Antenatal corticosteroids for preterm birth

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EPICE

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EXPRESS

Antenatal corticosteroids (ANS)

- Liggins & Howie 1972
- >8,000 babies included in RCTs

Antenatal corticosteroids (ANS)

- Liggins & Howie 1972
- >8,000 babies randomized

ANS decreases (in high-income settings):

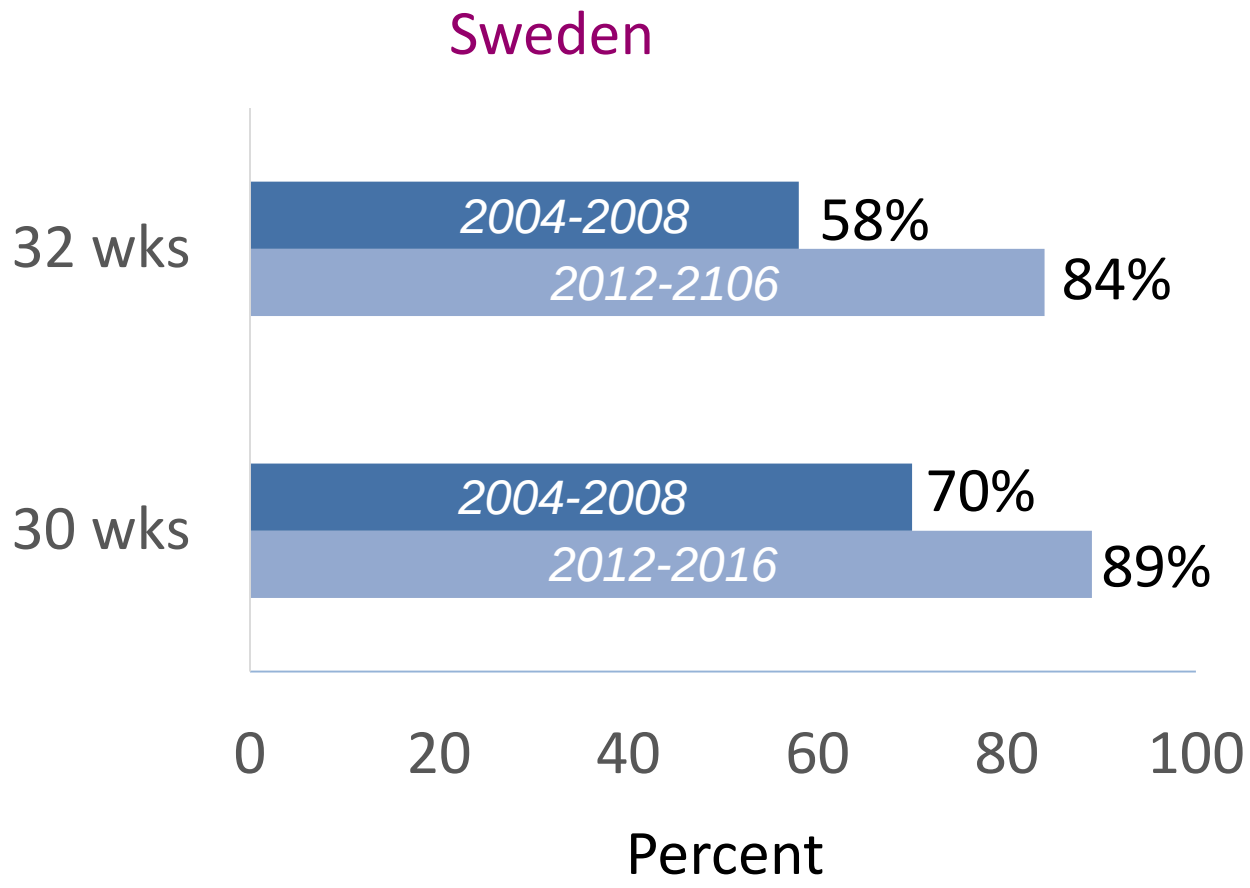
- Neonatal mortality (31%)
- RDS (34%)
- Need for mechanical ventilation (32%)
- IVH (45%)
- NEC (50%)
- Systemic infections <48h (40%)

Roberts D, Brown J, Medley N, Dalziel SR.
Cochrane Database of Systematic Reviews 2017;3:CD004454

Outline of talk

- Are they (ANS) used?
- Do they work in extremely preterm infants?
- Timing of ANS revisited

