Global Network
for Women's & Children's Health Research

Antenatal Corticosteroids Trial (ACT): trial summary

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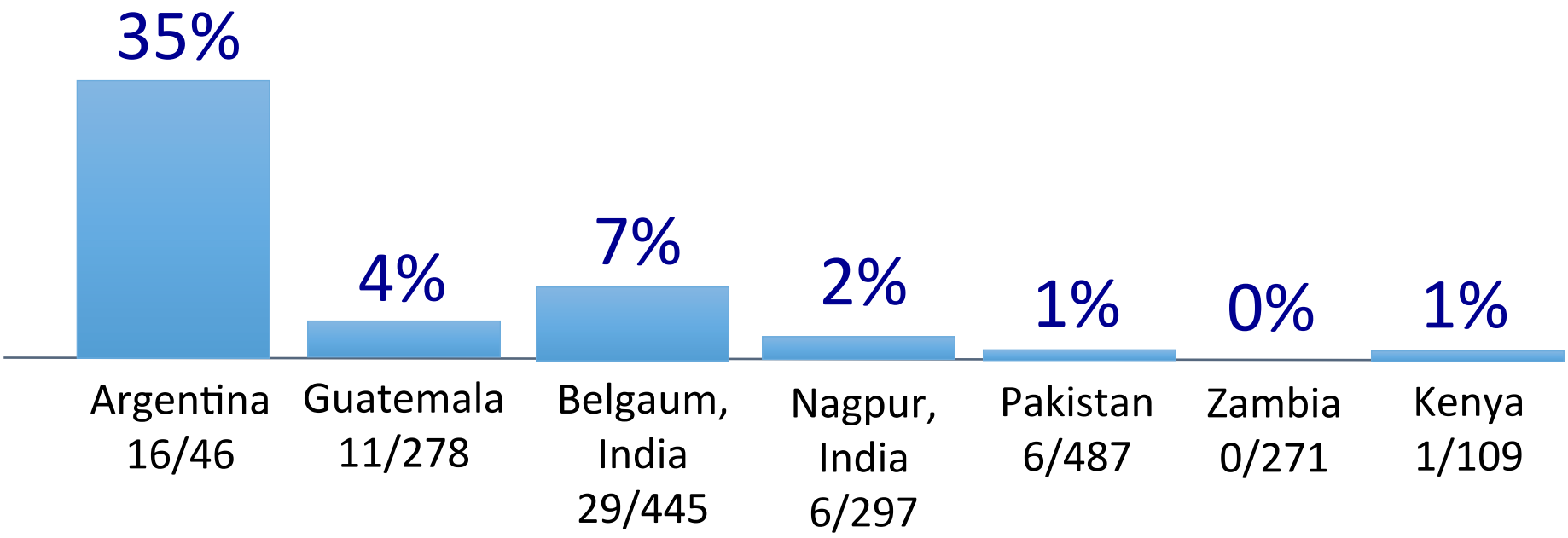
- No conflict of interest

2007

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?

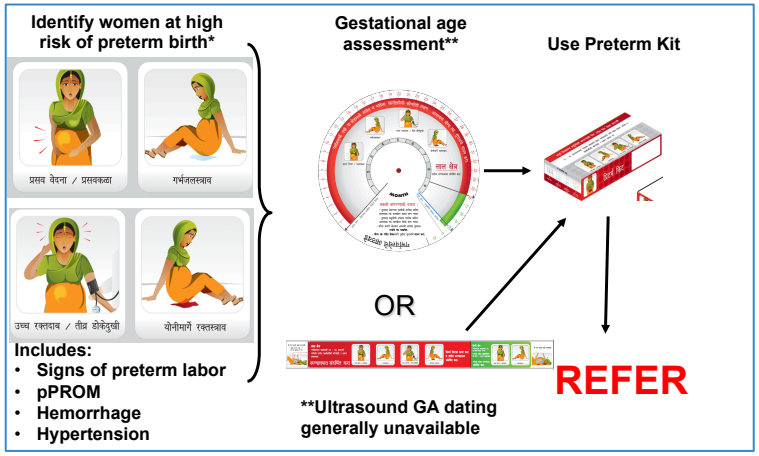
Use of ACS at six GN sites
(3-6 month baseline period in 2011)

