Acute Respiratory Infections and Asthma in U-5 Children: Improved Treatment to Reduce Morbidity and Mortality in Uganda; A Randomised Trial

- **Preliminary Results**

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Acute respiratory infections (ARI)

- Leading cause of mortality among children U-5 years of age globally.

- Case management algorithms used in resource limited countries are not robust enough to differentiate bacterial pneumonia from other causes of cough or difficult breathing

Acute respiratory infections (ARI)

- In most U-5 asthma is under-diagnosed and under-treated whereas bacterial pneumonia is over-diagnosed and over-treated *(Ostergaard MS, 2012)*

- Undiagnosed asthma could contribute to treatment failure and mortality

Hypotheses

- Treatment with inhaled corticosteroids (ICS) combined with the standard therapy reduces morbidity and mortality of children U-5 admitted with severe ALRI.

- The subgroup with asthma have a significantly larger efficacy than the other ALRIs group.

Objectives

- **On children U-5 admitted with severe ALRI and given standard treatment,**

  to determine the supplementary effect of ICS on

  - **mortality**
  - **time to normalization of respiratory rate**
  - **time to normalization of oxygen saturation**
  - **duration of hospitalization**

- Assess similar outcomes on children classified with asthma versus bacterial pneumonia

Sub-studies

- To determine the knowledge, attitude and perceptions of health workers to use of inhaled corticosteroids for the management of children U-5 years of age with ALRI.

- To determine the caretakers' satisfaction, attitude and perceptions to use of ICS for the management of children U-5 years of age with ALRI.

Methodology

Design

- A randomized controlled trial

- A cross sectional design for the substudies; using both qualitative and quantitative methods

