Supplemental Table 1: Characteristics of studies on child mortality

Author year	Country	Design	Comparison	No. clusters	Sample population	Frequency and duration	Follow-up	Child mortality[a]	OR/RR (95%CI)
Azithromycin MDA and child mortality reduction									
Chandramohan 2019[13]	Burkina Faso and Mali	Cluster–RCT	Azithromycin+ Antimalarials vs Placebo+Antimalarials	9,618 households	21,737 children (3–59 m)	3-day cycles, monthly for four months, 3y	3 years	24.8 vs 23.5, p=0.57	1.1 (0.88–1.3)
Keenan 2018[9] (MORDOR I)	Malawi, Niger, Tanzania	Cluster–RCT	Azithromycin vs Placebo	1,533 communities	190,238 children (1–59 m)	Biannual, 2y	2 years	14.6 vs 16.5, **p<0.001**	**0.86 (0.80–0.93)**
Porco 2009[17]	Ethiopia	Cluster–RCT	Azithromycin vs Untreated	48 communities	18,415 children (1–5 y)	Annual & Biannual & Quarterly, 1y	1 years	5.7 vs 12.1, **p=0.01**	**0.53 (0.26–0.84)**
Keenan 2011[15]	Ethiopia	Cohort	Azithromycin vs Untreated	24 subkebeles	5,507 children (1–5 y)	Single	26 months	All–cause: 2.79 vs 8.18, **p=0.06**	All–cause: **0.35 (0.17–0.74)** Infectious-cause: **0.20 (0.07–0.58)**
Repeated azithromycin MDA on mortality reduction									
Keenan 2019[14] (MORDOR II)	Niger	Cohort	3rd vs 1st year	594 communities	76,092 children (1–59 m)	Biannual, 1y	1 year	23.3 vs 24.0, p=0.55	Not available
Different frequencies of azithromycin MDA on mortality reduction									
O'Brien 2018[16]	Niger	Cluster–RCT	Annual vs Biannual-children only	48 communities	5304 children (6 m–12 y)	Annual vs Biannual, 3y	3 years	35.6 vs 29.0, p=0.07	All-cause: 0.81 (0.66–1.00) Infectious-cause: **0.73 (0.57–0.94)**

Porco 2009[17]	Ethiopia	Cluster–RCT	Annual vs Biannual vs Quarterly-children only	48 communities	18,415 children (1–9 y)	Annual vs Biannual vs Quarterly, 1y	1 year	3.2 vs 4.9 vs 4.7, p>0.05	Not available

2 OR, odds ratio; RR, rate ratio; CI, confidence interval; [a] child mortality,1000 person-years

Supplemental Table 2: Characteristics of studies on malaria

Author year	Country	Design	Comparison	No. cluster	Sample population	Frequency and duration	Follow-up	Outcome	OR/RR (95%CI)
Azithromycin MDA on malaria reduction									
Arzika 2019[6] [MORDOR]	Niger	Cluster–RCT	Azithromycin vs placebo	30 communities	315 children (1–59 m)	Biannual, 2y	2 years	Malaria parasitemia: 3.5% vs 4.8%; ***P*=0.02**	**0.54 (0.30–0.97)**
Chandramohan 2019[13]	Burkina Faso and Mali	Cluster–RCT	Azithromycin+Antimalarials vs Placebo+Antimalarials	9,618 households	21,737 children (3–59 m)	3-day cycles, monthly for four months, 3y	3 years	Malaria parasitemia	0.97 (0.93–1.01)
Hart 2020[20] [MORDOR]	Malawi	Cluster–RCT	Azithromycin vs placebo	30 communities	1200 children (1–59 m)	Biannual, 2y	2 years	Malaria parasitemia: *P*=0.78	0.89 (0.53–1.50)
Bloch 2019[18] [MORDOR]	Tanzania	Cohort	Azithromycin vs placebo	30 communities	738 children (1–35 m)	Biannual, 2y	2 years	Rapid diagnostic test: 13.2% vs 6.6%, *P* =0.34 Clinical malaria: 1.9% vs 1.2%, *P*=0.66	2.15 (1.16–3.99) 1.38 (0.38–4.95)
Hart 2014[19]	Gambia	Cluster–RCT	Azithromycin vs control	48 communities	3,646 children (0–5 y)	Annual, 3y	30 months	Spleen rate	**0.35 (0.15–0.82)**
Schachterle 2014[21]	Tanzania	Cohort	Azithromycin vs control	8 villages	1,986 residents (All age)	Single	1, 3, 4, 6 months	*Plasmodium falciparum*: Month 1: 1.6% vs 4.7% Month 3: 2.1% vs 2.5% Month 4: 0.8% vs 1.5% Month 6: 0.6% vs 0.7%	 **0.34 (0.17–0.64)** 0.83 (0.38–1.77) 0.52 (0.13–1.81) 0.95 (0.18–5.12)
Sadiq 1995[25]	Gambia, West Africa	Cluster–RCT	Azithromycin vs tetracycline eye ointment	8 villages	226 children (5-14 y)	Weekly, 3w	28 days	*Plasmodium falciparum*: 41% vs 74% *Plasmodium malaria*: 0% vs 11%	**0.56 (0.44–0.71)** 0 (0)

