

**Full Title: The role of Seasonal Malaria Chemoprevention in the effect of Azithromycin on Child Mortality: A Secondary Analysis of the CHAT Cluster Randomized Clinical Trial**

**Short Title: Seasonal Malaria Chemoprevention and Azithromycin for Child Mortality**

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## 21 Abstract

22 **Objective:** Mass treatment with azithromycin (AZ) and administration of seasonal malaria  
 23 chemoprevention (SMC) are both effective in reducing mortality among children under 5. However, it is  
 24 not clear whether the benefit of AZ for mortality varies in the presence of routine SMC administration.  
 25 The objective of this study was to examine whether the effect of mass AZ distribution on all-cause  
 26 mortality among children less than 5 years of age varies with SMC administration season or SMC  
 27 coverage.

28 **Methods:** This was a secondary analysis of the Community Health with Azithromycin Trial (CHAT), a  
 29 cluster randomized placebo-controlled trial of 341 communities in the Nouna District of Burkina Faso.  
 30 Communities randomized to intervention received treatment with twice yearly mass AZ while control  
 31 communities receive placebo. All communities received SMC as standard-of-care. SMC administration  
 32 and coverage data were provided from National Malaria Control Program. SMC administration season  
 33 was defined as the period during and immediately following SMC (July-December) versus the months  
 34 of no SMC (January-June). SMC coverage was assessed as proportion of the population covered and  
 35 by whether it was below or above a threshold of 80%. We used Poisson regression models with  
 36 person-time at risk used as an offset and robust standard error to analyze mortality rates by treatment  
 37 group and SMC subgroups and assessed interaction on both the multiplicative and additive scales.

38 **Results:** Mortality was higher in SMC seasons for both arms, with a mortality rate of 10.3 per 1,000  
 39 person-years (95% CI: 9.0 to 11.6) in SMC seasons and 7.9 (95% CI: 6.9 to 9.0) in non-SMC seasons.  
 40 Compared to placebo, the mortality rate in AZ clusters was 0.77 (95% CI: 0.60 to 0.98) during SMC  
 41 season, while it was 0.89 (95% CI: 0.68 to 1.15) during the non-SMC seasons. The effect of AZ  
 42 compared to placebo in clusters with <80% SMC coverage was 0.73 95%CI (0.56 to 0.96) and in  
 43 clusters with  $\geq$ 80% SMC coverage, it was 1.0 95%CI (0.59 to 1.69). The interaction between AZ and  
 44 SMC season or coverage was not statistically significant on the additive or multiplicative scales.

45 **Conclusion:** While our findings did not reach statistical significance, they raise the question of whether  
46 prioritizing MDA AZ during high transmission periods or in regions with low SMC coverage could be  
47 beneficial. Further research is needed to determine if targeting these periods or areas could lead to  
48 greater reductions in child mortality.

49 **Trial Registration:** ClinicalTrials.gov Identifier: NCT03676764

## 50 Introduction

51 Many regions of sub-Saharan Africa have high child mortality rates.[1] Infectious diseases, in  
 52 particular acute diarrheal and respiratory infections, and malaria, are the leading causes of illness  
 53 and death in children in low- and middle-income countries.[2] Antimicrobial-based strategies such as  
 54 mass drug administration of azithromycin (MDA AZ) and seasonal malaria chemoprevention (SMC)  
 55 have been used to reduce child mortality in these settings.[3, 4] Azithromycin (AZ) has been shown to  
 56 reduce all-cause mortality as well as infectious morbidity due to diarrhea, pneumonia, and malaria.[3,  
 57 5, 6] The MORDOR study which randomized communities in Malawi, Niger, and Tanzania to four  
 58 twice-yearly mass distributions of either oral AZ or placebo found that childhood mortality was lower  
 59 in communities randomized to AZ, with the largest effect (a relative reduction in all-cause mortality of  
 60 18.1%) seen in Niger, where SMC was not being distributed.[3] The Community Health with  
 61 Azithromycin Trial (CHAT) completed in 2023 and the AVENIR (Azithromycine pour la Vie des  
 62 Enfants au Niger: Implementation et Recherche) trial in Niger also demonstrated that mass  
 63 distribution of AZ remains effective at reducing child mortality in a setting receiving SMC.[7, 8] The  
 64 finding of these trials was consistent with MORDOR-Niger, showing a reduction in all-cause mortality  
 65 overall in communities randomized to AZ compared to placebo.[7]  
 66  
 67 SMC involves monthly administration of a 3-day regimen of sulfadoxine-pyrimethamine and  
 68 amodiaquine (SP-AQ) during the malaria season in regions with highly seasonal transmission, where  
 69 there is no evidence of resistance to these drugs.[9] SMC treats current infection and provides  
 70 protection against future infections for up to 3-4 weeks.[10] As of 2020, following the WHO policy  
 71 recommendation, 13 countries in Africa have adopted SMC with different scales of implementation.[11,  
 72 12] Large-scale evaluations have found SMC effective at reducing malaria infection and all-cause  
 73 mortality.[13, 14] Despite the adoption of SMC, it is not clear how the antimalarial, antibacterial, anti-  
 74 inflammatory and overall benefits of SP in SMC might affect the benefit of AZ for child mortality.[15]  
 75 Since Sulfadoxine is a broad-spectrum, long acting antibiotic, it may influence infections that AZ is

effective against. Previous evidence for the combined effect of AZ and SP in pregnant women showed that the combination of these drugs was superior in antimalarial activity compared to SP with chloroquine[16, 17] and SP alone.[18] A recent RCT found that children receiving the addition of AZ to SMC, versus placebo and SMC, had fewer episodes of gastrointestinal infections, upper respiratory tract infections, and nonmalarial febrile illnesses. However, there was no significant difference in incidence of death or hospitalization between these groups.[19] The lack of benefit of AZ for mortality observed in this trial raises questions about whether the mortality benefit of AZ may be lower when SMC is also administered. On a larger scale, these questions are relevant for the implementation of MDA AZ, particularly in relation to the timing of AZ administration (since SMC is administered seasonally) and for identifying communities that would benefit most based on SMC coverage. Communities with gaps in SMC coverage may also have other vulnerabilities and gaps in care, for which AZ might be particularly effective.[20]

The potential heterogeneity in the effect of AZ calls for further studies before its widespread use can be recommended.[21] Studies are needed to refine key aspects of implementation, such as the optimal dose, frequency, timing,[22] and the populations to target or prioritize.[23, 24] Additionally, understanding how malaria seasonality and the concurrent use of malaria interventions like SMC impact the effectiveness of MDA AZ programs can help in tailoring these interventions to enhance their benefits, use resources efficiently and develop integrated strategies.

Using data from the CHAT cluster-randomized controlled trial in Burkina Faso[7] and the country's National Malaria Control Program (NMCP) data on SMC administration and coverage, we examined whether the effect of mass AZ distribution on mortality among children aged 1-59 months varies with SMC administration season or SMC coverage. We hypothesized that the effect of AZ will vary with SMC season and coverage level.

