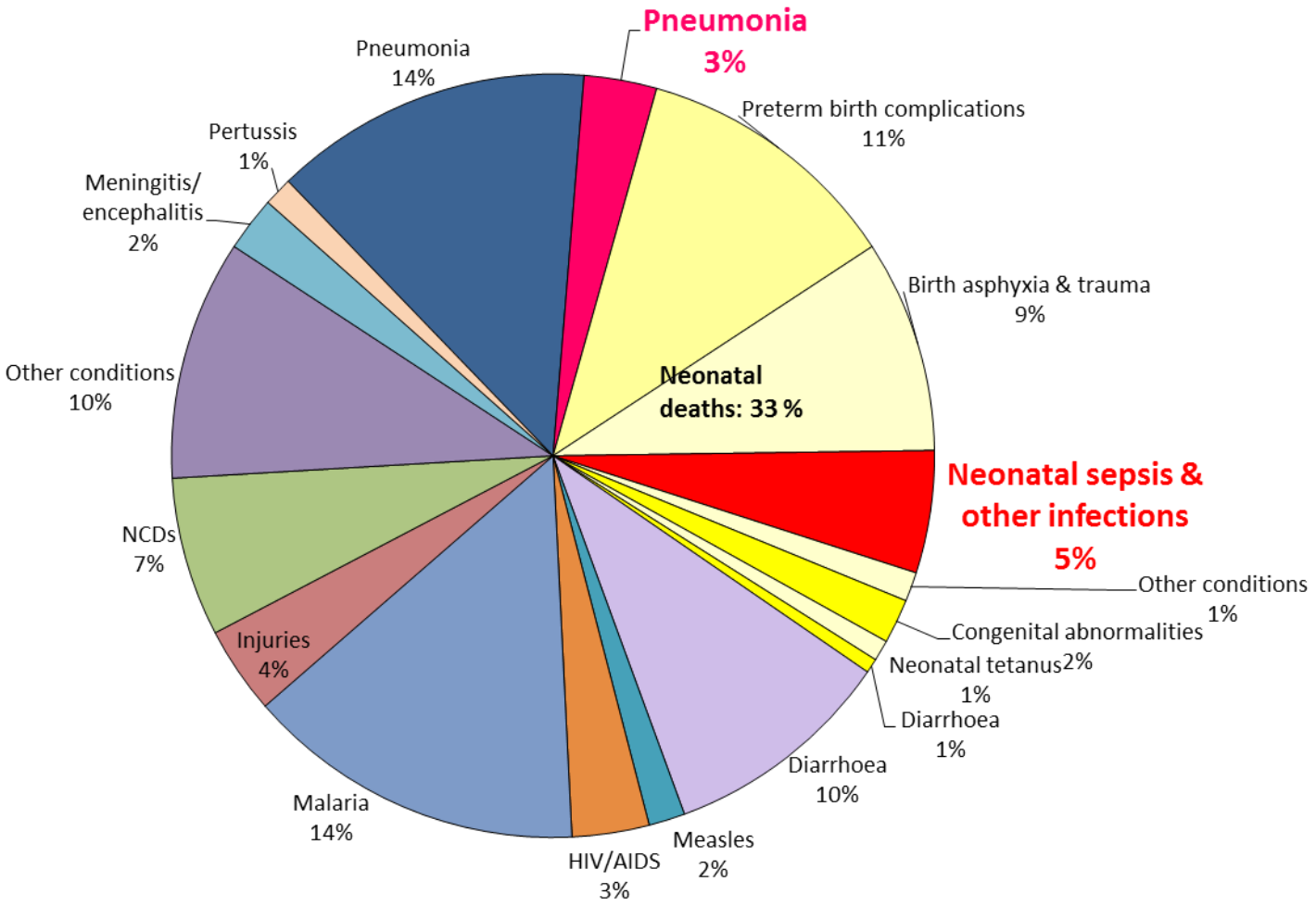
Simplified management of severe neonatal and young infant infections in outpatient settings:

A community-based multicentre randomised controlled trial in DR Congo, Kenya and Nigeria