Study site

- Mulago hospital paediatric wards

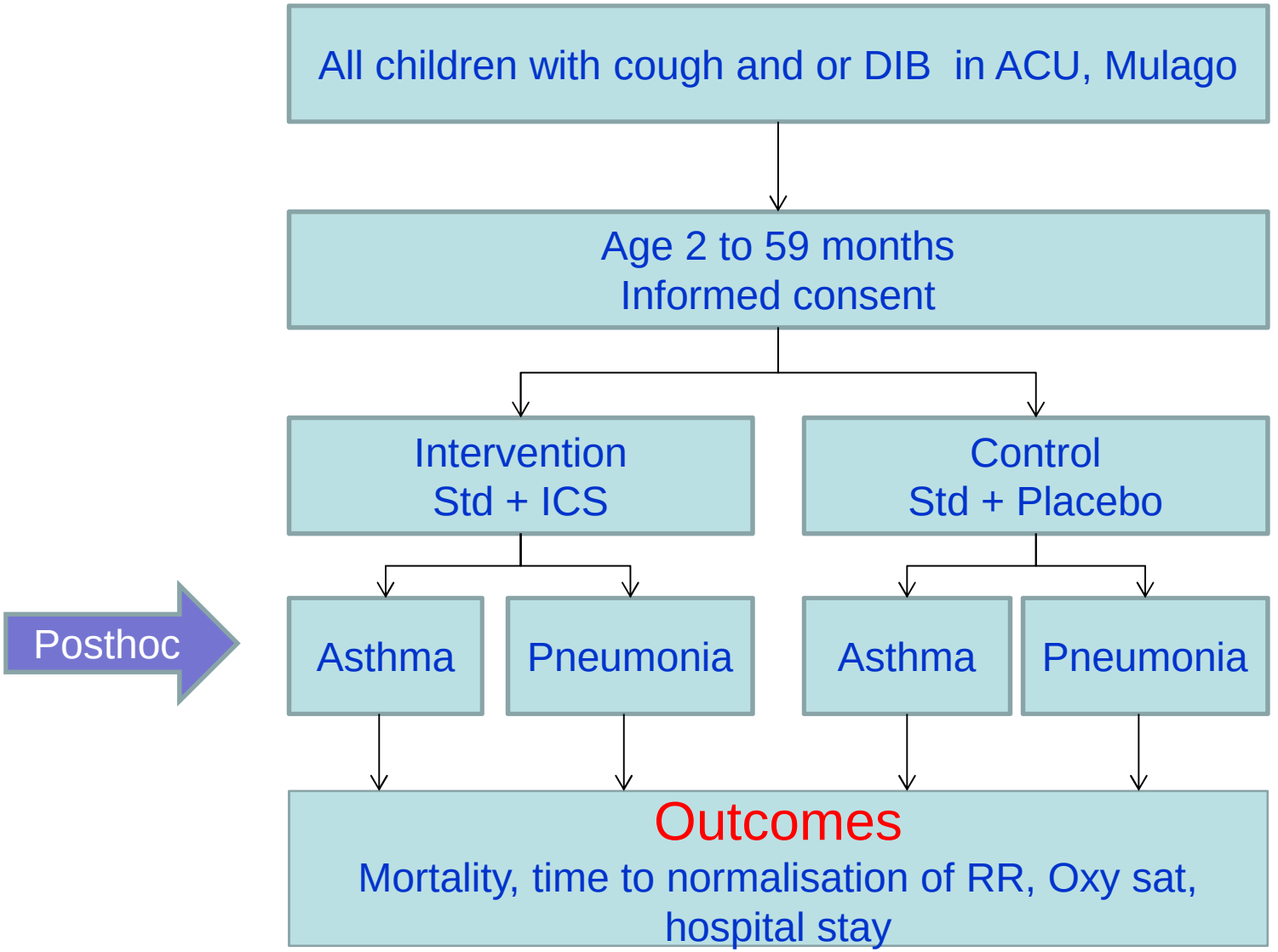
Inclusion criteria

- Children aged 2 to 59 months
- with cough and or difficult breathing
- Informed consent

Exclusion criteria

- A serious concurrent illness such as meningitis
- Congenital or acquired heart disease
- Severe anaemia
- Measles pneumonia
- Foreign body inhalation

Study Profile



Randomisation

- Random assignment to the intervention or placebo in a 1:1 ratio, in blocks of 8 to 20.
- Random nos in opaque envelopes, treatment assigned after randomisation
- Blinding: Caretakers and patients are blinded, canisters labelled A or B, in similar jackets.

Intervention

- Inhaled fluticasone vs placebo (Norflurane - tetrafluoroethane, non toxic propellant)
- Dose: 500 mcg twice a day.

- Administered using a face mask attached onto a spacer (babyhaler)


Flixotide™
inhaler 250mcg
Contains 250 micrograms
fluticasone propionate
per actuation
60 metered actuations
overseas foreign pharmacy
gsk GlaxoSmithKline


Flixotide
Evohaler
250 micrograms
120 metered actuations
GlaxoWellcome
134a aerosol
PLACEBO INHALER
200 doses
Contains :
norflurane
Store below 30°C
FOR
DEMONSTRATION
NOT FOR
THERAPEUTIC USE
GlaxoSmithKline

Administration of Inhaled fluticasone

Participant follow up

- First 48 hours: patients are monitored 6 hourly for temperature, respiratory rate and oxygen saturation

- After 48 hrs: monitor 12 hourly up to discharge from hospital

Safety and adverse event monitoring

- Participants are monitored for the presence of possible adverse effects such as dry mouth, hoarseness and oral thrush

