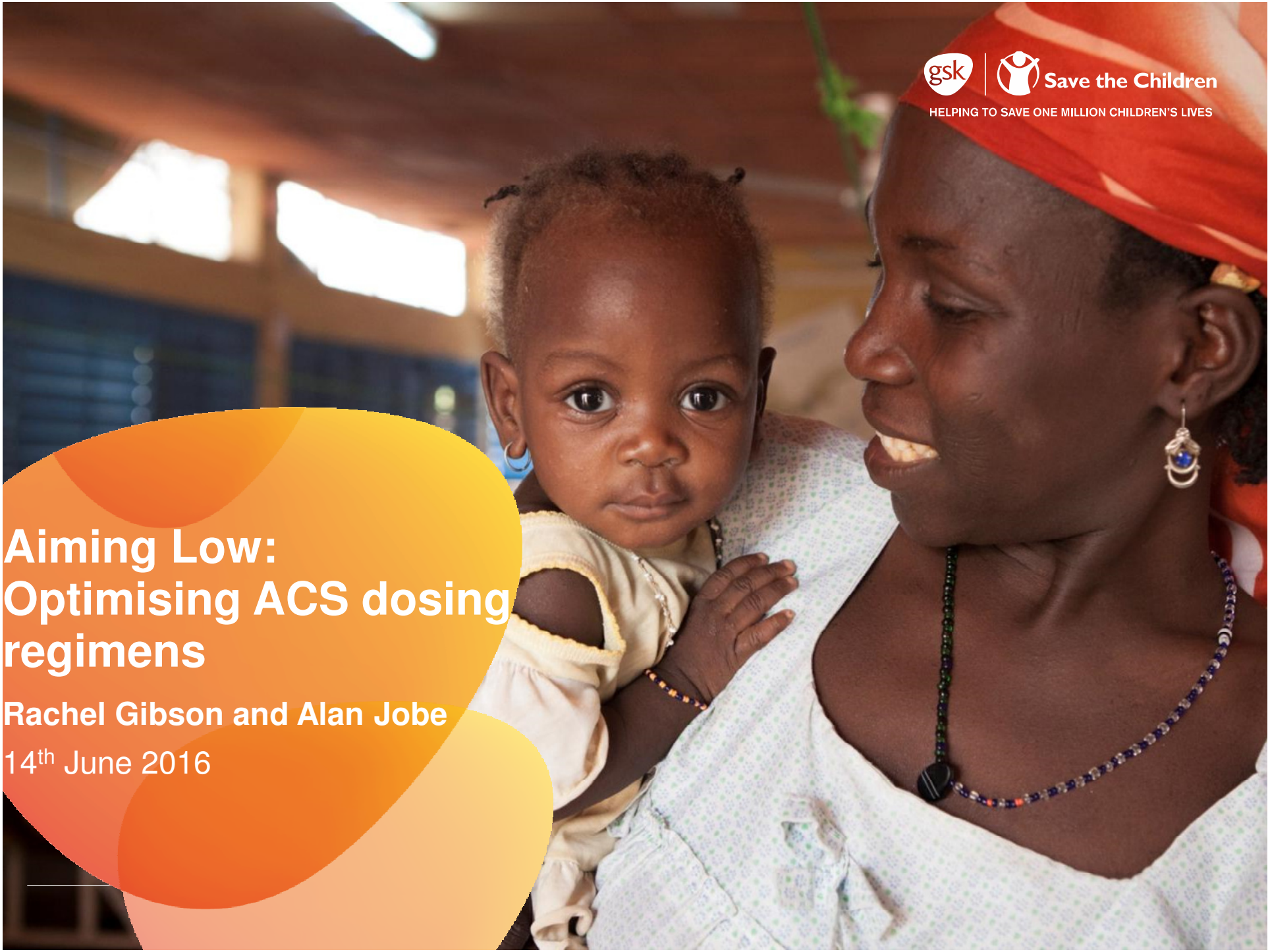


Aiming Low: Optimising ACS dosing regimens

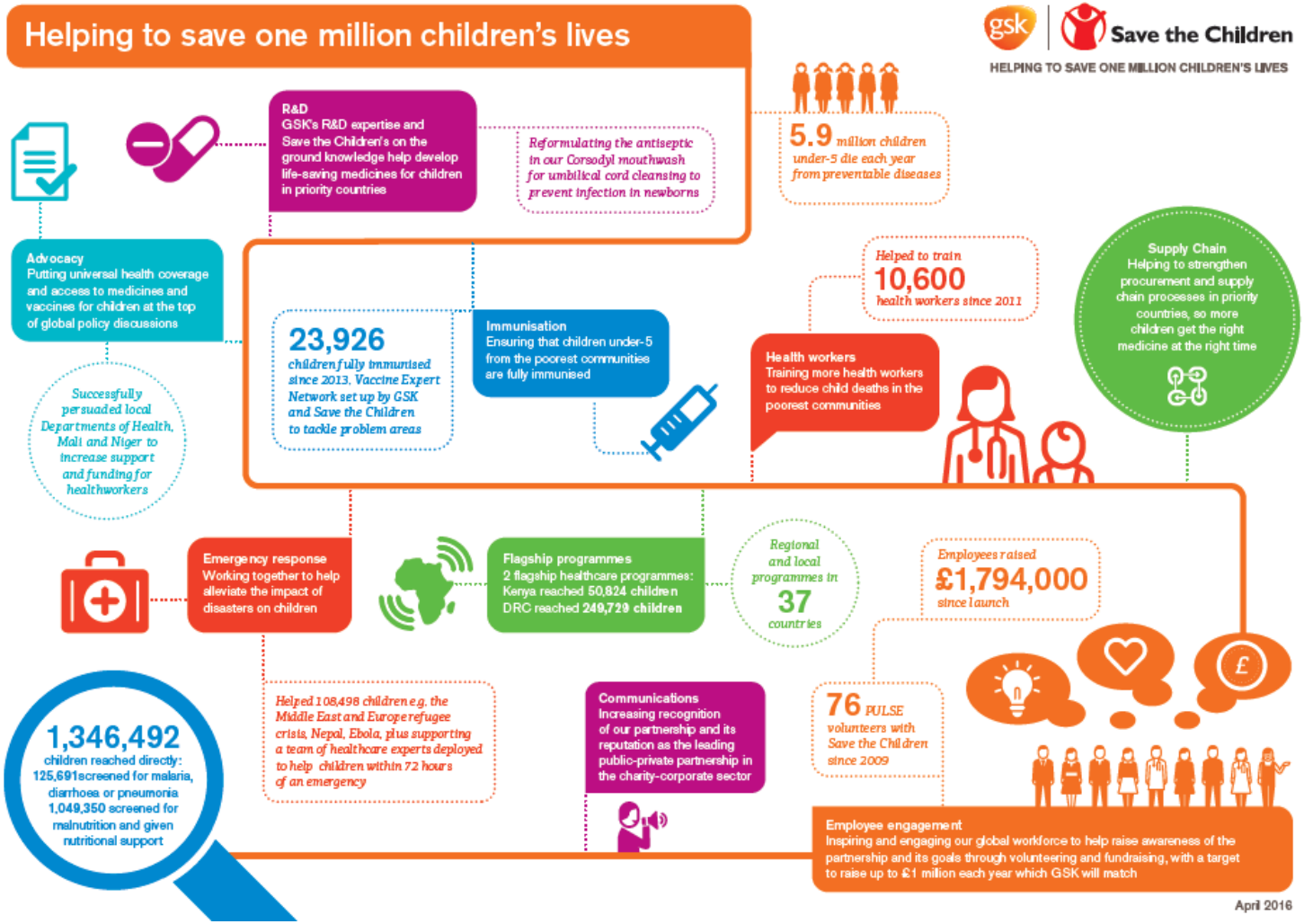
Rachel Gibson and Alan Jobe

14th June 2016

GSK / Save the Children Partnership

gsk | Save the Children

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES



GSK/Save The Children R&D Challenge 2014

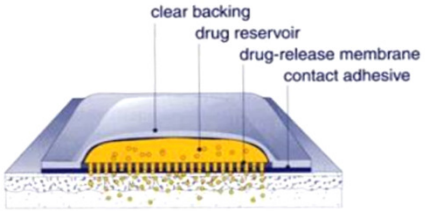
HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

Currently, Antenatal corticosteroids (ACS) are administered IM (intramuscular) for several doses over 48 hours

Idea: Could GSK support a time-bound piece of open innovation feasibility research on alternative ACS delivery methods?

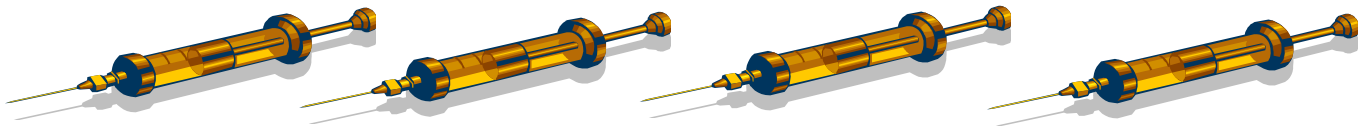
Tablet(s)