## Methods

### Study Design, Setting, Population and Data Collection

This was a post hoc secondary analysis of the CHAT trial (ClinicalTrials.gov, NCT03676764) and additionally included SMC data from NMCP. The methods and primary results have been reported in detail previously.[7, 25] Complete methods for the trial are also shown in the trial protocol (Supplement 1). In brief, CHAT was a cluster-randomized placebo-controlled trial designed to evaluate the efficacy of mass AZ strategies.[25] The trial was conducted from August 2019 to February 2023 and enrolled children aged 1-59 months in Nouna District of Burkina Faso. It covered both the Nouna Health and Demographic Surveillance Site (one third of Nouna District ),[26] as well as the non-HDSS area in Nouna.[25] A map of the study area is included in the primary analysis of the trial.[7] Communities were randomized in a 1:1 ratio to receive twice yearly distribution of a single oral dose of azithromycin or placebo. Children in these communities received their respective treatments for 3 years (from August 2019- February 2023). The overall coverage of MDA was approximately 90% for both AZ and placebo arms. Every 6 months, a census was conducted documenting births, deaths, pregnancies, and migration. CHAT had an open cohort design with children contributing different amounts of person time, and vital status recorded at each 6-month census (phases) for each child enrolled. Over the study period, 1,086 deaths over 119,139 person-years were observed (Figure 1).[7] Six rounds of census and treatment occurred during the study corresponding to the following phases: 0-6 months, 6-12, 12-18, 18-24, 24-30 and 30-36 months (Figure 2). Trial data were aggregated by cluster and these phases. All communities included in trial were included in these analyses.

Four monthly cycles of SMC were administered per local standard-of-care to children under 5 during the malaria transmission season from July through October each year. SMC was administered to the study area over a 3-4 day period.[27] NMCP records were reviewed to obtain SMC coverage data, including number of children treated during each cycle and the timing of treatment at the health post

(CSPS) level. Each community falls within a CSPS catchment area and was assigned the SMC coverage level of its corresponding CSPS.

The CHAT trial which served as basis for these analyses was reviewed and approved by the Institutional Review Boards at the University of California, San Francisco (IRB Number: 17-24230) and the Comité National d’Ethique pour la Recherche (National Ethics Committee of Burkina Faso (IRB Number: 2018-8-111) in Ouagadougou, Burkina Faso.

### Statistical analysis

The primary outcome for these analyses was all-cause mortality, assessed using a biannual census. The sample size was based on childhood mortality for the overall AZ versus placebo comparison in CHAT trial. Details of sample size calculation have been reported previously.[7] For the subgroup analysis, we calculated the minimum detectable effect (additive interaction effect per 1000 children) based on methods described by Hayes & Moulton for calculating power and sample size for examining interaction in cluster randomized trials, [28] This method accounts for clustering by using a randomization -unit level summary statistic.[28] Using parameters from CHAT data at 24 months, with 139 clusters per arm, 27 person-years of observation per cluster per subgroup, cluster standard deviation of 0.0223 and alpha of 0.05 for 2-sided test, we estimated that we would have 80% power to detect a delta of 1.16 (additive interaction effect of ~1 death per 1000 children). We conducted three analyses in which we assessed the effect of AZ (AZ vs placebo) in 1) the months of no SMC (January-June) versus months during and immediately following SMC (July-December), 2) by SMC coverage level (0-100%) on a continuous scale, and 3) by SMC coverage of below or above a threshold level of 80%, which was chosen a priori based on recommended WHO coverage levels. Descriptive analyses were used to report the mean number of children in each community, cluster-level mean percentages of children by age-group and sex, as well as SMC coverage levels. We used the interaction directed

152 acyclic graph[29] shown in Figure 3 to visualize the relationship between SMC and effect of AZ on  
153 under 5 mortality examined in the interaction analyses.

154  
155 For the analysis by season, the six phases were categorized as non-SMC (January-June) versus the  
156 SMC (July-December) seasons of the year, based on the timing of treatment and census. A Poisson  
157 regression model was used to analyze data at the cluster phase level with person-years included as an  
158 offset and robust standard error clustered at the cluster level to account for repeating phases. This was  
159 used to estimate the mortality rate in AZ and placebo groups, their rate ratio by season, and their  
160 interaction on the multiplicative scale. The margins command in Stata was used to estimate incidence  
161 rate differences (IRDs) with 95% CIs using the delta method. Number needed to treat to avert one  
162 death was calculated using the rate differences. Relative excess risk due to interaction (RERI) with  
163 bootstrap 95% confidence limits and 1000 repetitions was used to assess interaction on the additive  
164 scale.

165  
166 For the analysis by coverage, we updated the SMC coverage for 2020 and 2021 originally reported by  
167 NMCP using 2006 denominators (estimates of total number of children), by the corresponding census  
168 denominators from CHAT to obtain more accurate coverage estimates for each CSPA. The SMC  
169 coverage for each cycle in each year for each CSPA was calculated as the number of children treated  
170 (obtained from NMCP) divided by the total number of children in the CSPA catchment area.  
171 SMC coverage percentages for each cluster and each year (2019, 2020, 2021) were linked to the trial  
172 data by cluster. Since SMC coverage estimates for 2019 were not available and given the high  
173 correlation (>90%) in CSPA level coverage between 2020 and 2021, coverage estimates for 2020 were  
174 used for both 2019 and 2020. For the coverage estimate for each year, we used the average coverage  
175 level across the 4 cycles of SMC distributed during that year. Clusters with coverage estimates above  
176 100% (~8%) were capped to 100%. SMC coverage was scaled for each unit increase to represent 10%  
177 increase in coverage. Given the short duration of protection of SMC,[30] for the analysis by coverage,



we restricted the data to the second half of each year (July-December), the period during and immediately after SMC was administered. The analysis dataset included the treatment type (AZ vs placebo), number of deaths and person-time aggregated by cluster and phase year, along with the coverage estimate for each cluster and phase, in a longitudinal format.

For the analysis by coverage level of 80% or above, we used the dataset for the coverage analysis described above and dichotomized coverage level as below or 80% and above and examined whether the effect of AZ varied in these subgroups. We considered this cutoff reasonable since it has been noted that 69% of children receiving all SMC cycles or 90% receiving at least one cycle, can be considered high coverage.[31] For both analyses by coverage level, we used Poisson regression models with robust standard errors and similar methods described above for examining interactions on additive and multiplicate scales.

Due to the imbalance in SMC coverage between arms, we conducted sensitivity analysis adjusting for SMC coverage in the analysis by SMC season. Furthermore, we categorized the year into quarters, in a sensitivity analysis, to evaluate during which time of the year AZ distribution yielded the greatest benefit against mortality. Lastly, we examined the role of SMC coverage in the effect of AZ on child mortality, adjusting for age of children and distance to health facility, and their interactions with AZ,[29] as both may influence the level of SMC coverage and affect the benefit of AZ for mortality.[3, 20, 32]

We plotted the mortality rate and rate differences by SMC season, coverage level, and by a threshold coverage level of 80% to visualize changes in the effect of AZ, and in the mortality rates by arm. SAS 9.4 (SAS Institute, Cary, NC) was used for data cleaning and for generating the datasets for analyses. Stata version 14.2 (StataCorp, College Station, TX) was used for all other analyses.

