Title

The Impact of Mass Azithromycin Distribution and Seasonal Malaria Chemoprevention on Child Health: Heterogeneity of Treatment Effects, Wealth Disparities, and Broader Health Implications

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The Impact of Mass Azithromycin Distribution and Seasonal Malaria Chemoprevention on Child Health: Heterogeneity of Treatment Effects, Wealth Disparities, and Broader Health Implications

by

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DISSERTATION

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To my entire family,

your support made this possible.

To Sam and Liana,

my whole heart.

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The Impact of Mass Azithromycin Distribution and Seasonal Malaria Chemoprevention on Child Health: Heterogeneity of Treatment Effects, Wealth Disparities, and Broader Health Implications

Elisabeth Gebreegziabher

Abstract

Seasonal malaria chemoprevention (SMC) and mass azithromycin (AZ) distribution are two interventions shown to reduce child mortality in high-burden settings. While SMC is intended to prevent malaria through monthly administration of sulfadoxine-pyrimethamine and amodiaquine during the rainy season, it is unclear whether its benefit extends to non-malarial infections and overall child health. Additionally, although AZ has been effective in reducing child mortality, its effectiveness in the context of concurrent SMC use and the heterogeneity of its effects based on factors affecting access to treatment remains unclear.

The objective of this dissertation is to evaluate how mass distribution of AZ and SMC can be optimized to reduce infections and mortality among children under five in sub-Saharan Africa, with the goal of guiding mass drug administration program implementation.

This research combines national program records, clinic surveillance, and clinical trial data from 341 communities in Burkina Faso. Chapter 1 explores changes in non-malarial infections and antibiotic prescriptions following SMC to understand its indirect benefits and broader implications for reducing infections in real-world programmatic settings, including how its implementation may influence other interventions. Chapter 2 assesses the impact of concurrent administration of azithromycin and SMC on treatment outcomes, and whether the effect of AZ

on all-cause child mortality varies by SMC season and coverage. Chapter 3 examines the presence of a wealth gradient in child mortality and investigates heterogeneity in AZ treatment effects in relation to wealth-related health disparities at both the household and community levels.

With SMC being part of routine program delivery and mass distribution of azithromycin continuing to expand across sub-Saharan Africa, findings from this work provide insights into the broader impacts of these interventions and help offer guidance on optimizing their timing, targeting, and integration into health systems.

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List of Abbreviations

AVENIR: Azithromycine pour la Vie des Enfants au Niger: Implementation et Recherche

AZ: Azithromycin

CHAT: Community Health with Azithromycin Trial

CI: Confidence interval

CSPS: Centres de Santé et de Promotion Sociale

DAG: Directed acyclic graph

DHS: Demographic and Health Survey

HDSS: Health and Demographic Surveillance Site

IRD: Incidence rate difference

IRR: Incidence rate ratio

IRS: Indoor residual spraying of insecticide

KMO: Kaiser-Meyer-Olkin

LLIN: Long-lasting insecticidal net

MDA: Mass drug administration

MDA AZ: Mass drug administration of azithromycin

MORDOR: Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance

NMCP: National Malaria Control Program

PCA: Principal component analysis

RCT: Randomized controlled trial

RDT: Rapid diagnostic test

RERI: Relative excess risk due to interaction

RII: Relative index of inequality

RR: Risk ratio

SES: Socioeconomic status

SII: Slope index of inequality

SMC: Seasonal malaria chemoprevention

SP-AQ: Sulfadoxine-pyrimethamine and amodiaquine

WHO: World Health Organization

Chapter 1: Seasonal Malaria Chemoprevention and Its Indirect Effect on Non-Malarial Pediatric Infections and Routine Antibiotic Use: A Pre-Post Study with Positive and Negative Controls

INTRODUCTION

Infectious diseases, particularly acute diarrheal and respiratory infections, and malaria, are the leading causes of illness and death in children in low- and middle-income countries.[1] One strategy to prevent malaria infections and subsequent child mortality is the administration of seasonal malaria chemoprevention (SMC) for children under five. SMC involves administration of sulfadoxine-pyrimethamine and amodiaquine (SP-AQ) during the rainy season in areas with highly seasonal malaria transmission and regions where *Plasmodium falciparum* strains are sensitive to this antimalarial.[2] In most regions, SMC is administered in four or five monthly cycles, beginning July of each year.