OR



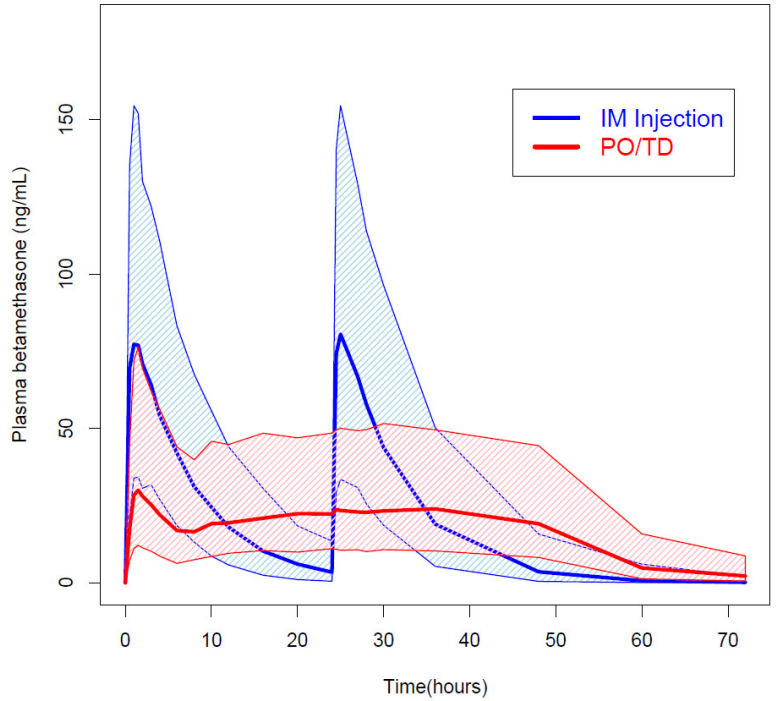
TDDS

Instead of….



What this might look like….

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES



- Betamethasone two 12 mg IM injections Q24 hours versus a 16 mg tablet + a patch delivering ~0.4 mg/hr for 48 hours.
- Projections based on literature data[1-4].
- Medians – thick lines, shaded areas – 95% prediction intervals.

Advantages

- No cold chain
- No Needles
- No expertise required for administration of ACS medication
- Flatter medicine profile
- Could remove patch in no longer in labour

1. Egerman RS et al. A Comparison of the Bioavailability of Oral and Intramuscular Dexamethasone in Women in Late Pregnancy. Obstet Gynecol 1997, 89, p276-80.
2. Egerman RS. A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. AJOG. 1998.
3. Della Torre et al. Betamethasone in Pregnancy:Influence of maternal body weight and multiple gestation on pharmacokinetics AJOG, 2010.
4. Kubota et al. Plasma concentrations of betamethoasone after topical application of betamethasone 17-valerate. Br. J. Clin. Pharmacy, 1994

Context is everything

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

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

Fernando Althabe, José M Belizán, Elizabeth M McClure, Jennifer Hemingway-Foday, Mabel Berrueta, Agustina Mazzoni, Alvaro Ciganda, Shivaprasad S Goudar, Bhalachandra S Kodkany, Niranjana S Mahantshetti, Sangappa M Dhaded, Geetanjali M Katageri, Mrityunjay C Metgud, Anjali M Joshi, Mrutyunjaya B Bellad, Narayan V Honnungar, Richard J Derman, Sarah Saleem, Omrana Pasha, Sumera Ali, Farid Hasnain, Robert L Goldenberg, Fabian Esamai, Paul Nyongesa, Silas Ayunga, Edward A Liechty, Ana L. Garces, Lester Figueroa, K Michael Hambidge, Nancy F Krebs, Archana Patel, Anjali Bhandarkar, Manjushri Waikar, Patricia L Hibberd, Elwyn Chomba, Waldemar A Carlo, Angel Mwiche, Melody Chiwila, Albert Manasyan, Sayury Pineda, Sreelatha Meleth, Vanessa Thorsten, Kristen Stolka, Dennis D Wallace, Marion Koso-Thomas, Alan H Jobe, Pierre M Buekens

Summary

Background Antenatal 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 of a multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels of health care in low-income and middle-income countries.

Lancet 2015; 385: 629–39
Published Online
October 15, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61651-2

- **ACT Cluster Randomised Trial**
- Multi-faceted strategy to increase ACS treatment with higher upper gestation age threshold of 36 weeks.
- .Despite increased use of antenatal corticosteroids in low-birth weight infants in the intervention groups, neonatal mortality did not decrease in this group, and increased in the population overall.
- For every 1000 women exposed to this strategy, an excess of 3·5 neonatal deaths (12%) occurred, and the risk of maternal infection seems to have been increased.

- Challenges of gestational age assessment and appropriate prescribing of ACS
- Absence of any dose-ranging data to support current ACS dosing recommendations.
- ACS are accepted therapy worldwide for over 40 years. ACS are only known to be approved for fetal indications in very few countries including Australia, and New Zealand. In nearly all other countries, antenatal use is off-label.
- The drug choice, dosing, and route of treatment not optimised to current pharmaceutical standards.