## Results

203 The CHAT trial involved 341 communities. Of these, 171 were randomized to receive Azithromycin,  
 204 with 146 being analyzed, while 170 communities were randomized to receive placebo, with 139 being  
 205 analyzed (Figure 1). Characteristics of communities included in the trial are presented in Table 1.  
 206 Around 30% of the children in each arm were aged 12-23 months. The age and sex distributions were  
 207 similar across arms. The SMC coverage estimates that were updated by recent denominators showed  
 208 variability, with an overall average coverage of 79% (SD 0.59). The average SMC coverage across  
 209 rounds was slightly higher in treatment versus placebo arm, 82% versus 73%, respectively. In both  
 210 arms, SMC coverage level was slightly higher in the 4<sup>th</sup> cycle compared to other cycles. In the CHAT  
 211 trial, the mortality rate in the azithromycin group was 8.2 deaths per 1000 person-years while in the  
 212 placebo group, it was 10.0 deaths per 1000 person-years.[7]

213  
 214 For both arms, mortality rate was higher in the SMC seasons: 7.9 per 1000 person-years, 95% CI (6.9  
 215 to 9.0) in the first half of the year, compared to 10.3 per 1000 person-years, 95%CI (9.0 to 11.6) in the  
 216 second half of the year (Figure 4a) In both SMC and non-SMC seasons, mortality rate was higher in  
 217 placebo arm (Table 2). The interaction between AZ and SMC season was not statistically significant on  
 218 either the multiplicative or additive scale. The effect of AZ compared to placebo was 0.77, 95%CI (0.6  
 219 to 0.98) in SMC season vs 0.89 (0.68 to 1.15) in non-SMC season (Figure 4b).

220  
 221 Table 3 shows the mortality rates by arm and the effect of AZ at different SMC coverage levels. The  
 222 interaction between AZ and SMC coverage (both on continuous scale and dichotomous at 80%  
 223 coverage threshold) was not statistically significant on either the multiplicative or additive scale  
 224 ( $P>0.05$ )., However, the benefit of AZ appeared to slightly lower with increasing SMC coverage (Figure  
 225 5a and 5b). The effect of AZ compared to placebo in clusters with <80% SMC coverage was 0.73  
 226 95%CI (0.56 to 0.96) and in clusters with  $\geq 80\%$  SMC coverage, it was 1.0 95%CI (0.59 to 1.69).

227

Although the interaction was not statistically significant, the mortality rate was lower in the AZ arm compared to the placebo arm (IRR AZ vs placebo=0.73, 95%CI (0.56 to 0.96) in clusters with SMC coverage below 80%. No significant difference in the mortality rate was observed between the AZ and placebo arms in clusters with SMC coverage of 80% or above: IRR=1.0, 95%CI (0.59 to 1.69), Table 4, Figure 6a and 6b).

In the sensitivity analysis, we found that adjusting for coverage in the analysis by season generated similar findings in which the effect of AZ compared to placebo was 0.77 95%CI (0.6 to 0.98) in SMC season vs 0.89 95%CI (0.68 to 1.15) in non-SMC season (Supplementary Table 1, Supplementary Figure 1).

In the sensitivity analysis by quarters, the interaction between AZ and quarter did not reach statistical significance (P=0.203). However, the benefit of AZ appeared to be more pronounced when administered in the last 3 months of the year (October–December); IRD = -4.0 per 1,000 person-years (95% CI: -7.9 to -0.11) (Supplementary Figure 2). In the analysis in which we examined the role of SMC coverage in the effect of AZ on child mortality, adjusting for age of children and distance to health facility and their interaction with AZ, we found that the results were similar in which we did not reach statistical significance but the benefit of AZ appeared to slightly lower with increasing SMC coverage (Supplementary Figure 3).

## Discussion

We evaluated how the effect of AZ changes by seasons of SMC administration and coverage. We found that the interaction between AZ and SMC season or coverage did not reach statistical significance on both the additive or multiplicative scales. Mortality rates appeared higher during SMC seasons for both AZ and placebo-treated clusters. Although not significant, the benefit of AZ may have been higher during these high-mortality SMC seasons. Mortality rates appeared to decrease with

increasing SMC coverage in placebo clusters but not in AZ clusters. Compared to placebo, our results suggested that AZ may have had an increasing benefit as SMC coverage decreased. Its effect was also more pronounced in clusters with <80% versus  $\geq 80\%$  SMC coverage.

The effect of AZ appeared higher during and after the months when SMC was administered, particularly towards the end of the year. This is likely due to the high malaria transmission and associated high child mortality during this period.[33] Since AZ may provide short-term infection prevention and treatment by clearing infections,[5, 34] its impact may be higher when administered around peak morbidity and mortality periods. It is suggested that optimal administration of AZ requires targeting asynchronous peaks in morbidity and mortality from various causes, as AZ is not specific to a single pathogen.[34] Although other infectious diseases treated by AZ, such as pneumonia and diarrhea, may follow different seasonal patterns than malaria,[35, 36] AZ appeared to have a larger effect during this period of elevated malaria transmission and mortality. Previous studies in this region have found that malaria rates remained high in November and December, extending beyond the final cycle of SMC in October.[37] Furthermore, the sensitivity analysis (Supplementary Figure 2) suggests that the effect of AZ may be more pronounced during these late months of the year, compared to the third quarter when SMC is primarily administered. While the overall benefit of AZ appeared greater in the post-SMC period (July–December), its enhanced effect may have been concentrated in the final quarter, when malaria and potentially mortality rates remain high without further cycles of SMC. This likely higher benefit however may also be due to a higher number of deaths to be prevented or greater statistical power to detect an effect of AZ, given the higher mortality during this season. Given concerns about the frequency of AZ in relation to resistance,[21, 22] as well as its short-term effects, future studies should examine whether fewer rounds of AZ, but administered during the malaria transmission and SMC season, particularly when mortality is elevated, could be beneficial.

278 Although the interaction was not statistically significant, the slightly higher effect of AZ in clusters with  
 279 lower SMC coverage may suggest that the benefit of AZ may be greater in areas with gaps in SMC  
 280 coverage. A likely contributing factor could be that SMC coverage may be related to engagement with  
 281 the healthcare system, with low-coverage areas likely facing obstacles to care.[32] AZ MDA has been  
 282 found more effective for children who often have less access to preventive and curative care. [20]  
 283 Therefore, the lower SMC coverage may reflect broader gaps in community and facility resources  
 284 related to SMC administration. Previous studies have identified several barriers to SMC uptake,  
 285 including local shortages, challenges reaching mobile populations and underserved areas, and issues  
 286 related to community distributors' working conditions, such as workload and incentives.[32, 38]  
 287 Therefore regions with lower SMC coverage may also have other gaps in routine child health  
 288 interventions and care, where AZ may be particularly helpful. Although it did not reach statistical  
 289 significance, the higher benefit of AZ in low SMC communities suggests that prioritizing AZ treatment in  
 290 areas with inadequate SMC coverage might be beneficial.,

291 The slightly reduced benefit of AZ in areas with high SMC coverage may also partly be due to reduction  
 292 in malaria disease burden following SMC administration.[27] In regions with lower SMC coverage,  
 293 important gaps in malaria prevention remain,[31] making AZ MDA likely beneficial as it may have some  
 294 efficacy against both malaria and bacterial infections. Although the effect of AZ on malaria infections  
 295 has been inconsistent,[39] analysis of causes of death from the MORDOR trial found that malaria was  
 296 one of the primary causes of mortality against which AZ was beneficial.[6] With effective malaria  
 297 interventions like SMC, the impact of AZ may be less apparent.[40] This is also consistent with the lack  
 298 of observed benefit of AZ for mortality in the household randomized trial, where all enrolled children  
 299 received SMC.[19]

