When to start ART in children aged 2-5 years?

A collaborative causal analysis of cohort studies from Southern Africa

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Background

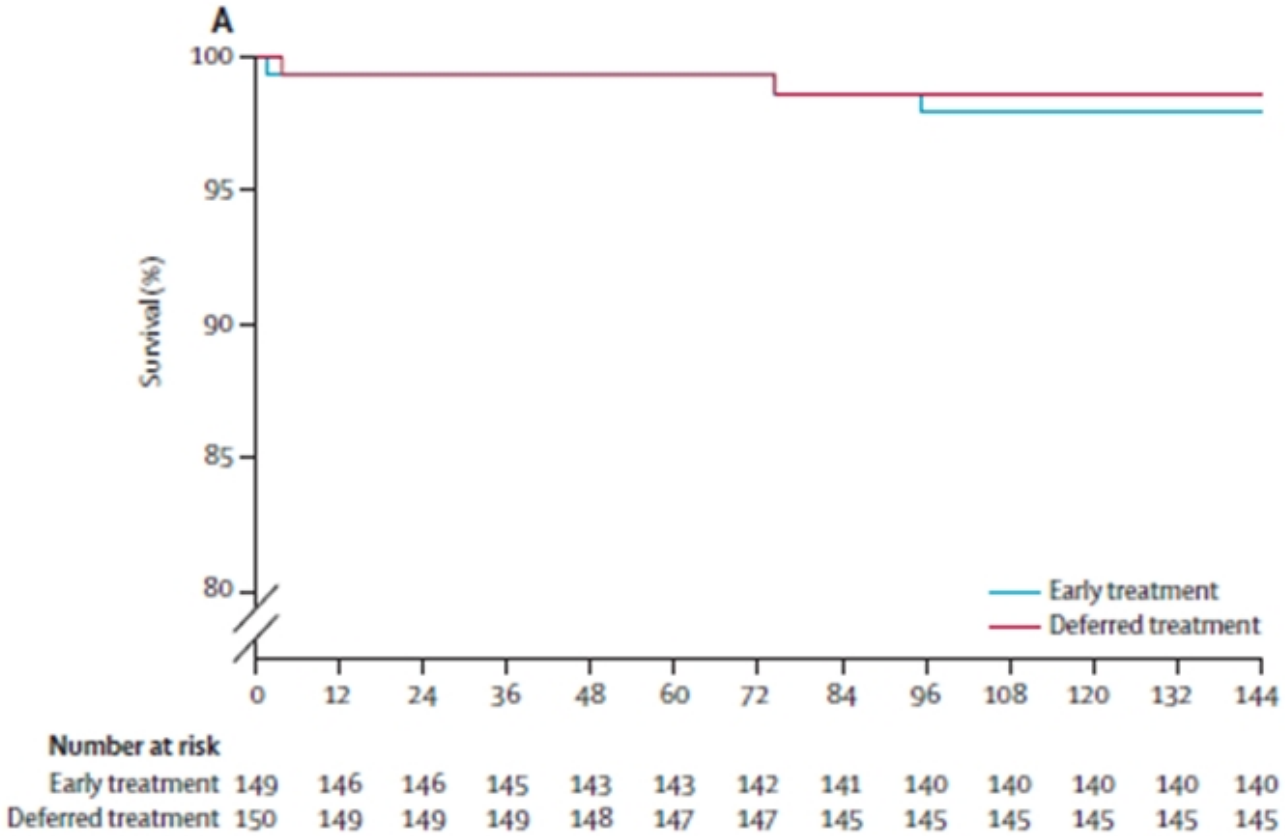
- Limited evidence from RCTs on when to start ART in children age 2-5 years

- CHER study: Early ART initiation in infants $<$ 3 months of age $\rightarrow$ 76% mortality reduction *Violari et al. (2008), NEJM*

