

Universal vs. conditional follow-up for children with unclassified fever at the community level: a cluster randomised, community based non- inferiority trial in SNNPR, Ethiopia (and DRC)

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RESEARCH ARTICLE

Universal versus conditional day 3 follow-up for children with non-severe unclassified fever at the community level in Ethiopia: A cluster-randomised non-inferiority trial

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RESEARCH ARTICLE

Universal versus conditional day 3 follow-up for children with non-severe unclassified fever at the community level in the Democratic Republic of the Congo: A cluster-randomized, community-based non-inferiority trial

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Rationale

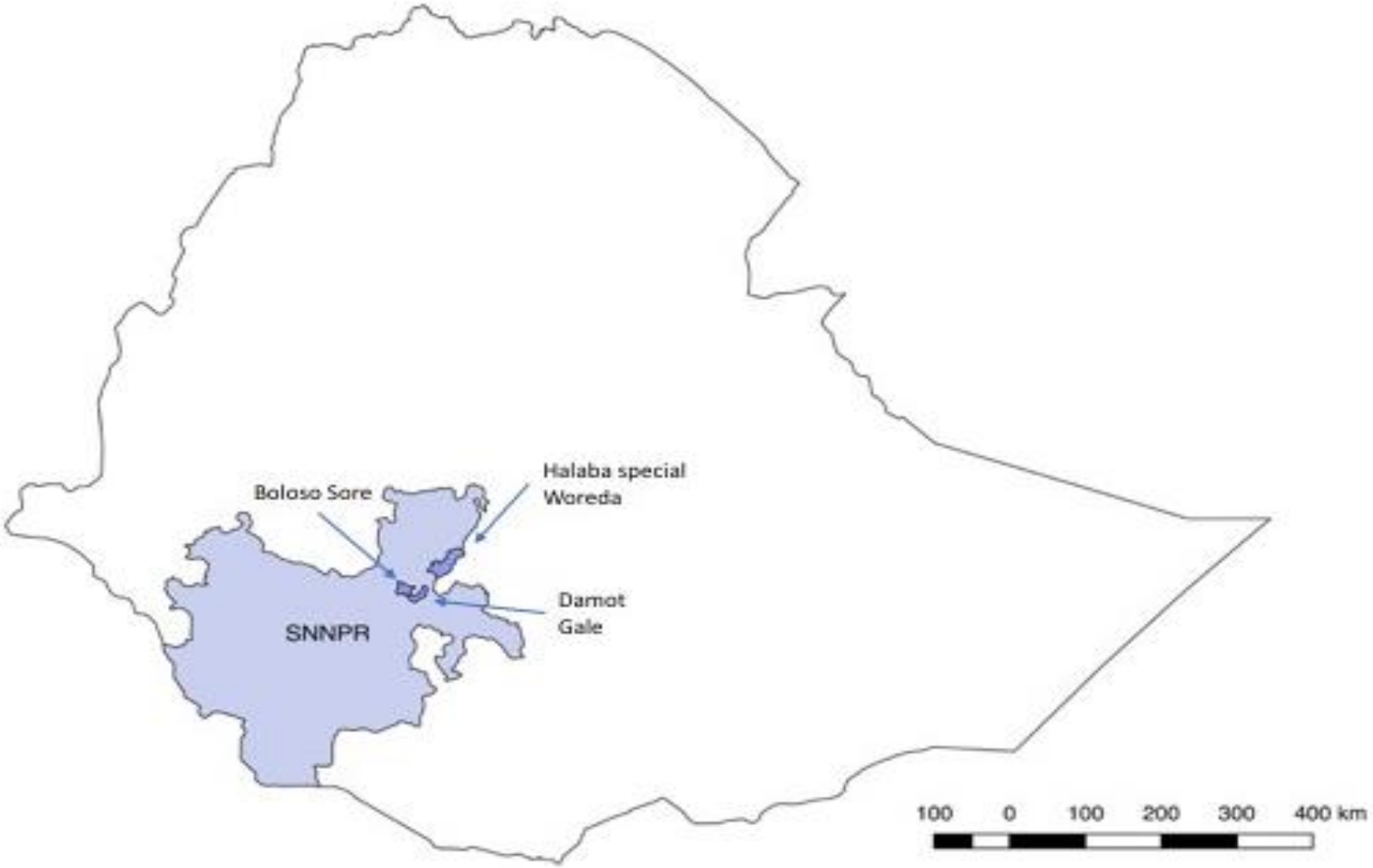
- As a result of declining malaria prevalence and increased use of malaria diagnostic tests, it is becoming more common for children seen by community health workers (CHWs) to have non-severe unclassified fever.
- Caregivers of children seen on day 1 with non-severe unclassified fever are advised to bring the child back to the CHW on day 3 for reassessment, regardless of whether symptoms have resolved or not (universal follow-up), burdening both the family and health system.
- As many such non-severe unclassified febrile illnesses self-resolve, the advice given to caretakers could be simplified to return only if the illness continues or worsens.
- This study assessed the safety of CHWs following-up children with non-severe unclassified fever only when symptoms have not resolved (conditional follow-up), hypothesizing that the conditional follow-up would be as safe as universal follow-up.

