# Could statistical methods matter?

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# Outline

- Key statistical considerations in randomised trials
  - Binary outcome of preterm birth alone not desirable
  - Taking time from vaccination to birth is better
  - Time of vaccination affects risk of prematurity

- Suggestions for analysis
  - statistical methods should be optimal
  - statistical methods should reflect clinical relevance
  - graphical presentations help understanding

Thanks to Professor Patrick Royston (MRC Clinical Trials Unit, London) for considerable help with Stata programming and discussions

# Binary outcome of preterm birth alone not desirable

- Dichotomising a continuous variable as an outcome leads to loss of power
    - *Ragland DR. Epidemiology. 1992 3(5):434-40*
- Preterm birth as <37 weeks gestation is an international standard
  - Extremely preterm birth (<28 weeks' gestation) also used
- Using 3 ordered categories may be better
- Gestational age (GA) needed for definition
  - GA has considerable measurement error, especially in LMICs

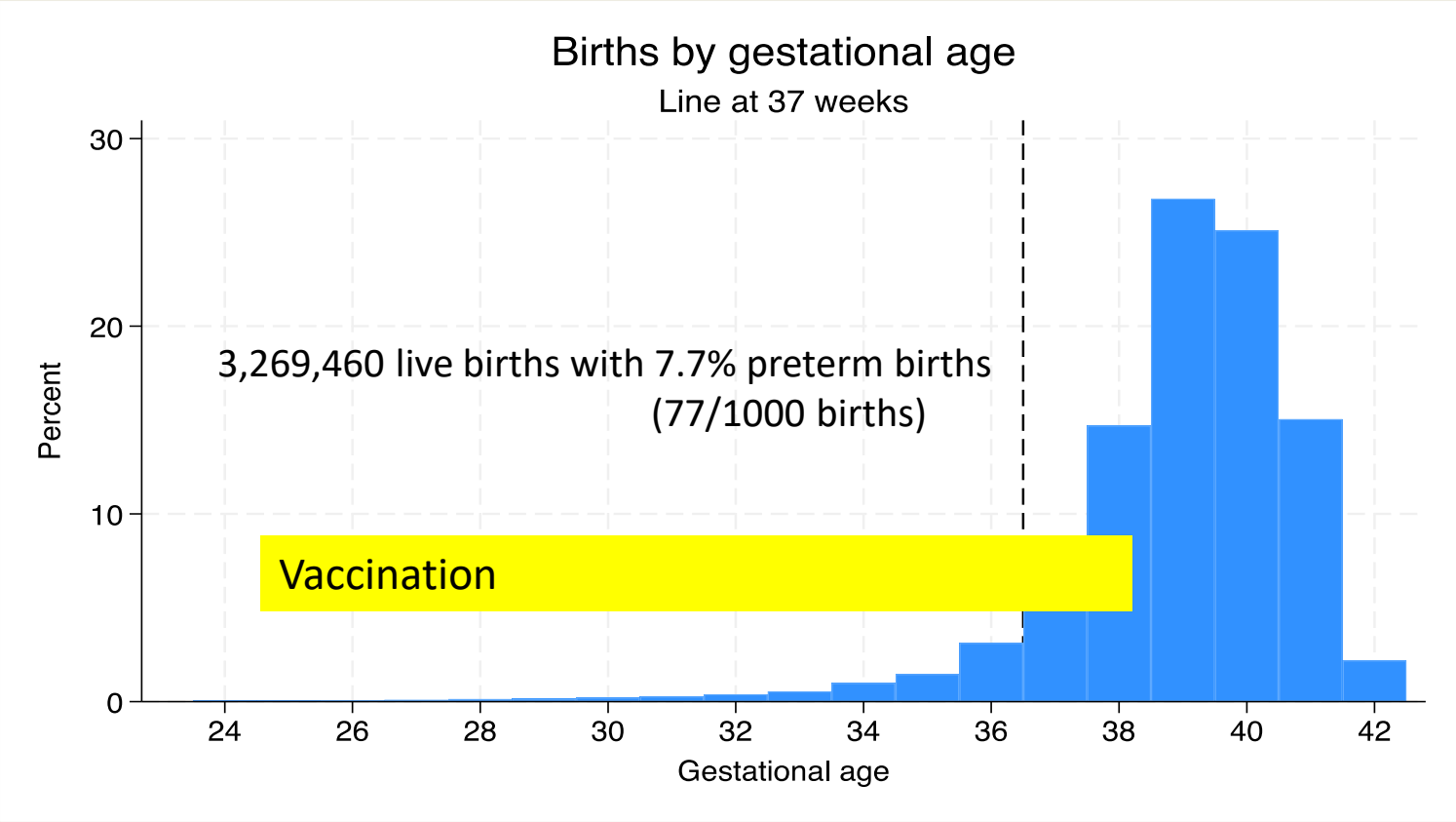
# Taking account of time from vaccination to birth is better

