

Antenatal Corticosteroids Trial (ACT): trial summary

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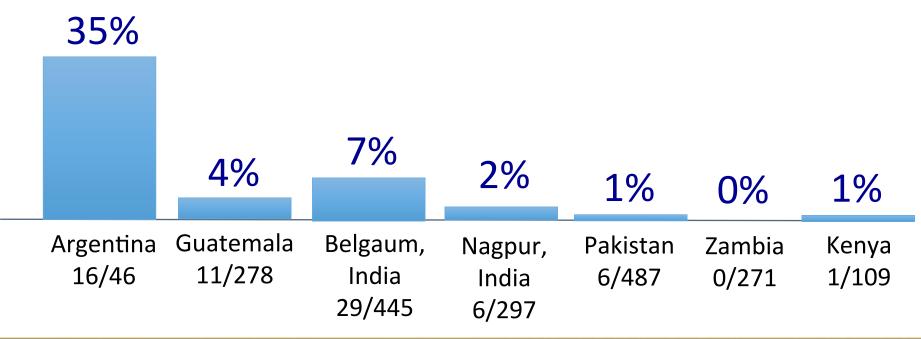
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Why is an intervention proven to be effective, safe, easy to administer, and inexpensive in most high and a few middle income countries, still underused in low and middle income countries?



Use of ACS at six GN sites (3-6 month baseline period in 2011)

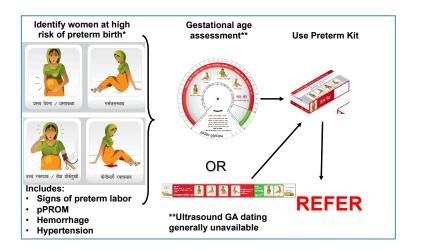
Among women with babies <5th percentile BW





ACT Trial (2011-2014)

- 6 countries
- **102** clusters
- 99,742 mothers enrolled
- **100,705** babies
- 18-month intervention



A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT clusterrandomised trial



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Background Anienabl corticosteroids for pregnant women at risk of preterm birth are among the most effective hospital based interventions to reduce neonatal mortality. We aimed to assess the feasibility, effectiveness, and safety Newson Comof a multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels of health care in w-income and middle-income countries

on in this 15-month, cluster-randomized trial, we randomly assigned (1:1) rural and semi-urban clusters within six countries (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia) to standard care or a multifaceted Intervention including components to improve identification of women at risk of preterm birth and to facilitate appropriate use of animatal corticosteroids. The primary outcome was 23-day neonatal mortality among infants less than the 5th percentile for birthweight is peary for preterm birth) across the clusters. Use of animutal corticosteroids and suspected maternal infection were additional main outcomes. This trial is registered with ClinicalTitals.gov, number NCT00084096

Findings The ACT total took place between October, 2011, and March, 2014 (start dates varied by site). S1 intervention clusters with 47.344 healtrias (2520 [555] less than 586 percentile for intrinsequity and 50 control clusters with 50.745 levelarths (2520 [555] less than 586 percentile) completed follow-up. 1052 [6555] of 23.27 women in intervention clusters who delivered less-than 585 percentile infants received antennals controlleration, compared with 125 [075] of 2705] of 2062. In control clusters [a-c0-0001]. Among the less-than-5th-percentile infinits, 23-day securial mortality was 225 per 1000 brehitrih for the intervention group and 232 per 1000 brehitrih for the control group [minite risk [RR]] 0-96, 95% C10-87-1-96, p-0-053 and suspected matternal infection was reported in 236 (10%) of 2264 women in the intervention group and 133 (0%) of 2064 in the control group [odds ratio [OR] 1-07, 1-33-2-96, p-0-0001]. Among the whole population, 25-day meanatal mortality was 27-4 per 1000 livebirths for the intervention group and 23-9 per 1000 livebirths for the control group (RR 1-12, 1-02-1-22, p-0-0127) and suspected maternal infection was reported in 1207 (3%) of 48239 women in the intervention group and 867 (2%) of 51523 in the control group (OR 1-45, 1-33-1-58, pc0-0001).

ion Despite increased use of animabl corticosteroids in low-birthweight infants in the ini neonatal mortality did not decrease in this group, and increased in the population ownsil. For every 1000 women exposed to this strategy, an excess of 3-5 neonatal deaths occurred, and the risk of maternal infection seems to have been increased.