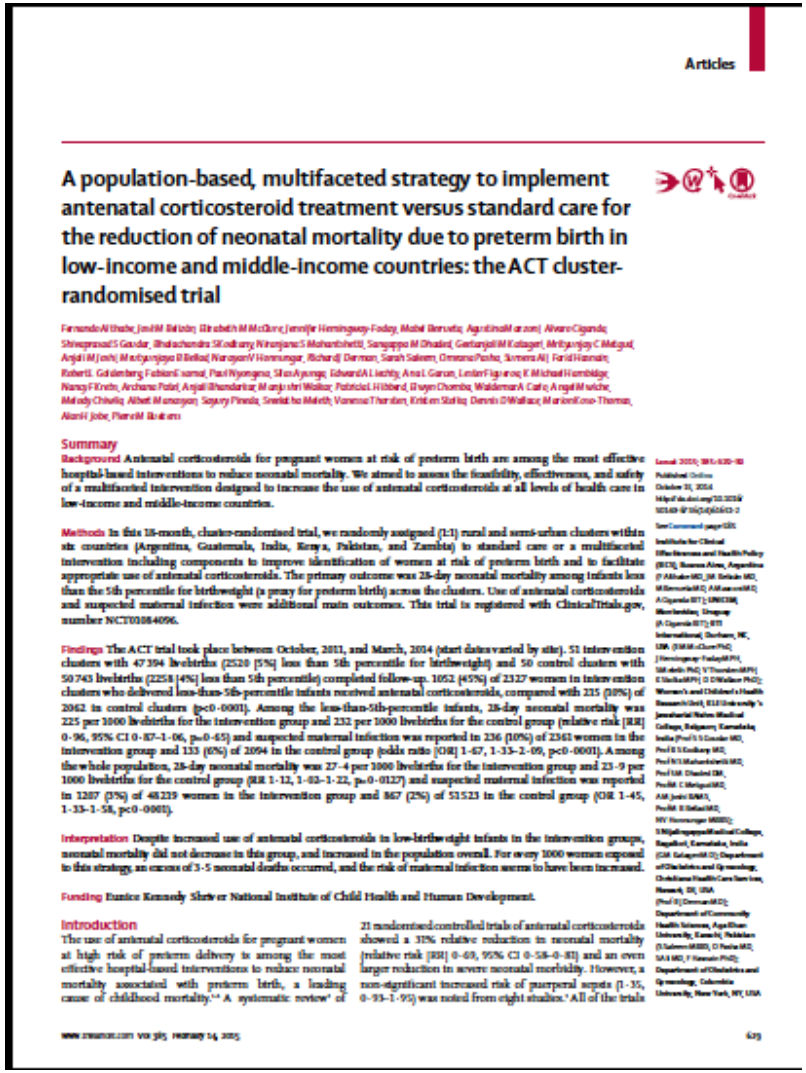
Among women with babies <5th percentile BW



ACT Trial (2011-2014)