- Using continuous data generally better
  - A “survival” model like a Cox model helps
- Dates of vaccination and birth known precisely
  - No need for estimation of GA for the outcome
- Births at say 30 weeks are different to those at 36 weeks, but both “Preterm”

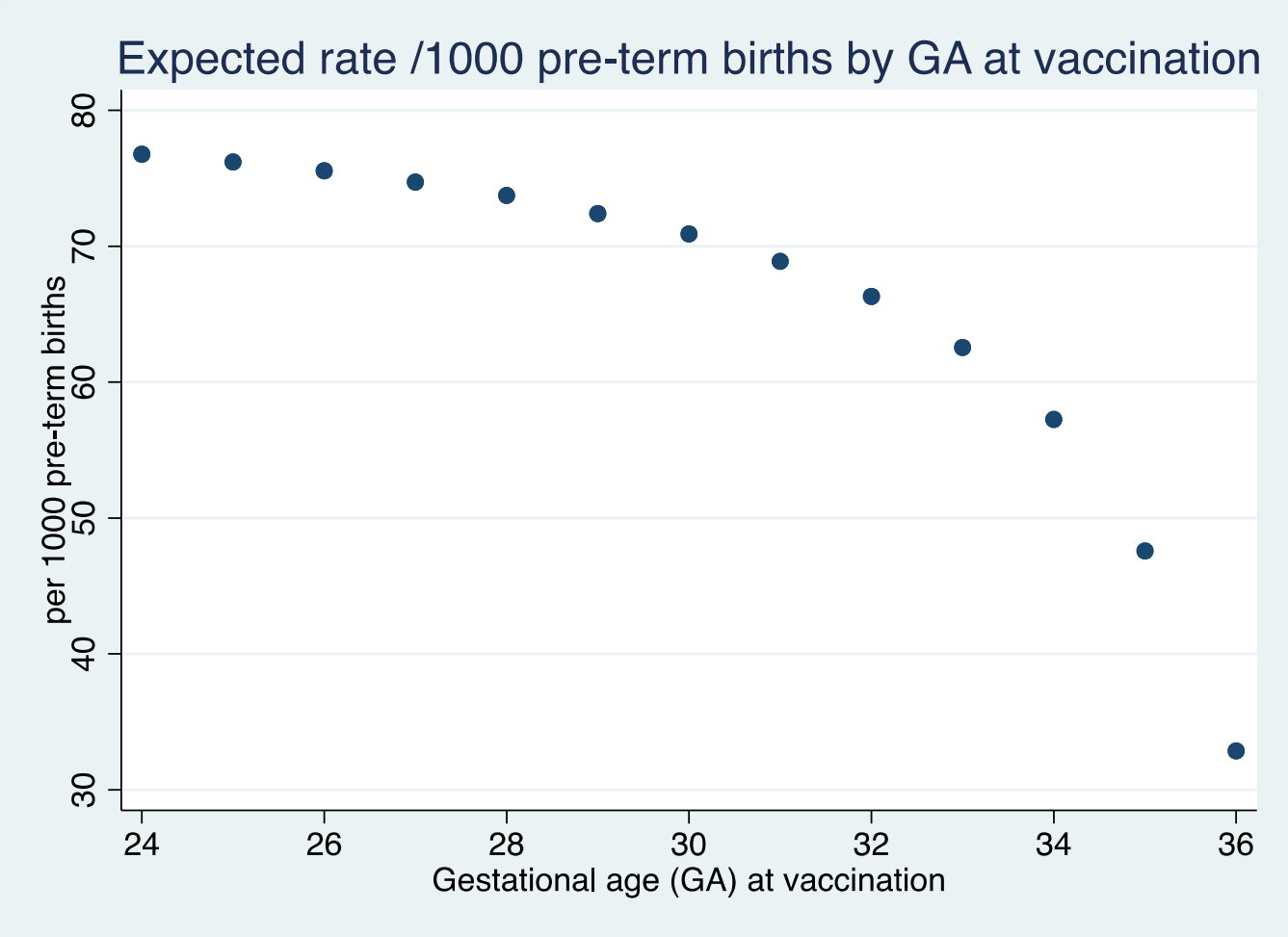
# Time of vaccination affects risk of prematurity