Funding Eunice Rennedy Shriver National Institute of Child Health and Human Development

The use of anismatal corticosteroids for program women showed a 35% relative reduction in neonatal mortality at high risk of preterm delivery is among the most prelative risk [RR] 0-60, 95% CI 0-58-0-81] and an even most subset (resulting the hospital-based interventions to reduce neonatal argor reduction in severe neonatal merbidity. However, a Department of the larger reduction in severe neonatal merbidity.

21 randomised controlled trials of antenntal corticosteroids mortality associated with preferre birth, a leading non-significant increased risk of pumperal septis (1-35, cause of childhood mortality." A systematic review of 0-93-1-95) was noted from eight studies. "All of the trials

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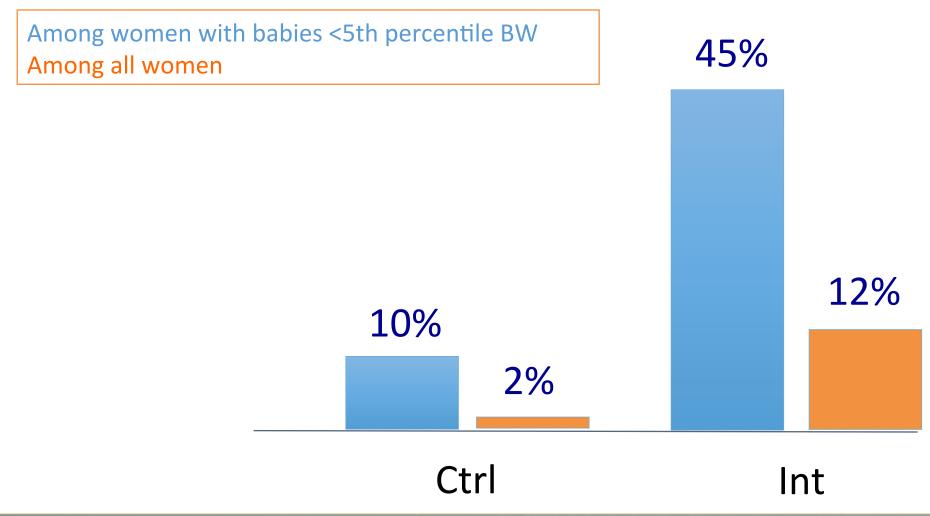


Trial Questions

- Was it feasible under routine conditions to scale up ACS at all levels of care in LMIC?
- Were ACS effective to reduce neonatal mortality in low resource settings in the absence of newborn intensive care?
- Were ACS safe for the mother and/or newborns if scaled up at all levels of care?