								Clinical malaria:15% vs 32% Spleen rate: 27% vs 55%	**0.45 (0.27–0.75)** **0.5 (0.36–0.70)**
Gaynor 2014[22]	Niger	Cluster–RCT	Annual vs Biannual	24 communities	1030 children (< 1–72 m)	Annual or biannual, 1y	12 months	Malaria parasitemia: 29.8% vs 19.5%, ***P*=0.03** Parasite density: 354 vs 74, ***P*=0.03** Gametocytemia: 1.5% vs 0%, *P*=0.29 Hemoglobin: 10.0 vs 10.2, *P*=0.20	Not available
O'Brien 2017[23]	Niger	Cluster–RCT	Annual vs Biannual	24 communities	1032 children (6–60 m)	Annual or biannual, 3y	3 years	Malaria parasitemia: 54.5% vs 54.5%, *P*=0.995 Parasite density: 7,710 vs 4,930, *P*=0.11 Gametocytemia: 0.5% vs 0.7%, *P*=0.63 Hemoglobin: 9.4 vs 9.4, *P*=0.87	Not available
Oldenburg 2018[24]	Niger	Cluster–RCT	Annual vs Biannual	24 communities	1037 children (6 m–12 y)	Annual or biannual, 3y	3 years	Malaria prevalence 50.6% vs 42.6%, *P*=0.29 Parasite density: 6,260 vs 10,660, *P*=0.57 Clinical malaria 6.8% vs 5.9%, *P*=0.69 Hemoglobin 9.2 vs 9.5, *P*=0.21	Not available

OR odds ratio; RR rate ratio; CI confidence interval

6 **Supplemental Table 3: Characteristics of studies on general morbidity or condition**