300

301 This study has some limitations. First, it may have been underpowered to detect significant interaction  
 302 between AZ and SMC on the mortality outcome. For the analysis by coverage level, the data was

further restricted to SMC seasons, which further reduced our sample size. However, we still observed patterns suggestive of a differential effect of AZ by season and SMC coverage. Considering the lack of statistical power, is it possible that the slight differences we observed may be due to chance. These findings should be confirmed in larger studies and examined in different settings. Second, the SMC data used in our analysis were programmatic data, not prospectively collected for research purposes and therefore had less specificity and details such as daily doses or whether treatment was directly observed. Additionally, the data were provided at the health post level, and any differences in coverage levels between clusters were not captured. The absence of data for 2019 is also another limitation in our analysis. Furthermore, although we adjusted for distance to facility and age group of children, there may be other unknown factors that can affect SMC coverage as well as the effect of AZ on child mortality. However, since the goal of this these analyses was to identify subgroups that potentially benefitted the most from AZ treatment, only confounding of the primary exposure-outcome (AZ-mortality) relationship needs to be taken into account.[41] We would not expect confounding to be an issue for the AZ-mortality effect due to the randomized nature of the intervention. There may also be measurement error in our coverage level estimates of SMC. To minimize this, we updated denominators using recent census estimates of the number of children and capped outliers. Lastly, since the CHAT trial included rural communities, the generalizability of these findings may be limited to such settings.

## Conclusion

Although the interactions did not reach statistical significance, our findings raise the question of whether MDA AZ programs could be more effective if prioritized during the latter part of the year, when malaria transmission and mortality are elevated. Additionally, regions with lower SMC coverage may represent a useful target for AZ MDA interventions. Future studies should explore whether prioritizing AZ administration in these high-risk periods or areas with gaps in SMC coverage leads to greater reductions in child mortality.

## 328 **Ethics Approval**

329 The CHAT Randomized controlled trial was reviewed and approved by the Institutional Review Boards  
330 at the University of California, San Francisco and the Comité National d'Ethique pour la Recherche  
331 (National Ethics Committee of Burkina Faso) in Ouagadougou, Burkina Faso.

332

## 333 **Data Availability**

334 The datasets analyzed during the current study are not yet publicly available but will be made  
335 accessible through the Open Science Framework (OSF) repository upon finalization. The data will be  
336 shared in accordance with relevant open data sharing guidelines. A link to the repository will be  
337 provided once the data is available.

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347 **Conflict of Interest:** None declared

348 **Tables and Figures**

349 **Table 1-** Characteristics of communities in CHAT trial

	<b>Azithromycin group (146 communities)</b>	<b>Placebo group (139 communities)</b>
Number of Children	34,399	33,847
Age groups (mean %, SD)		
1–11 months	17.7% (3.8)	17.1% (3.6)
12–23 months	30.6% (4.3)	30.4% (4.4)
24–35 months	15.0% (2.7)	15.2% (3.1)
36–47 months	14.0% (2.7)	14.1% (2.9)
48–59 months	14.0% (3.2)	14.8% (3.8)
Male sex (mean %, SD)	50.2% (4.2)	50.0% (4.0)
SMC coverage (mean %, SD)	82% (0.66)	73% (0.49)
Cycle 1 (July)	80% (0.65)	71% (0.47)
Cycle 2 (August)	80% (0.66)	72% (0.5)
Cycle 3 (September)	83% (0.66)	74% (0.5)
Cycle 4 (October)	84% (0.69)	75% (0.51)

350



**Table 2-** Effect of Azithromycin vs Placebo Distribution on Child Mortality by overall and by SMC season

	<b>Overall (Jan-Dec)</b>	<b>Non-SMC (Jan-Jun)</b>	<b>During/Post-SMC (Jul-Dec)</b>
Mortality rate per 1000 PY (all clusters)	9.1 (8.1 to 10.1)	7.9 (6.9 to 9)	10.3 (9 to 11.6)
Mortality rate per 1000 PY in AZ	8.2 (7.1 to 9.4)	7.5 (6.1 to 8.8)	9 (7.5 to 10.4)
Mortality rate per 1000 PY in Placebo	10.0 (8.4 to 11.7)	8.4 (6.8 to 10.1)	11.7 (9.5 to 13.9)
IRR (AZ vs placebo)	0.82 (0.66 to 1.01)	0.89 (0.68 to 1.15)	0.77 (0.6 to 0.98)
IRD (AZ vs placebo)	-1.82 (-3.8 to 0.14)	-0.97 (-3.07 to 1.14)	-2.7 (-5.32 to -0.07)
Number Needed to treat to prevent one death	549	1037	371
Interaction Coeff multiplicative	0.87 (0.65 to 1.16), p= 0.335		
Interaction Coeff additive	-0.21 (-0.57 to 0.16), P=0.268		