- If all vaccinations are given at 37 weeks GA then no births can be preterm
- The earlier the vaccination, the more time for a preterm birth to occur
  - In a randomised trial (RCT) overall result will not be biased, but within trial subgroup and between-trial comparisons may be biased

# Distribution by gestational age (truncated at 24 & 42, data from )



# Preterm birth rate/1000



# Suggestions for analysis

- Allowance for GA at vaccination (GAV)
  - Bias slight in RCTs but strong in Non-Randomised Studies
- Utilise time from vaccination
  - can use birth, or 37 weeks GA, as end event
  - can use ordinary regression methods with GA at vaccination as covariate (examine residuals)
  - can use e.g. Cox model with GAV as covariate
    - suggest using different endpoints for sensitivity
    - e.g. 36,37,38 weeks & birth

# Statistical methods should be optimal

- If an effect exists, it should be detected as soon as possible
- Bias within the overall result may be minimal
  - subgroup comparisons and between-trial comparisons are not randomised comparisons
- Using best statistical methods may allow for possible prognostic factors (.e.g. region, past medical history etc) to be studied

# Statistical methods should reflect clinical relevance

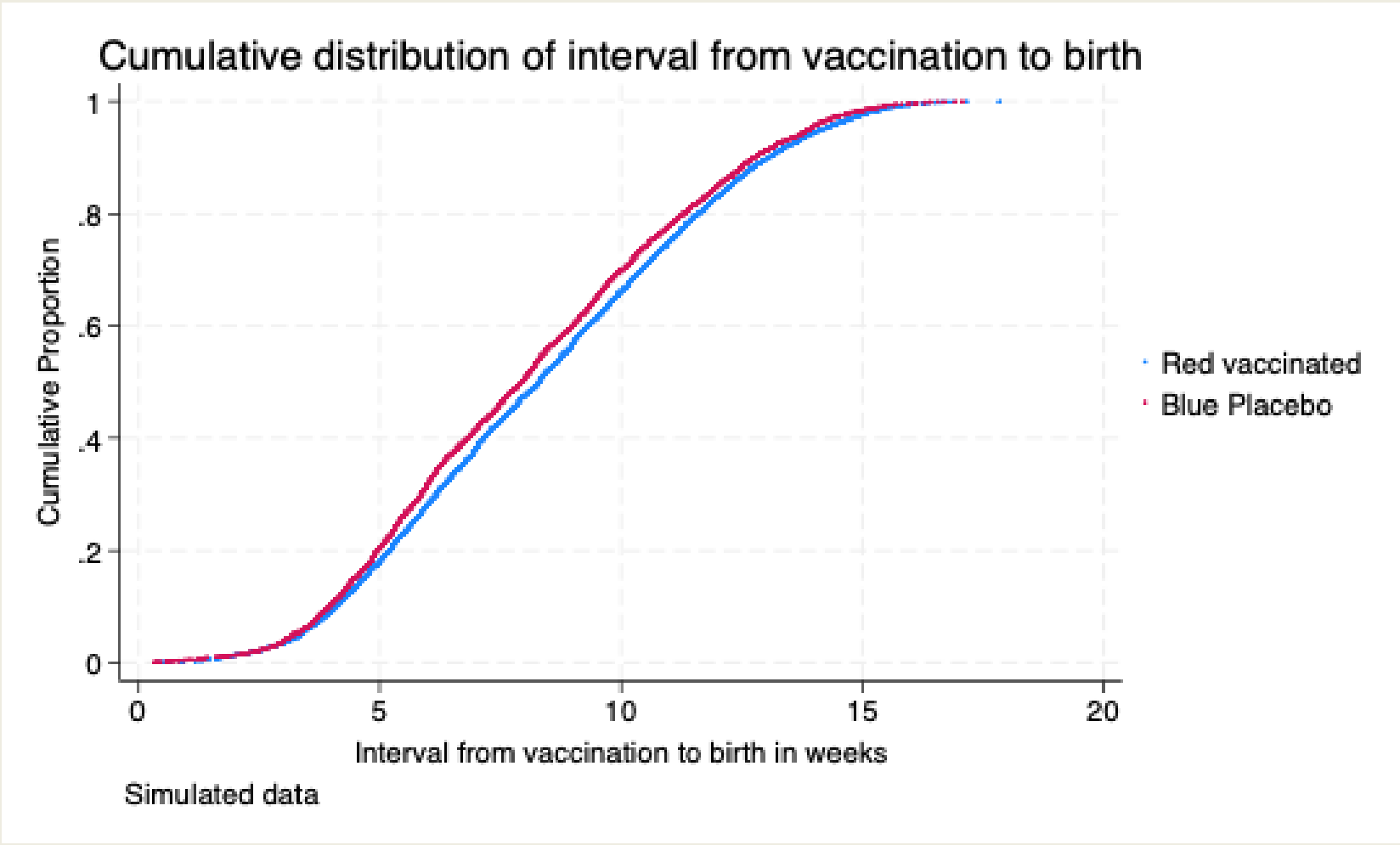
- Very small differences in time from vaccination to birth may be irrelevant
  - The association between GA at birth and adverse outcomes is not totally causal
- Differences in GA at birth at <37 weeks should be studied
- Differences in GA at birth at >37 weeks may be irrelevant