- PREDICT study:
  - Enrolled children age 1-12 years with CD4% of 15-24% without CDC Stage C disease
  - Randomized to immediate ART vs. ART when CD4 $<$ 15%
  - No difference in mortality, AIDS-free survival, new category B and C events, neurodevelopmental outcomes, rates of hospital admission or drug related adverse events

Puthanakit et al. (2012), Lancet Infectious Diseases

Background: PREDICT results



- Low event rate for the primary outcome
  (5 CDC category C events, 3 in early treatment group; 1 death)
- 96 children in 2-5 year age group

IeDEA Southern Africa
International epidemiologic Databases to Evaluate AIDS

Objective

To use observational data from children age 2-5 years in the IeDEA-SA collaboration to estimate mortality for up to 3 years after first clinic visit related to the strategies of

- starting ART immediately (irrespective of CD4 criteria)
- starting ART when CD4 drops below different thresholds, e.g. 750 cells mm^3 or 25%
- starting ART not at all

Methods

Inclusion and exclusion criteria:

- Age 2-5 years at first visit to HIV care & treatment facility
- ART naive children (except for PMTCT exposure)
- At least 1 follow-up visit
- Excluded cohorts where all children initiated ART (i.e. no children died/LTFU prior to ART initiation)

Missing covariate data:

- longitudinal multiple imputation ...after carrying forward for up to 9 months

Methods

Data situation:

- Outcome: Time from first visit to death
- Interventions: ART initiation at different CD4 thresholds
- Time-dependent confounders (which influence both mortality and ART initiation in children): CD4 count, CD4%, Stage [weight-for-age z-score as proxy]

Causal modelling analysis using g-computation:

- The observed associations in the data are used to simulate and evaluate a counterfactual dataset that would have been observed under a certain initiation rule

G-computation

Step 1: After t=1,3,6,... months of follow-up:

a) model the association of *each* time-dependent confounder (CD4 count, CD4%, stage ≈ weight-for-age) at time t with

- disease progression history before time t (CD4, WFA at time $t-1\ldots$),
- baseline characteristics (CD4,WFA,HFA),
- and demographics (age,sex,region,...),
- and the intervention (ART)

b) also model the association of the outcome (death) at time t with risk factors (history) and ART intervention as well