Ebunoluwa Aderonke Adejuyigbe
Professor of Paediatrics,
Dean, Faculty of Clinical Sciences,
Obafemi Awolowo University, Ile-Ife, Nigeria
On behalf of the African Neonatal Sepsis Trial (AFRINEST) Group

Accra, Ghana

Major causes of death in neonates and children under-five in the African Region



Globally 700,000 neonatal deaths occur due to sepsis, pneumonia and meningitis

–Source: WHO. Global Health Observatory (http://www.who.int/gho/child_health/en/index.html)
–

Reasons for these studies

- Inpatient Hospital treatment - not accessible to all
- In circumstances where referral was not possible
  - Procaine penicillin and gentamicin injection have been used
  - 7days and on outpatient basis
- Make accessible safe and effective treatment to all the sick young infants

Aim of the study

To identify, in time sick young infants and find the simplest treatment which is:

- as effective as standard treatment,
- deliverable, and
- acceptable to families.

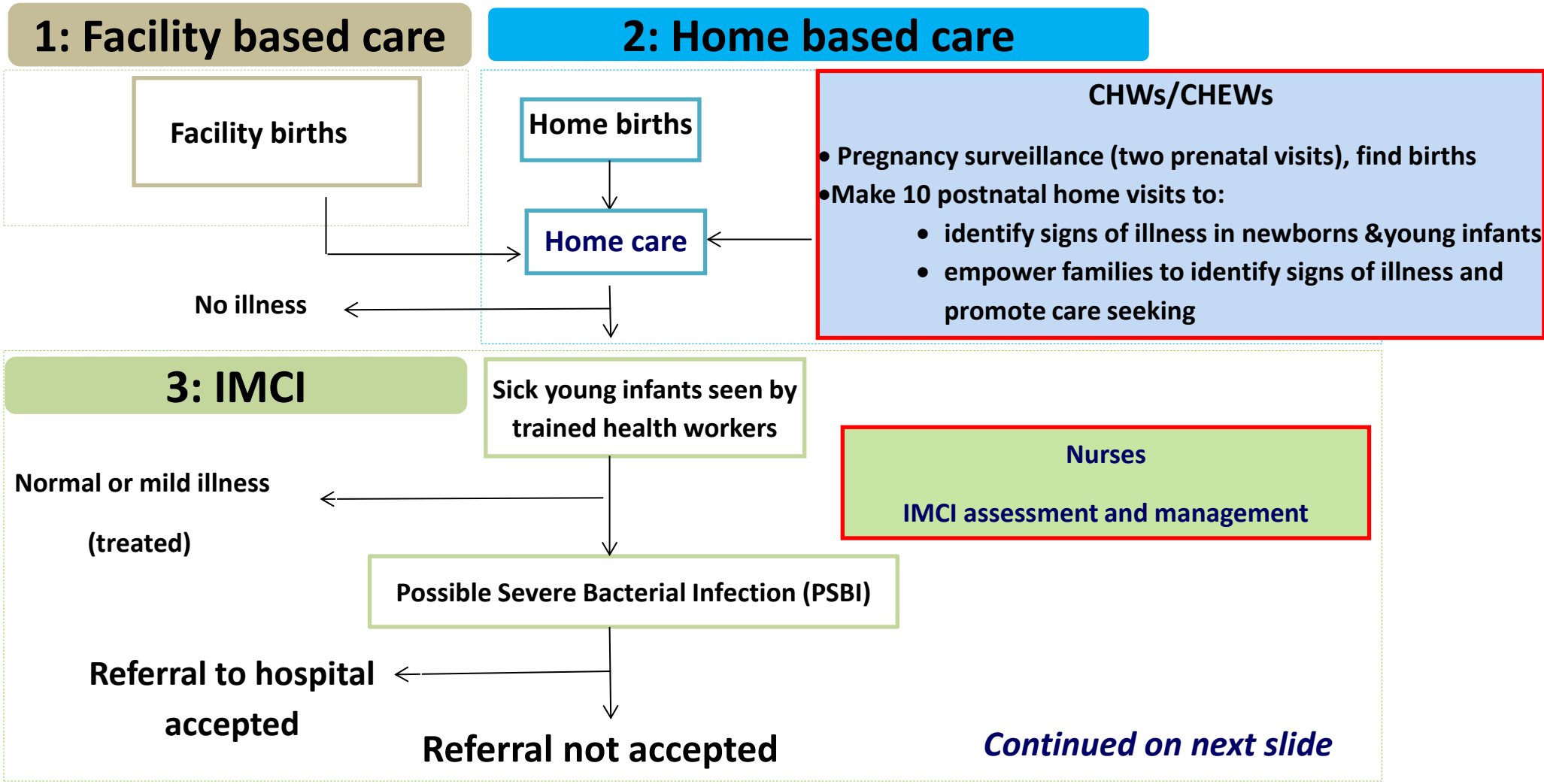
Study concept

- Promote appropriate care seeking among pregnant women
- Early identification of infections through postnatal home visits by community health workers
- Encourage hospitalization
- Standard or simpler antibiotic regimens on outpatient basis where referral is not possible
- Study set up within the country-specific health systems

Primary Objective

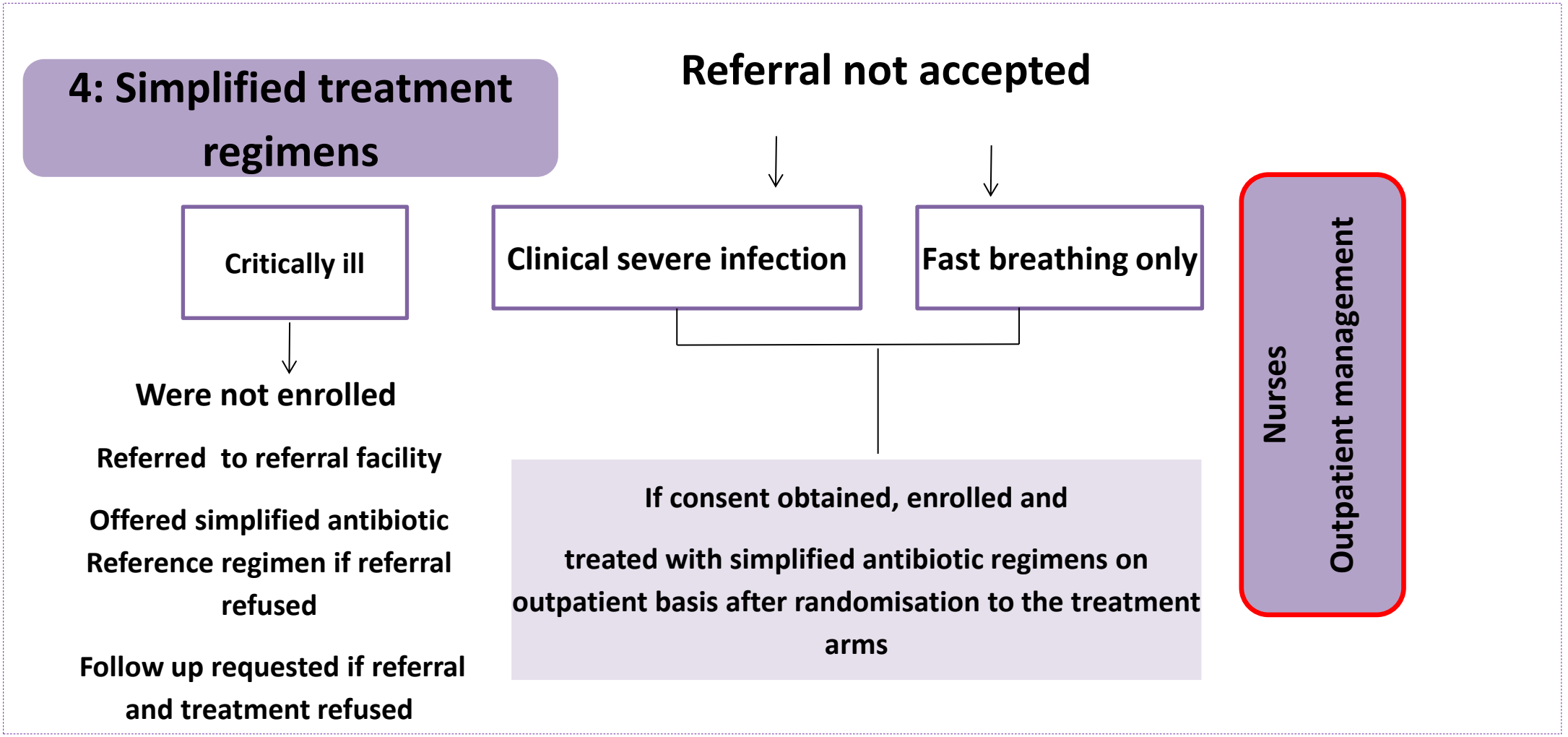
Evaluate **simple, safe and effective** antibiotic regimens for use at **first level facilities and in the community** for young infants with possible serious bacterial infection (PSBI) whose **families do not accept or cannot access referral level care**.