Updated WHO Recommendations 2015

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

Antenatal corticosteroid therapy is recommended for women at risk of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met:

- Ability to accurately assess gestational age (GA)
- Ability to determine high risk of imminent preterm birth
- Adequate obstetrical care of during child birth
- Adequate care available for preterm newborns (e.g. resuscitation, thermal care, feeding support, treatment of infection, safe oxygen use)
- No clinical evidence of maternal infection

Other ACS Work

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

A*STEROID

Of the two main ACS medicines (dexa and beta), neither has been definitively shown to be superior to the other - results expected 2017

Crowther et al. BMC Pregnancy and Childbirth 2013, 13:104
http://www.biomedcentral.com/1471-2393/13/104

BMC Pregnancy & Childbirth

STUDY PROTOCOL Open Access

Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol

ALPS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2016 VOL. 374 NO. 14

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, A.T.N. Tita, U.M. Reddy, G.R. Saade, D.J. Rouse, D.S. McKenna, E.A.S. Clark, J.M. Thorp, Jr., E.K. Chien, A.M. Peaceman, R.S. Gibbs, G.K. Swamy, M.E. Norton, B.M. Casey, S.N. Caritis, J.E. Tolosa, Y. Sorokin, J.P. VanDorsten, and L. Jain, for the NICHD Maternal–Fetal Medicine Units Network*

- Improved study respiratory composite score at 72 hours
- No impact on newborn mortality, RDS, or IVH outcomes
- Infants were more likely to have hypoglycaemia than those in the placebo group (24 percent vs. 14.9 percent).
- Need to address whether this short term benefit may be associated with any long term benefits or risks. (*Crowther and Harding (2016) NEJM*)
- Funding being sought for longer term follow-up

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HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

Aiming Low: Development of New ACS Formulations

Alan H. Jobe, MD, PhD

Cincinnati Children's Hospital

University of Cincinnati

Cincinnati, Ohio

UNIVERSITY OF Cincinnati

Cincinnati Children's Hospital Medical Center

Conflicts of Interest Declaration

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

	Source:	Purpose:
Grants	B&M Gates Foundation	Antenatal steroid studies
	GSK (Matt Kemp)	Steroid Pharmacokinetics
Gifts for Research	Chiesi	Budesonide for BPD, Surfactant
	Merck	Betamethasone
Consulting	B&M Gates Foundation	Infant mortality in low resource environments
	Chiesi	New treatments for BPD

Why develop new ACS treatments for low resource environments?

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

– Availability – the gold standard Celestone has limited availability; Higher cost and less stability that Dex. Phos.

– Ease of treatment – Celestone (Beta-Acetate + Beta-Phos) is 2 injections, Dex-Phos is 4 injections (WHO) – ideal treatment would be 1 exposure.

Why develop new ACS treatments for low resource environments?

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

- Peak free Beta or Dex levels are high and continuous lower exposure better than repeated treatments (animal models).

- Risks of high peak levels.
  - Unanticipated deaths in low resource environments – possibly infection related (ACT Trial).
  - Hypoglycemia in newborn (ALPS Trial).
  - Concerns about developmental effects – lack of follow –up.

Which Steroid for Antenatal Treatment?

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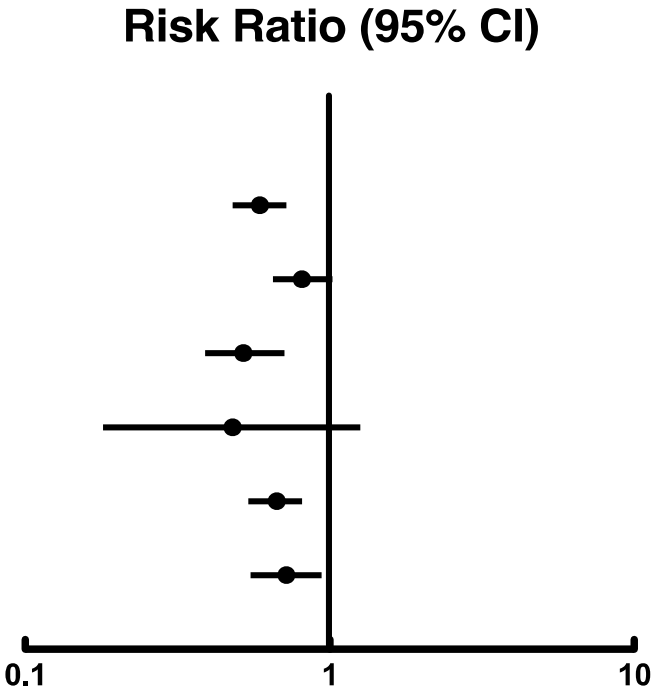
- **Beta Acetate + Phos-12 mg given as 2 doses – 24h interval**
  - **Most tested against placebo**
  - **Exclusively used for repeated dose studies**
- **Dex Phosphate – 6 mg 12h x 4**
  - Less effective in some trials
  - Cheaper and more available
- Dex Phos – 12 mg 24 hr. x 2 – A* Steroid Trial (Crowther)

Comparison of Trials for Dex·PO_4 or Celestone (Beta·PO_4 + Beta·Ac)

Outcomes	Number of Trials		Events
RDS	Beta	18	3115
	Dex	6	1457
IVH	Beta	8	2169
	Dex	5	703
Death	Beta	15	2880
	Dex	6	1468



NZ and Australia Clinical Practice Guidelines 2015

We compared in preterm fetal sheep the clinical dosing of Celestone (Beta-Ac+ Beta-Phos) – 0.25 mg/kg – 2 doses 48 and 24 hours before preterm delivery with equivalent doses of Beta-Phos or Dex-Phos.