In 2012, the World Health Organization recommended the adoption of SMC, and since then, several countries in Africa have implemented, with over 50 million children receiving it in 2023.[3-5] Recent guidelines have introduced more flexibility, allowing for adjustments in age groups, dosages, and treatment frequency based on local conditions.[6] Evidence from randomized controlled trials (RCTs) and observational studies show that SMC is an effective malaria control strategy.[7-9]

Although SMC has been shown to prevent clinical malaria and reduce all-cause mortality,[10,11] its effect on non-malarial infections is not clear. While SMC primarily targets malaria, the SP

component has weak antimicrobial/antibiotic properties that may help prevent or treat other infections.[12,13] It remains unclear whether there are additional mechanisms through which SMC might lower all-cause mortality beyond its effects on malaria. Additionally, malaria may increase susceptibility to other infections through indirect effects on the immune system,[14] anemia,[15] and nutrition/growth[16]. Therefore, by reducing malaria morbidity and susceptibility to other infections, malaria control efforts such as SMC may have potential to offer broader health benefits for children beyond those directly linked to malaria reduction.

Previous research suggests that clearance of chronic malaria was associated with lower overall illness, decreased antibiotic use and improved immunocompetence against non-malaria infections among children.[17] Effective malaria control interventions may reduce other infections and routine antibiotic use,[17] potentially contributing to improvements in overall health and a reduction in selection for antibiotic resistance from routine use. Therefore, examining the impact of SMC on overall infection burden, common infections such as pneumonia and diarrhea, and subsequent antibiotic use, can help determine whether it reduces non-malarial illnesses, offers broader health benefits beyond malaria, and potentially help in designing integrated health interventions.

Furthermore, previous research shows variability in the effectiveness of SMC across cycles, with the greatest benefit against malaria observed in the fourth and final cycle.[18] Understanding whether any indirect benefits SMC may have vary over the course of administration may help health programs optimize and integrate malaria interventions with broader infectious disease control efforts.

To explore this, we assessed the short-term effects of SMC on non-malarial outcomes in the weeks following treatment by analyzing routine surveillance data on diagnoses for children under five from primary healthcare facilities in Nouna, Burkina Faso. The objectives of this study were to 1) to determine whether and how non-malarial outcomes such as pneumonia, diarrhea, and acute malnutrition among children under five change following SMC administration; 2) compare overall antibiotic use at the population level in the weeks before and after SMC; and 3) assess whether changes, if any, in non-malarial outcomes following SMC, or indirect health benefits, vary by month of administration. We hypothesized that SMC could have indirect benefits and help lower non-malarial diagnoses and antibiotic prescription rates.

METHODS

Study Setting and Population

Health posts (n=51) in the rural northwestern district of Nouna in Burkina Faso, including both the Nouna Health and Demographic Surveillance Site (HDSS),[19] and the surrounding non-HDSS area[20] were included in the analysis. In Burkina Faso, children under five years of age receive free care at Centres de Santé et de Promotion Sociale (CSPS), which are government-run, nurse-led primary healthcare facilities offering basic preventive and treatment services, including antenatal care, postnatal care, and vaccinations for children. These centers are often the first line of care and provide referrals for more advanced cases. The median rate of healthcare visits in the villages served by these health posts in 2020 was 6.7 per 100 child-months with the most common reasons for visits being pneumonia (37.5%), malaria (25.1%)

and diarrhea (9.1%) infections.[21] In this analysis, we included data on diagnoses from 2020 and 2021 for children aged 1-59 months, as reported by the health posts in the study area.