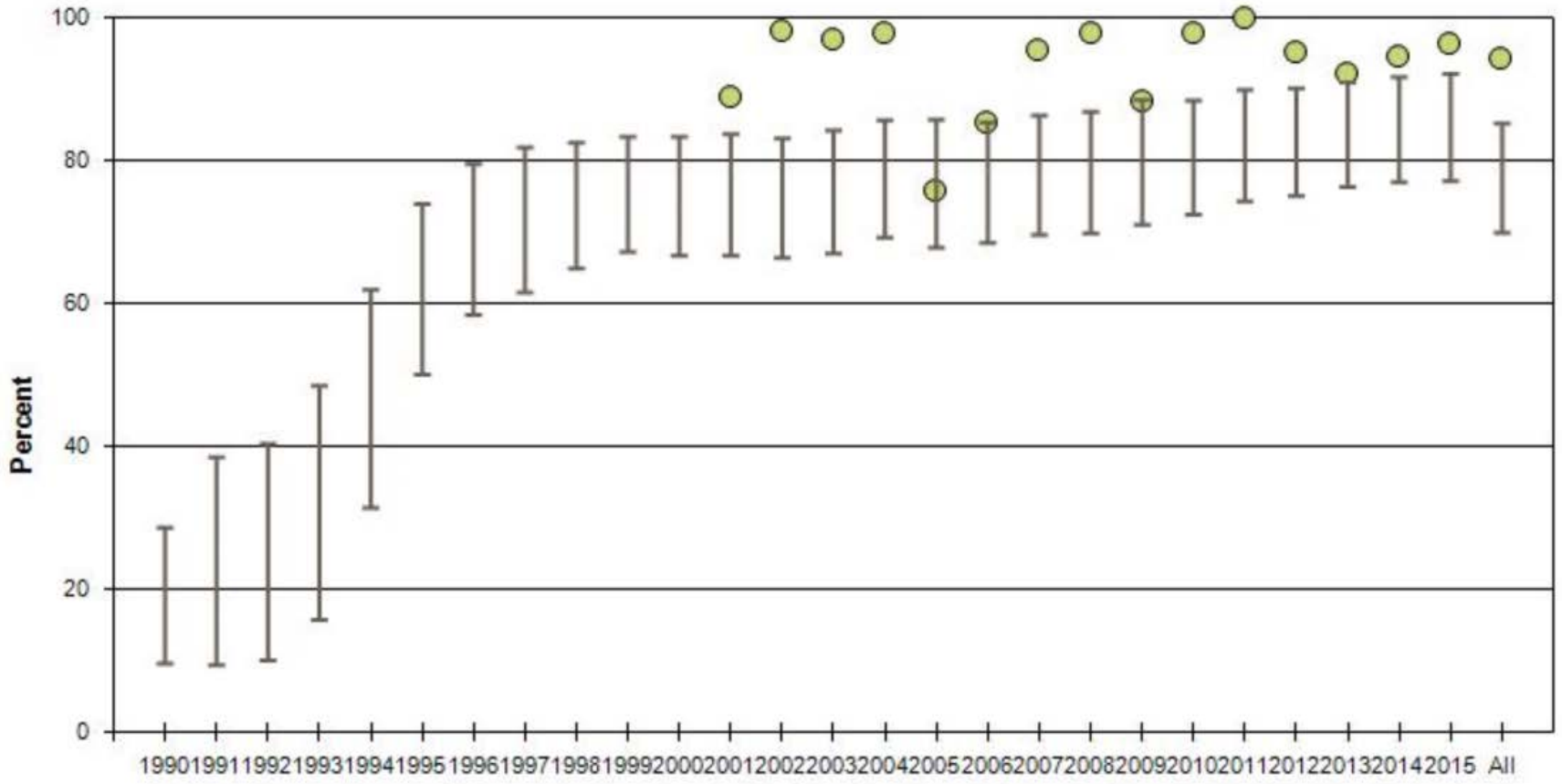
Are ANS used?



