Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Keenan JD, Bailey RL, West SK, et al. Azithromycin to reduce childhood mortality in sub-Saharan Africa. N Engl J Med 2018;378:1583-92. DOI: 10.1056/NEJMoa1715474

APPENDIX

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Table S1: Aggregate treatment coverage by arm and period for all three countries

Inter-census period	Mean (± SD)	
	Azithromycin	Placebo
1	92.7% (±10.9%)	92.8% (±10.6%)
2	86.5% (±11.3%)	86.7% (±10.8%)
3	90.1% (±11.2%)	90.5% (±10.5%)
4	91.7% (±7.7%)	91.8% (±7.1%)
All	90.3% (±10.6%)	90.4% (±10.1%)

Coverage over all countries, all phases, and both arms was 90.4% (±10.4%).

Table S2: Treatment coverage by country, arm, and period

Inter-census period	Malawi Mean (± SD)		Niger Mean (± SD)		Tanzania Mean (± SD)	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
1	88.0% (±6.5%)	88.5% (±6.8%)	98.0% (±5.3%)	97.5% (±7.8%)	89.9% (±14.1%)	90.5% (±12.7%)
2	89.9% (±6.2%)	89.9% (±7.0%)	91.5% (±6.4%)	91.8% (±6.2%)	80.0% (±13.7%)	80.2% (±12.3%)
3	93.6% (±4.7%)	93.8% (±4.3%)	95.8% (±4.9%)	96.2% (±4.5%)	82.8% (±13.6%)	83.4% (±12.3%)
4	94.6% (±4.5%)	94.0% (±5.4%)	92.9% (±5.2%)	92.4% (±6.2%)	89.2% (±10.0%)	90.1% (±8.2%)
All	91.5% (±6.1%)	91.5% (±6.4%)	94.5% (±6.0%)	94.5% (±6.7%)	85.5% (±13.6%)	86.1% (±12.3%)

Table S3. Census results

Category	All Countries		Malawi		Niger		Tanzania	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
Census enrollments	**371592**	**358815**	**139150**	**141300**	**161257**	**143280**	**71185**	**74235**
Died	2404	2616	502	542	1727	1888	175	186
Moved	24415	23123	8351	7710	10084	8760	5980	6653
Unknown	18809	17587	11845	12160	6087	4508	877	919
Alive	325964	315489	118452	120888	143359	128124	64153	66477

S4: Verbal Autopsy

Cause	Malawi	Niger	Tanzania
Diarrhea/Possible Diarrhea	6/39	1/48	12/16
Dysentery/Possible Dysentery	1/1	1/2	4/2
Injury	7	5	13
Malaria/ Possible Malaria	48/55	84/38	65/19
Malnutrition	9	3	24
Measles	0	1	1
Meningitis	11	11	8
Other Infection	9	10	1
Pneumonia/Possible Pneumonia	8/18	8/8	27/20
Unspecified	38	30	38

Random sample of 250 deaths per country

P<0.001 (permutation p-value clustered by community)

Table S5. Deaths and person-time-at-risk by age group. (Totals can be affected by rounding.)

Age (mos)	Malawi Deaths / Person-years		Niger Deaths / Person-years		Tanzania Deaths / Person-years	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
1-5	57 / 3617	82 / 3739	202 / 5653	244 / 5148	21 / 2189	31 / 2229
6-11	102 / 5747	98 / 5912	286 / 7901	340 / 7143	41 / 3599	39 / 3595
12-23	131 / 11639	136 / 11897	491 / 15207	511 / 13573	54 / 7562	57 / 7924
24-59	212 / 34269	226 / 34738	748 / 48113	793 / 42860	59 / 19162	59 / 19886

Table S6 (for Figure 3, main text): Reduction of mortality with oral azithromycin by age group