The study was reviewed and approved by the Institutional Review Boards at the University of California, San Francisco and the Comité National d'Ethique pour la Recherche (National Ethics Committee of Burkina Faso) in Ouagadougou, Burkina Faso. Written informed consent was obtained from the caregiver of each participant.

Data Sources and Measures

We used three data sources for this analysis: 1) primary healthcare surveillance, 2) Community Health with Azithromycin Trial (CHAT) census data,[22] and 3) Burkina Faso's National Malaria Control Program (NMCP) data.

Primary Healthcare Surveillance: Passive surveillance was conducted at each CSPS (health post) in the study area. Each visit by a child under five was recorded, including the reason for the visit (e.g., fever, diarrhea, malnutrition, etc.), the village of residence, the child's age and sex, the diagnosis (e.g., malaria, pneumonia, etc.), the treatment provided (e.g., antibiotics, antimalarial agents, etc.), and the timing of the visit (e.g., first versus follow-up visit). Data were routinely collected by facilities on paper forms and were entered into an electronic database. Clinic visit counts for malaria, pneumonia, diarrhea, acute malnutrition and injury cases were used to determine diagnosis rates for their respective outcomes. Malaria was typically diagnosed using a rapid diagnostic test (RDT) and based on symptoms during stockouts.[23] Other diagnoses were determined based on the WHO community management of childhood illness algorithms, but the

accuracy of these diagnoses was not captured.[23] Acute malnutrition included both moderate and severe forms of acute malnutrition, which were combined due to the low number of cases. Injuries included various types, such as bites, burns, and wounds. Treatments prescribed by healthcare providers were grouped by type at entry, and the counts of antibiotics and antimalarials were analyzed. We restricted the surveillance data to villages in Nouna where the census was conducted and to the year 2020 and 2021, for which SMC administration data were obtained.

CHAT Trial Data: CHAT was a cluster RCT of 285 villages, designed to evaluate the efficacy of mass and targeted azithromycin strategies for reducing child mortality.[22] It was conducted for 3 years (2019-2023). The census performed for the CHAT trial was used to generate the population denominator for this study. CHAT's methods, including the setting and size of the study, have been described in detail previously.[20,22] In this trial, a census was conducted every 6 months documenting births, deaths, pregnancies, and migration. The 2020 and 2021 census data were used as denominator to derive the number of children in each health post, which was then used to calculate diagnoses rates.

NMCP Data: these data were used to obtain SMC administration dates and the corresponding epidemiological (epi) weeks for each round of treatment in 2020 and 2021. Epi week or a CDC week begins on a Sunday and ends on Saturday and is a standardized method of counting weeks to allow comparison of data year after year.[24] In 2020, SMC was administered on July 13- 16 (epi-week 29), August 12 - 15 (epi-week 33), September 11- 14 (epi-week 37) and October 10-13 (epi-week 41). In 2021, it was administered on July 6- 9 (epi-week 27), August 3 - 6 (epi-

week 31), August 31- September 2 (epi-week 35) and September 28- October 1 (epi-week 39). During each round, SMC was administered to the entire study area during the same epi week over a 3-4 day period.

Study Design and Statistical Analysis Methods

We used a one-group pretest-posttest design with multiple follow-up measurements,[25] that were then combined into a post-treatment period. We compared diagnoses and treatment prescription rates during the administration weeks with rates in the three weeks following administration. The three weeks were combined as post-intervention weeks since SMC is conducted every 4 weeks, and the effect has also been shown to last for only the few weeks after administration.[26,27] We used a conceptual framework (Figure 1) to show the relationships between variables and how SMC could be related to changes in other infections and antibiotic prescription rates. However, in the analyses, we only adjusted for the cycle (month of administration), a time-related factor, as some of these diagnoses are seasonal, with the month potentially influencing these rates. Since our assessment examines rates in the same population over time, it minimizes bias from time-invariant factors at the population level, which is one of the benefits of pre-post comparisons.[28] To evaluate potential influence of unmeasured confounding from other factors that may change over time, we used both negative and positive control outcomes.[29,30] Specifically, since we did not have a control group to account for changes in the absence of intervention, we used these control outcomes to help identify the presence of unmeasured confounding or other factors influencing outcomes. We used malaria as the positive control outcome, as it is the outcome for which SMC is intended and has been proven effective.[7,8] Injury rate was used as a negative control outcome as it would share the same potential sources of bias (given that these were