Altman M, J Pediatr 2011; Swed Neonatal Quality Registry

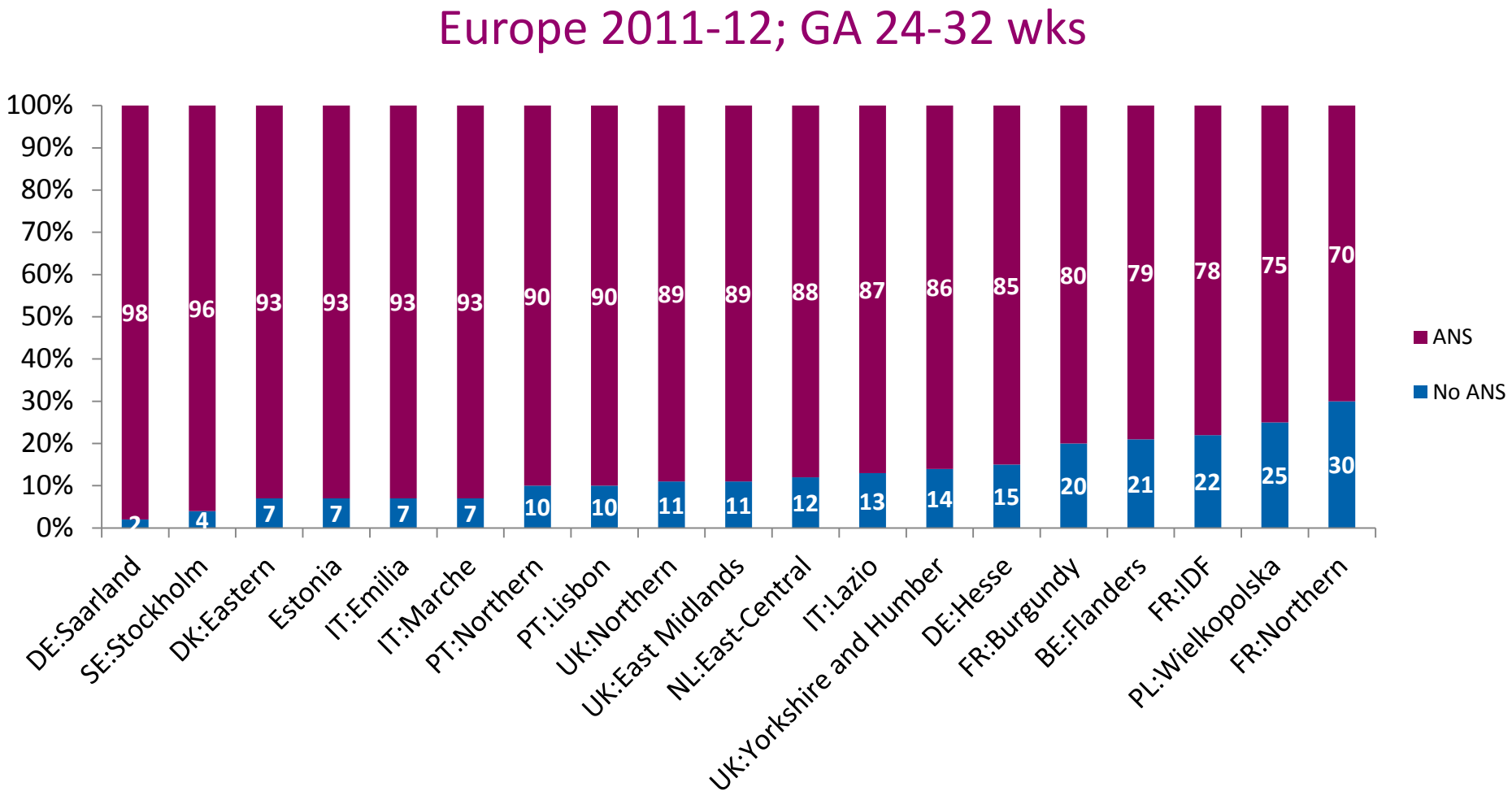
Antenatal Steroids - Antenatal Steroids: Ga 24 to 33
Birth Year

Chart Type: Center and Group Quartiles Chart



VON; Green dots Turku Univ Hosp Finland

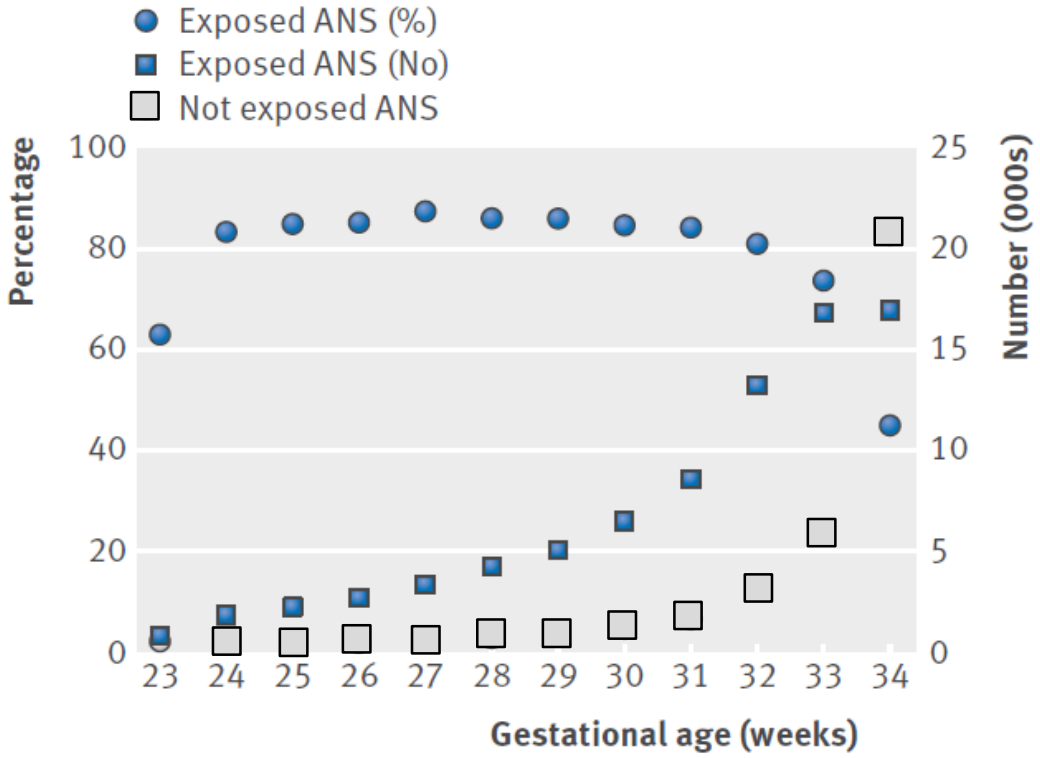
Regional variations



Norman M et al, JAMA Peds 2017

ANS and GA

USA (Pediatrix Medical Group); 2009-13; GA 23-34 wks



Travers CP et al: BMJ 2017

Summary part I

- 65-100% of pregnant women delivering at 24-32 weeks of GA receives ANS
- Practice varies:
  - over time
  - between hospitals, regions and countries
  - by gestational age

What should be the target?