Author year	Country	Design	Comparison	No. cluster	Sample population	Frequency and duration	Follow-up	Outcome	OR/RR (95%CI)
General morbidity and symptom									
Chandramohan 2019[13]	Burkina Faso and Mali	Cluster –RCT	Azithromycin+Antimalarials vs Placebo+Antimalarials	9,618 households	21,737 children (<5 y)	3–day cycles, monthly for four months each year, 3y	3 years	Respiratory tract infection	**0.85 (0.81–0.89)**
								Diarrhea	**0.85 (0.79–0.91)**
								Fever	**0.79 (0.72–0.86)**
Coles 2012[7]	Tanzania	Cohort	Azithromycin vs untreated	8 communities	1,036 children (<5 y)	Single	1,3,6 months	Respiratory tract infection at 1 m	**0.62 (0.43–0.91)**
								Respiratory tract infection at 3 m	0.91 (0.69–1.20)
								Respiratory tract infection at 6 m	1.00 (0.76–1.30)
Coles 2011[8]	Tanzania	Cohort	Azithromycin vs untreated	8 communities	1,036 children (<5 y)	Single	1,3,6 months	Diarrhea at 0–1 m	**0.61 (0.39–0.95)**
								Diarrhea at 1–3 m	0.76 (0.54–1.07)
								Diarrhea at 3–6 m	0.85 (0.60–1.20)
Fry 2002[33]	Nepal	Cohort	Azithromycin vs untreated	8 villages	458 children (1–10 y)	Single	10 days	Respiratory tract infection	**0.59 (0.41–0.90)**
								Diarrhea	0.79 (0.49–1.27)
								Fever	**0.46 (0.28–0.76)**
								Abdominal pain	0.91 (0.59–1.40)
								Vomiting	0.62 (0.33–1.16)
								Headache	**0.50 (0.27–0.93)**
Whitty 1999[26]	Gambian	Cluster –RCT	Azithromycin vs topical tetracycline	8 villages	804 children (<14 y)	Weekly, 15 d	28 days	Respiratory tract infection	0.87 (0.70–1.08)
								Diarrhea	**0.26 (0.15–0.46)**
								Fever	**0.80 (0.72–0.88)**
								Abdominal pain	0.80 (0.62–1.03)
								Vomiting	**0.59 (0.46–0.77)**
								Headache	**0.78 (0.68–0.89)**

Oldenburg 2018[42]	Niger	Cluster –RCT	Azithromycin vs placebo	30 communities	1,712 children (1-5 m)	Single	2 weeks	Diarrhea **19.3% vs 28.1%, *P*=0.03** Abdominal pain: 9.1% vs 10.2%, *P*=0.75 Vomiting: 15.9% vs 21%, *P*=0.07	**0.68 (0.49–0.96)** 0.90 (0.45–1.77) 0.76 (0.56–1.02)
Carriage of pathogenic organisms									
Batt 2003[30]	Tanzania	Cross–section	Before vs after treatment	1 village	1,402 residents	Single	2, 6 months	*Sp* carriage at baseline: 11% *Sp* carriage at 2 m: 12%, *P*>0.05 *Sp* carriage at 6 m:7%, *P*>0.05	Not available
Burr 2014[31]	Gambia	Cross–section	Azithromycin vs untreated	30 villages	1575 residents	Annual, 3y	1, 6 months after the last MDA	*Sp* carriage at 1 m *Sp* carriage at 6 m	**0.30 (0.22–0.42)** 1.09 (0.80–1.48)
Coles 2013[32]	Tanzania	Cohort	Azithromycin vs untreated	8 communities	1015 children (<5 y)	Single	1, 3, and 6 months	*Sp* carriage at 1 m: 41.4% vs 38.5% *P*>0.05 *Sp* carriage at 3 m: 22.0% vs 35.1%, *P*>0.05 *Sp* carriage at 6 m: 51.8% vs 50.9%, *P*>0.05	Not available
Fry 2002[33]	Nepal	Cohort	Azithromycin vs untreated	8 villages	458 children (1–10 y)	Single	180 days	*Sp* carriage at 10 d: **42% vs 85%, *P*<0.05** *Sp* carriage at 180 d: 89% vs 85%, *P*>0.05	Not available
Haug 2010[34]	Ethiopia	Cross-section	Azithromycin vs untreated	8 villages	120 children (1–5 y)	Biannual, 3y	36 months	*Sp* carriage: *P*>0.05	Not available
Leach 1997[29]	Australia	Cross–section	Before vs after treatment	1 community	79 children (<15 y)	Single	3 weeks, 2 and 6 months	*Sp* carriage at baseline: 68% *Sp* carriage at 3 w: **29%, *P*<0.05** *Sp* carriage at 2 m: 78%, *P*>0.05 *Sp* carriage at 6 m: 87%, *P*>0.05	Not available
Skalet 2010[35]	Ethiopia	Cluster –RCT	Azithromycin vs untreated	24 communities	110 children (<10 y)	Quarterly, 1y	12 months	*Sp* carriage 78% vs 81.7%, *P*>0.05	Not available
Doan 2020[36]	Niger	Cluster –RCT	Azithromycin vs placebo	30 communities	890 children (<5 y)	Biannual, 3y	3 years	Coronavirus burden: ***P*<0.05** Coronavirus prevalence: *P*>0.05	Not available
Doan 2018[27]	Niger	Cluster	Azithromycin vs	30 villages	1,125 children	Biannual, 2y	30 months	Gut microbial structure: ***P*<0.001**	Not available