reported by the same facilities using the same process) and is an outcome that cannot be related to treatment (SMC).[29,30] Additionally, we examined how antimalarial prescription rates in 2020 and 2021 changed following SMC administration (which were expected to change with malaria), to serve as a positive control outcome for antibiotic prescription rates. We used methods similar to those used in the main analyses described below to examine changes in control outcomes following SMC administration, compared to administration weeks.

Statistical Analysis

Diagnoses for each year (2020 and 2021) were aggregated to counts by epi week for each of the 51 health posts (CSPS) in the study area. Person-weeks were calculated using the total number of children in each CSPS for each year based on the census data. The surveillance and census data at the health post level were joined by CSPS. For each CSPS, weekly diagnoses counts were included in a longitudinal format. We estimated incidence rates and 95% confidence intervals for several epi weeks before and after administration to describe diagnoses and treatment prescription trends during and after SMC distribution in 2020 and 2021.

For the pre-post comparison, the administration weeks (8 epi-weeks across the 51 health posts) served as reference against which the rates for the post administration period (the three weeks after (24 epi-weeks)) were compared. Approximately 10% of the epi weeks across all health posts did not have recorded counts of diagnoses and treatments. Given the limited amount of missing data, we conducted a complete-case analysis.

We used a Poisson regression model with person-weeks used as an offset and standard errors clustered by health post. We calculated marginal effects, expressed as incidence rate ratios (IRR) and incidence rate differences (IRD) across all health posts. To examine whether the effect of SMC varied across cycles, we included an interaction term between post-SMC period and SMC-cycle in the models. Results were considered statistically significant at an alpha level of $p < 0.05$. To adjust for multiple comparisons, we used the Romano-Wolf method with 1000 repetitions, which uses bootstrap resampling to control for the familywise error rate.[31]

Since the benefit of SMC for malaria has been shown to decline in the weeks following administration,[27,32] as a sensitivity analysis, we examined how rates of diagnoses and treatment prescriptions following SMC changed in the first, second and third week post administration. SAS 9.4 (SAS Institute, Cary, NC) was used for data cleaning and for generating the dataset for analysis. Stata version 14.2 (StataCorp, College Station, TX) was used for all other analyses.

RESULTS

The characteristics of the health posts included in the analysis are shown in Table 1. The average number of children 1 to 59 months of age across the 51 health post catchment areas was 2,246. The average age was 38.3 months (3.2 years), and approximately 50% of the children were male. Among diagnoses, malaria, pneumonia and diarrhea were most frequent with average rates of 6.0 (95% CI: 5.2–6.9), 4.3 (95% CI: 3.5–5.2), and 1.1 (95% CI: 0.8–1.4) cases per 1,000 person-weeks, respectively. Acute malnutrition and injury were rare with average rates of 0.12 (95% CI: 0.07 –0.18) and 0.16 (95% CI: 0.13–0.19) cases per 1,000 person-weeks. Anti-malarial prescription rates closely mirrored that of malaria with an average rate of 6.0 (95% CI: 5.1 – 6.9)

prescriptions per 1,000 person-weeks, while antibiotic prescription rates were slightly higher, at 6.9 (95% CI: 5.7 – 8.0) prescriptions per 1,000 person-weeks. By quarter of year, malaria and pneumonia diagnoses as well as treatment prescription rates were highest in the fourth quarter (Oct-Dec) while diarrhea rates were relatively higher in the first (Jan-Mar) and third (July-Sep) quarter of the year.

