Antenatal corticosteroids to reduce preterm deaths in low-income settings

In their Comment (April issue),[1] Kishwar Azad and Anthony Costello raise questions that should be answered before antenatal corticosteroid treatment is scaled up to reduce preterm deaths in low-income countries. We share their concerns about the unknown overall effect of this treatment on mortality and potential safety issues in the mother. To answer these questions, we have initiated the Antenatal Corticosteroids Trial[2] to assess whether or not a multifaceted intervention to increase the use of antenatal corticosteroids reduces neonatal mortality at 28 days of age, and maternal morbidity due to infections. Enrolment has been completed and data from more than 90 000 births have been collected.

We disagree with Azad and Costello's comment about the effect of antenatal corticosteroid treatment on respiratory distress in infants at 34 weeks' gestation. This statement is based on a subgroup analysis from a systematic review.[3] However, the same review presents data showing a decreased risk of respiratory distress syndrome in infants with first dose of corticosteroids administered to mothers at 33–35 weeks' gestation (relative risk [RR] 0·53, 95% CI 0·31–0·91), and a non-significant decrease in the risk of respiratory distress in infants (0·61, 0·11–3·26) with first dose at 35–37 weeks' gestation. The findings suggest a reduction in respiratory distress syndrome is present according to gestational age at first delivery of corticosteroids.[3]

Prevention of respiratory distress syndrome in infants born at 33–36 weeks' gestation without access to specialised high-quality level 2 care might create a substantial health-care burden in low-income countries. The Antenatal Corticosteroids Trial[2] will assess the administration of steroids to mothers up to 36 weeks' gestation. Data from this trial will be available in the second half of 2014. We hope that several of the concerns expressed in the Comment by Azad and Costello will be addressed.

We declare that we have no competing interests.

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Antenatal corticosteroids to reduce preterm deaths in low-income settings

The Comment[1] by Kishwar Azad and Anthony Costello opposing scale-up of antenatal corticosteroids misdirects the discussion of this topic towards speculation about differences in low-income settings. Our experience in Malawi provides a concrete example of the rapid scaling up of antenatal corticosteroid treatment with dexamethasone.

Malawi has the highest estimated preterm birth rate worldwide.[2] In Bwaila Maternity Hospital, Lilongwe, that has more than 15 000 deliveries annually with more than 2900 preterm, we increased targeted coverage of antenatal corticosteroids from 8% to 80% in 16 weeks in women at risk of preterm delivery from 24 to 34 weeks' gestation. After this pilot study, we began programmes in three other hospitals, reaching 59–83% coverage from a baseline of 1–6% within 6 weeks. This intervention has thus far been associated with a drop in preterm neonatal mortality contribution from 60% to 24% at 0–6 days of age. Although this intervention was not done as part of a trial, and focuses only on quality improvement, we noted no increase in the rate of maternal or neonatal infections.

Antenatal corticosteroids induce fetal lung maturation through the same biological mechanism in low-income settings as in high-income settings and reduce the need for neonatal mechanical ventilation.[3] Although antenatal corticosteroids might not be a so-called magic bullet as a standalone vertical intervention, no biological basis exists to presume that babies born preterm in resource-poor settings will succumb to respiratory distress syndrome any more than do those in resource-rich countries. I support the existing recommendation of a single-course of antenatal corticosteroids to mothers at high risk of preterm birth between 24 weeks and 33 weeks' gestation, but question Azad and Costello's unrealistic prerequisite for round-the-clock access to level 2 care in a low-income setting.

Low-income settings, which have the highest burden of preterm neonatal deaths, urgently need proven beneficial interventions, not the assessment of therapeutic efficacy on the basis of resource profiling that could delay treatment. Contrary to Azad and Costello's speculation,[1] antenatal corticosteroids are likely to have a greater effect in the absence of level 2 care, not a lesser effect.[4] The difference between low-income and high-income settings is not biology, but an increased burden of disease and reduced access to even basic health care. Our experience in Malawi offers a powerful example for generalising this standard of care to the regions where it will save the most lives and also reduce neonatal disability.

I declare no competing interests.