Part II: ANS for extremely preterm infants

Only about 100 deliveries <28 wks GA included in the >20 RCTs on ANS

Jobe A, PAS 2017

Previous meta-analysis: no reductions of mortality & morbidity prior to 26 wks

Onland W et al, Am J Perinatol 2011

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Previous meta-analysis: no reductions of mortality & morbidity prior to 26 wks

Onland W et al, Am J Perinatol 2011

More recent studies: indicate similar or even more pronounced benefits from ANS for extremely preterm births

Carlo WA et al, JAMA 2011; Mori R et al, J Pediatr 2011; Melamed N et al, Obstet Gynecol 2015

ANS@22-24 wks (review of 8 high quality non-RCTs)

Table 2. Summary of finding for pooled data as per GRADE guidelines.

Outcome	Gestational age	Absolute risk		Relative effect OR (95% CI)	Number of participants	Quality of evidence GRADE
		Estimated risk in control group	Corresponding risk in intervention group			
Mortality	22–24 weeks	619 per 1,000	**433 per 1,000** (388 to 476)	**OR 0.47** (0.39 to 0.56)	10109 (7 studies)	Moderate

Deshmukh M, Patole S: PLOS ONE 2017

VON 2012-2015, survival rates by GA and ANS

GA	Life support only	Life support and ANS	aRR
22 wks	382 (18.4%)	391 (38.6%)	2.10
23 wks	946 (35.9%)	3980 (55.2%)	1.54
24 wks	933 (59.9%)	7467 (71.2%)	1.19
25 wks	909 (76.1%)	8600 (82.9%)	1.09

Ehret D, PAS abstract 2017

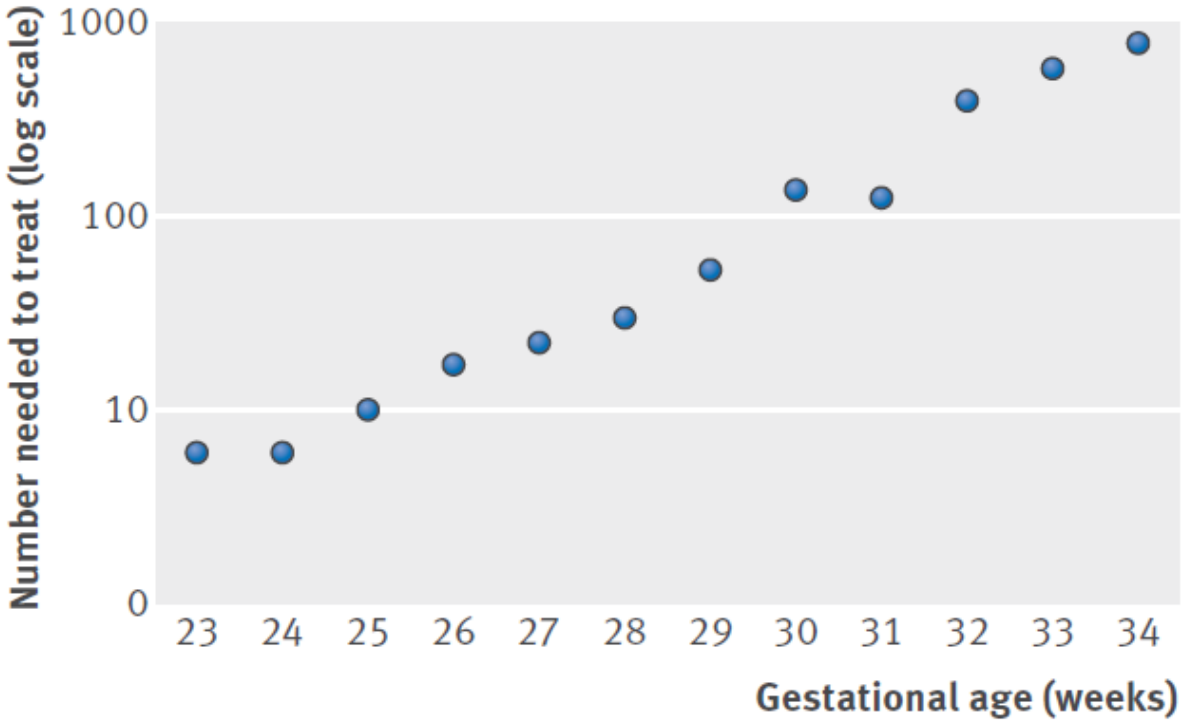


Fig 2 | Number needed to treat with antenatal corticosteroids to prevent one death before discharge in infants with gestational age 23 0/7 to 34 6/7

Travers CP et al: BMJ 2017

Summary part II

- Observational data indicate that ANS may be effective also for extremely preterm birth
- Confounding by indication may be a problem ->

  effect on survival larger than on morbidity (other way around in meta-analyses of RCTs)

Why should not all extremely preterm births be treated with ANS?