Summary of follow-up guidelines

Guideline:	Return for follow-up visit in*:
International	
WHO iCCM	3 days
IMCI	2 days, if fever persists (in no malaria risk areas) 3 days, if fever persists (in low and high risk malaria areas)
Ethiopian	
IMNCI	2 days, if fever persists

In 3 days* is interpreted as on day 4 after being seen at health provider (on day 1). ***In 2 days* is hence on day 3 after initial visit (on day 1).

Study area


Boloso Sore
Halaba special Woreda
Damot Gale
SNNPR
100 0 100 200 300 400 km

Inclusion criteria and follow-up advice

- Child 2-59 months with fever with a negative malaria rapid diagnostic test, and in whom the HEW did not diagnose pneumonia or diarrhoea or identify other symptoms requiring referral on day 1

Universal follow-up arm:

- Caregivers counselled to return on day 3

Conditional follow-up arm:

- Caregivers counselled to return only if symptoms persist

Caregivers in both arms were advised to go to the health centre immediately if danger signs developed.

Restricted randomisation

	Conditional (intervention)			Universal (control)			
		Min	Max		Min	Max	P-value
Total health centres	12			13			
Health posts per health centre (mean)	5.2	2	14	6.4	3	11	0.27
HEWs per health centre per health centre (mean)	8.9	3	22	10.7	6	19	0.36
U5 population per health centre (mean)*	4,175	1,575	12,557	4,449	2,814	8,040	0.79
Person-distance to referral facility (mean)*	71,810	12,557	219,817	79,658	18,708	235,719	0.75
RDT positive U5s/health centre/year (mean)*	538.8	31	3,092	560.5	29	886	0.93

Annual average RDT positivity rate: 21%

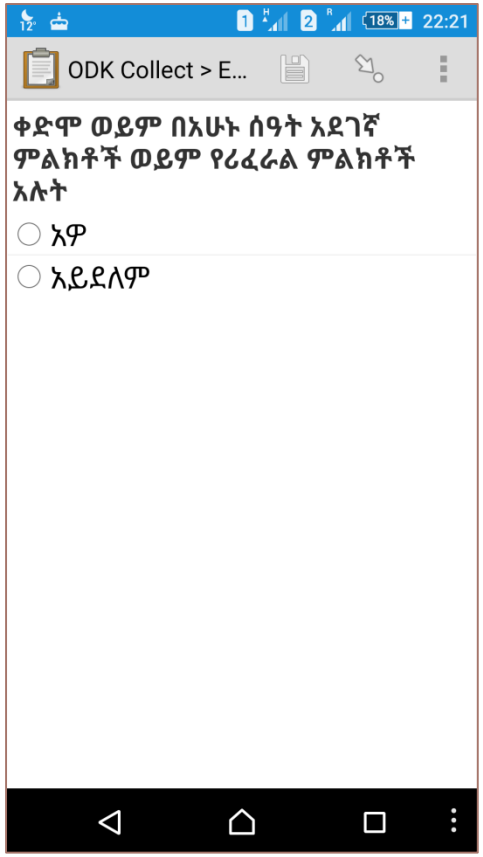
Training and data collection

- Training of 284 HEWs from 144 health posts was done in November 2015
- Data collection started in the first week of December 2015 and finished last week of December 2016
- Ongoing sensitisation and discussion with district health office, research assistants and HEWs conducted to increase case flow