- The physiologic assessment of lung increased greatly with Celestone.
- The Beta-Phos and Dex-Phos increased lung function similarly from control values – but the effect was less that for the Celestone.

Schmidt and Jobe, Submitted

We compared in preterm fetal sheep the clinical dosing of Celestone (Beta-Ac+ Beta-Phos) – 0.25 mg/kg – 2 doses 48 and 24 hours before preterm delivery with equivalent doses of Beta-Phos with the intervals of treatment of 6h, 12h, or 24h.

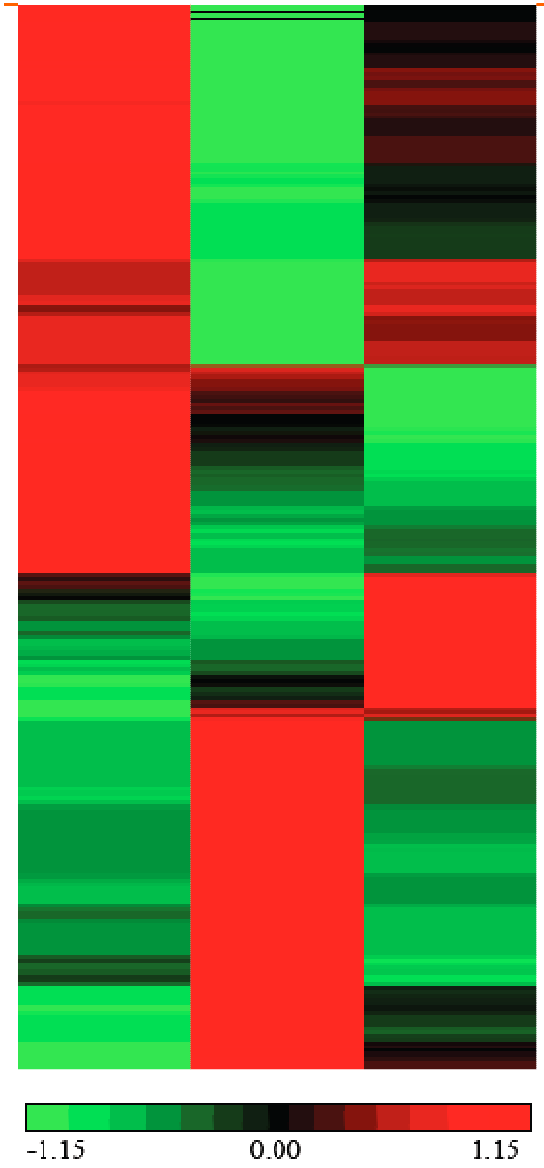
- The three different intervals of dosing improved lung function similarly relative to control but the effect was less than the Celestone.
- These experiments in sheep suggest that neither Beta-Phos nor Dex-Phos are as effective as the combined preparation that contains Beta-Ac.