Part III: current concepts about timing

- Maximized benefits -> ANS administered 24-48 hours to 7 days before delivery

Cochrane 2006, AJOG 2004, 2005, 2007, 2011 & 2015, Obstet & Gynecol 2001 & 2013

Concepts about timing

- Neonatal benefits maximized when ANS are administered 24-48 hours up to 7 days before delivery

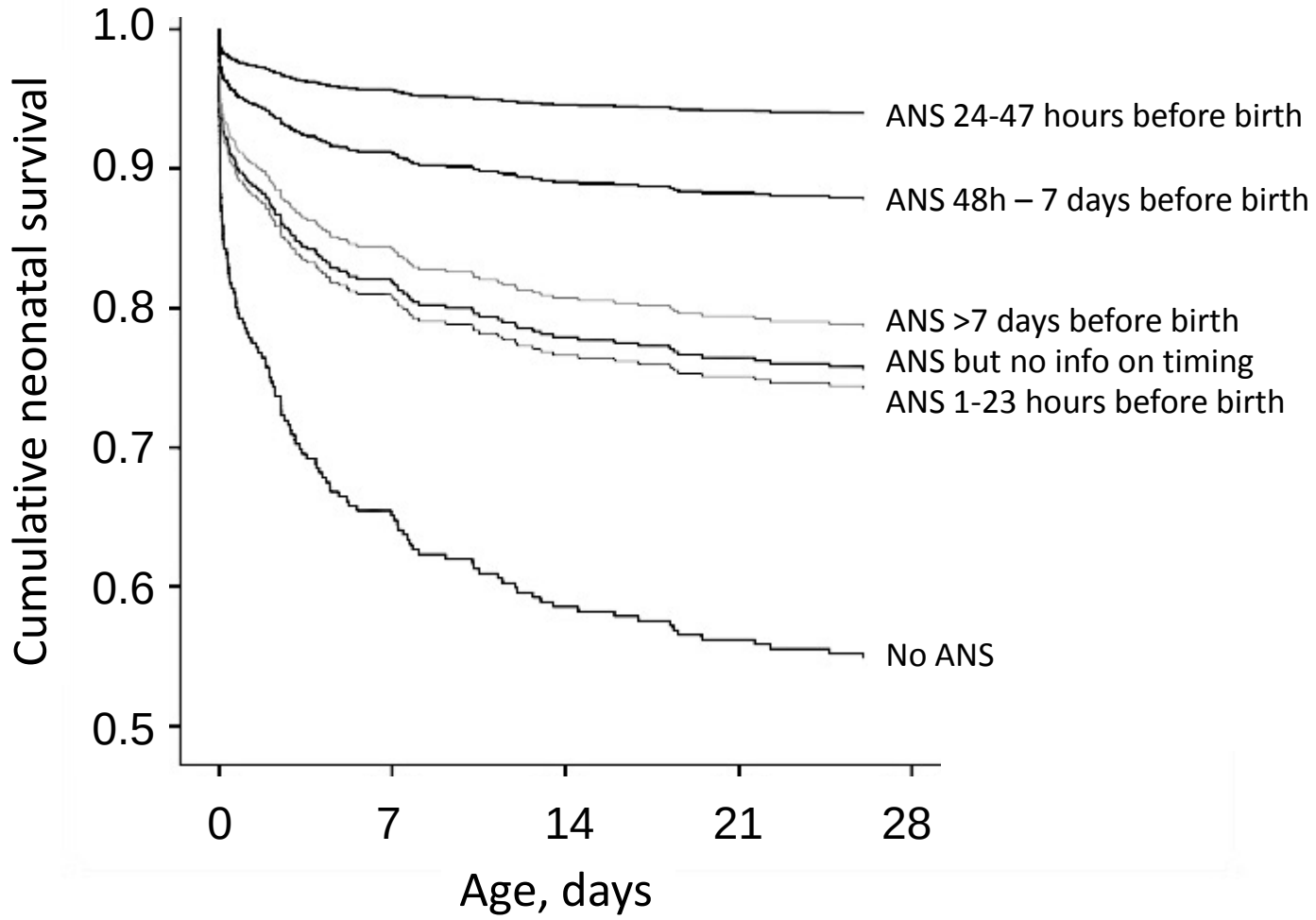
  Cochrane 2006, AJOG 2004, 2005, 2007, 2011 & 2015, Obstet & Gynecol 2001 & 2013

- Administration-to-birth intervals <24 (-48) hours described and considered as **incomplete, suboptimal or partial**

  AJOG 2004, J Maternal-Fetal & Neonatal Medicine 2009, Obstet & Gynecol 2015

Neonatal survival[a] in EXPRESS by ANS administration-to-birth intervals

(n=707, GA 22-26 wks, 84% exposed to ANS)



[a] Adjusted for maternal smoking, maternal HT/PE, placenta previa, placental abruption, PPROM, regionalization of care, gestational age, small for gestational age, infant gender and surfactant <2h after birth

Hanna Norberg, BJOG 2016

The problem

Timely prediction of preterm delivery unresolved

- most women deliver outside the “optimal” interval
- many deliver before 24 (-48) hours have passed from admin of ANS