Research in programme setting



Study Design: Randomized trial

Two open-label equivalence trials



Study Sites

	DRC	Kenya	Nigeria
Site	Equateur Province	Western province	Ibadan, Ile-Ife, Zaria
Study population	300,000 2 districts	350,000 8 districts	600,000 5 Local Government Authority areas
Expected Births/year	12,000	12500	25,000
Expected sick infants/year	2000	2000	3000

Gemena Town, DRC

Treatment regimens

Control arm for both studies (reference treatment)

- **A** : IM Gentamicin and Procaine Penicillin once daily for 7 days

  14 injections

Experimental interventions

Clinical severe infection study

- **B**: IM Gentamicin once daily and Oral Amoxicillin twice daily for 7 days

  7 injections

- **C**: IM Gentamicin and Procaine Penicillin once daily for 2 days, thereafter oral Amoxicillin twice daily for 5 days

  4 injections

- **D**: IM Gentamicin once daily and Oral Amoxicillin twice daily for 2 days, thereafter oral Amoxicillin twice daily for 5 days

  2 injections

Fast breathing study

- **E**: Oral Amoxicillin twice daily for 7 days

  No injections

Inclusion and exclusion criteria

Inclusion criteria

- **Clinical severe infection study**

  One or more of the following signs:
  - Stopped feeding well
  - Movement only when stimulated
  - Severe chest in-drawing
  - Temperature >38.0^{o}C or <35.5^{o}C
  - Consent given by parents

- **Fast breathing study**
  - –Respiratory rate 60 or more per minute
  - –Consent given by parents

Exclusion criteria

- **Clinical severe infection study**

  One or more of the following:
  - –Signs of critical illness
  - –Previous inclusion in the study
  - –Hospitalization in the last 2 weeks

- **Fast breathing study**

  One or more of the following:
  - –Signs of critical illness
  - –Signs of clinical severe infection
  - –Previous inclusion in the study
  - –Hospitalization in the last 2 weeks

Outcomes

- **Primary outcome**
  - Treatment failure within 7 days of randomization
- **Secondary outcomes**
  - Death within 2 weeks of enrolment
  - Relapse of signs/symptoms present at enrolment during 2nd week
  - Adverse effects due to study drugs
  - Adherence to study therapy

Outcome assessed by nurses not involved with intervention:

- *Scheduled on days 4, 8, 11 and 15*
- *Additionally when treatment health workers feel the need*

Treatment Failure – Both studies

IN THE FIRST WEEK AFTER RANDOMIZATION

- **Death**
- **Hospitalization**
- **Serious adverse effect** of the study antibiotics
- **Clinical deterioration** defined as emergence of any sign of critical illness, a (new) sign of severe infection
- **No improvement** by day 4
- **Not recovered** by day 8
- **Re-emergence** of any presenting sign after disappearance on day 4 (only in “clinical severe infection study” – not in “fast breathing study”)

Study Oversight bodies

- Technical Advisory Group (TAG) established with membership that included
  - External experts
  - Site Principal Investigators
  - Technical experts from WHO
  - Funding agencies (BMGF, USAID, SNL)
- Data Safety Monitoring Board (DSMB)
  - 5 external independent members (multicountry experts)