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





Articles

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 cluster-randomised trial

Summary

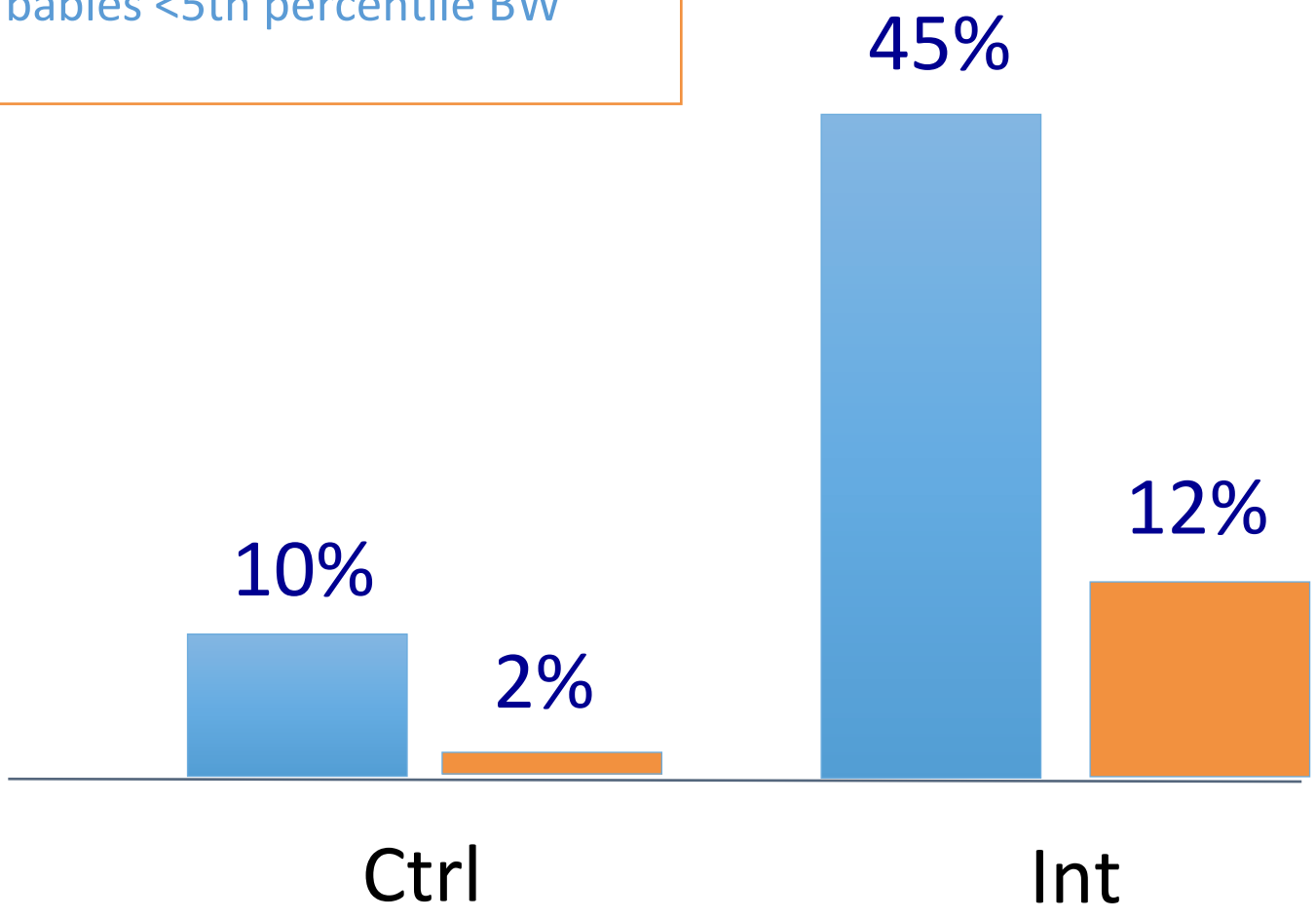
Introduction

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

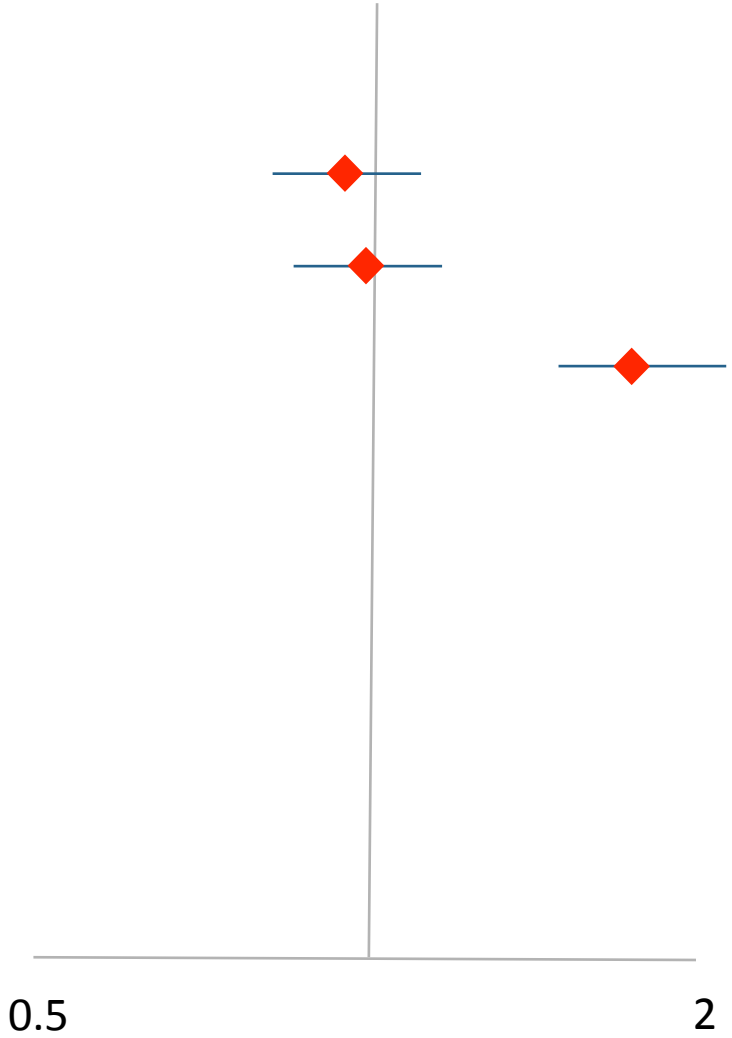
Among women with babies <5th percentile BW
Among all women