# Graphical presentations help understanding

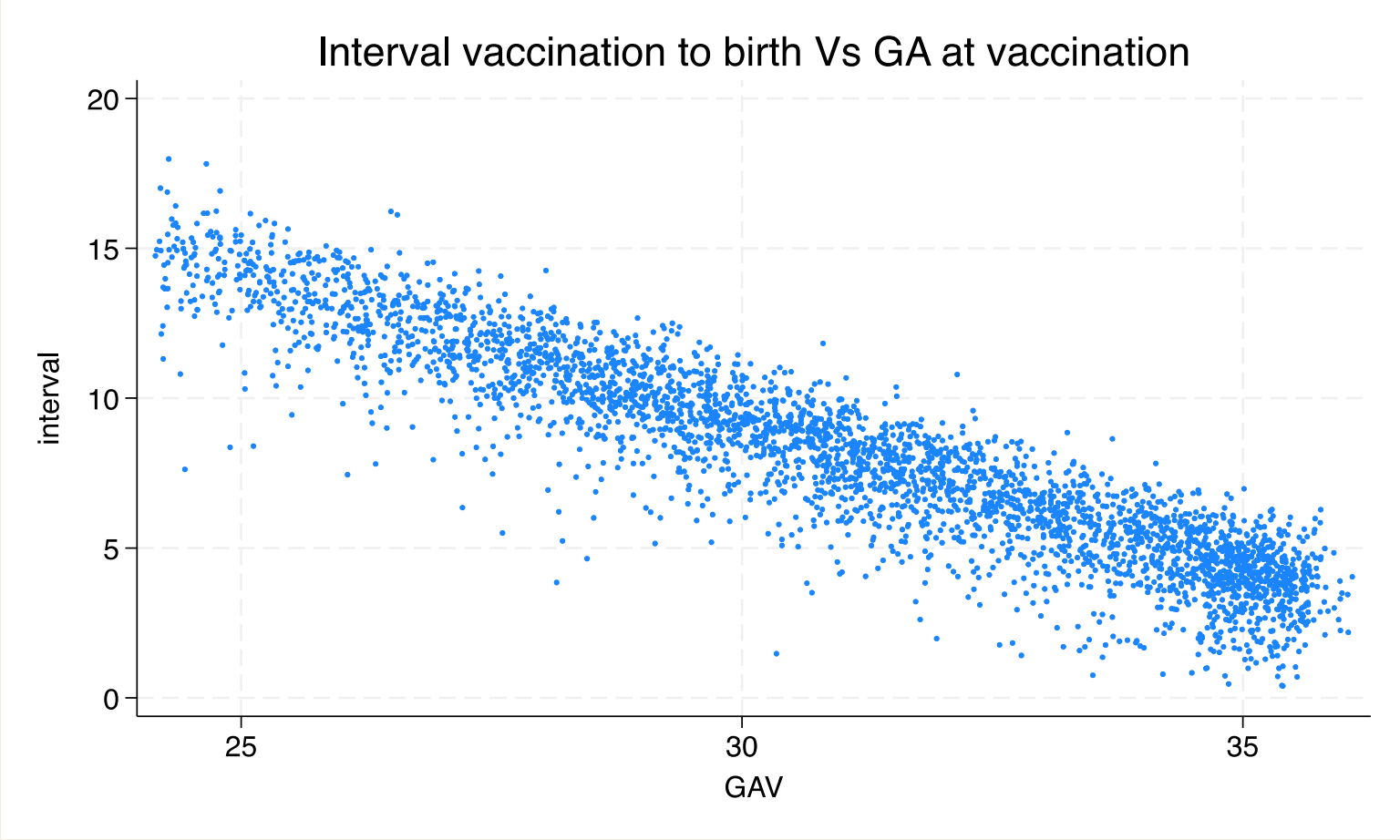
- Cumulative proportions of births post-vaccination should be plotted using exact interval from vaccination to birth
  - Between group differences should be seen
  - Pattern of any difference at early times
- Scatter diagram (with fitted lines) of interval vs estimated GA at vaccination
  - groups identified
- Cumulative proportion vaccinated by estimated GA
  - Different regions identified?