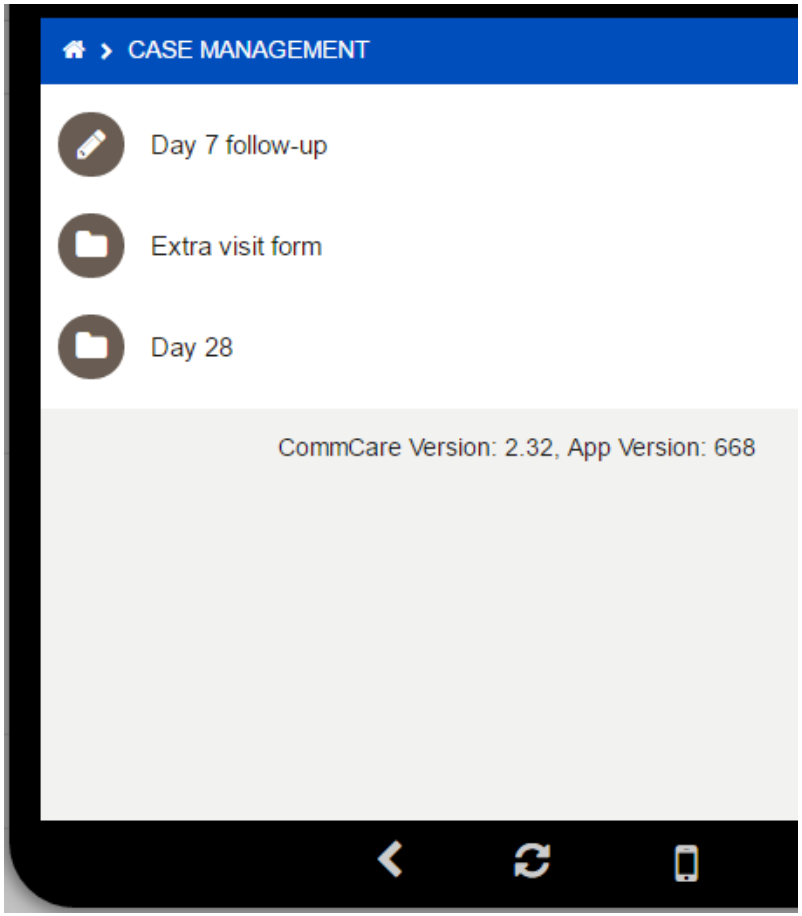
A very similar sister study was conducted by the IRC and Johns Hopkins Bloomberg School of Public Health in the Tanganyika Province, Democratic Republic of the Congo

The electronic data management system

HEW app for enrolling children



Independent evaluator app for assessing children at FU



Analytical approach

Per-protocol population defined:

1. Child having eligible symptoms at enrolment (fever with no malaria, no pneumonia, no diarrhoea and no danger signs)
2. Mother stating receiving follow-up advice in line with the cluster allocation of her CHW
3. Primary outcome collected on day 8 ± 1

Primary outcome definitions of treatment failure

Treatment failure 1:

Any of: Danger sign, admitted, dead, malaria, pneumonia, diarrhoea, **reported fever**

Alternative more stringent definitions
Treatment failure 2: Any of: Danger sign, admitted, dead, malaria, pneumonia, diarrhoea, **reported fever >3 days**
Treatment failure 3: Any of: Danger sign, admitted, dead, malaria, pneumonia, diarrhoea, **measured fever (≥37.5)**
Treatment failure 4: Any of: Danger sign, admitted, dead, malaria, pneumonia, diarrhoea