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Antenatal corticosteroids to reduce preterm deaths in low-income settings

Kishwar Azad and Anthony Costello[1] suggest the use of extreme caution in scaling up of antenatal corticosteroid treatment in low-income settings. They raise three important questions with respect to the efficacy, safety, and the appropriate gestational age at which to give corticosteroids to patients in low-income countries.

Firstly, in terms of efficacy, there is high-quality evidence on the benefits of antenatal corticosteroids for lung maturation in utero. A large decrease in neonatal mortality was reported in trials in four middle-income countries, including those in Africa and the Middle East (relative risk [RR] 0·47, 95% CI 0·35–0·64), compared with 14 studies in high-income countries (0·79, 0·65–0·96).[2,3] Antenatal corticosteroids actually reduced the need for level 2 care, including mechanical ventilation or continuous positive airway pressure in four studies (0·69, 0·53–0·90) and intensive care in two studies (0·80, 0·65–0·99) suggesting that, in regions where mechanical ventilation is not available, substantial benefits could be expected.[2,3] We agree that more research is needed but in view of the biological basis for the effect of antenatal corticosteroids on infant mortality, it is extremely unlikely, statistically, that antenatal corticosteroids would be shown not to work in African or Asian babies.

Secondly, we agree with Azad and Costello that potential harm to the patient is always a critical issue. However, a one-off course of antenatal corticosteroids (<48 h) poses a very low risk of adverse effects. The Cochrane systematic review[2] discussed by Azad and Costello shows antenatal corticosteroids are associated with major reductions in, death, severe disability and lower rates of retinopathy of prematurity so their concerns with respect to perinatal death or disability are hard to justify. Repeat antenatal corticosteroids have been linked to learning disabilities compared with a single dose,[4] and late-onset metabolic syndrome might also be a risk.[5] With respect to maternal outcomes there is no robust evidence of increased infections.[6] Because preterm deaths are now the leading cause of child deaths at 1 million per year, the balance lies in the direction of reducing mortality rather than the unknown risks of less severe outcomes.

Thirdly, although the proven benefit of antenatal corticosteroids is when they are administered to patients at 28–33 weeks' gestation, this gestational age band is partly due to enrolment criteria in the original trials.[2,3] The gestational-age limit for antenatal corticosteroids in high-income countries has been extended with guidelines supporting use at less than 26 weeks' gestation. More than 85% of preterm infants are born at least 32 weeks' gestation,[7] and although few have major preterm birth complications, this amounts to a large proportion of infants potentially at risk. The upper gestational-age limit for corticosteroid use is a critical question yet to be answered, especially in health-care settings where mechanical ventilators are not widely available and antenatal corticosteroids are more likely to be life-saving. WHO is presently reviewing the recommended upper and lower gestational-age cutoffs for antenatal corticosteroid treatment. When gestational-age of an infant is unknown or is imprecisely known, the balance of risks needs to be considered and in high mortality settings the balance will be in favour of treatment.

High-income countries have at least 90% coverage of antenatal corticosteroids, with most women in preterm labour being treated, and clinicians would be sued for non-use. Yet countries with the highest rates of preterm births have negligible coverage of antenatal corticosteroids. We support the call for more research, especially on how to reach the poorest women and how to increase long-term health for both women and their babies. In the meantime, the evidence strongly supports giving a single, short course of corticosteroids to women at risk of preterm birth in hospitals everywhere, not just in high-income countries.

Prof Joy E Lawn is co-lead of ACS Technical Reference Team for UN Commission on Life Saving Commodities and wrote this Correspondence on behalf of the group.