		–RCT	placebo		(<5 y)			Diversity of the gut microbiome: ***P*=0.005**	
Doan 2019[28]	Niger	Cluster –RCT	Azithromycin vs placebo	30 villages	600 children (<5 y)	Biannual, 2y	24 months	Diversity of the gut microbiome: *P*=0.08 Reduction of 35 gut pathogenic species: ***P*< 0.01**	Not available
Nutrition									
Amza 2013[37]	Niger	Cluster –RCT	2 vs 1 MDA	24 communities	1,030 children (6 m–5 y)	Annual or biannual, 1y	1 year	Wasting Low MUAC Stunting Underweight	0.75 (0.46–1.23) 0.93 (0.59–1.46) 0.89 (0.65–1.22) 0.81 (0.57–1.16)
Amza 2014[39]	Niger	Cluster –RCT	2 vs 1 MDA	24 communities	1,034 children (6 m–5 y)	Annual or biannual, 3y	3 years	Wasting Low MUAC Stunting Underweight	0.89 (0.53–1.49) 0.62 (0.32–1.17) 0.78 (0.54–1.13) 0.88 (0.66–1.19)
Burr 2014[40]	Gambia	Cluster –RCT	3 vs 1 MDA	48 clusters	2,886 children (1–4 y)	Annual, 3y or 1y	3 years	Wasting Stunting Underweight	1.07 (0.81–1.40) 1.12 (0.90–1.41) 1.10 (0.89–1.37)
Gore-Langton 2020[41]	Burkina Faso and Mali	Cluster –RCT	Azithromycin+Antimalarials vs Placebo+Antimalarials	9,618 households	4,000 children (3–59m)	3–day cycles, monthly for four months each year, 3y	3 years	Wasting Low MUAC Stunting Underweight	0.94 (0.81–1.08) 0.79 (0.62–1.01) 0.92 (0.83–1.02) 1.01 (0.90–1.13)
Keenan 2019[38]	Ethiopia	Cluster –RCT	Azithromycin vs untreated	24 communities	530 children (< 5 y)	Biannual, 3y	3 years	Height Weight	p=0.60 p=0.54

SP Streptococcus pneumoniae; OR, odds ratio; RR, rate ratio; CI, confidence interval; MUAC, mid-upper arm circumference.

Supplemental Table 4: Risk of bias of studies on child mortality

Study	Confounding		Selection bias		Misclassification bias	Performance bias		Detection bias	Attrition bias	Reporting bias
	Bias due to confounding (O)	Selection into study (O)	Random sequence generation (R)	Allocation concealment (R)	Bias in intervention classification (O)	Bias due to deviations from interventions (O)	Masking of participants and personnel (R)	Masking of outcome assessors (R, O)	Incomplete outcome data (R, O)	Selective reporting (R, O)
RCT										
Chandramohan 2019[13]	NA	NA	Unclear	Low	NA	NA	Low	Low	Low	Low
Keenan 2018[9]	NA	NA	Low	Low	NA	NA	Low	Low	Low	Low
O'Brien 2018[16]	NA	NA	Low	Unclear	NA	NA	Unclear	Unclear	Low	Low
Porco 2009[17]	NA	NA	Moderate	Unclear	NA	NA	Unclear	Low	Low	Low
Non-RCT										
Keenan 2011[15]	Unclear	Moderate	NA	NA	Moderate	Unclear	NA	Low	Low	Low
Keenan 2019[14]	Moderate	Low	NA	NA	Low	Unclear	NA	Low	Low	Low