Use of ACS

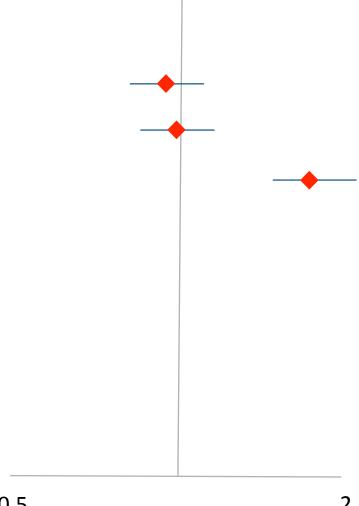




Maternal and Perinatal Outcomes

Among births <5th percentile

- Neonatal deaths 28d
- Stillbirths
- Suspected Maternal Infection*



0.5





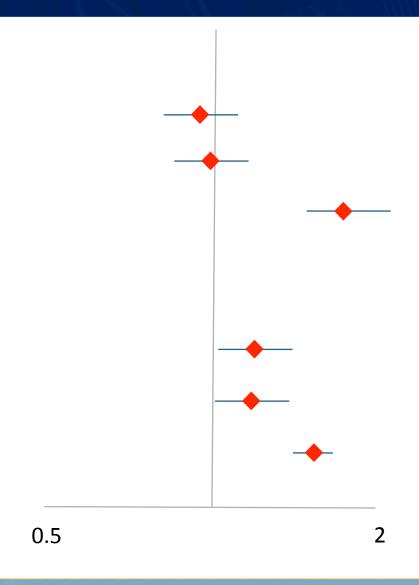
Maternal and Perinatal Outcomes

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Among <u>all</u> births

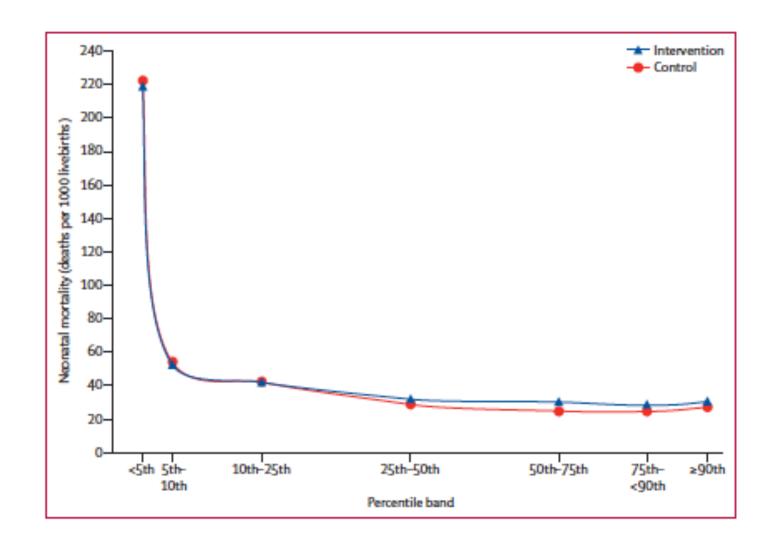
- Neonatal deaths 28d
- Stillbirths
- Suspected Maternal Infection*



*Odds ratio



Effect on Neonatal Mortality by BW Percentiles





Interpretation

Absence of positive effect on NM (<5th percentile)

- Partial coverage of ACS (45%)
- 50% late preterms
- Absence of neonatal intensive care
- Newborns suffering other co-morbidities (infection)?



Interpretation

Harmful effects on the overall population

- Overtreatment with ACS (only 16% of treated delivered a small/preterm baby)
- Hypothesis: increased susceptibility to infection?
- Hypothesis: worse quality of care in the intervention group?



Post-hoc secondary Analysis

Identify which components of the complex intervention might have caused the increased mortality by:

- Analyzing the use of steroids in the deaths to see if could have caused excess mortality;
- Exploring the process of care to see if the intervention effect on mortality was mediated by co-interventions related to antenatal care or delivery care.



Post-hoc secondary Analysis

Gain a better understanding of the mechanism of action through which ACS might have increased mortality:

 The factors related to ACS administration associated with perinatal deaths e.g. timing of steroid use, number of doses and time to delivery.

 Whether regional or site differences in health system, population baseline risk, intervention implementation were associated with the observed effects.



Post-hoc secondary Analysis

To analyze the effect of the intervention on:

- neonatal infectious morbidity and mortality
- stillbirth rates, including assessment of macerated, intrapartum stillbirth



Thank You!

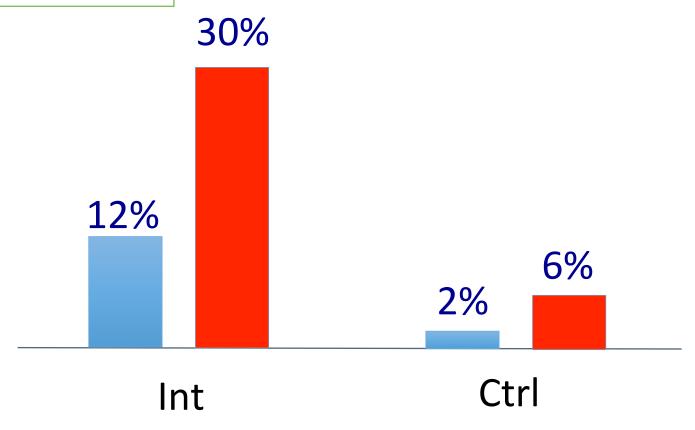




To identify which components of the complex intervention might have caused the increased mortality

ACS use among all women

ACS use among neonatal deaths





To identify which components of the complex intervention might have caused the increased mortality

 Did the ACT intervention affect the quality of care in the intervention compared to the control group?