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In their Comment[1] on the use of antenatal corticosteroids to reduce preterm infant deaths, Kishwar Azad and Anthony Costello advise "extreme caution" before scale-up in low-income settings. They emphasise maternal sepsis as a concern but cite only one trial in which dexamethasone resulted in a significant increase in fever that required antibiotic treatment compared with controls (relative risk [RR] 2·05, 95% CI 1·14–3·69; 118 women).[1,2] We suggest that this finding alone does not reflect a balanced assessment of the paucity of evidence available.[2]

In a systematic review of antenatal corticosteroid treatment to accelerate fetal lung maturation, only four of 21 randomised controlled trials report on puerperal sepsis outcomes for dexamethasone versus no antenatal corticosteroids and these show moderate heterogeneity (I^2 38%) (RR 1·74, 95% CI 1·04–2·89; 536 women).[2] Only two trials were in low-income to middle-income countries and had very different results: the Dexiprom trial from South Africa (0·57, 0·17–1·89; 204 women) and one trial from Jordon (4·19, 0·94–18·68; 139 women). Incidence of maternal postnatal fever did not differ in two trials, the US Collaborative trial (0·93, 0·56–1·53; 682 women) and the Dexiprom trial in South Africa (1·00, CI 0·36–2·75; 204 women). Most reassuringly, no significant difference was reported in the incidence of chorioamnionitis in four trials of dexamethasone (1·35, 0·89–2·05; 575 women) or postnatal fever in two trials of dexamethasone (0·94, 0·60–1·47; 886 women).[2] No trials of dexamethasone reported on maternal intrapartum fever when antibiotics were given.

Trials of betamethasone versus dexamethasone in accelerating fetal lung maturation have not reported on maternal infectious outcomes.[3] We are currently undertaking a large-scale trial to compare the efficacy of intramuscular dexamethasone versus betamethasone in reducing childhood neurosensory disability, with maternal infection as a secondary outcome.[4] Currently, no published data suggest a major risk of maternal infection with the use of antenatal corticosteroids and none are available to allow confident assertion that dexamethasone increases the risk. According to present recommendations, the major safety concern surrounding the use of antenatal corticosteroids is repeat doses.[5]

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CC is an author of two of the Cochrane systematic reviews cited in this Correspondence and is principal investigator for the A*STEROID randomised controlled trial (ACTRN12608000631303).

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Authors' reply

We agree with many of the correspondents' points. First, we concur that antenatal corticosteroid treatment can reduce respiratory distress in infants born at less than 34 weeks' gestation. Second, we welcome the rapid scale-up of its use in hospitals in Malawi, as described by Stephen Kaliti, and look forward to the published assessment of its effect on mortality in preterm infants. Third, we agree that more research is needed to explore the best methods for scale-up in hospitals and to assess the risks and benefits to patients through community studies in low-income regions. Particularly, we anticipate findings of a trial of antenatal corticosteroid treatment that is underway in several countries and in which 90 000 infants have been enrolled.

Conversely, we are not in agreement with Joy Lawn and colleagues who suggest that it is, "extremely unlikely, statistically, that antenatal corticosteroids would be shown not to work in African or Asian babies". Our point about the potential risks associated with antenatal corticosteroid scale-up was not a question of efficacy, or ethnicity, but instead the underlying risks and benefits of antenatal corticosteroids to populations in low-income regions and different levels of access to health care. These factors can strikingly change the benefit-to-risk ratio of interventions. For example, in low-income regions in south Asia and Africa, dietary vitamin A supplementation in rural populations and participatory women's groups had a large effect on child survival, but there is no evidence of a similar effect in populations in high-income regions in the USA or Europe.[1,2]

Our concern arose because of reports implying that antenatal corticosteroids could be scaled up as a vertical treatment administered to women with signs of preterm labour by community health-care workers, or at outreach clinics without specialised level-2 health-care facilities. Two potential risks from this setting could outweigh the benefits: the possibility that the number needed to treat, to save the life of a preterm infant, could increase the incidence of serious sepsis in mothers, and second, death or disability might occur later as a result of suboptimal preterm care.

Globally, 40 million women deliver their babies at home every year and many more face formidable economic, cultural, and geographical barriers to accessing good-quality maternity health care. Many of these women live in low-income regions and rural populations in Africa and south Asia and endure high levels of malnutrition, especially a lack of micronutrients and protein, malaria, anaemia, and worm infestations that combined with the immunosuppressive effect of pregnancy or HIV infection might increase their vulnerability to sepsis. In the USA, chorioamnionitis affects 9% of pregnancies, but the burden of placental infection is much higher in Africa and Asia.[3,4] We agree with Caroline Crowther and Julie Brown that a paucity of evidence exists for the effect of dexamethasone on maternal infection, anywhere, and a complete absence of evidence exists in low-income settings. Health-care workers need to be sure, however, that antenatal corticosteroids do not exacerbate the severity, or the dissemination, of maternal infections in these communities.