Summary of analytic approach for outcome

- Calculate proportion treatment failure in each group meeting the definition
- Risk difference estimated by subtracting the proportion in "Universal" ***from*** the proportion in "Conditional" (i.e. $p_{cond} - p_{univ}$)
- Use GLM binomial regression with identity link function, treating cluster as a random effect
- We applied a statistical non-inferiority test using a CI approach, using the exact binomial CI for the difference in overall treatment failure between study arms.
- Non-inferiority was claimed if the upper bound of the 95% CI lay on the negative side of the 4% margin, using a 1-sided test at 2.5% significance level.
- We also report cluster-level analysis (i.e. t-test on aggregate, cluster-specific failure rate)

Results

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Intervention compliance - Follow-up advice (Ethiopia)

Outcome	Arm			
	Universal		Conditional	
	N	Percent	N	Percent
Any follow-up advice given by HEW	2,017	98.2	2,047	98.2
Follow-up advice given in line with cluster allocation	1,971	97.7	1,992	97.3
Returned to the HEW	1,907	94.6	153	7.5

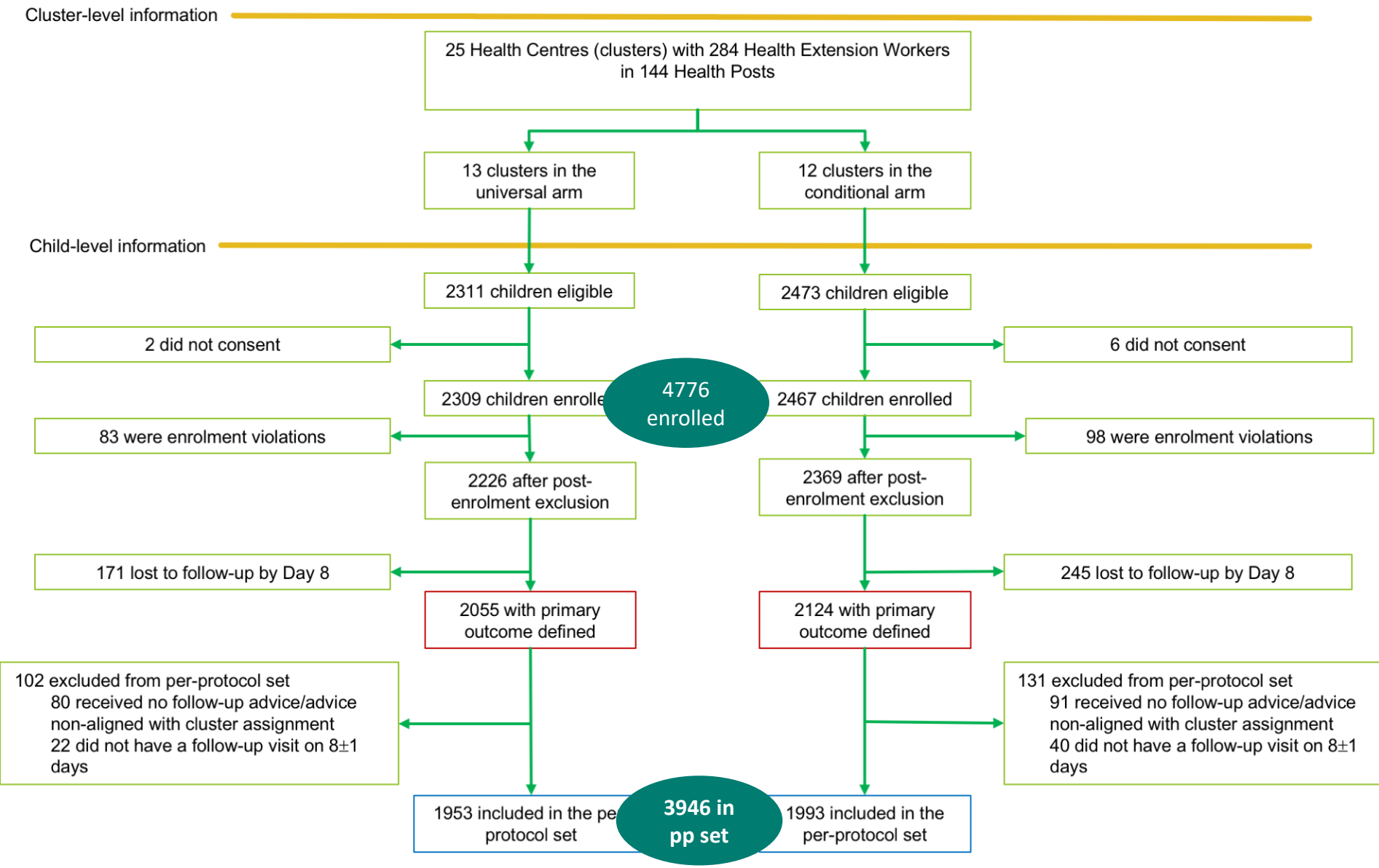
Intervention compliance - Follow-up advice (DRC)