Maternal and Perinatal Outcomes

Among births <5th percentile

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



*Odds ratio

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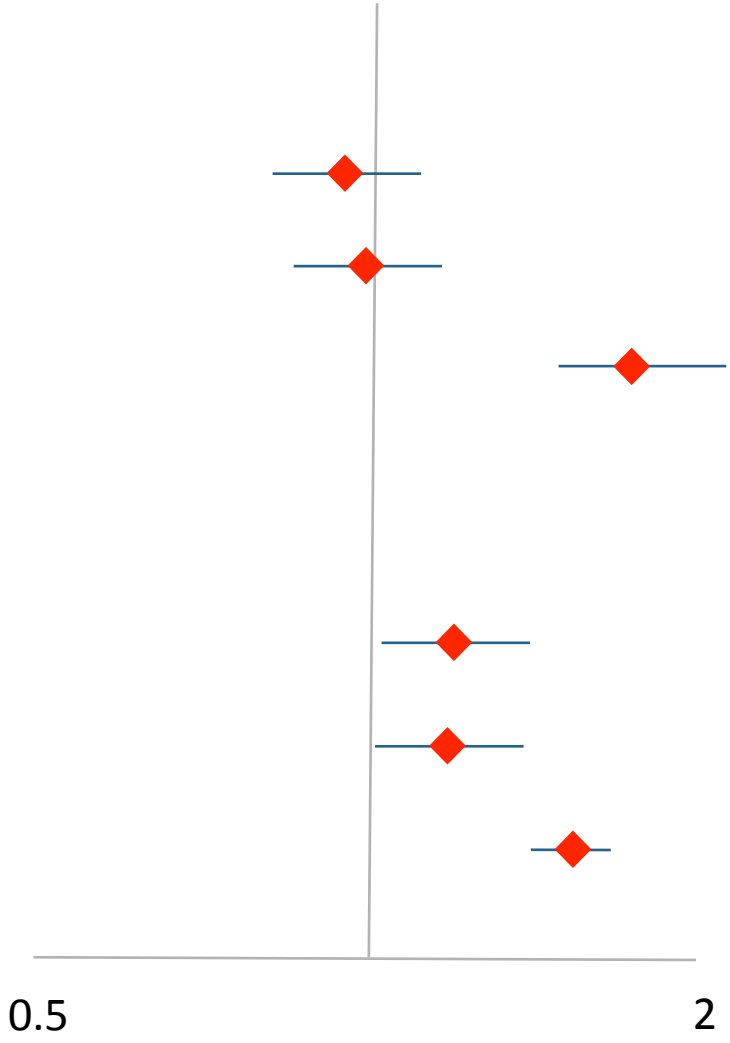
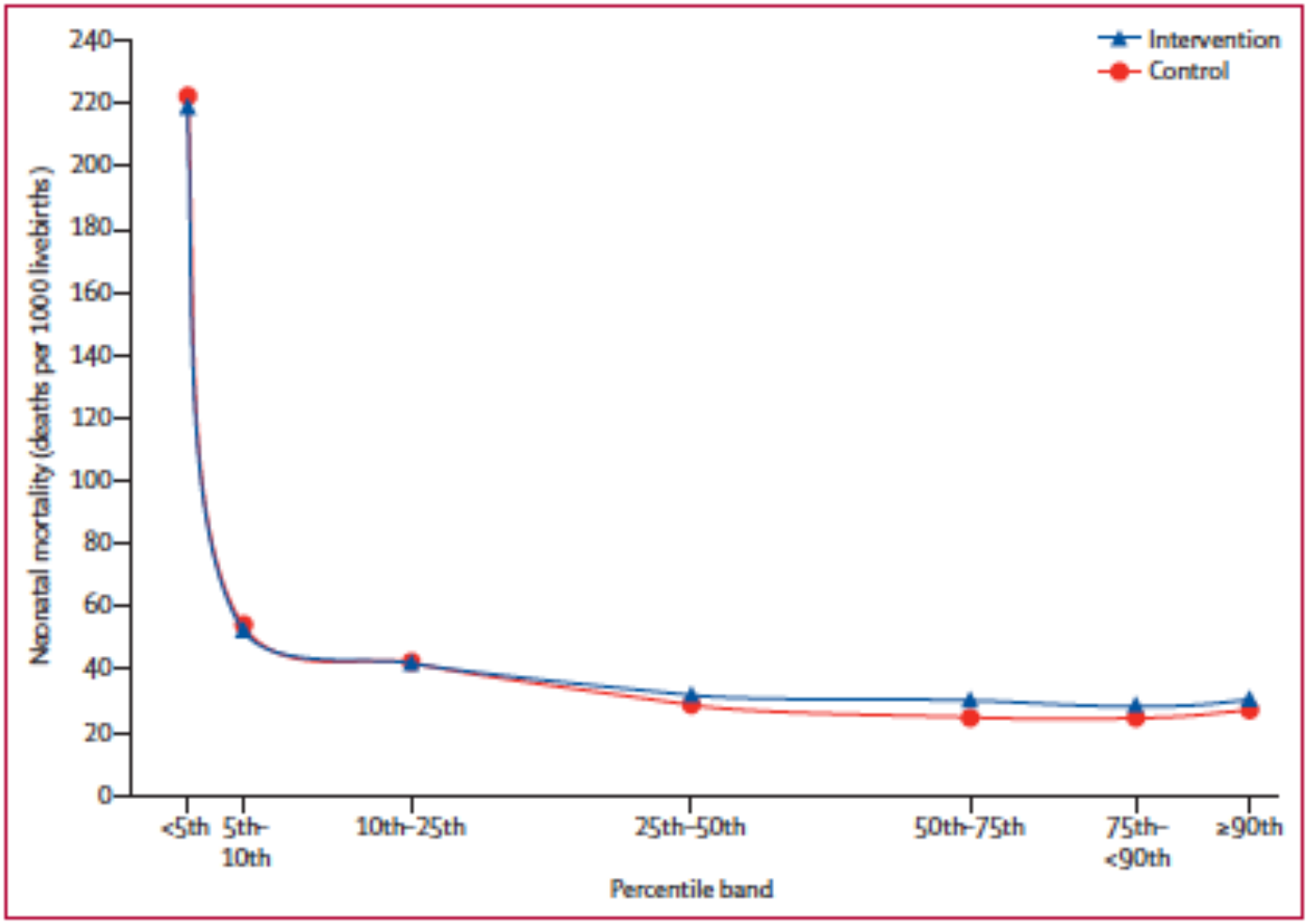


*Odds ratio

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.