Abbreviations: O, observational, non-randomized studies; R, randomized studies

Supplemental Table 5: Risk of bias of included studies on malaria

Study	Confounding		Selection bias		Misclassification bias	Performance bias		Detection bias	Attrition bias	Reporting bias
	Bias due to confounding (O)	Selection into study (O)	Random sequence generation (R)	Allocation concealment (R)	Bias in intervention classification(O)	Bias due to deviations from interventions (O)	Masking of participants and personnel (R)	Masking of outcome assessors (R, O)	Incomplete outcome data (R, O)	Selective reporting (R, O)
RCT										
Arzika 2019[6]	NA	NA	Low	Low	NA	NA	Low	Low	Low	Low
Chandramohan 2019[13]	NA	NA	Unclear	Low	NA	NA	Low	Low	Low	Low
Gaynor 2014[22]	NA	NA	Low	Low	NA	NA	High	Low	Low	Low
Hart 2014[19]	NA	NA	Moderate	Unclear	NA	NA	Moderate	Low	Low	Low
Hart 2020[20]	NA	NA	Low	Low	NA	NA	Unclear	Unclear	Low	Low
O'Brien 2017[23]	NA	NA	Low	Unclear	NA	NA	Unclear	Low	Low	Low
Oldenburg 2018[24]	NA	NA	Low	Low	NA	NA	High	Low	Low	Low
Sadiq 1995[25]	NA	NA	Unclear	Unclear	NA	NA	High	Low	Low	Low
Non-RCT	NA	NA								
Bloch 2019[18]	Low	Low	NA	NA	Low	Low	NA	Low	Unclear	Low
Schachterle 2014[21]	Moderate	Moderate	NA	NA	Low	Moderate	NA	Unclear	Low	Low

Abbreviations: O, observational, non-randomized studies; R, randomized studies

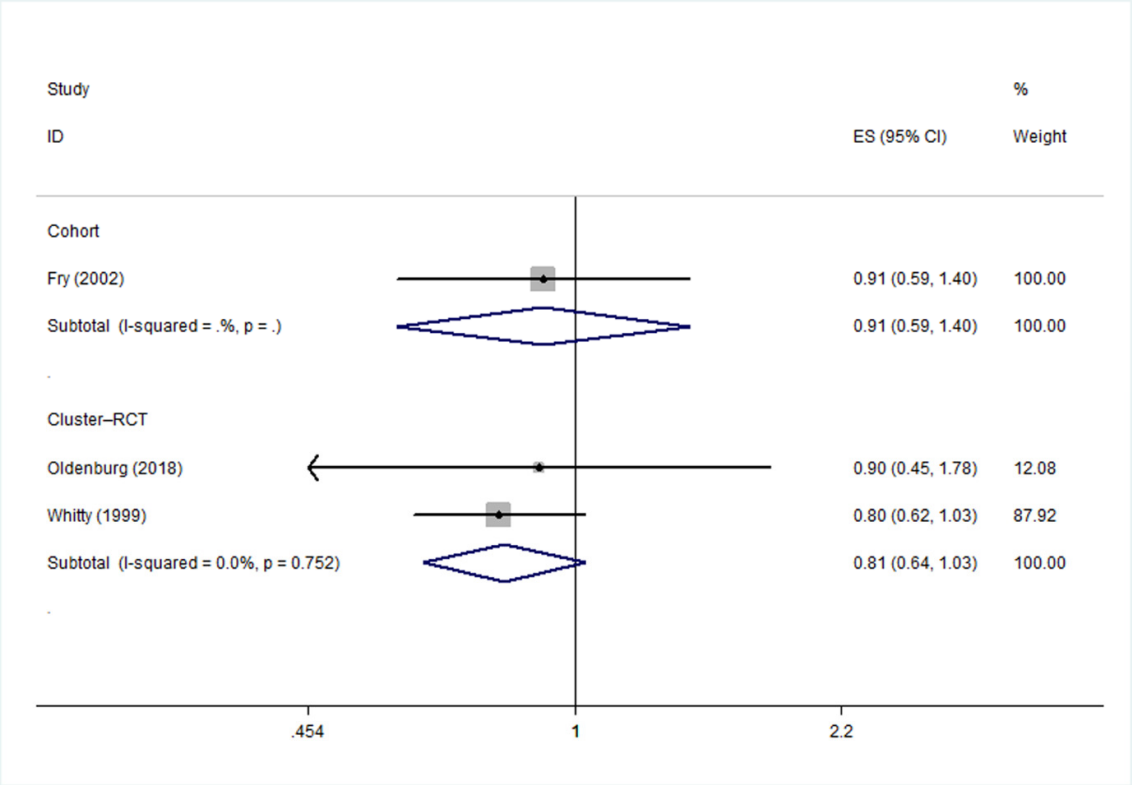
Supplemental Table 6: Risk of bias of included studies on general morbidity or condition