Quality control and internal validity

Internal (site team)

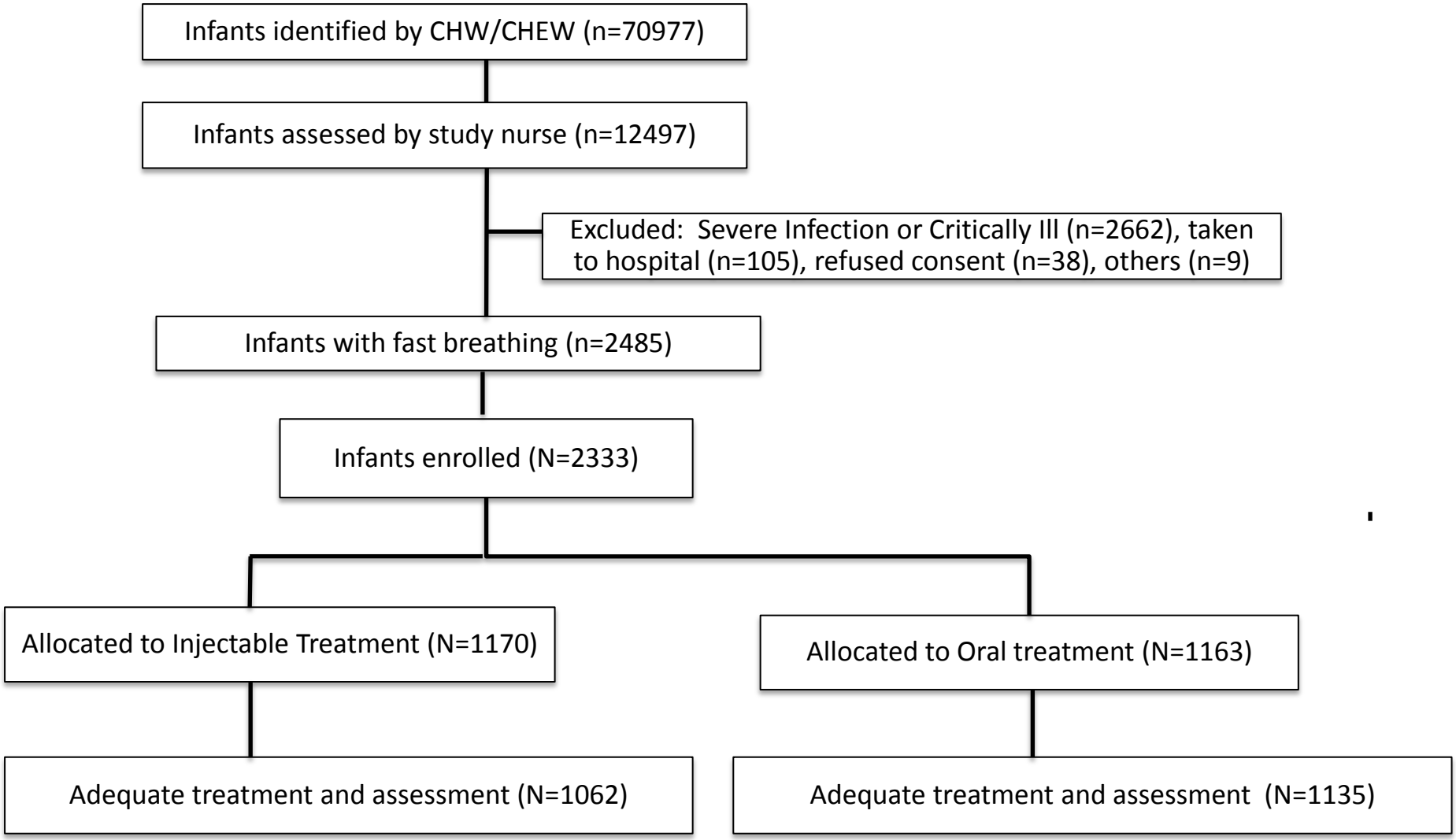
- Initial and periodic standardization exercises for CHWs and Nurses
- Supervisory visits and independent checks
- Quality monitoring by PI and co-investigators - random checks
- Data based monitoring