# We can simulate a trial

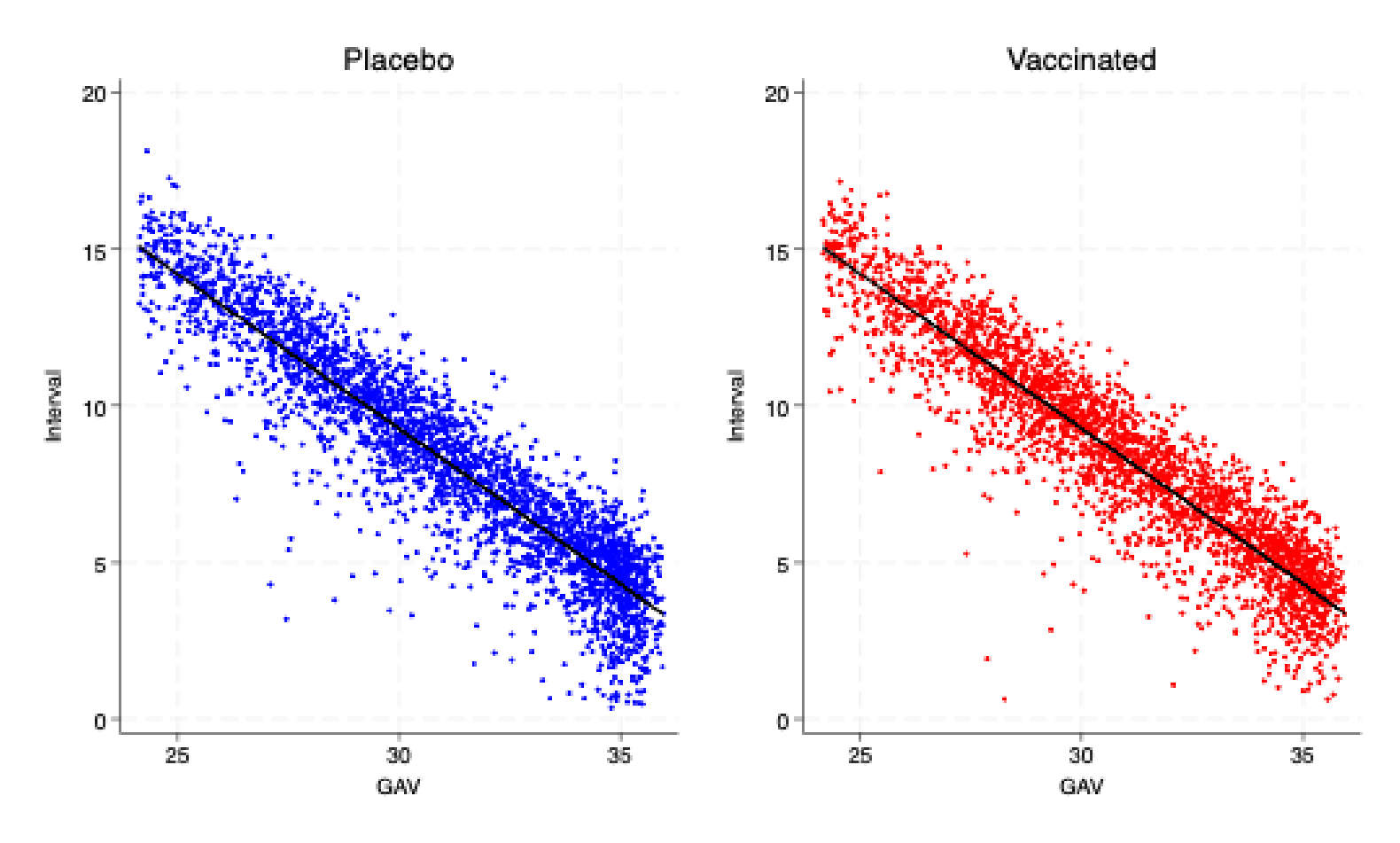
- Can fit the distribution of GA at vaccination
- Can fit the distribution of GA at birth
- Can obtain intervals (GAB – GAV)
- Problem of fitting an effect of vaccination
  - we don't know a plausible mechanism
  - we don't know the pattern of any effect over time
    - for illustration we just change GAB by a measured amount (with a distribution)


Cumulative distribution of interval from vaccination to birth
Cumulative Proportion
0
.2
.4
.6
.8
1
0
5
10
15
20
Interval from vaccination to birth in weeks
Red vaccinated
Blue Placebo
Simulated data