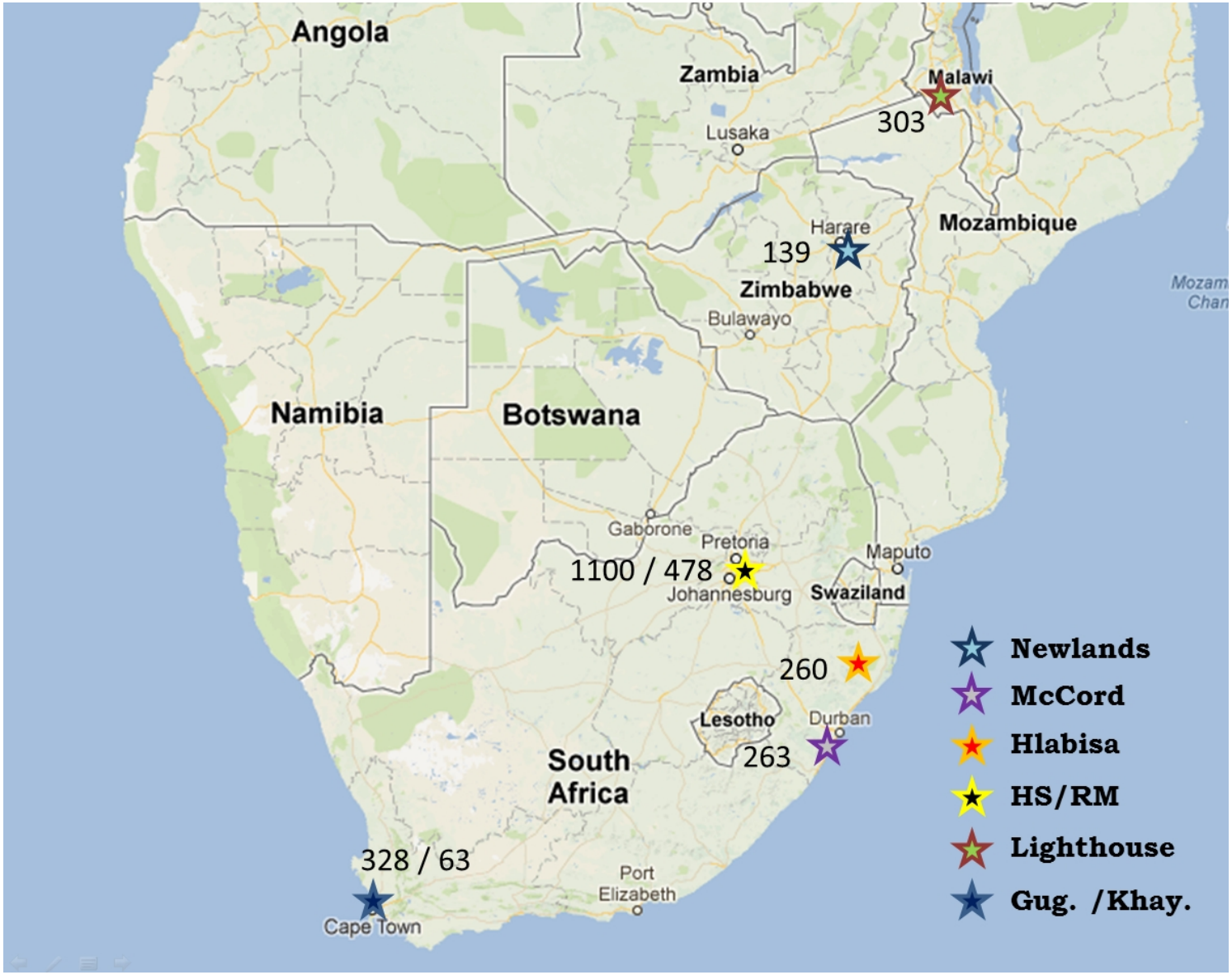
Step 2: Take baseline data ($t = 0$), and simulate time-dependent confounders and outcome 'forward in time' ($t = 1, 3, 6, \ldots$)

- based on the models of step 1,
- any 'forced' intervention of interest,
  i.e. give ART ($\rightarrow$ set ART $\equiv 1$) only if *simulated* CD4% < 20%

St. 3-6: Evaluate what would have happened under this intervention of interest, repeat for all interventions, and use bootstrapping and imputation rules to obtain final estimates.