BMJ 2016

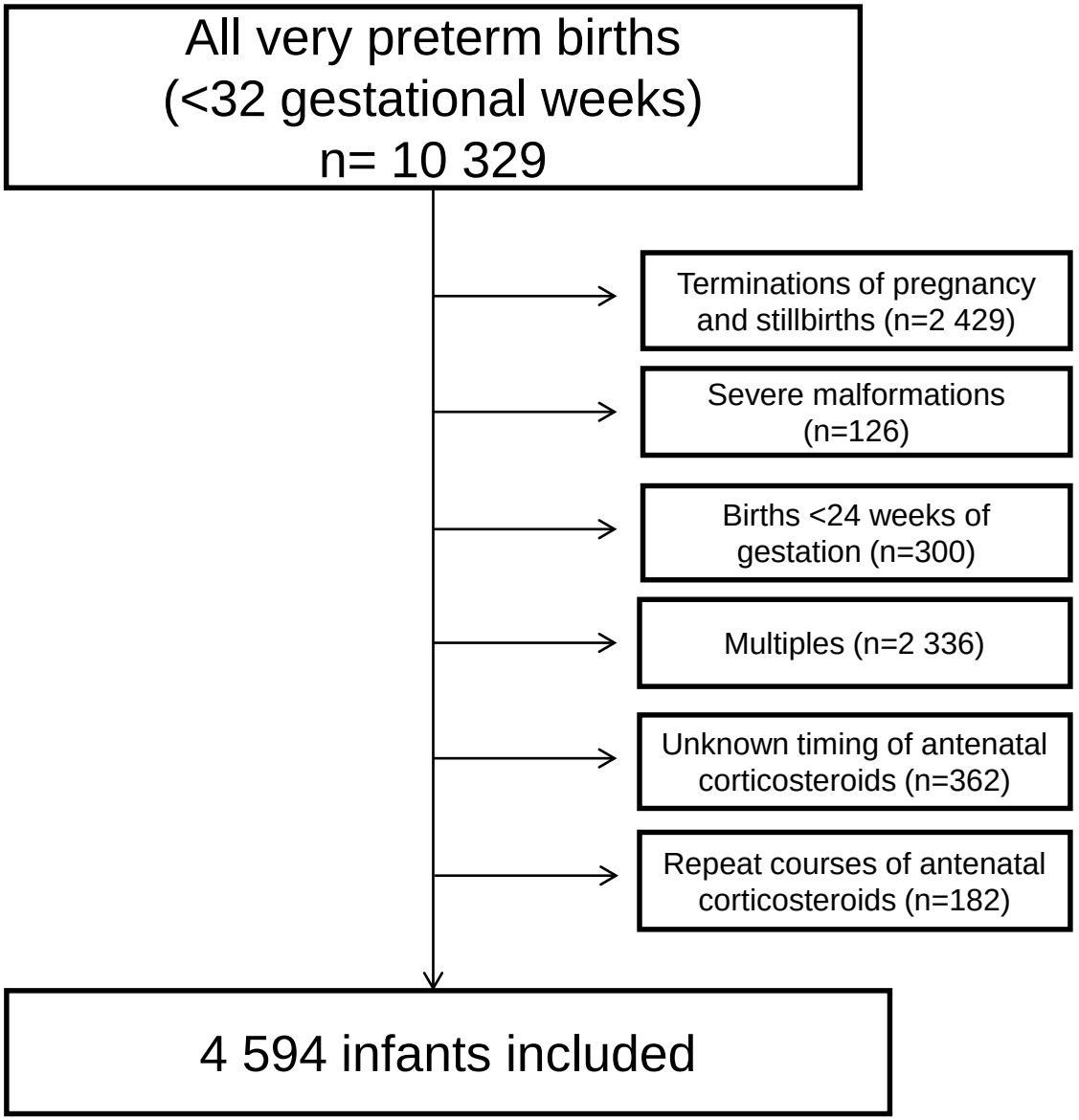
Research question

What is the shortest administration-to-birth interval of antenatal corticosteroids to promote survival in very preterm infants?

EPICE COHORT

Effective Perinatal Intensive Care in Europe

- Overall aim: to study implementation of evidence based practices in perinatal and neonatal medicine
- 19 regions from 11 European countries
- GA<32 weeks
- All deliveries in 2011-2012


All very preterm births
(<32 gestational weeks)
n= 10 329
Terminations of pregnancy and stillbirths (n=2 429)
Severe malformations (n=126)
Births <24 weeks of gestation (n=300)
Multiples (n=2 336)
Unknown timing of antenatal corticosteroids (n=362)
Repeat courses of antenatal corticosteroids (n=182)
4 594 infants included

Design

Exposure: ANS administration-to-birth interval in hours

Outcomes:

1) In-hospital mortality

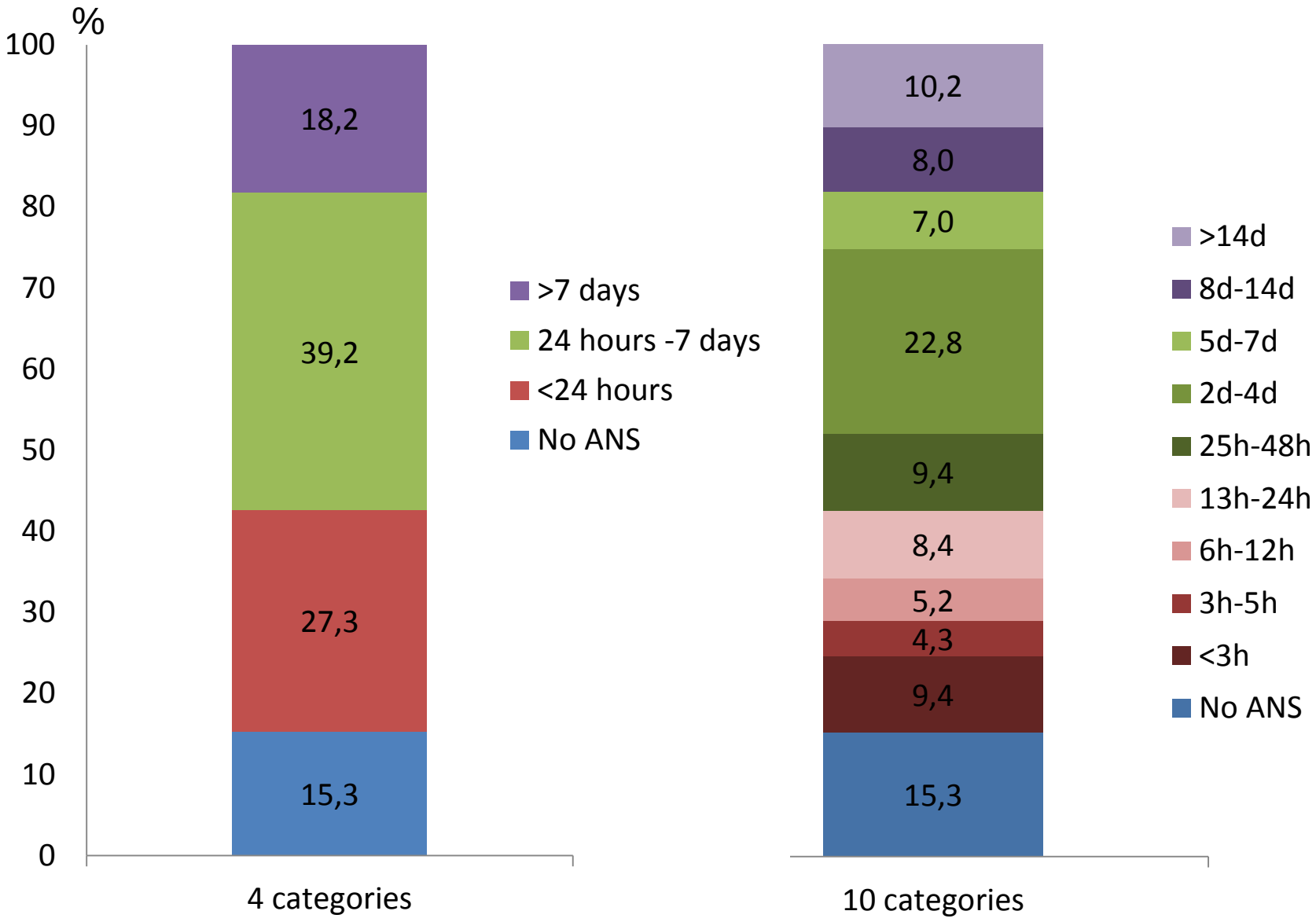
2) Mortality or severe neonatal morbidity (IVH ≥3, cPVL, NEC or ROP stage ≥3)

3) Severe neonatal brain injury ((IVH ≥3 or cPVL)

Co-variates:

- maternal age
- parity
- pregnancy complications
- GA
- small for gestational age
- infant sex
- delivery on day of admission
- mode of delivery
- delivery in level III unit