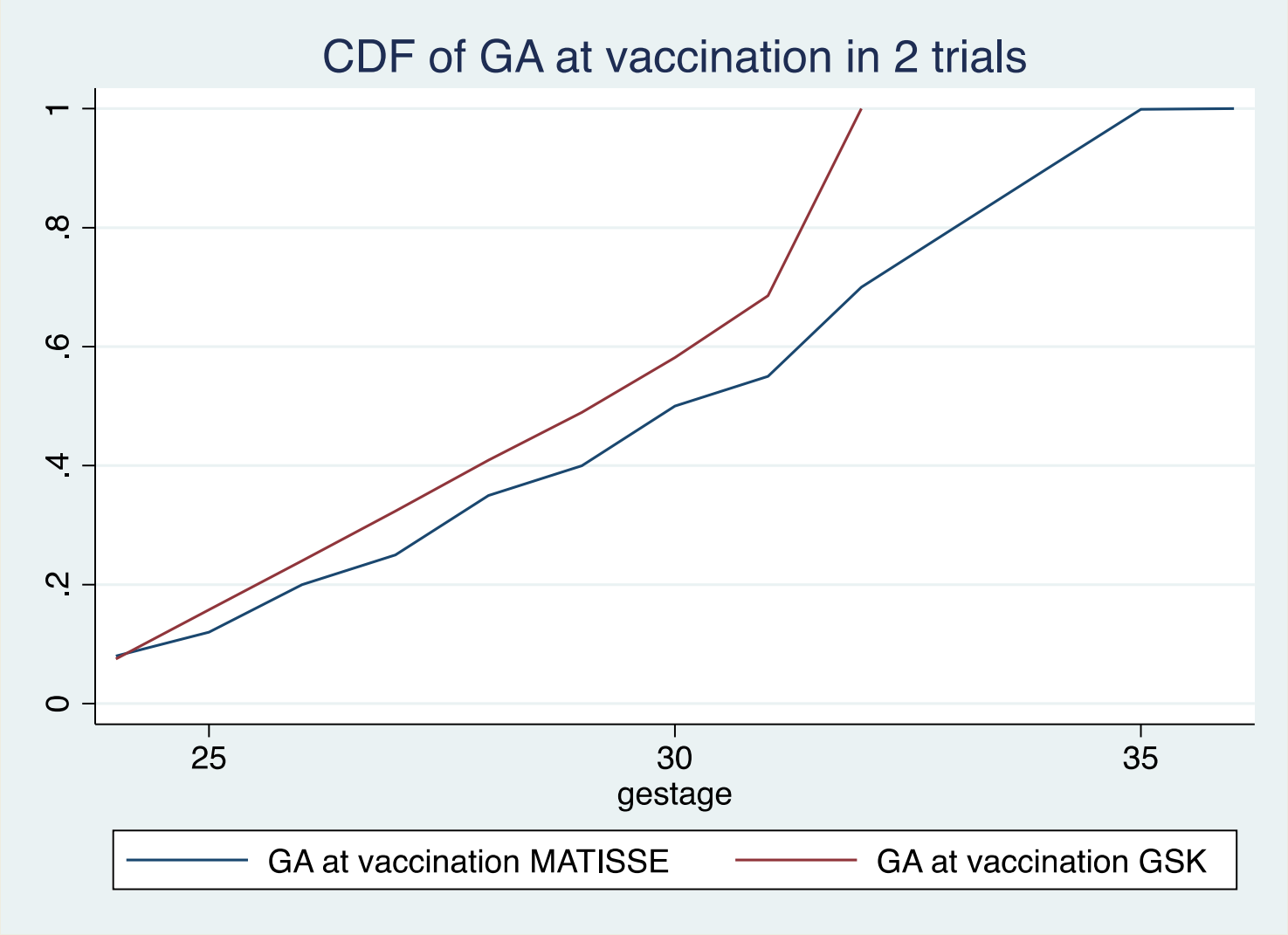
# Simulation of continuous interval
# A single group



# Simulation of two groups



# Overall difference between trials in age at vaccination



# Time from vaccination to delivery (only in pre-term) Matisse trial

**Table S19. Time from vaccination to delivery among preterm deliver**

| | RSVpreF (N*=3577) n† (%) | Placebo (N*=3570) n† (%) |
|---|---|---|
| Number of preterm deliveries‡ | 229 | 198 |
| Time from vaccination to delivery | | |
| ≤7 days | 11 (4.8) | 16 (8.1) |
| >7 days to ≤30 days | 81 (35.4) | 71 (35.9) |
| >30 days | 137 (59.8) | 111 (56.1) |

Kampmann B, Madhi SA, Munjal I, et al.
Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants.
N Engl J Med 2023;388:1451-1464.

# Statistical Methods

- Use the best
  - may need multiple analyses if mechanism not known
- May or may not make a large difference
- Reduces bias
- Improves statistical power