Stephen Kaliti suggests that, "antenatal corticosteroids are likely to have a greater effect in the absence of level 2 care, not a lesser effect", but the evidence to support this statement is weak. Any policy to extend antenatal corticosteroid delivery to mothers through community health-care workers in regions where access to good-quality specialised care is not available (and where the assessment of gestational age and duration of pregnancy is often unreliable) should be on the basis of randomised community effectiveness trials. The risks and benefits can then be measured in the same way that those of dietary vitamin A, chlorhexidine, and zinc supplementation have been assessed in populations in low-income regions.[5,6] We urge funders to support these studies.

We declare that we have no competing interests.

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Extreme caution is needed before scale-up of antenatal corticosteroids to reduce preterm deaths in low-income settings

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The great American epidemiologist Bill Silverman taught us that the road to hell is paved with good intentions. From 1942, during a 12-year period, more than 10 000 infants were blinded through retinopathy of prematurity because paediatricians recommended a minor increase in the concentration of supplemental oxygen for preterm infants in incubators.[1] Later, "untold thousands of premature infants succumbed in the first few days of life because incubator temperatures were set slightly too low (to avoid overheating)".[2] Indeed, Silverman's trial of adrenocorticotrophic hormone to treat retinopathy of prematurity showed no benefit and an increased death rate in the intervention group. He warned that we need trial evidence for any new preterm intervention. No shortcuts can be used—care of the preterm infant is a delicate and integrated process.

Recently, antenatal corticosteroid treatment has been widely promoted to reduce preterm deaths in developing countries. On the face of it, the argument seems to be persuasive. Worldwide, 15 million infants are born prematurely every year, and south Asia accounts for two-thirds and Africa for three-quarters of deaths in these infants.[3] The 2013 State of the World's Mothers report says: "Prenatal corticosteroids cost as little as 51 cents per treatment… are ready for rapid scale-up now…using skilled birth attendants…and could save 340 000 newborn lives each year".[4] This estimate does not come from trials but rather from a Lives Saved Analysis tool.[4]

The evidence is far more nuanced. A systematic review of 21 studies in high-income and middle-income country hospitals, which included a total of 3885 women and 4269 infants, showed that one course of corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth reduced neonatal deaths by 31% (relative risk [RR] 0·69, 95% CI 0·58–0·81; in 18 studies of 3956 infants) and respiratory distress syndrome by 34% (0·66, 95% CI 0·59–0·73; in 21 studies of 4038 infants).[5] Nonetheless, the statement made by the Healthy Newborn Network that "administering antenatal steroids to a mom in preterm labour, helps her baby speed up lung development, reducing the risk of newborn death by more than 50% in low-resource facilities"—is speculative. The clamour to roll out a so-called magic bullet treatment must be resisted until three crucial questions have been answered.

The first of these questions is whether antenatal corticosteroids actually work for mothers and infants at 33 weeks' gestation or less in poor populations? All studies in the systematic review were from hospitals in which infants had access to "level 2" special care: 24-h availability of skilled nursing; thermal stability; monitoring of blood gases, glucose, electrolytes, infection indicators, and bilirubin; apnoea alarms; oxygen and ventilatory support; and antibiotics and other essential drugs for infection and shock. Similar reductions in case-fatality rate are highly unlikely in settings where level 2 care is not available. Coverage of good-quality level 2 care in low-income settings is tiny—few facilities exist outside capital cities. One study of 1000 low-birthweight infants in Dhaka, Bangladesh, showed that even in a teaching hospital that provided level 2 care, three-quarters of neonates born at less than 33 weeks' gestation died during the neonatal period.[6] The causes of death were manifold and not just attributable to respiratory distress. Indeed, respiratory distress syndrome might be less prevalent in poor countries than in wealthy nations because intrauterine growth retardation causes fetal cortisol concentrations to rise, which might accelerate the production of lung surfactant.