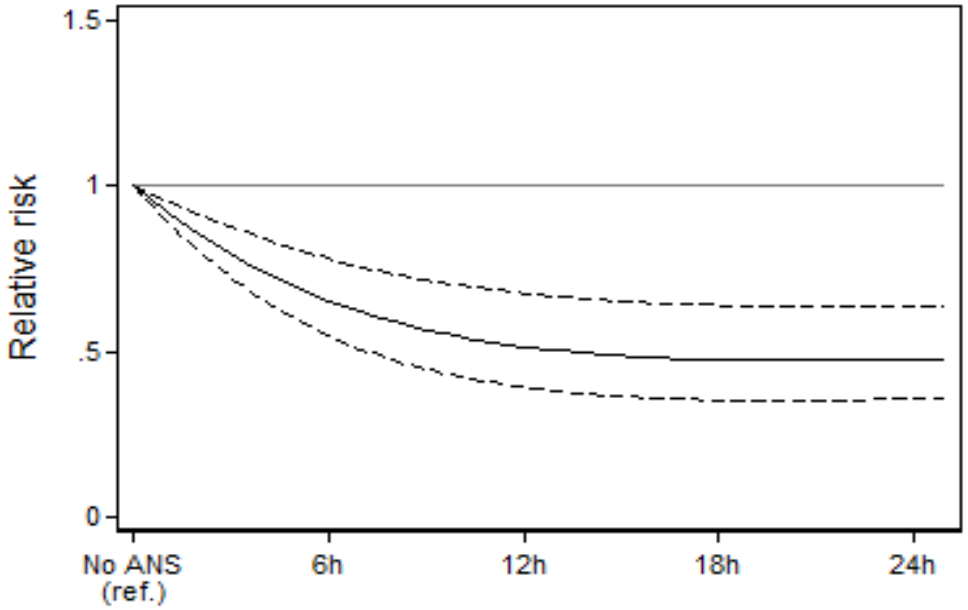
Results

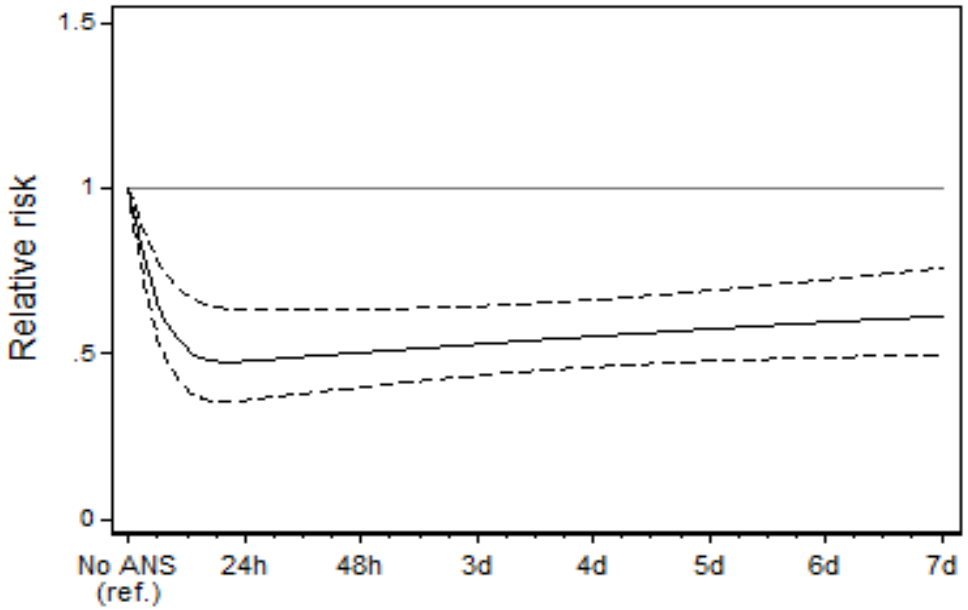

%
100
90
80
70
60
50
40
30
20
10
0
18,2
39,2
27,3
15,3
>7 days
24 hours -7 days
<24 hours
No ANS
4 categories
10,2
8,0
7,0
22,8
9,4
8,4
5,2
4,3
9,4
15,3
>14d
8d-14d
5d-7d
2d-4d
25h-48h
13h-24h
6h-12h
3h-5h
<3h
No ANS
10 categories

Main finding

Infant mortality by ANS administration-to-birth intervals

*RR adjusted for **patient case-mix** (maternal age; parity; pregnancy complications including preeclampsia, eclampsia and HELLP-syndrome and PPROM; GA; small for gestational age and infant sex) and factors related to **management** (delivery on day of admission, mode of delivery, delivery in hospital with level III neonatal unit)*





Norman M et al, JAMA Peds 2017

Summary III

77% of women did not receive ANS or received ANS outside of the desired administration-to-birth interval, i.e., 2 to 4 days

ANS associated with immediate and rapid decline in mortality

Under the assumption of a causal relationship, a simulation of ANS given 3 hours before delivery to infants who did not receive ANS
-> their estimated decline in mortality would be 26%

Infants with an ANS administration-to-birth interval >7 days (19% of all infants in our study) exhibited 40% higher mortality than those with ANS given 1-7 days before birth

Conclusion

ANS may be effective even if given only hours before delivery

meaning

Infants of pregnant women at risk of imminent/immediate very preterm delivery may benefit from its use

Topic for future research?

Given the suggestion of very rapid actions, immediate postnatal corticosteroid rescue for very preterm infants unexposed to ANS may be interesting to test

Compare PREMILOC-trial by Baud O et al, Lancet 2016

BELGIUM: Flanders (E Martens, G Martens, P Van Reempts); **DENMARK**: Eastern Region (K Boerch, A Hasselager, L Huusom, O Pryds, T Weber); **ESTONIA** (L Toome, H Varendi); **FRANCE**: Burgundy, Ile-de France and Northern Region (PY Ancel, B Blondel, A Burguet, PH Jarreau, P Truffert); **GERMANY**: Hesse (RF Maier, B Misselwitz, S Schmidt), Saarland (L Gortner); **ITALY**: Emilia Romagna (D Baronciani, G Gargano), Lazio (R Agostino, D DiLallo, F Franco), Marche (V Carnielli), M Cuttini; ; **NETHERLANDS**: Eastern & Central (C Koopman-Esseboom, A van Heijst, J Nijman); **POLAND**: Wielkopolska (J Gadzinowski, J Mazela); **PORTUGAL**: Lisbon and Tagus Valley (LM Graça, MC Machado), Northern region (Carina Rodrigues, T Rodrigues), H Barros; **SWEDEN**: Stockholm (AK Bonamy, M Norman, E Wilson); **UK**: East Midlands and Yorkshire and Humber (E Boyle, ES Draper, BN Manktelow), Northern Region (AC Fenton, DWA Milligan); **INSERM**, Paris (**Jennifer Zeitlin**, M Bonet, A Piedvache).

Thank you for your attention

Questions?