caregivers in tertiary hospital settings

In the United States, Leviton et al. studied the dissemination of ANCS following the NIH consensus Conference held in 1994 across 27 American tertiary care facilities.[xxxiii] The control group of 14 institutions received the "usual dissemination practices" including mailings of NIH brochures outlining the conference findings. The recommendations were also published in JAMA and elsewhere. These publications, other research literature, lectures, and word of mouth constituted the way NIH usually disseminated its recommendations. In the 13 active dissemination institutions, an influential physician and a nurse coordinator led a program consisting of grand rounds, a chart reminder system, group discussion of case scenarios, monitoring, and feedback. Not surprisingly, the active dissemination institutions achieved higher rates of adoption at the endline survey.

Figure 5. Comparison of coverage of ANCS after usual dissemination and active dissemination in the US (Leviton et al)



Less is known about the drivers of ANCS use in developing world contexts, and especially at lower level facilities where caregivers may have more sparse professional networks and lower levels of access to published literature, and active dissemination, mentoring, text reminders and other approaches may be even more important.

WHO has conducted a trial in 22 hospitals in Mexico and 18 hospitals in Thailand to evaluate the effect of a multifaceted educational strategy to promote the use of the WHO Reproductive Health Library (RHL 2005) on several obstetric practices, including the use of antenatal corticosteroids in preterm births <34 weeks.[xxxiv] The mean post-intervention use rate was 24% in participating

hospitals in Mexico and Thailand, which while an increase from baseline, suggested that more was needed than simply giving out information.

7.3 Feasibility of providing antenatal corticosteroids more peripherally in the health care system

Provision of ANCS in the peripheral health system of developing countries is neither well studied nor well understood. There are research questions regarding the best way to help lower skilled caregivers identify preterm labor and properly administer the drug, as suggested in section 5 above. Additionally, however, there are some questions about the theoretical possibility of risks that are not significant in high income settings. For example, steroids including betamethasone and dexamethasone are known to increase the risk of infection. In environments where the risk of iatrogenic infection is higher, ANCS may compound this risk. NICHD's Global Network for Women's and Children's Health has designed and is implementing a study to look at this and several other questions relating to use in settings with low antenatal steroid. The study focuses on contexts where deliveries occur at mostly at primary health care facilities or at home. The evaluation design is a cluster randomized controlled trial in 102 health regions in 6 countries (http://gn.rti.org/).

8. Monitoring and Evaluation

A number of metrics may be useful in monitoring the progression of ANCS from an overlooked opportunity to a routine part of maternal and neonatal care. Table 4 suggests a few possible metrics:

Table 4: Indicators for tracking the scale up of antenatal corticosteroids for preterm labor

Supply Metrics	• Number of manufacturers producing betamethasone or dexamethasone • Number of countries with dexamethasone on essential drug list for fetal indications
Demand Metrics	• Number of countries with policies/guidelines on ANCS for preterm labor • % of public and private maternity facilities with ANCS in stock • % of maternity care providers with correct knowledge of the use of ANCS • % of women of reproductive age (or pregnant women) who know the use of ANCS in management of preterm labor
Correct Use Metrics	• % of women with indications to receive ANCS who received ANCS • % of women in preterm labor/with indications to receive ANCS who received ANCS course at 24 hours to 7 days before birth • % of women with indications to receive ANCS where a complete and correct dose was administered
Impact Metrics	• Neonatal mortality rate • Preterm specific neonatal mortality rate • Predischarge case fatality rate for preterm (<37 weeks) and extreme preterm (<28 weeks)

9. Recommendations

Priority actions to be considered by the Commission:
The following recommendations have the potential to help save almost half a million lives in a relatively short time period:

1. ***Prioritize immediate scale up of dexamethasone for use to reduce deaths for preterm babies:*** Betamethasone is simpler to administer in only two injections, and may have some advantage in efficacy (not statistically established), yet its lower availability and much higher cost are serious challenges. Dexamethasone is far less expensive, and already more widely available than betamethasone including in low income countries. If an affordable betamethasone were to be produced, and the clinical data established a definite advantage over dexamethasone, then betamethasone could replace dexamethasone at a future date but in the meantime many lives could be saved with rapid scale up of dexamethasone.

2. ***Add fetal lung maturation to the indications for dexamethasone on the WHO Essential Medicines list:*** Although few national regulatory bodies have approved ANCS for fetal lung maturation, there are decades of evidence to show its safety and efficacy, such that failure to prescribe ANCS for preterm labor in a high income country could result in litigation. Corticosteroids are already on the Priority Medicines list for this indication of reducing the risk of deaths due to preterm birth but the Essential Medicines List is closely linked to policy change in many countries. Further analysis is required to determine if national registration for fetal use is important to pursue given the widespread precedent of off-label usage for fetal lung maturation in the wealthy world.

3. ***Increase policy awareness and provider support to correctly administer ANCS:*** Strong policy promotion and provider education was crucial to the adoption of ANCS in the wealthy world, and is a key opportunity now for rapid adoption in the rest of the world as well. Currently it has received little attention from global policy leaders including the relevant UN organizations. Empowering midwives to provide ANCS for women in preterm labor would immediately increase access.

4. ***Invest in rigorous implementation research:*** Scaling up this cost-effective intervention will require investment in understanding context-specific, local barriers, in designing innovative strategies capable of overcoming those barriers, and in conducting rigorous research to measure effectiveness and cost of ANCS at all levels of the healthcare system, in varying contexts, through various providers and linked to other cost-effective care options to reduce deaths among preterm babies such as Kangaroo Mother Care. In addition research is required to improve the coverage and process data tracking to promote accountability for provision of this high impact intervention.

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