Study	Confounding		Selection bias		Misclassification bias	Performance bias		Detection bias	Attrition bias	Reporting bias
	Bias due to confounding (O)	Selection into study (O)	Random sequence generation (R)	Allocation concealment (R)	Bias in intervention classification(O)	Bias due to deviations from interventions (O)	Masking of participants and personnel (R)	Masking of outcome assessors (R, O)	Incomplete outcome data (R, O)	Selective reporting (R, O)
RCT										
Amza 2014[39]	NA	NA	Low	Low	NA	NA	High	Low	Low	Low
Amza 2013[37]	NA	NA	Low	Unclear	NA	NA	High	Unclear	Low	Low
Burr 2014[40]	Low	Low	NA	NA	Low	Low	NA	Unclear	Low	Low
Chandramohan 2019[13]	NA	NA	Unclear	Low	NA	NA	Low	Low	Low	Low
Doan 2020[36]	NA	NA	Low	Low	NA	NA	Unclear	Low	Low	Low
Doan 2019[28]	NA	NA	Low	Low	NA	NA	Low	Low	Low	Low
Doan 2018[27]	NA	NA	Low	Low	NA	NA	Low	Low	Low	Low
Gore-Langton 2020[41]	NA	NA	Unclear	Unclear	NA	NA	High	Unclear	Low	Low
Keenan 2019[38]	NA	NA	Low	Low	NA	NA	Unclear	Low	Low	Low
Whitty 1999[26]	NA	NA	Unclear	Unclear	NA	NA	Unclear	Unclear	Low	Low
Oldenburg 2018[42]	NA	NA	Low	Unclear	NA	NA	Low	Low	Low	Low
Skalet 2010[35]	NA	NA	Low	Unclear	NA	NA	High	Low	Low	Low
Non-RCT										

Batt 2003[30]	Unclear	Unclear	NA	NA	Low	Low	NA	Unclear	Low	Low
Burr 2014[31]	Unclear	Low	NA	NA	Low	Low	NA	Unclear	Low	Low
Coles 2013[32]	Unclear	Unclear	NA	NA	Low	Unclear	NA	Unclear	Low	Low
Coles 2012[7]	Low	Low	NA	NA	Low	Low	NA	Unclear	Low	Low
Coles 2011[8]	Low	Low	NA	NA	Low	Low	NA	Unclear	Low	Low
Fry 2002[33]	Low	Low	NA	NA	Low	Low	NA	Unclear	Moderate	Low
Haug 2010[34]	Low	Unclear	NA	NA	Unclear	Unclear	NA	Unclear	Low	Low
Leach 1997[29]	Unclear	Unclear	NA	NA	Low	Low	NA	Unclear	Low	Low

16 Abbreviations: O, observational, non-randomized studies; R, randomized studies

Supplemental Figure 1: Forest plot for azithromycin MDA and abdominal pain



Supplemental Figure 3: Forest plot for azithromycin MDA and vomiting