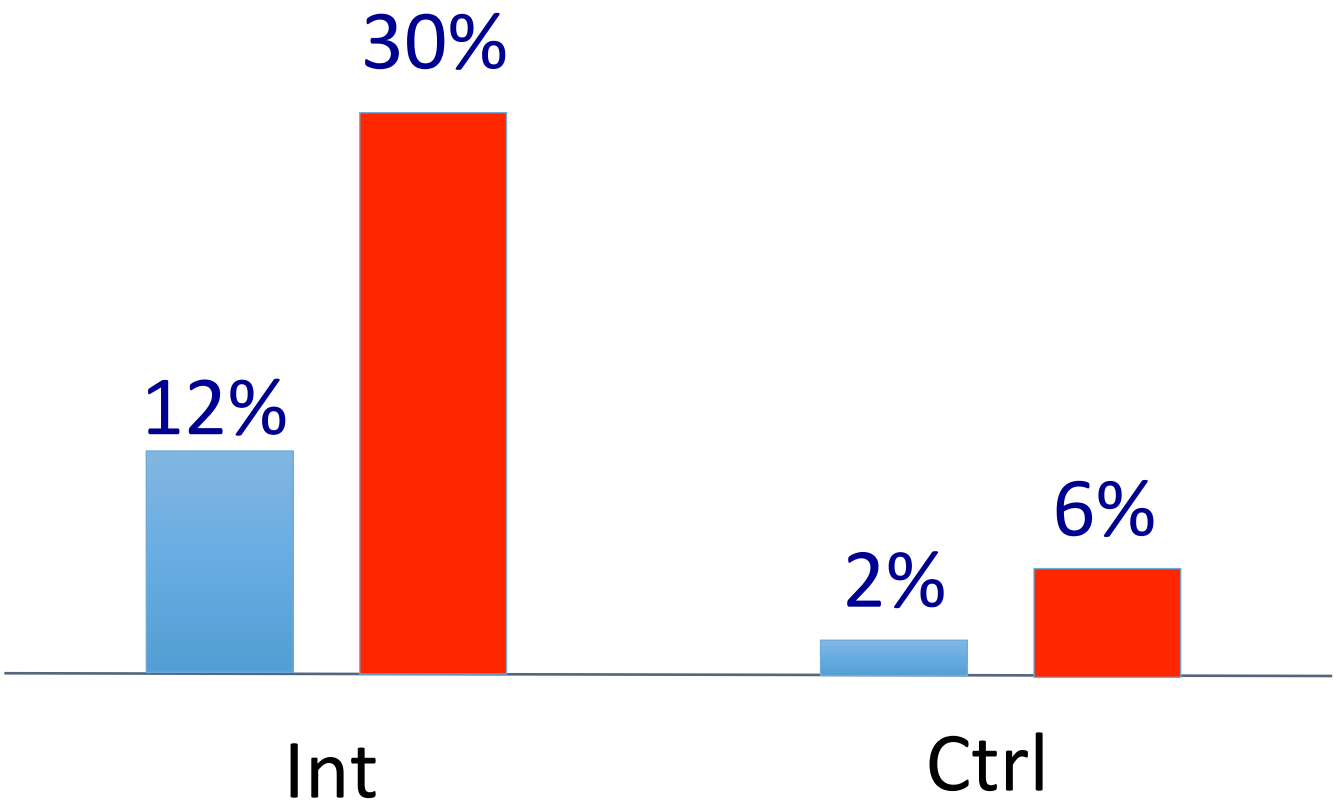
Post-hoc secondary Analysis

- 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:

	Livebirths < 5th percentile birthweight		All livebirths	
Characteristic, n (%)	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 minute or more	Breathing problems; 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