Study population

We included 2,934 children from 8 cohorts

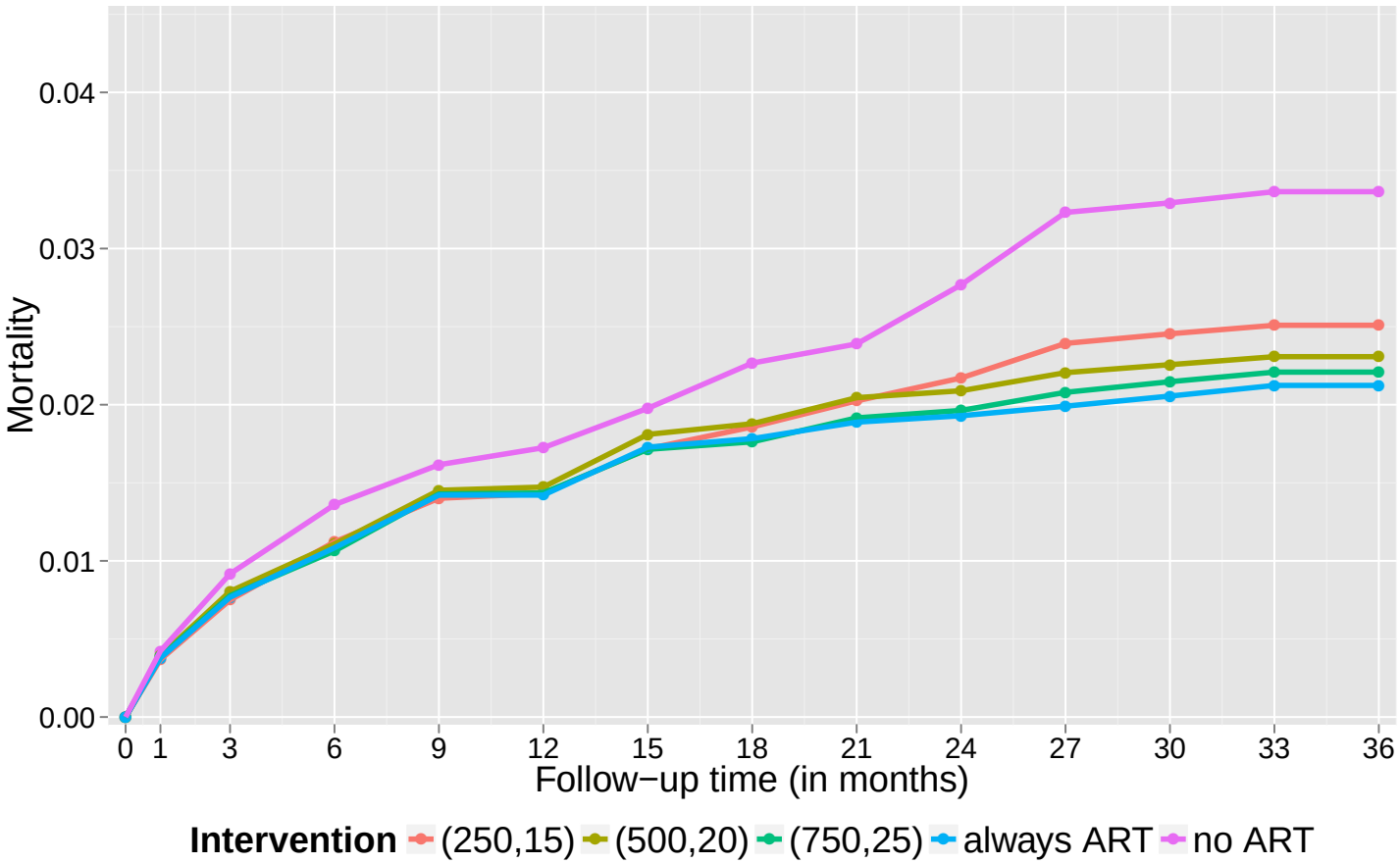


Characteristics of patients

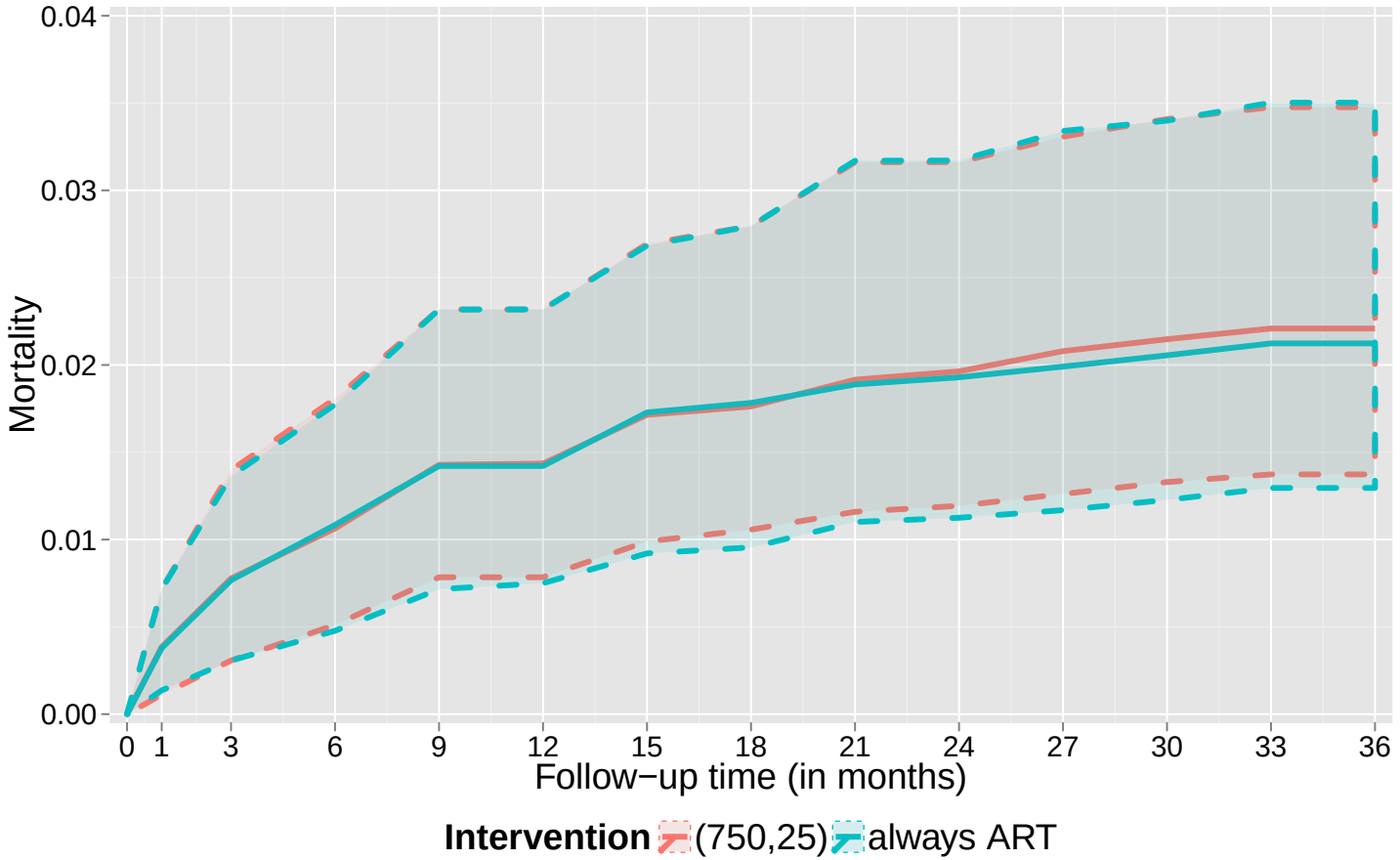
Characteristic	Median (IQR)
Age (in years)	3.3 (2.6; 4.1)
CD4 count	592 (356; 895)
CD4 percent	16 (10; 23)
Weight-for-age z-score	-1.4 (-2.3; -0.5)
Height-for-age z-score	-2.6 (-3.5; -1.6)

Characteristic	n (%)
Male sex	1501 (51%)
Initiated ART	2227 (75.9%)
below 750/25%	1716 (77%)
above 750/25%	100 (4.5%)
unknown	411 (18.5%)