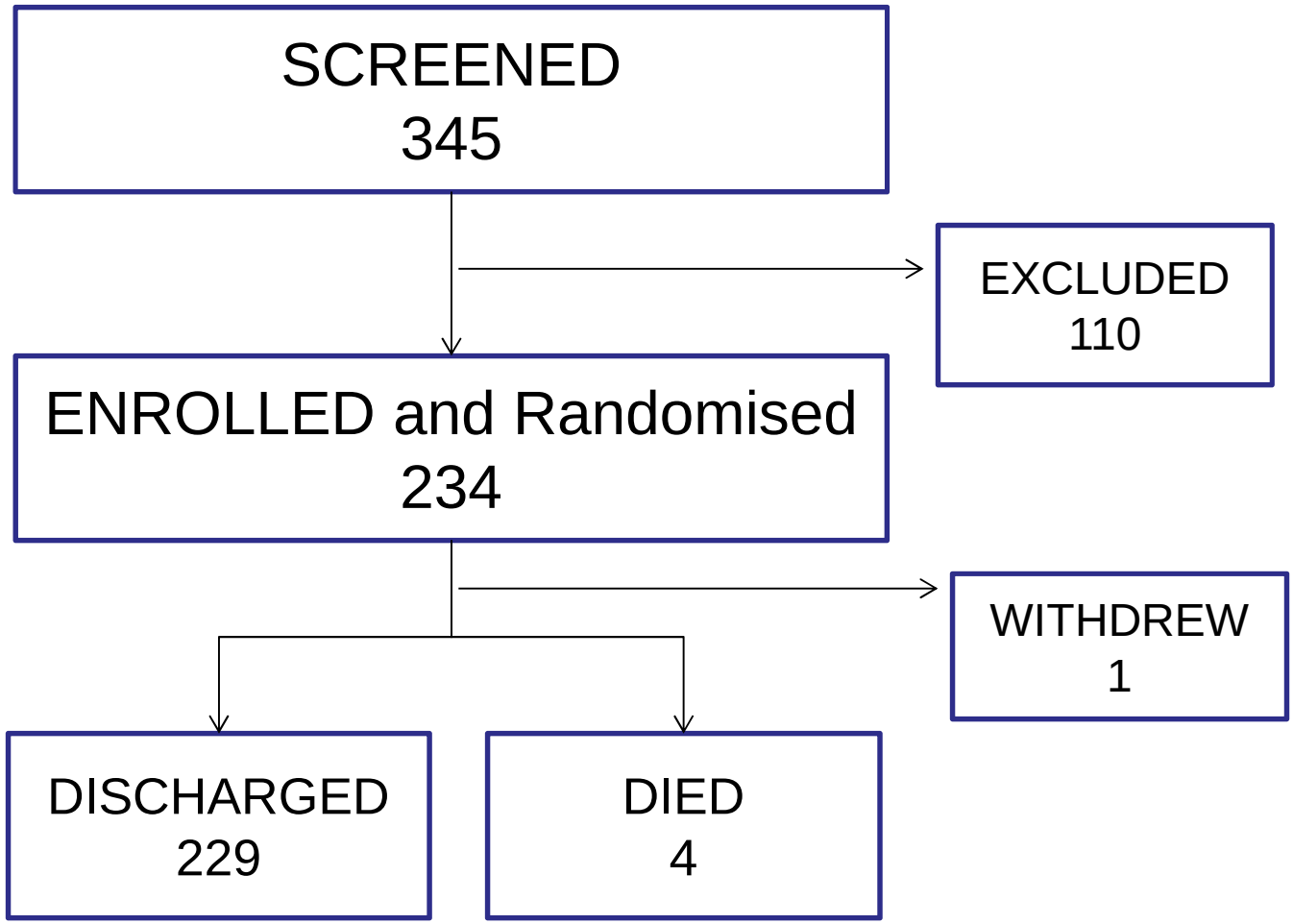
- These are recorded on an adverse event form, summarised and submitted to IRB and DSMB on a monthly basis

Sample size calculation

Assumptions:

- 40% effect size,
- A two-sided significance level (1-alpha) 95%
- Power (1-beta, % chance of detecting a difference)80%
- Allocation ratio 1:1
- Mortality without intervention12% *(Srinivasan et al 2012)*
- Mortality with intervention 7.2%
- Odds Ratio 0.57
- Required sample size: 635 in each group
- 10% attrition 64 children
- **Total sample size: 1398**

PRELIMINARY RESULTS


SCREENED
345
EXCLUDED
110
ENROLLED and Randomised
234
WITHDREW
1
DISCHARGED
229
DIED
4

Reasons for exclusion (n=110)

- Not eligible for admission (OPD) – 42
- Over 5 years and under 2 mo age – 26
- Severe anaemia – 15
- Previously enrolled – 12
- Congenital heart disease – 9
- Severe dehydration – 2
- Meningitis – 2
- Measles pneumonia – 1
- Did not consent – 1

Demographic characteristics of study participants (N=234)

Variable	No	Percentage
Sex		
Male	106	45.3
Female	128	54.7
Caretaker		
Mother	228	97.4
Other	6	2.5
District		
Kampala	174	74.4
Wakiso	50	21.4
Others	10	4.2
Urban	210	89.7
Rural	24	10.3

F:M ratio = 1.2:1

Characteristics of illness

Variable	No	Percentage
Cough < 21 days	218	93.2
Onset gradual	183	78.2
Disease started with changes in breathing	109	46.6
Onset associated with wheezing/whistling	59	25.2
Onset associated with fever	187	79.9
Previous asthma diagnosis	15	6.4

Duration of cough and or difficult breathing 1 -90 days,
Median (IQR): 4 (3-7) days

Use of medicines before hospitalisation

198/234 (84.6%) of caretakers gave medicines before hospitalisation

- Commonly used drugs:
  - Paracetamol (138)
  - Antibiotics (104)
  - Cough syrups (89)
  - Antimalarials (69)
  - A few had taken steroids (17) or salbutamol (14).

