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Hot or not?
Management of unclassified fever in children in sub-Saharan Africa

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Key messages

- Conditional follow-up of children with non-severe unclassified fever in a low-malaria endemic setting was non-inferior to universal follow-up advice through day 7.
- Allowing community health workers (CHWs) to advise caregivers to return only when a child has continued symptoms can be a more efficient use of resources.

Introduction

- More children seen by CHWs have unclassified fever, as a result of declining malaria prevalence and increased use of malaria diagnostic test.
- Caregivers of children seen with non-severe unclassified fever are advised to take the child to a CHW after two days for re-assessment.
- This study assessed the safety of conditional vs. universal follow-up of children with unclassified fever, hypothesising that the conditional arm does not have a higher treatment failure rate.

Methods

- This two-arm cluster-randomised controlled non-inferiority trial in Southwest Ethiopia randomised 25 health facilities, with 282 CHWs, to universal or conditional follow-up.
- CHWs enrolled children aged 2-59 months with fever and without malaria, pneumonia, diarrhoea or danger signs.
- Caregivers received advice to return after two days (universal arm), or to only come back if symptoms persisted (conditional arm).
- Clinical outcomes were assessed on day 7, and at day 14 and 28 if the child had not recovered; vital status of all children was assessed at day 28.
- Analysis was per-protocol with non-inferiority margin of 4% for treatment failure by day 7, using generalised linear models.
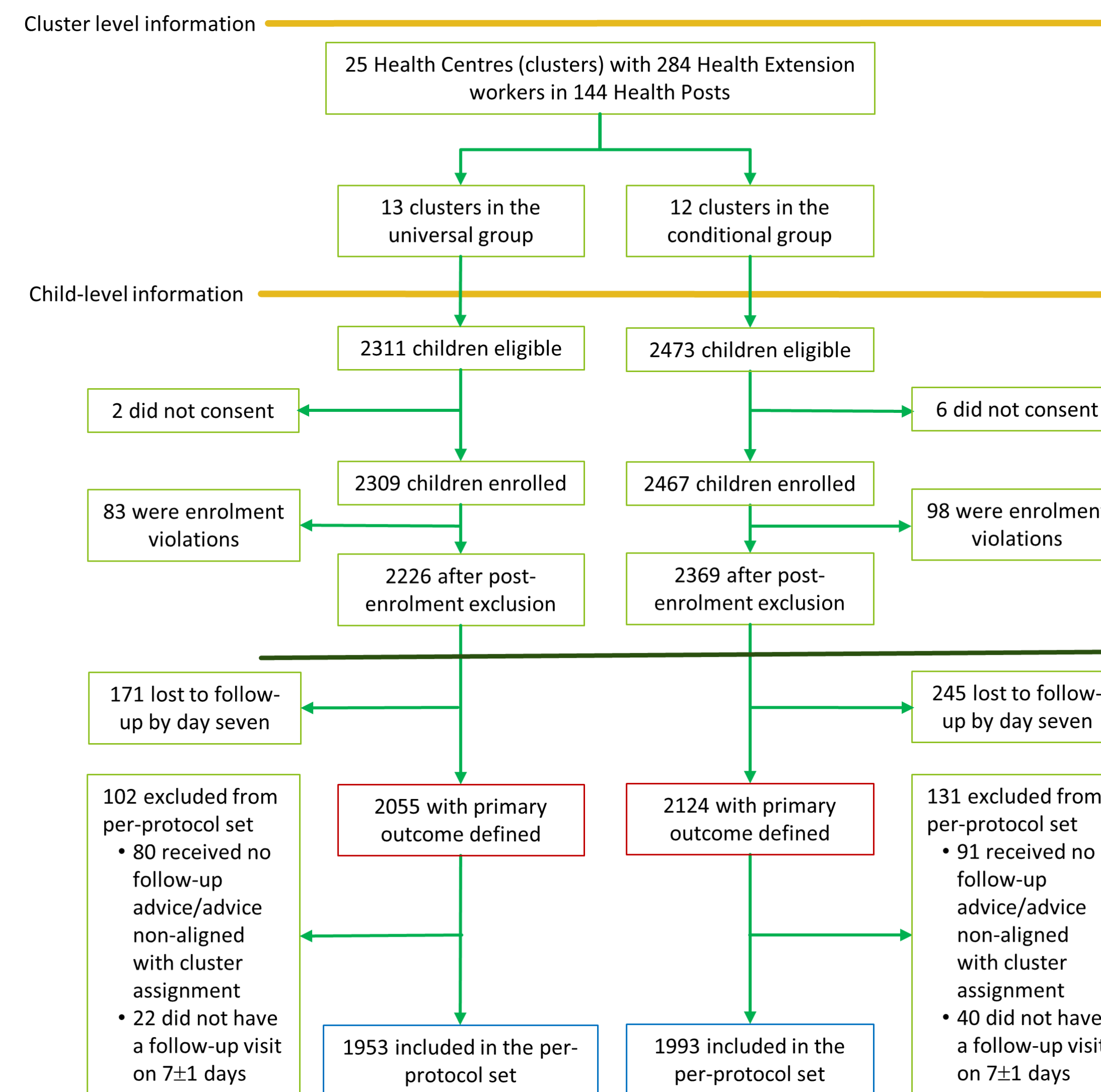
Results