Changes in Diagnosis and Treatment following SMC

Figure 2 shows the rates of diagnoses and treatment prescriptions in 2020 and 2021 during the multiple weeks before and after SMC administration. Pneumonia diagnosis and antibiotic prescription rates showed some seasonality, with relatively higher rates toward the end of the year (after the administration of the fourth round of SMC). In contrast, acute malnutrition rates remained relatively constant in the weeks before, during, and after the SMC, while diarrhea rates were slightly higher around the weeks of SMC administration, with small fluctuations in trends (Figure 2).

For the control outcomes, malaria and antimalarial prescription rates showed high seasonality, with higher rates toward the end of the year, while injury rates remained relatively constant throughout the weeks (Supplementary Figure 1).

In the pre-post comparison, compared to the administration weeks, the rates of pneumonia, diarrhea, and acute malnutrition declined by 14% (95% CI: 7%–21%), 17% (95% CI: 7%–26%), and 29% (95% CI: 3%–49%), respectively (Table 2). Following SMC administration, antibiotic prescription rates declined by 12% (95% CI: 6%–17%).

For control outcomes, malaria rates (the positive control outcome) declined by 38% (95% CI: 31% to 44%), while injury rates (the negative control outcome) remained unaffected during the post-SMC administration period, as expected (Table 2). Antimalarial prescription rates (the positive control outcome) decreased by 37% (95%CI: 31% to 44%), mirroring changes in malaria rates.

The statistical significance of the findings remained unchanged after adjusting for multiple comparisons using Romano-Wolf P-values, with all outcomes except injury rates remaining statistically significant (Table 2).

Variation in Changes in Outcomes by Month of Administration

For the comparison of changes across SMC cycles, the change in rates following SMC administration varied by month (cycle) for pneumonia, diarrhea, and antibiotic prescriptions (P values for the global test of interaction= 0.000, 0.047, and 0.002, respectively; Figure 3, Supplementary Table 1). Among the four cycles, the change in rates following SMC administration was most pronounced in October for pneumonia and antibiotic prescriptions, and in August for diarrhea. No significant variation was observed for acute malnutrition.

For the control outcomes, the reduction in rates following SMC was also highest in October for both malaria incidence and antimalarial prescription rates, while no significant variation was observed for injury (Supplementary Figure 2).

Although the cycles with the highest reduction varied slightly by outcome, the last round (October) was the period during which the reductions following SMC were seen for most outcomes.

In the sensitivity analyses examining changes in diagnoses and prescription rates in each of the three weeks following administration, rates of diarrhea, acute malnutrition, and antibiotic use declined most in the second week post-administration, while pneumonia rates declined most in the third week post-administration (Supplementary table 2). Rates of the control outcomes, malaria and antimalarial prescription rates also declined most in the second week post-administration.

DISCUSSION

We evaluated the short-term changes in non-malarial outcomes following SMC administration under routine program conditions in Burkina Faso. We found modest declines in rates of pneumonia, diarrhea and acute malnutrition in the post-SMC period. Additionally, there was a small reduction in antibiotic prescription rates. The change in rates of pneumonia, diarrhea, acute malnutrition and antibiotic prescription following SMC varied by the month of administration, with its overall benefits appearing more pronounced in October (after the final round of administration).

The modest reductions in non-malarial outcomes following SMC may be partially explained by the antimicrobial properties of sulfadoxine-pyrimethamine (SP). In a previous study, SP had a clinically significant effect on concurrent infectious diseases in pregnant women and has demonstrated antibacterial effects in vitro, particularly against pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae*.[13] This suggest that sulfadoxine-pyrimethamine may have

an effect against some bacterial pathogens, potentially contributing directly to reductions in pneumonia and diarrhea.