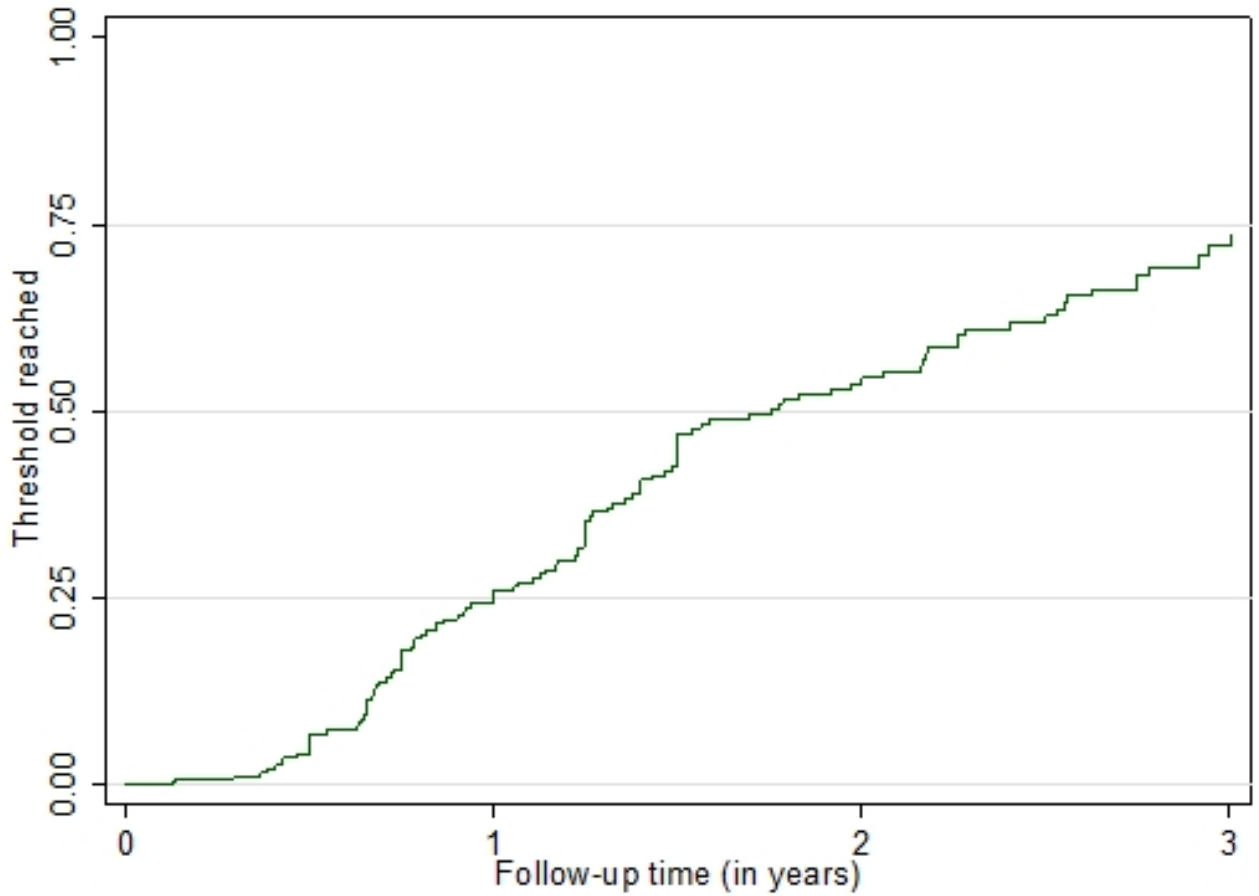
Comparing mortality for different interventions



Comparing mortality for immediate ART vs. deferred ART (750,25%)



Time to fall below the CD4 threshold of 750 cells/mm^3 or 25% [1]



Time	1 year	2 years	3 years
Threshold reached (in%)	26.0 (20.4-32.7)	54.5 (47.2-62.2)	72.2 (64.3-79.6)

[1]The figure is based on 322 children presenting with a CD4 count of 750 or above and a CD4% of 25% or above. Only pre-ART follow-up is considered.

Conclusions

- There is a trend in that interventions that start ART late lead to higher mortality than interventions that start ART early.
- However, there is no major difference in mortality between ART irrespective of CD4 compared to deferring to WHO 2010 guidelines criteria (<750 cells/mm^3 or 25%)

Limitations

- Loss to follow-up – under-ascertainment of deaths
  - sensitivity analysis: imputed survival time for those LTFU in 3 cohorts based on linkage data from the SA death registry
  - mortality estimates for all interventions 2-3$\times$ higher, but relative differences after 3 years same
- Unmeasured confounding
  - used weight-for-age as proxy for clinical stage
  - other unmeasured confounders
- Other issues
  - Generalizability to rural areas and sub-Saharan African countries with less well-resourced health care systems
  - Long term outcomes as well as other outcomes
  - .....

Acknowledgements

- All children and their caregivers from participating sites
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