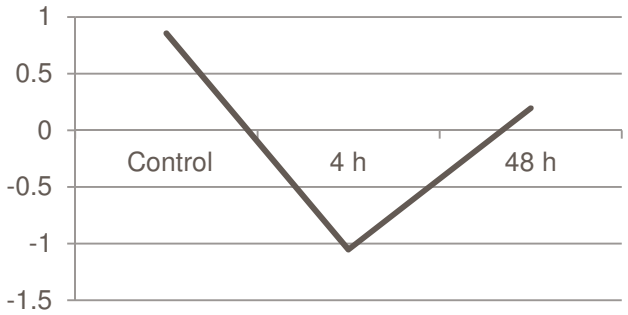
Schmidt and Jobe, Submitted

Rhesus Lung

Celestone 0.25mg/kg

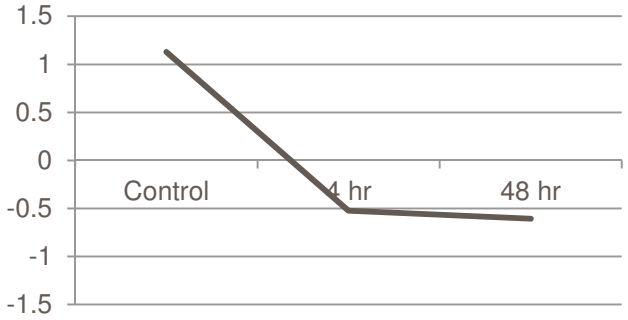
Control 4h 48h



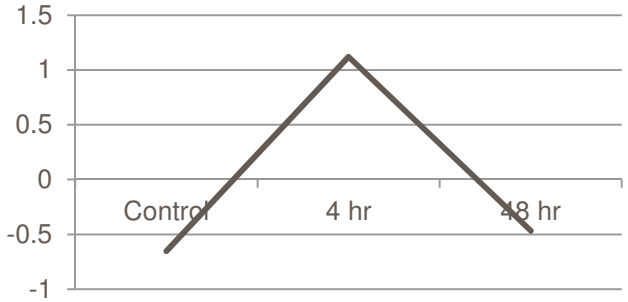


Apoptotic signaling

Morphogenesis



Vascular development



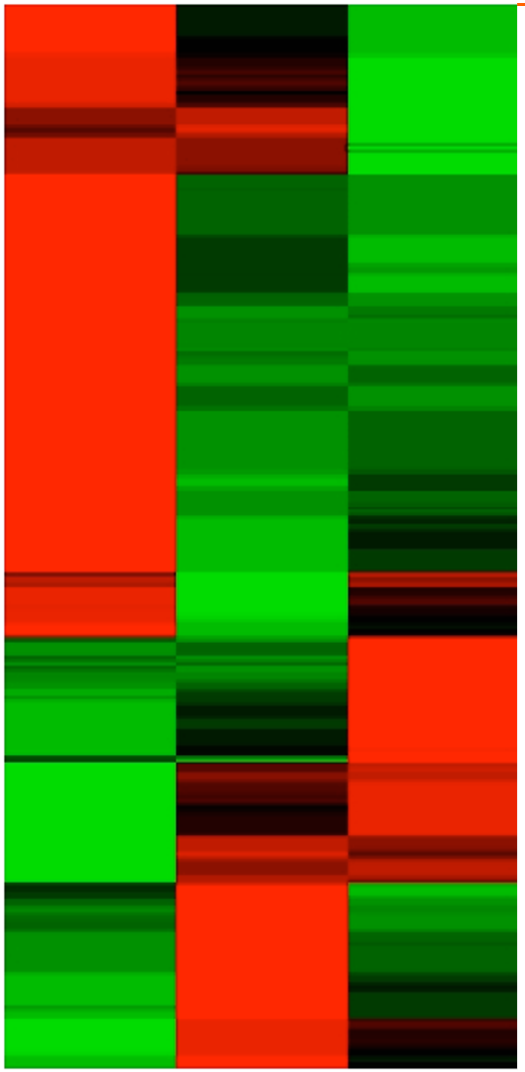
Lipid transport

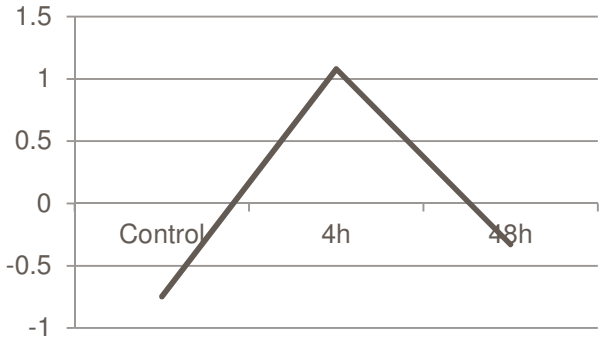
Extracellular matrix

Schmidt - Unpublished

Celestone 0.25mg/kg **Rhesus Placenta**

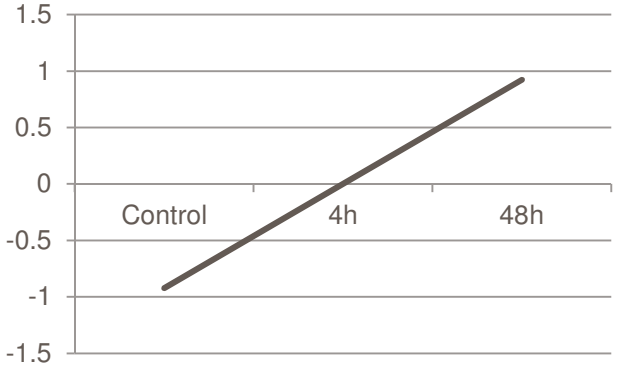
Control 4h 48h





Ceramide breakdown – fetal growth restriction

Anion transporter



Cell cycle arrest

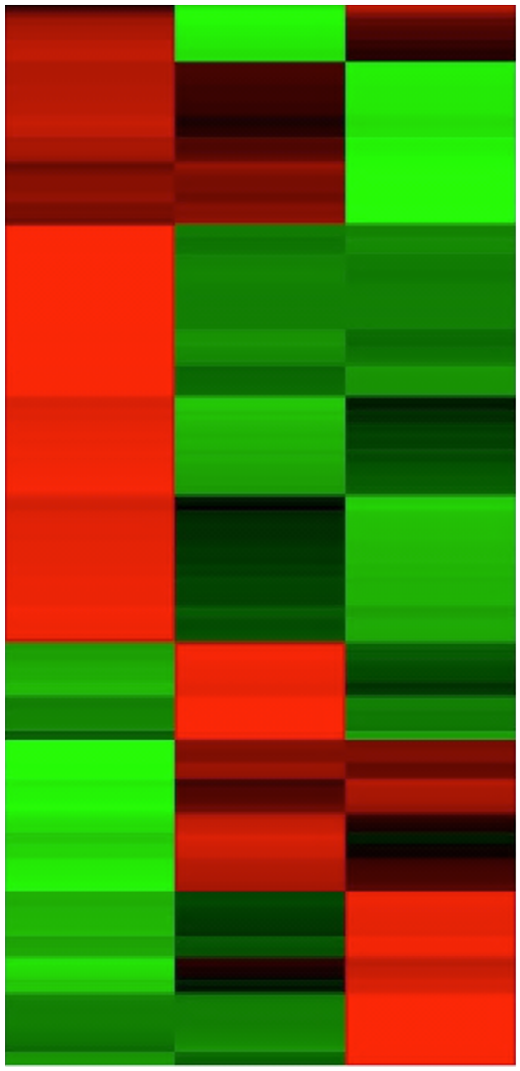
Small placenta

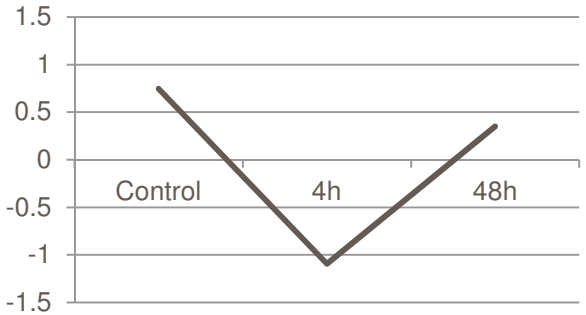
Hypoglycemia

Schmidt - Unpublished

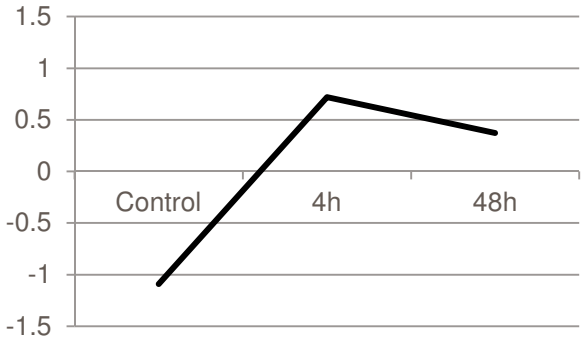
Celestone 0.25mg/kg **Rhesus Hippocampus**

Control 4h 48h





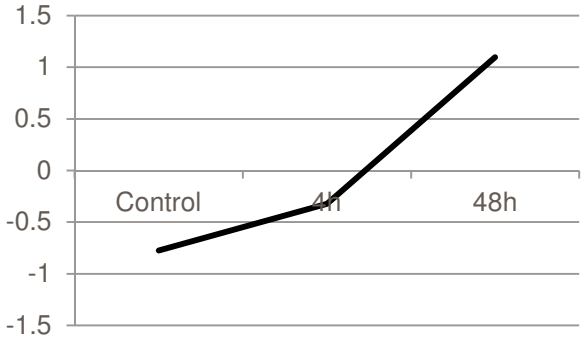
Glial cell differentiation



Negative regulation of neuron differentiation

Negative regulation of neurogenesis

Neuron projection



Neuron degeneration

Abnormal electrophysiology

Decreased tissue mass

Schmidt - Unpublished

Strategies to Develop New ACS Dosing

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

- Use IV infusions to evaluate fetal blood levels and responses – GSK.

- Evaluate Beta-Ac for slow release – Bill & Melinda Gates.

- Consider alternate methods or steroids for achieving exposure.

Infusions of Beta-Phos for 3 or 12 hr. using 0.125 mg/kg, 0.04 mg/kg or 0.0125 mg/kg:

- Achieved peak maternal Beta levels that were linearly proportionate to dose.
- Fetal levels of about 1/10 of maternal plasma levels were measurable only for the 0.125 mg/kg dose.
- Despite the very low fetal exposures, surfactant protein and ion transport gene expression increased except at the lowest dose. This increased gene expression indicates lung maturation.

These infusion demonstrate studies that the fetus can respond to longer and lower peak drug levels.