External (WHO technical experts, monitors)

- Site monitoring visits by external expert
- Cross-site WHO technical staff visits
- Data-based monitoring by data management centre and WHO
- Monitoring visits by WHO technical staff

EARLY UNPUBLISHED RESULTS

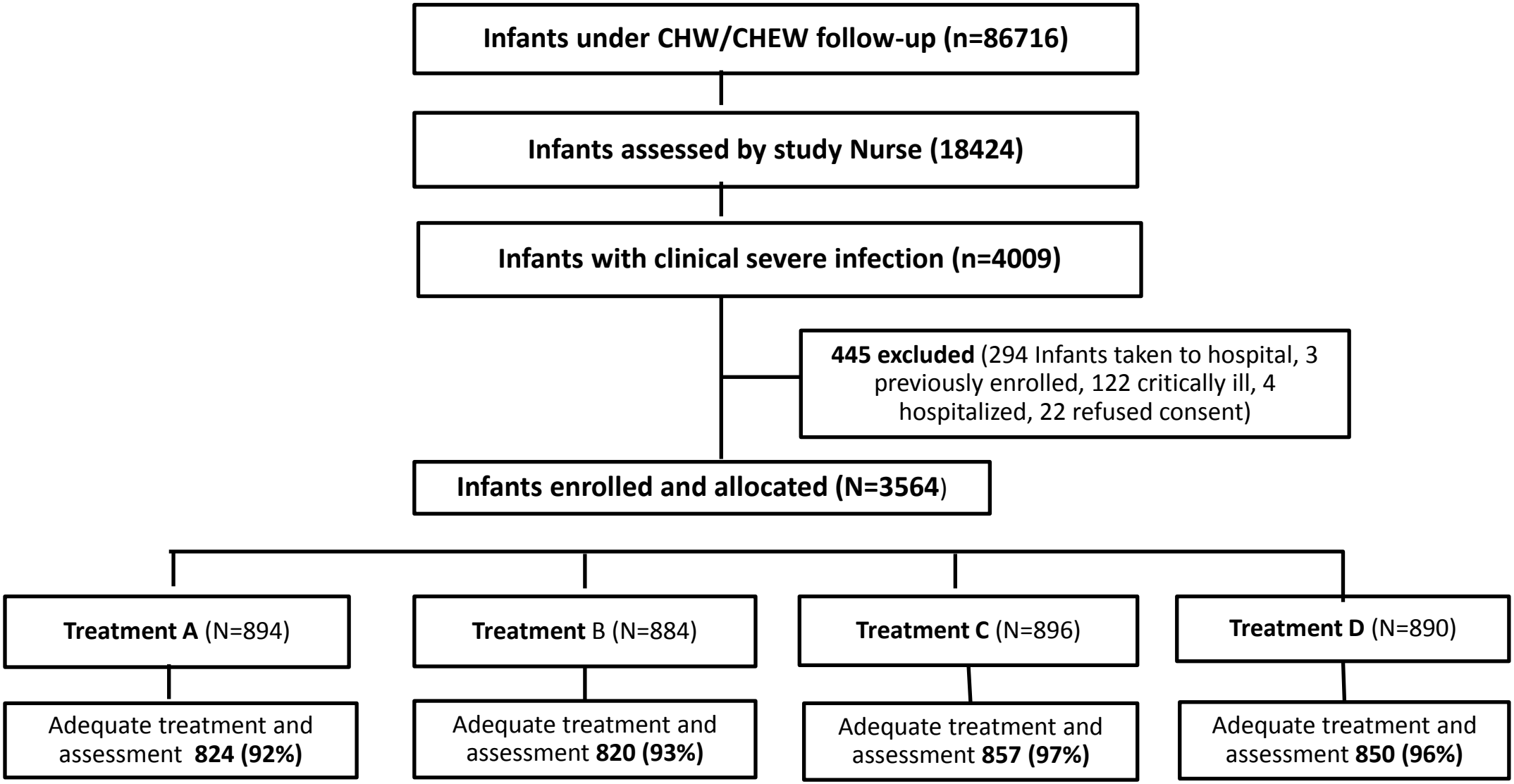
CONSORT diagram for fast breathing



Is Oral Amoxicillin equivalent to Inj. Gentamicin & Procaine Penicillin for treatment of fast breathing?