Young Infants Clinical Signs Study Group. Lancet 2008

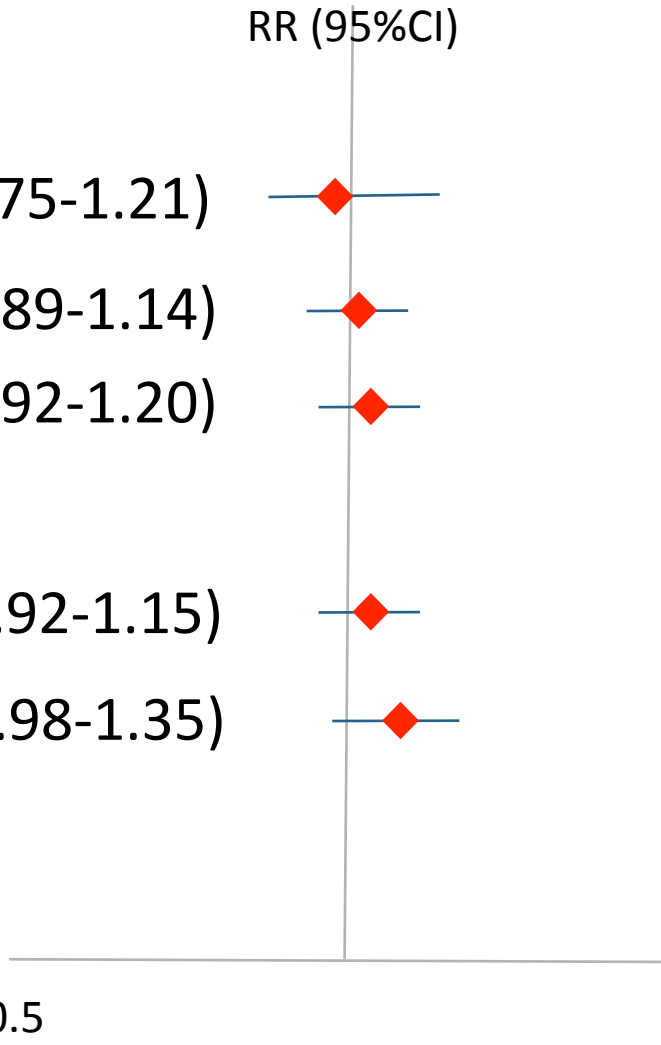
pSBI

pSBI

- Pre-trial 12.4% 14.2% 0.95 (0.75-1.21)
- Trial 14.8% 13.9% 1.01 (0.89-1.14)
  - Adjusted by pre-trial 1.05 (0.92-1.20)

○ <25th BW %ile* 1.03 (0.92-1.15)

○ ≥25th BW %ile* 1.15 (0.98-1.35)

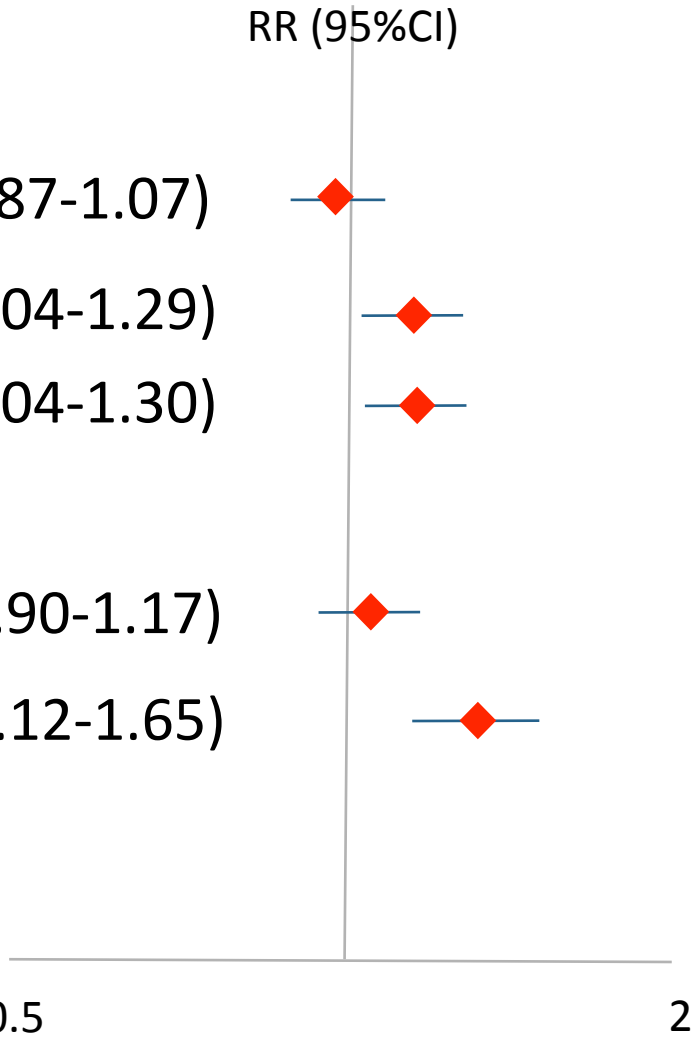


*Adjusted by pre-trial

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*			1.03 (0.90-1.17)
○ ≥25th BW %ile*			1.36 (1.12-1.65)



*Adjusted by pre-trial

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.