- Commonly used antibiotics: Amoxycillin, cotrimoxazole, ceftriaxone

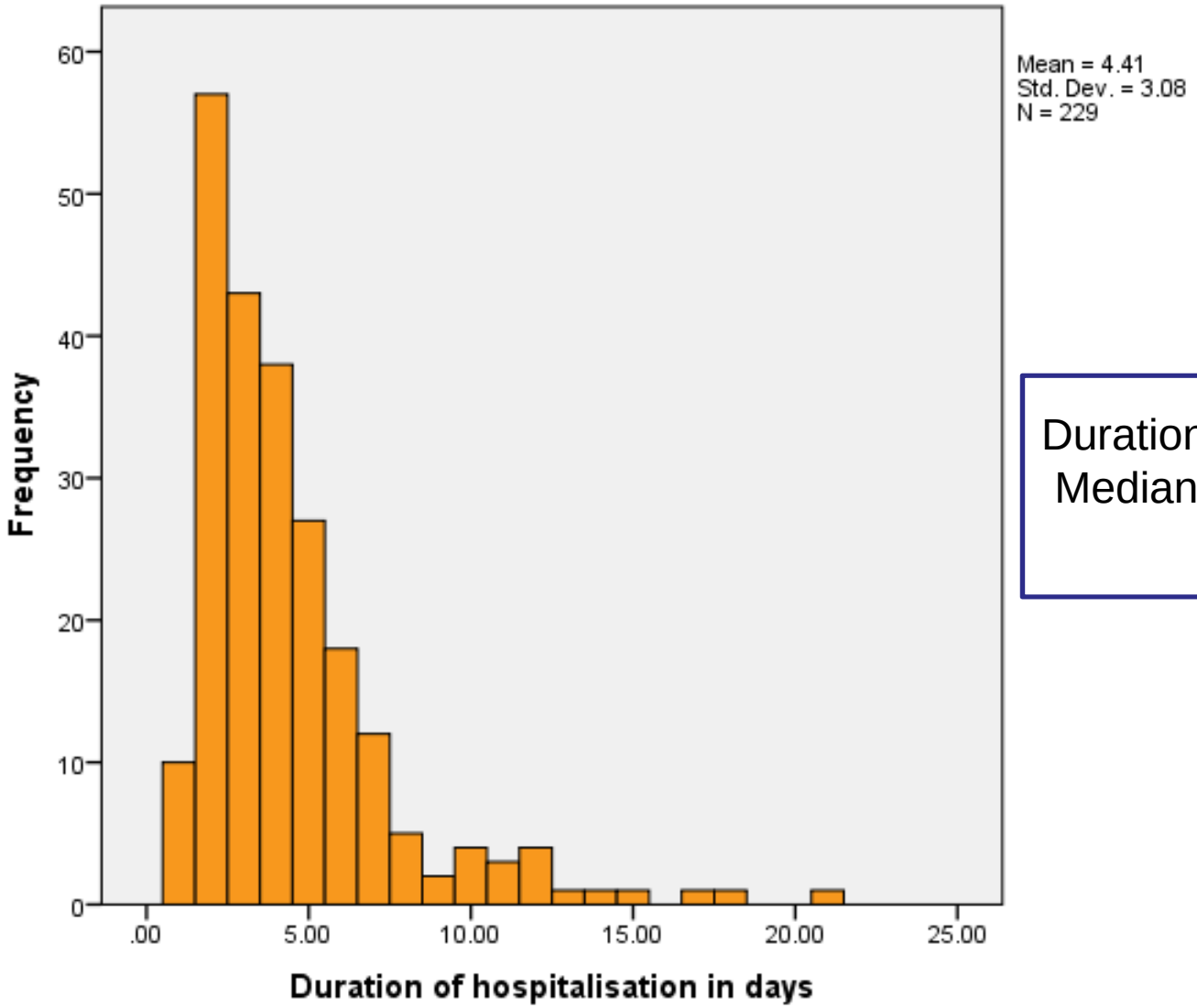
Clinical characteristics

Variable	No	percentage
Temperature ≥37.5	129	55.1
Tachypnoea	222	94.9
Oxy sat < 92%	59	25.2
Audio wheeze	38	16.2
Auscultatory wheeze	86	36.8
Crepitations	130	55.6

Outcome of 234 children with severe ALRI

Outcome	No	percentage
Discharged	229	97.9
Hospitalisation ≥ 14 days (n=229)	5	2.2
Died	4	1.7
Withdrew	1	0.4

Duration of hospitalisation for 229 participants with severe ALRI in Mulago hospital



Duration 1 – 21 days
Median (IQR): 4 (2-5)

Adverse events

- Cough on administration of study medicine – 2
- Dry mouth – 1
- Oral thrush – 1 (appeared on 2nd day and resolved by day 5).

Discussion

- Mortality rate low (1.7%)
- Majority of patients are discharged within 5 days
- Adverse events are very few
- Serious adverse events less likely to be related to the intervention

Strengths and limitations

Strengths

- Most probably the first study investigating use of ICS in children with ARI in Uganda
- A randomised trial

Limitations

- Single blinding versus double blinding
- Sample size based on studies that reported higher mortality rates – ?? Power of study

Acknowledgements

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