	Gentamicin & Procaine penicillin inj.	Oral Amoxicillin	Risk difference (95% CI)
	1063	1145	(oral – injections)
Treatment failure	235 (21%)	221 (19%)	-3% (-6% to 1%)
Individual Signs of failure			
Death during 2 week f/up	4	4	
Clinical deterioration	21 (2%)	20 (2%)	
Persistence of FB on day 4	193 (18%)	197 (16%)	
Recurrence of FB day 5-8	17 (2%)	20 (2%)	
Severe adverse events	0	0	
Relapse during 2nd week	18 (2%)	22 (2%)	

Study flow: clinical severe infection



Are simplified regimens equivalent to reference treatment?

	Gentamicin & Pen injections 14 injections	Gentamicin & Oral Amoxicillin 7 injections	Gentamicin & Pen injections 4 injections	Gentamicin & Oral Amoxicillin 2 injections
	N= 824	**N= 820**	**N= 858**	**N= 850**
Treatment failure (Risk Difference)	61 (7.4%)	43 (5.2%) -2% (-5% to 0.2%)	56 (6.5%) -1% (-3% to 2%)	44 (5.2%) -2% (-5% to 0.1%)
Death during 2 weeks	11 (1%)	10 (1%)	17 (2%)	11 (1%)
Clinical deterioration	13 (2%)	11 (1%)	13 (2%)	15 (2%)
SAE	1	0	0	0
Hospitalization	4	3	4	1
Not improved by day 4	36 (4%)	24 (3%)	24 (3%)	18 (2%)
Not recovered by day 8	8 (1%)	6 (1%)	8 (1%)	4 (1%)
Relapse in 2nd wk	8 (1%)	7 (1%)	2 (0.3%)	9 (1%)

Summary of key findings

- Fast breathing as a single sign constitute about 40% of all infants referred based on WHO criteria for PSBI
- In infants with fast breathing only, treatment failure, clinical deterioration and deaths in those with oral amoxicillin was similar to that with procaine penicillin and gentamicin injections.
- Overall, In infants with clinical severe infection, treatment failure, clinical deterioration and death in those with 2, 4 or 7 antibiotic injections given with oral antibiotics, was similar to those with a regime that had 14 injections.

Conclusions

- Where referral is not possible, Infants with fast breathing as a single sign can be safely and effectively treated as outpatient with oral amoxicillin under supervision
- Where referral is not possible, infants with severe infection can be safely and effectively treated as outpatients
- Community health workers can serve as a link between the families and health providers who provide outpatient treatment
- No infant with infection should be left untreated

Implications

- Potential to transform the current limited access of young infants
- WHO guidelines are in the process of being updated and will be available in 2014.

Study teams of Investigators and sponsors

Democratic Republic of Congo

- Prof. Antoinette Tshefu
- Dr. Cyril Engmann
- Dr Adrien L. Longombe

Kenya

- Prof. Fabian Esamai
- Dr. Peter Gisore
- Prof. Edward Liechty

Nigeria

- **Ibadan**
  - Dr. Adejumoke Ayede
  - Prof. Adegoke G. Falade
- **Ile Ife**
  - Prof. Ebunoluwa Adejuyigbe
  - Prof. A. Odebiyi
  - Dr. Henry.C Anyabolu
- **Zaria**
  - Prof. Robinson Wammanda
  - Prof. William Ogala
  - Dr. Clara L. Ejembi

- ***Data Management:*** *London School of Hygiene and Tropical Medicine, London (Lu Gram and Simon Cousens)*
- ***Technical Support and Coordination:*** *Department of Maternal, Newborn, Child & Adolescent Health, WHO Geneva & CAH AFRO (S. Qazi, R. Bahl, N. Rollins, S. Yoshida, K Mwinga)*
- ***Funding and support:*** *Bill and Melinda Gates Foundation (Gary Darmstadt)*