No evidences were found to support such hypothesis



Did the intervention increase the risk of neonatal severe infection in the intervention compared to the control group?

Infection as a cause of neonatal death:

Characteristic, n (%)	Livebirths < 5 th percentile birthweight		All livebirths	
	Intervention	Control	Intervention	Control
Neonatal deaths <28 days, N	566	524	1,300	1,211
Birth asphyxia	42 (7.4)	45 (8.6)	303 (23.3)	278 (23.0)
Low birthweight/prematurity	380 (67.1)	362 (69.1)	430 (33.1)	404 (33.4)
Neonatal sepsis/infection	28 (4.9)	15 (2.9)	121 (9.3)	95 (7.8)
Major malformation	15 (2.7)	14 (2.7)	47 (3.6)	47 (3.9)
Other	73 (12.9)	64 (12.2)	306 (23.5)	276 (22.8)
Cause not identified	28 (5.0)	24 (4.6)	93 (7.2)	111 (9.2)

Supplementary table 4: Cause of 28-day neonatal deaths among all births



Did the intervention increase the risk of neonatal severe infection in the intervention compared to the control group?

• We adapted WHO YICSS algorithm to define possible severe bacterial infection (pSBI).

 We compared pSBI rates, and the pSBI plus death rates in intervention vs. control groups, controlling for pre-trial imbalances.



Methods: pSBI Definition

WHO YICSS symptom	GN MNHR symptom		
Temperature ≥ 37.5° C	High fever (> 38° C)		
Temperature < 35.5° C	Hypothermia (< 35° C)		
History of difficulty feeding	Feeding problems;		
	Stopped suckling/feeding		
History of convulsions	Convulsions		
Respiratory rate of 60 breaths per	Breathing problems;		
minute or more	Difficulty breathing		
Severe chest indrawing	Breathing problems;		
	Difficulty breathing		
Movement only when stimulated	-		
	Bleeding/pus-like discharge from		
	umbilicus		
	Infection COD; Text indicating		
	infection, sepsis, possible sepsis, septic		
	conditions, meningitis, pneumonia		



pSBI

pSBI

- Pre-trial 12.4%
- 14.2%
- 0.95 (0.75-1.21)

RR (95%CI)

Trial

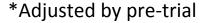
- 14.8%
- 13.9%
- 1.01 (0.89-1.14)

Adjusted by pre-trial

1.05 (0.92-1.20)

- <25th BW %ile*</p>
- ≥25th BW %ile*

- 1.03 (0.92-1.15)
- 1.15 (0.98-1.35)



pSBI *plus* death

pSBI plus death

- Pre-trial
- 2.3%
- 2.4%
- 0.96 (0.87-1.07)

Trial

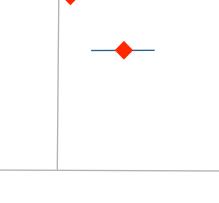
- 2.4%
- 2.0%
- 1.16 (1.04-1.29)

Adjusted by pre-trial

1.17 (1.04-1.30)

- <25th BW %ile*</p>
- ≥25th BW %ile*

- 1.03 (0.90-1.17)
- 1.36 (1.12-1.65)



RR (95%CI)

*Adjusted by pre-trial

0.5

Summary

- Compared to other components of the multifaceted intervention, ACS may have been more likely involved in the observed increased neonatal mortality,
- ACS may be associated with the observed increased risks of potential severe infections and death reported in this paper.
- These interpretations should be considered cautiously and no practical implications can be derived from them.
- However, they support that further trials are urgently needed to clarify the effectiveness and safety of ACS on neonatal health in low resource settings.
- Neonatal infection should be included as a main outcome in such trials.