**Table 3-** Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC coverage level

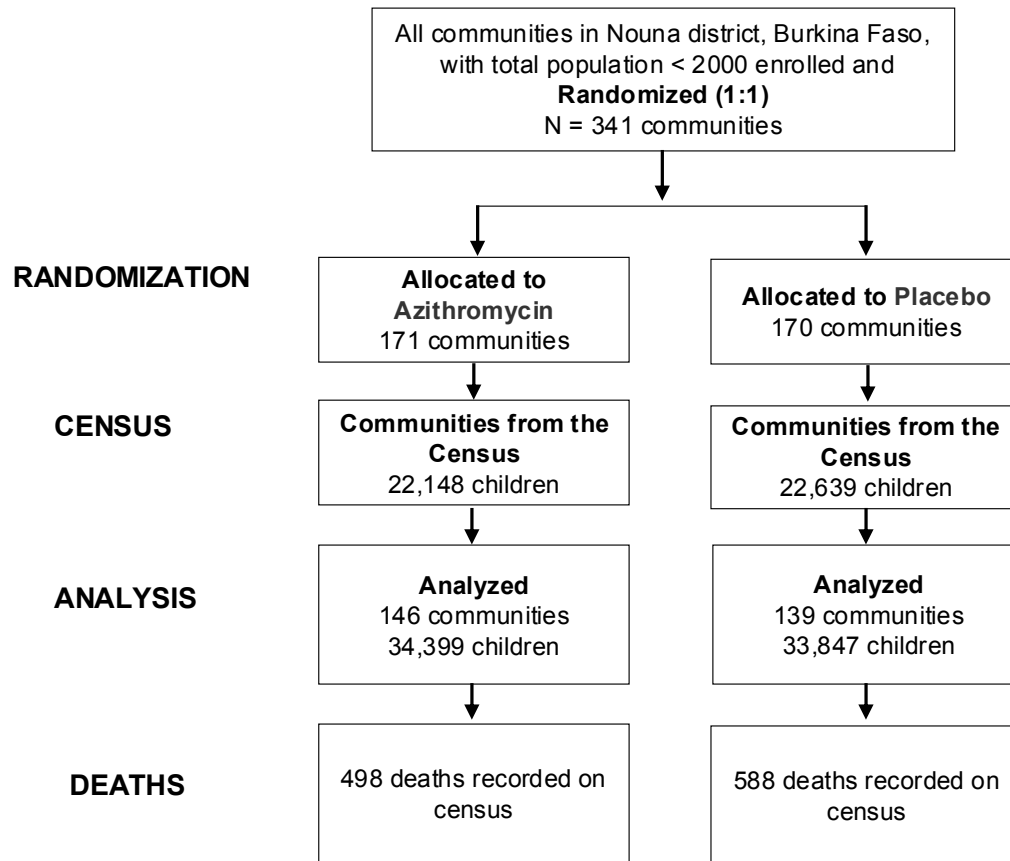
<b>SMC coverage</b>	<b>Mortality rate per 1000 PY (all clusters)</b>	<b>Mortality rate per 1000 PY in AZ</b>	<b>Mortality rate per 1000 PY in Placebo</b>	<b>IRR (AZ vs placebo)</b>	<b>IRD (AZ vs Placebo) per 1000 PY</b>	<b>Number needed to treat to prevent one death</b>
Overall	10.3 (9.1 to 11.6)	9.0 (7.5 to 10.4)	11.6 (9.6 to 13.6)	0.77 (0.6 to 0.98)	-2.6 (-5.0 to -0.1)	387
30%	11.6 (7.6 to 15.7)	8.5 (4.8 to 12.3)	14.9 (7.6 to 22.2)	0.57 (0.2 to 0.95)	-6.4 (-14.6 to 1.8)	157
40%	11.2 (8.2 to 14.2)	8.6 (5.7 to 11.6)	13.9 (8.6 to 19.2)	0.62 (0.3 to 0.94)	-5.2 (-11.3 to 0.8)	191
50%	10.8 (8.7 to 12.9)	8.8 (6.6 to 11)	12.9 (9.3 to 16.5)	0.68 (0.42 to 0.93)	-4.2 (-8.4 to 0)	240
60%	10.4 (9 to 11.8)	8.9 (7.3 to 10.5)	12 (9.7 to 14.4)	0.74 (0.54 to 0.93)	-3.2 (-6.0 to -0.3)	318
70%	10.1 (8.9 to 11.3)	9 (7.5 to 10.5)	11.2 (9.4 to 13)	0.80 (0.62 to 0.99)	-2.2 (-4.5 to 0.2)	456
80%	9.8 (8.3 to 11.2)	9.2 (7.2 to 11.1)	10.5 (8.3 to 12.6)	0.88 (0.62 to 1.14)	-1.3 (-4.2 to 1.6)	775
90%	9.5 (7.5 to 11.5)	9.3 (6.5 to 12.1)	9.7 (6.9 to 12.6)	0.95 (0.56 to 1.35)	-0.4 (-4.4 to 3.5)	2274
100%	9.3 (6.7 to 11.8)	9.4 (5.7 to 13.2)	9.1 (5.5 to 12.6)	1.04 (0.46 to 1.62)	0.4 (-4.8 to 5.5)	2743
Interaction Coeff multiplicative scale		1.1 (0.9 to 1.3), P=0.297				
Interaction Coeff additive scale		0.08 (-0.06 to 0.21), P= 0.264				

**Table 4-** Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC coverage threshold of 80%

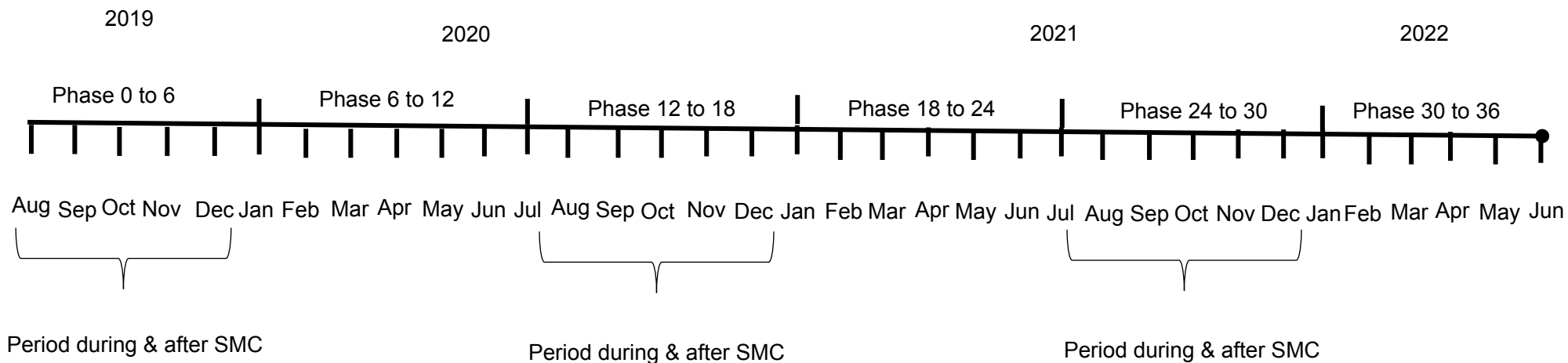
	<b>Across all clusters (N=285)</b>	<b>Coverage below 80% (N=222)</b>	<b>Coverage 80% or above (N=86)</b>
Mortality rate per 1000 PY (all clusters)	10.3 (9 to 11.5)	10.5 (9 to 11.9)	9.2 (6.8 to 11.7)
Mortality rate per 1000 PY in AZ	9.0 (7.5 to 10.4)	8.9 (7.3 to 10.5)	9.2 (5.9 to 12.6)
Mortality rate per 1000 PY in Placebo	11.5 (9.4 to 13.6)	12.1 (9.6 to 14.7)	9.2 (5.8 to 12.7)
IRR (AZ vs placebo)	0.78 (0.61 to 0.99)	0.73 (0.56 to 0.96)	1.0 (0.59 to 1.69)
IRD (AZ vs placebo)	-2.49 (-5.03 to 0.05)	-3.3 (-6.2 to -0.3)	0.01 (-4.8 to 4.9)
Number Needed to treat to prevent one death	402	308	119,306
Interaction Coeff multiplicative	1.37 (0.76 to 2.48), P= 0.301		
Interaction Coeff additive	0.27 (-0.19 to 0.72), P=0.247		

Note: Some clusters may appear in both high and low coverage counts if their estimates were above the threshold in one year and below the threshold in another year.