Response	Universal follow-up		Conditional follow-up	
	N	Percent	*N*	Percent
Advice given by CHW (as reported by caregiver)				
Come back on day 3	2,352	99.4	19	0.9
Come back if still sick on day 3	12	0.5	2,044	98.8
Don't recall	2	0.1	5	0.2
Return was made	1,861	78.7	187	9.0
Reason for return visit				
Child's illness worsened	43	2.3	30	16.0
Child was not improving	31	1.7	115	61.5
CHW directed me to return	1,778	95.5	41	21.9
Other/missing	9	0.5	1	0.5

CHW, community health worker.

https://doi.org/10.1371/journal.pmed.1002552.t003

Flowchart


Cluster-level information
25 Health Centres (clusters) with 284 Health Extension Workers in 144 Health Posts
13 clusters in the universal arm
12 clusters in the conditional arm
Child-level information
2311 children eligible
2473 children eligible
2 did not consent
6 did not consent
2309 children enrolle
4776 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 8
245 lost to follow-up by Day 8
2055 with primary outcome defined
2124 with primary outcome defined
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 8±1 days
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 8±1 days
1953 included in the pe protocol set
3946 in pp set
1993 included in the per-protocol set

Primary outcome between treatment groups at one week - Ethiopia

Primary outcome	Universal, n (%)	Conditional, n (%)	Difference	Upper limit 95% CI	P-value*
Treatment failure 1	90 (4.61)	16 (0.80)	−3.81%	0.65	0.002
Treatment failure 2	25 (1.28)	12 (0.60)	−0.68%	0.43	<0.001
Treatment failure 3	14 (0.72)	10 (0.50)	−0.22%	0.42	<0.001
Treatment failure 4	3 (0.15)		0.20%	0.55	<0.001

*P-value for test of non-inferiority

Primary outcome between treatment groups at one week - DRC

	Arm				
Primary outcome	**Universal, n (%)**	**Conditional, n (%)**	**Difference**	**Upper limit 95% CI**	**P-value***
Treatment failure 1	230 (10.41)	188 (9.74)	−0.67%	5.05%	0.089
Treatment failure 2	200 (9.05)	159 (8.23)	−0.82%	4.08	0.053
Treatment failure 3	160 (7.24)	113 (5.85)	−1.39%	2.52	0.012
Treatment failure 4	147 (6.65)	108 (5.59)	-1.06%	2.85	0.017

*P-value for test of non-inferiority

Conclusions

- ➔ Advising caregivers of children under 5 years old with non-severe unclassified fever to return on day 3 only if signs persisted resulted in similar rates of clinical failure in the week after presentation when compared with universal follow-up visits on day 3.
- ➔ In the DRC, the statistical strength of the evidence for non-inferiority was greater for measured fever, danger signs requiring referral, or other clinical outcomes, rather than caregivers' report of fever.
- ➔ When clear case management instructions are provided, using unclassified fever as a diagnostic term, CHWs feel more empowered to withhold medicines and to reassure caregivers that their child was cared for (Funk et al 2018).
- ➔ An update to the global guidelines for iCCM could be considered, as simplified advice regarding return visits may reduce unnecessary follow-up visits, saving resources for families and health workers.

Thank you

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