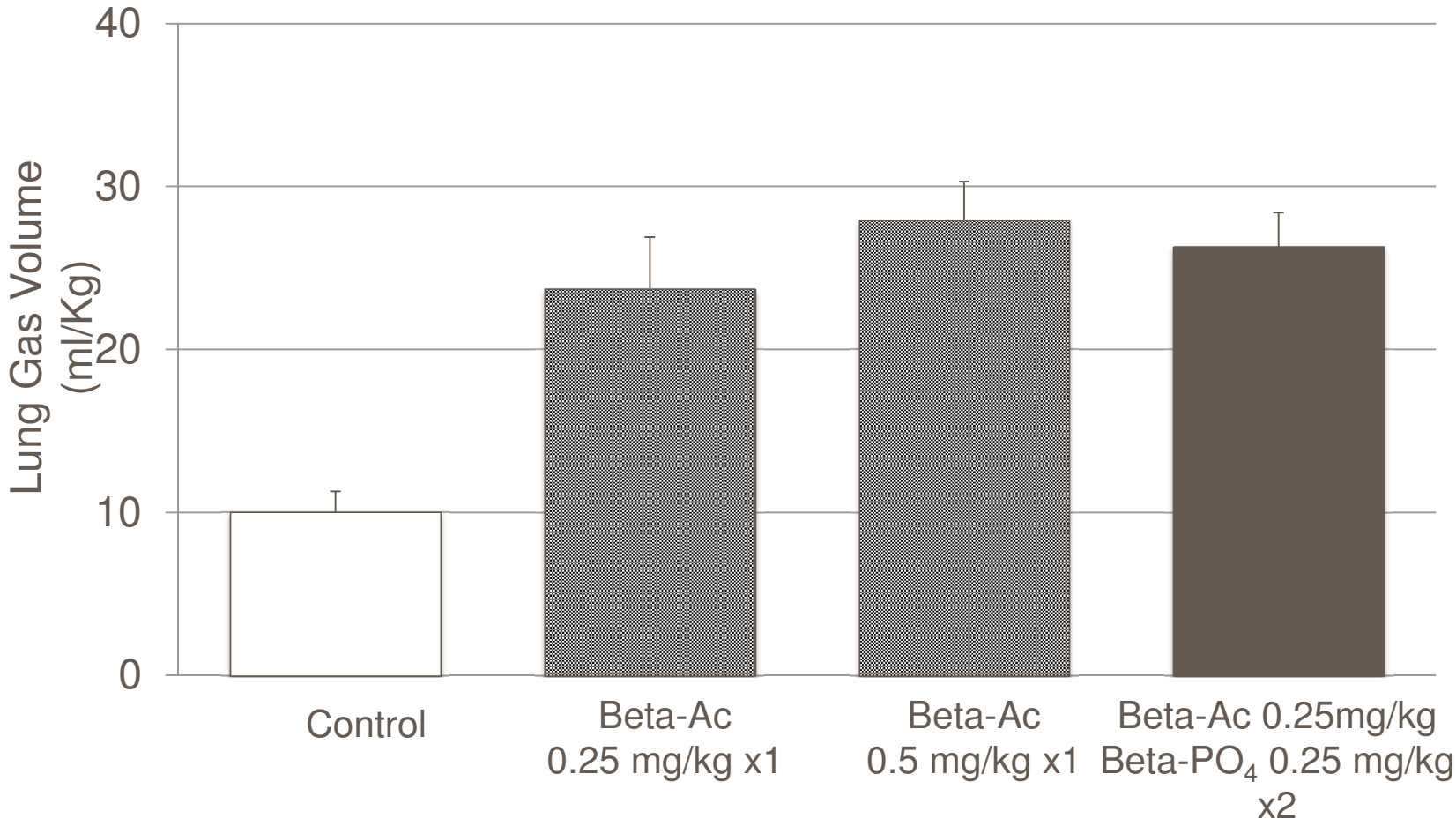
Peak Blood Levels of Free Betamethasone in Ewes and Fetuses with Equivalently Effective Treatments for Lung Maturation

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

	Celestone – 0.5 mg/kg Beta·Phos + Beta·Acetate	Beta·Acetate – 0.25 mg/kg
Maternal	130 μg/ml	13
Fetal	10 μg/ml	< 1 μg/ml

Jobe, AJOB Gyn., 2009

Beta-Acetate response relative to Celestone for V40 at 48h



Total Beta Dose 0 0.25mg/kg 0.5mg/kg 1 mg/kg

Jobe et al. AJOG 2009

In initial experiments, we compared lung maturation responses to single doses of Celestone (0.25 mg/kg) and its Beta-Ac component (0.125mg/kg) in preterm Rhesus monkeys.

- Relative to vehicle control, after a 5 day interval from treatment to delivery; the pressure – volume curves of the fetal lungs increased equivalently for Celestone and Beta-Ac.
- This study suggest that the Beta-Ac alone is equivalent in fetal response to Celestone.

July – Perth, Australia
Plans for 2016

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

– Constant dose Beta infusions for 12 hr. – Pharmacokinetics and Efficacy (GSK)

– Single dose Beta AC doses vs Celestone for efficacy (Gates funding, Beta Ac a gift from Merck)

Recommendations from the GSK team

HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

- GSK recognise that this has important implications for both developed and low resource settings.
- How best to deliver steroid?
  - Is a topical patch of interest?
- Should dose optimisation be taken forward clinically?
  - Need for a co-ordinated partnership approach (Such as a public private pre-competitive collaboration)
    - Will require a detailed scientific / project plan with clear deliverables
    - Resourcing
    - Regulatory Input
    - Drug supply (GSK does not manufacture an ACS)
    - Large non-inferiority study
  - Identify a co-ordination body and partners to deliver this strategy

Questions/comments