**Figure 1- Cluster and Participant Flow Diagram**

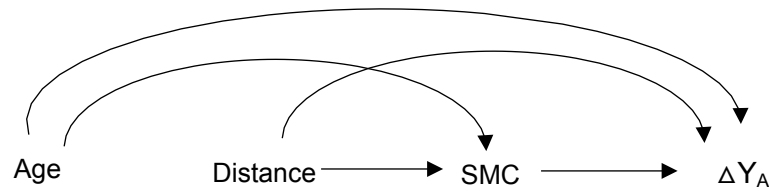


**Figure 2-** Timeline of census and AZ treatment phases in CHAT trial and SMC seasons



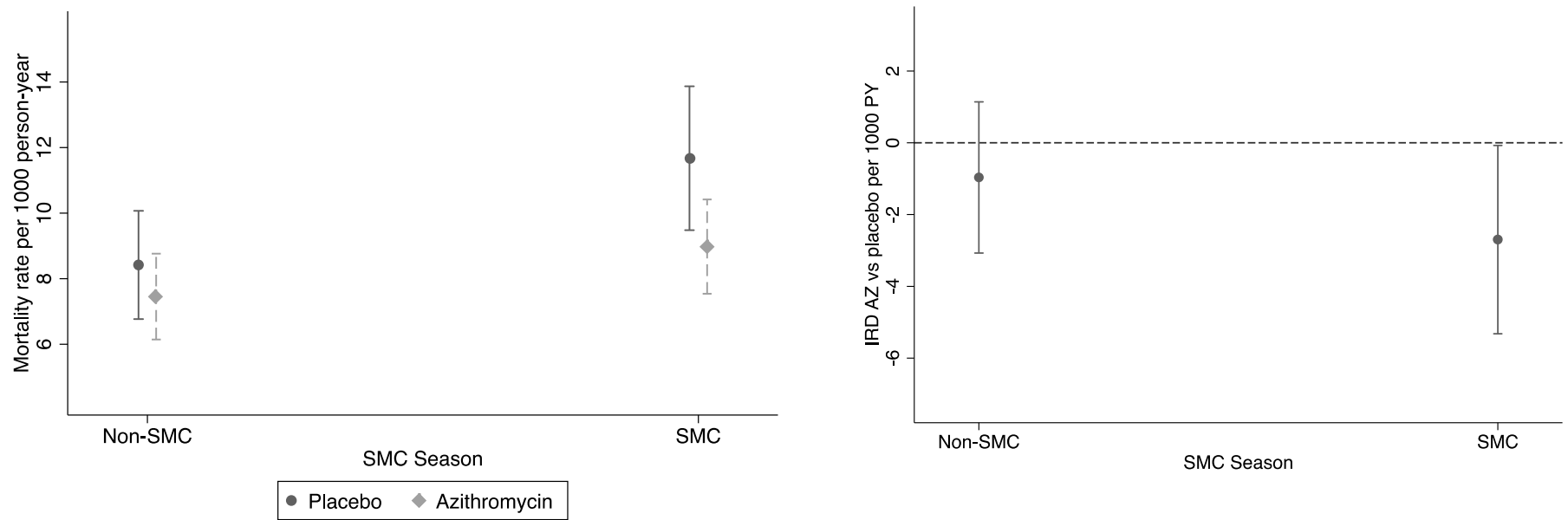
**Note:** AZ treatment and census occurred during each phase (biannual). There were four rounds of SMC treatment (July to October, one each month) each year

**Figure 3-** Interaction Directed Acyclic Graphs Illustrating the Interaction Between Mass AZ Treatment and SMC



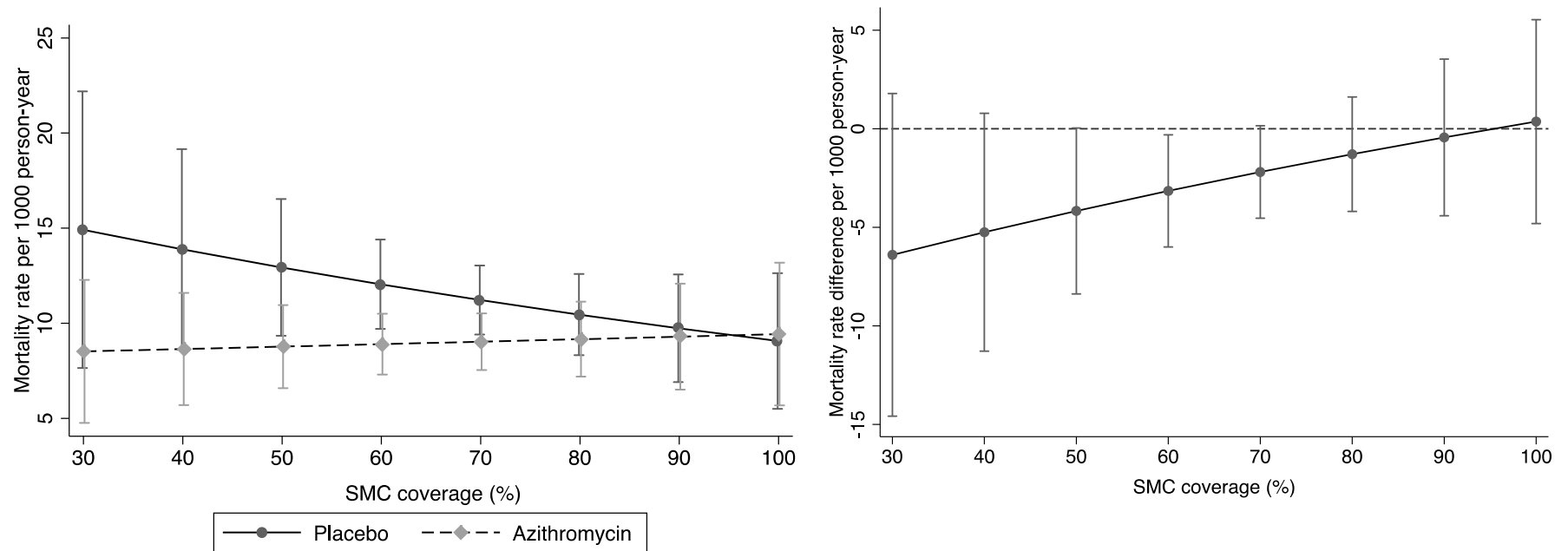
**Note:** Age-age of children, Distance-distance to health facility, SMC-SMC coverage level, Y-under-five mortality, A- AZ treatment,  $\Delta Y_A$ -effect of AZ on child mortality. The figure shows how SMC may modify the effect of AZ on child mortality, with potential confounders including the interaction of distance to a health facility with AZ, and the interaction of child age with AZ on child mortality. Adjusted analyses are presented in Supplementary Figure 3

**Figure 4-** a) Mortality rate by treatment and SMC season and b) Mortality rate difference (AZ vs Placebo) by SMC season