Age (mos)	All Countries		Malawi		Niger		Tanzania	
	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*
1-5	24.9% (10.6% to 37.0%)	0.001	27.6% (-4.1% to 49.7%)	0.08	23.1% (4.9% to 37.8%)	0.02	31.2% (-22.7% to 61.4%)	0.21
6-11	14.2% (0.0% to 26.3%)	0.05	-6.2% (-43.2% to 21.2%)	0.69	23.3% (7.4% to 36.3%)	0.01	-1.4% (-67.1% to 38.5%)	0.96
12-23	10.0% (-1.9% to 20.4%)	0.10	0.7% (-29.5% to 23.9%)	0.96	14.0% (0.1% to 26.0%)	0.048	0.9% (-45.0% to 32.3%)	0.96
24-59	12.6% (3.6% to 20.8%)	0.01	5.0% (-16.1% to 22.2%)	0.62	16.5% (6.1% to 25.8%)	0.003	-3.3% (-50.4% to 29.0%)	0.86

Mortality reduction was estimated from a negative binomial regression modeling community-specific deaths as a function of treatment arm, age group, and the treatment by age group interaction, with person-time at risk used as an offset. Positive numbers indicate a mortality reduction with azithromycin relative to placebo.

Table S7. Deaths and person-time-at-risk by inter-census period. (Totals can be affected by rounding.)

Inter-census period	Malawi Deaths / Person-years		Niger Deaths / Person-years		Tanzania Deaths / Person-years	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
1	118 / 12068	105 / 11998	531 / 23318	557 / 20549	64 / 9016	61 / 9311
2	159 / 15861	159 / 15935	382 / 17281	427 / 16015	53 / 8773	57 / 8948
3	97 / 12146	115 / 12678	439 / 18753	466 / 16744	38 / 7439	46 / 7767
4	128 / 15197	163 / 15676	375 / 17521	438 / 15415	20 / 7284	22 / 7608

Table S8 (for Figure 4, main text): Reduction of mortality with oral azithromycin by inter-census period

Inter-census period	All Countries		Malawi		Niger		Tanzania	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
1	7.3% (-5.9% to 18.8%)	0.26	-14.1% (-57.7% to 27.3%)	0.42	15.0% (0.6% to 27.3%)	0.04	-7.1% (-56.7% to 26.8%)	0.72
2	11.2% (-1.1% to 22.1%)	0.07	-0.0% (-29.5% to 22.8%)	>0.99	17.0% (2.1% to 29.5%)	0.03	5.1% (-38.4% to 34.9%)	0.79
3	15.7% (3.7% to 26.2%)	0.01	12.2% (-17.4% to 34.3%)	0.38	16.9% (2.6% to 29.2%)	0.02	13.8% (-32.8% to 44.1%)	0.50
4	22.0% (10.6% to 31.9%)	<0.001	19.3% (-4.1% to 37.4%)	0.10	24.1% (10.3% to 35.7%)	0.001	5.1% (-74.0% to 48.2%)	0.87

Mortality reduction was estimated from a negative binomial regression modeling community-specific deaths as a function of treatment arm, inter-census period, and the treatment by inter-census period interaction, with person-time at risk used as an offset. Positive numbers indicate a mortality reduction with azithromycin relative to placebo.

Table S9. Adverse events. Serious adverse events (hospitalizations or deaths reported to study staff within 1 week of study drug administration) were documented according to Pfizer's adverse event reporting system. Non-serious adverse events were managed at local health facilities with guidance from the World Health Organization Integrated Management of Childhood Illness manual. Although village informants and health facilities were encouraged to report possible adverse events, in practice very few adverse events were brought to the attention of study staff.

	Malawi		Niger		Tanzania	
Condition	**Azithromycin**	**Placebo**	**Azithromycin**	**Placebo**	**Azithromycin**	**Placebo**
Malaria	0	0	0	0	4	3
Respiratory infection	0	0	0	0	1	2
Diarrhea	0	0	0	1	0	0
Ileus	0	0	0	0	1	0
Dehydration	0	0	0	0	0	2
Coma	0	0	1	0	0	0
Death	0	1	1	0	3	0