The second crucial question asks whether safety issues exist in poor settings. If steroids are given to millions of women in preterm labour in poor populations, can we be sure that there will be no significantly increased risk of maternal sepsis, perinatal death, or childhood disability? The 2006 systematic review showed that, from eight trials and 1003 women with data for puerperal sepsis, 57 of 496 treated mothers had sepsis, compared with 44 of 507 controls (RR 1·35, 95% CI 0·93–1·95). More worrying is the evidence from trials that used dexamethasone (the low-cost treatment recommended for scale-up), which significantly increased both puerperal sepsis (RR 1·74, 95% CI 1·04–2·89; in four trials of 536 women) and fever that needed antibiotics (2·05, 1·14–3·69; in one trial of 118 women), in comparatively wealthy populations.[7] These findings

For the **Healthy Newborn Network** see www.healthynewbornnetwork.org/topic/antenatal-corticosteroids

ring alarm bells for scale-up in populations in which the prevalence of malnutrition and the risk of sepsis are much higher and access to antibiotics is low. In infants born at a gestation of at least 36 weeks, an almost significant trend was recorded towards an increase in combined fetal and neonatal death (RR 3·25, 95% CI 0·99–10·66; in two studies of 498 infants).

Another major concern is that a substantially increased risk of disability can occur in cases where preterm survival is accompanied by suboptimum care. Historically, outcomes for preterm infants born at weights of less than 1500 g in developed countries showed that mortality rates and the prevalence of major disability in survivors were very high until after 1960 when level 2 care improved on a wide scale.

The third crucial question is whether there is any evidence of benefit for the great majority of preterm infants born at more than 33 weeks? A recent working paper for the UN Commission on Life-Saving Commodities for Women and Children promotes scale-up of steroids by suggesting "the effect is greatest between 31 weeks and 36 weeks gestation" although no evidence shows an effect beyond 33 weeks.[7] Three-quarters of the 12·6 million preterm infants worldwide each year are born after 33 completed weeks of gestation. In this group, the systematic review of antenatal steroids[5] showed no reduction in fetal or newborn deaths. For deaths in newborn babies alone, there was no benefit for babies born at 34 weeks or more (RR 1·58, 95% CI 0·71–3·50; two studies, 808 infants) or for babies born at 36 weeks or more (2·62, 95% CI 0·77–8·96, three studies, 514 infants). Moreover, there was no reduction in respiratory distress at more than 34 weeks, as we might expect from the timing of maturation of surfactant production. For these reasons, the American Academy of Obstetrics and Gynecology and the British Royal College of Obstetrics and Gynaecology both recommend steroid treatment for mothers only up to 33 weeks' gestation.

With no evidence of benefit after 33 weeks in any setting, questionable benefit at less than 33 weeks in poor populations, potential risks of sepsis in mothers, and unknown disability levels in babies in cases where level 2 care standards are not met, we urge extreme caution. Millions of mothers in poor populations could soon be given steroid injections each year which carry risks that could substantially exceed the benefits. We support the existing recommendation to restrict single-dose antenatal steroids to mothers who are at 33 weeks' gestation or less, in preterm labour, and with easy access to good quality, round-the-clock level 2 care. We need clear evidence for benefit in other settings. One multicountry trial at established research sites in Argentina, Guatemala, Kenya, India, Pakistan, and Zambia is underway.[8] Other trials in poor and inaccessible populations are needed before we can be certain of the risk–benefit ratio.

No quick fix exists to ensure preterm survival without serious disability. The global priority remains greater coverage of round-the-clock provision of high-quality level 2 care. The scope for low-cost innovation in district facilities is tremendous—eg, kangaroo care, the use of nursing aides to support scarce nursing staff, simple technology for blood sugar and bilirubin estimation, electricity-free syringe pumps, and low-cost incubators for babies too ill to manage skin-to-skin care. However, technology and drugs alone are dangerous without the provision and retention of skilled and motivated staff—the biggest challenge of all.

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We declare that we have no competing interests.

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