Figure 1: Trial profile

Cluster level information

25 Health Centres (clusters) with 284 Health Extension workers in 144 Health Posts

13 clusters in the universal group — 12 clusters in the conditional group

Child-level information

2311 children eligible — 2473 children eligible

2 did not consent — 6 did not consent

2309 children enrolled — 2467 children enrolled

83 were enrolment violations — 98 were enrolment violations

2226 after post-enrolment exclusion — 2369 after post-enrolment exclusion

171 lost to follow-up by day seven — 245 lost to follow-up by day seven

102 excluded from per-protocol set
- 80 received no follow-up advice/advice non-aligned with cluster assignment
- 22 did not have a follow-up visit on 7±1 days

2055 with primary outcome defined — 2124 with primary outcome defined

131 excluded from per-protocol set
- 91 received no follow-up advice/advice non-aligned with cluster assignment
- 40 did not have a follow-up visit on 7±1 days

1953 included in the per-protocol set — 1993 included in the per-protocol set

- From 01 Dec 2015 to 30 Nov 2016, 4,179 children were enrolled; 2,055 (49.2%) in the universal arm and 2,124 (50.8%) in the conditional arm.
- Caregivers' adherence with advice given by CHWs was high; 4,064 (97.3%) received follow-up advice, of which 3,801 (93.5%) followed advice in line with the cluster allocation.
- By day 7, 2.7% of per-protocol population had treatment failure; 0.8% in the conditional follow-up arm and 4.6% in the universal follow-up arm, with a difference of -3.81% (95%CI -∞, -0.65%).
- There were no deaths recorded by day 28.

Table 1: Comparison of the primary outcome between groups at day 7

Primary outcome	Arm			
	Conditional, n (%)	Universal, n (%)	Difference	Upper limit, 95% CI
Treatment failure*				
Per-protocol	16 (0.80)	90 (4.61)	**-3.81%**	0.65%
Intention-to-treat	19 (0.89)	94 (4.57)	**-3.67%**	0.57%

*Any of: danger sign, admitted, child death, malaria, pneumonia, diarrhoea, reported fever

An independent assessor conducting a follow-up assessment on day 7

Discussion

- A strength of this study was the randomised controlled trial design and compliance to the study protocol was high among CHWs and caregivers.
- Insufficient clinical data was collected on children at enrolment to understand which other symptoms or diagnoses were present.
- However, most children were followed up until day 28. None of them died or were referred, indicating that no child deteriorated to a severe condition.
- We recommend that Ethiopian guidelines, which stipulate conditional follow-up of children with unclassified fever, remain unchanged as best practice in this context.

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