Note: IRD- Incidence rate difference

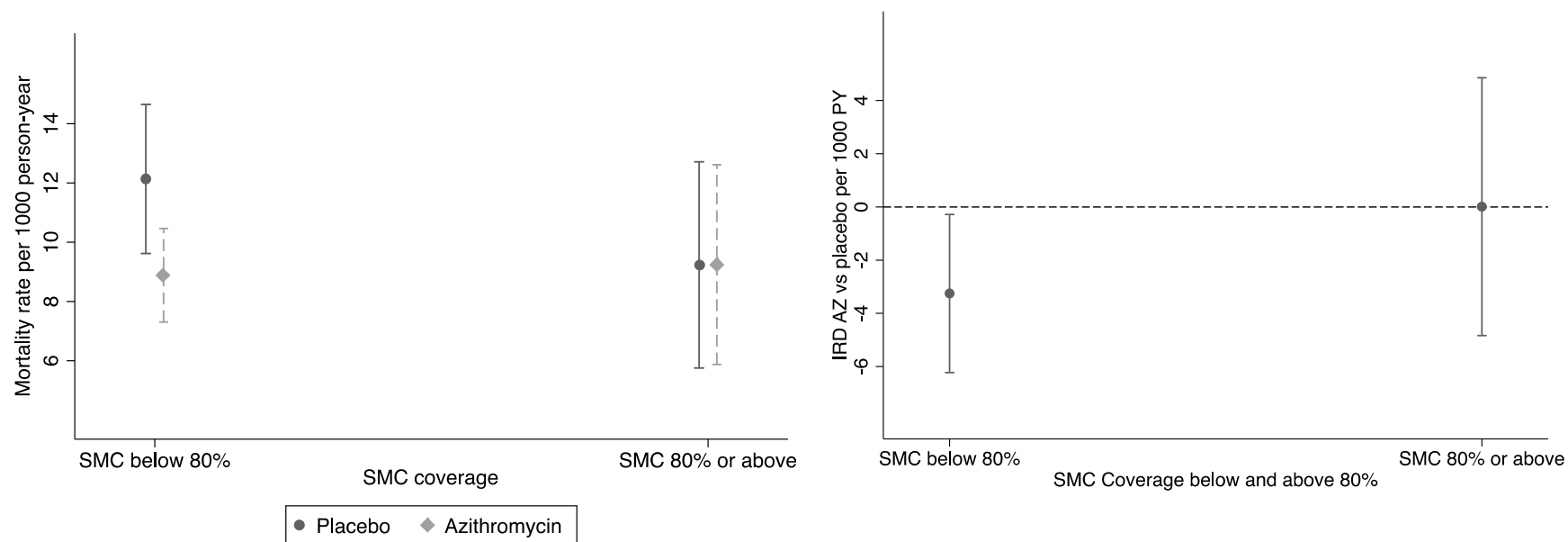
**Figure 5-** a) Mortality rate by treatment arm at each level of SMC coverage and b) difference in mortality rate (AZ vs Placebo) by SMC coverage



Note: This analysis was restricted to months during and after SMC distribution (July-December). The lowest SMC coverage was 30%.



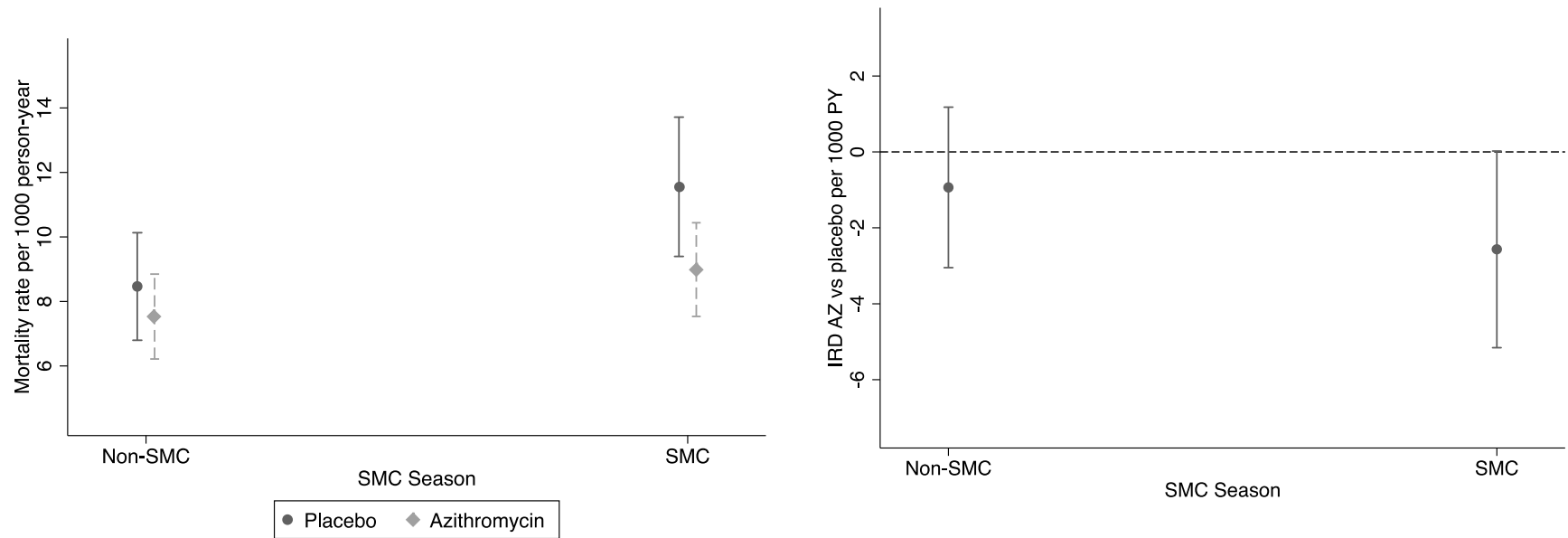
**Figure 6-** a) Mortality rate by treatment and SMC coverage and b) Mortality rate difference (AZ vs placebo) by SMC coverage threshold of 80%



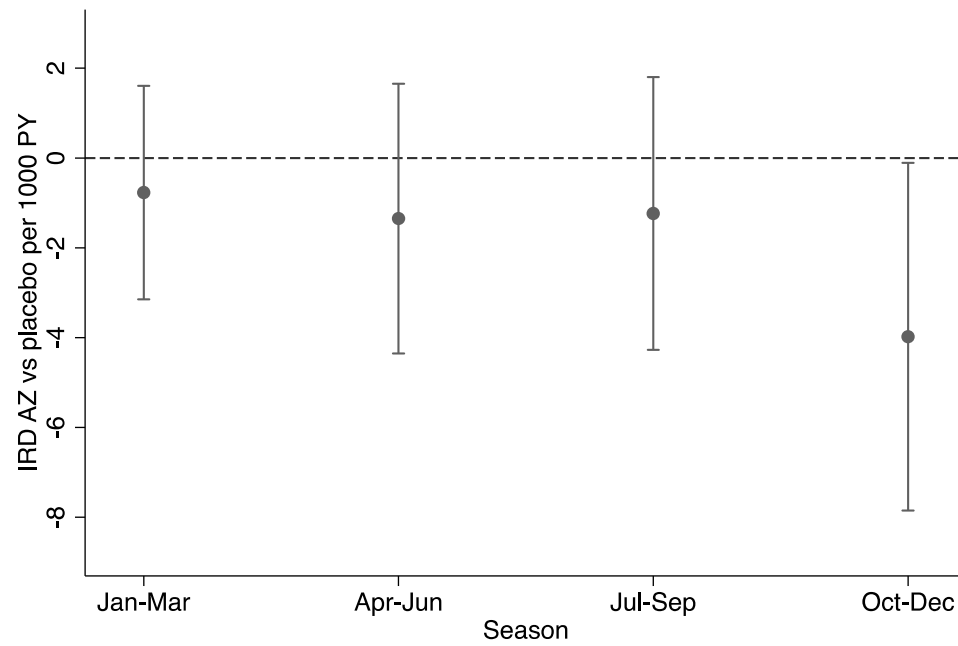
Note: IRD- Incidence rate difference

## Supplementary Figures

**Supplementary Figure 1-** a) Mortality rate by treatment and SMC season and b) Mortality rate difference (AZ vs Placebo) by season adjusting for SMC coverage level

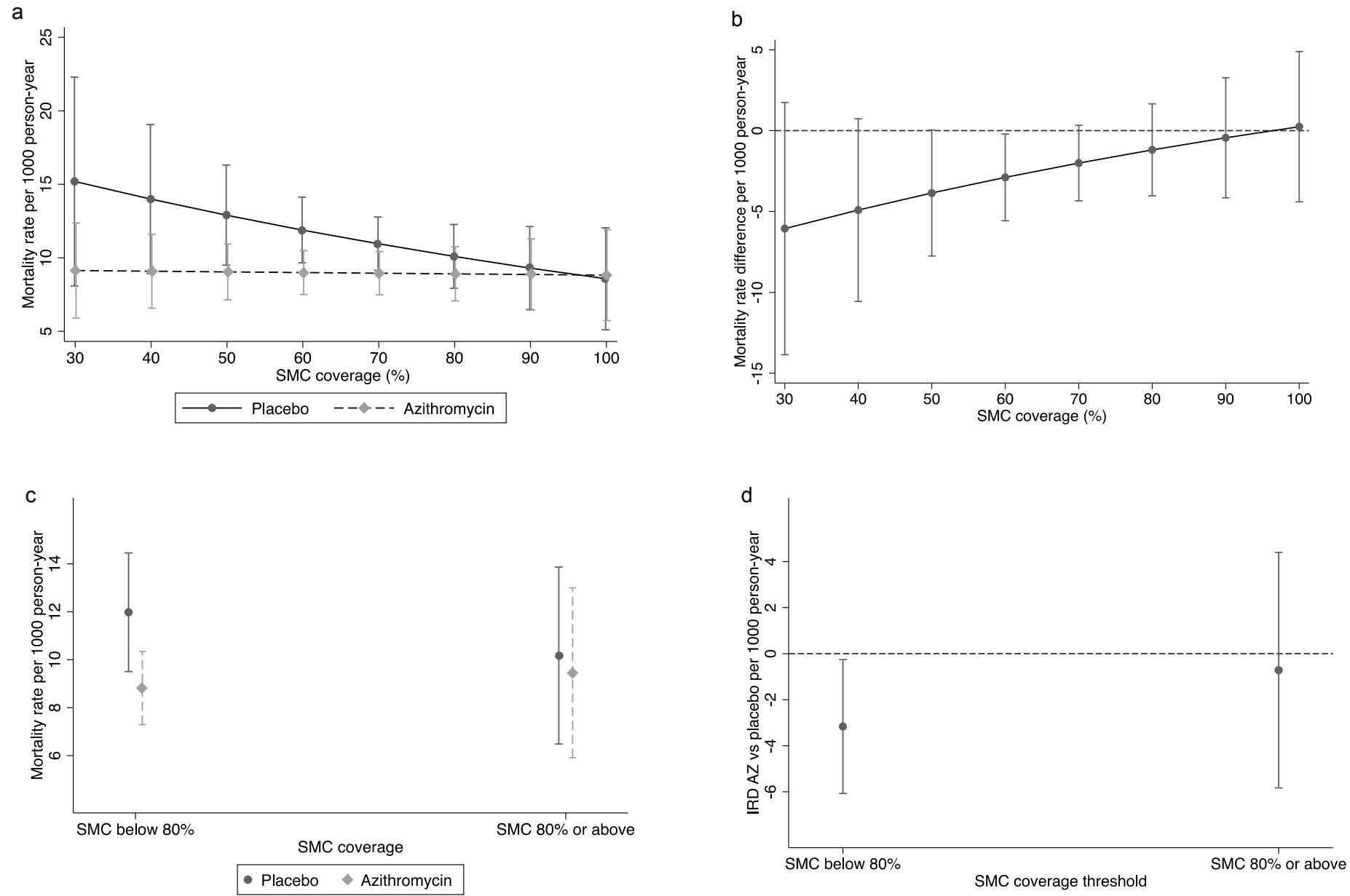


**Supplementary Figure 2 - Mortality rate difference (AZ vs placebo) by quarter of year**



Note: P value for the interaction between AZ and quarter was 0.203 on the multiplicative scale and 0.148 on the additive scale

**Supplementary Figure 3- Mortality Rate by Treatment and SMC Coverage: a) Continuous Scale and c) Threshold Level; Mortality Rate Difference (AZ vs. Placebo) by SMC Coverage: b) Continuous Scale and d) Threshold Level, Adjusting for Distance to Facility, Age of Children, and Their Interaction.**



## Supplementary Tables

**Supplementary Table 1-** Effect of Azithromycin vs. Placebo on Child Mortality by Season, Adjusting for SMC Coverage

	<b>Non-SMC (Jan-Jun)</b>	<b>SMC (Jul-Dec)</b>
Mortality rate per 1000 PY (all clusters)	7.9 (6.9 to 9.0)	10.3 (9 to 11.6)
Mortality rate per 1000 PY in AZ	7.5 (6.1 to 8.8)	9.0 (7.5 to 10.4)
Mortality rate per 1000 PY in Placebo	8.4 (6.8 to 10.1)	11.7 (9.5 to 13.9)
IRR (AZ vs placebo)	0.89 (0.68 to 1.15)	0.77 (0.6 to 0.98)
IRD (AZ vs placebo)	-0.97 (-3.07 to 1.14)	-2.7 (-5.3 to -0.07)
Number Needed to treat to avert one death	1037	371
Interaction Coeff multiplicative scale	0.87 (0.65 to 1.16), p= 0.335	
Interaction Coeff additive scale	-0.21 (-0.57 to 0.16), p=0.268	

Note: Table showing results from sensitivity analyses adjusting for coverage

## Legends

### Tables:

**Table 1-** Characteristics of communities/clusters in CHAT trial

**Table 2-** Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC season

**Table 3-** Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC coverage level

**Table 4-** Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC coverage threshold of 80%

### Figures:

**Figure 1-** Cluster and Participant Flow Diagram

**Figure 2-** Timeline of census and AZ treatment phases in CHAT trial and SMC seasons

**Figure 3-** Interaction Directed Acyclic Graphs Illustrating the Interaction Between Mass AZ Treatment and SMC

**Figure 4-** a) Mortality rate by treatment and SMC season and b) Mortality rate difference (AZ vs placebo) by SMC season

**Figure 5-** a) Mortality rate by treatment arm at each level of SMC coverage and b) difference in mortality rate (AZ vs Placebo) by SMC coverage

**Figure 6-** a) Mortality rate by treatment and SMC coverage and b) Mortality rate difference (AZ vs placebo) by SMC coverage threshold of 80%

## Supplementary material

**Supplement 1-** CHAT Trial Manual of Operations

### Figures

**Supplementary Figure 1-** a) Mortality rate by treatment and SMC season and b) Mortality rate difference (AZ vs Placebo) by season adjusting for SMC coverage level

**Supplementary Figure 2-** Mortality rate difference (AZ vs placebo) by quarter of year

**Supplementary Figure 3-** Mortality Rate by Treatment and SMC Coverage: a) Continuous Scale and c) Threshold Level; Mortality Rate Difference (AZ vs. Placebo) by SMC Coverage: b) Continuous Scale and d) Threshold Level, Adjusting for Distance to Facility, Age of Children, and Their Interaction.

**Tables: Supplementary Table 1-** Effect of Azithromycin vs. Placebo on Child Mortality by Season, Adjusting for SMC Coverage

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