SMC may also indirectly lower susceptibility to other infections by reducing malaria burden. Malaria control strategies may contribute to a reduction in other infections by reducing malaria-related immunosuppression.[33] Malaria can weaken the immune system because repeated or long-term infections can lead to a dysregulated immune response, making the body less effective at fighting off new or other types of infections.[33] Previous evidence shows that children with recent or acute malaria are at an increased risk of bacterial infections, with those experiencing both malaria and invasive bacterial infections facing a substantially higher risk of mortality.[34]

Malaria can also exacerbate malnutrition, which in turn increases risk of infections, illness and mortality in children.[35] A previous study showed that children who received chemoprophylaxis with chloroquine had fewer episodes of severe malnutrition compared to the control group.[36] Our findings also show modest declines in acute malnutrition following SMC. Therefore, the reduction in malaria burden following SMC could lead to improvements in immunocompetence, malnutrition and overall health, further reducing the risk of other infections or concurrent illnesses.

These indirect health benefits may contribute to reductions in mortality associated with SMC administration. Previous studies have found that SMC reduces all-cause hospitalization and death,[10,11] although it is not clear whether its effect on all-cause mortality is due primarily to its impact on severe malaria or if it also reduces mortality from other infections. Our findings

suggest that SMC's impact on non-malaria infections may contribute to its previously demonstrated effect on all-cause mortality,[11] as rates of the most common non-malaria illnesses appear to lower following SMC administration. Future studies should further investigate its role in reducing mortality from non-malarial causes to better understand its broader effects on all-cause mortality in children and its potential integration with other health interventions.

The reductions in antibiotic use following SMC administration may be due to a decrease in febrile illnesses related to malaria, as well as a reduction in non-malarial infections. A previous study assessing indication for antibiotic prescriptions in health facilities in rural Burkina Faso found that 5% of all antibiotic prescriptions were for malaria diagnoses.[23] Overall, 7.3% of malaria diagnoses received an antibiotic prescription while 97% of pneumonia diagnoses and 92% of dysentery diagnoses resulted in an antibiotic prescription.[23] While broad-spectrum antibiotic treatment is recommended for children with severe malaria,[37] some of the antibiotic prescriptions for malaria may be unnecessary or the result of misdiagnosis, as pneumonia and malaria can present with similar clinical signs, including fever.[23,38]

The lower rate of antibiotic prescriptions following SMC may therefore reflect a reduced need for antibiotics, indicating a decrease in the overall burden of infections. This, in turn, could help lower pressure on healthcare systems, particularly in facilities serving multiple communities. A study on the healthcare burden in Burkina Faso showed that infectious illnesses not only strain healthcare systems but also significantly impact households, forcing families to deplete savings, sell livestock or reduce consumption to afford treatment.[39] Therefore, reducing infections and

improving overall health could potentially help ease the burden on health systems and lower treatment costs for families.

Additionally, the reduction in antibiotic prescriptions following SMC could have implications for antibiotic resistance. Estimates of the global burden of bacterial antimicrobial resistance (AMR) indicate that AMR is a major issue in sub-Saharan Africa.[40,41] A study examining antibiotic prescription rates following universal distribution of long-lasting insecticidal nets (LLIN) and indoor residual spraying of insecticide (IRS) also observed a reduction in antibiotic use and highlighted the potential for effective malaria interventions to help mitigate antibiotic resistance resulting from routine use of antibiotics.[17] Therefore, there is potential for SMC administration to help reduce subsequent routine antibiotic use at the population level.

The relatively higher benefits of SMC observed in October for pneumonia and antibiotic prescriptions, may be partly due to the seasonality of infections. Rates for these outcomes were higher during the last round of SMC compared to prior rounds (Figure 2). Consequently, the observed benefit of SMC in October may appear more pronounced because the baseline (pre-administration) rates were higher, leading to a larger reduction in infection burden and subsequent treatment prescriptions. A previous study in Togo also found that the greatest reduction in malaria compared to the first round was during the peak periods, in the last round of SMC in October.[18] Similarly, diarrhea rates particularly in 2020, were slightly higher around the second round of SMC, during which the largest reduction in diarrhea rates following SMC was observed. Although antibiotic prescription rates were slightly higher, the trends mirrored those of

pneumonia diagnoses (Figure 2), as the majority of pediatric antibiotic prescriptions in this area of Burkina Faso are related to pneumonia.[23]

This study has some limitations. First, although we used negative and positive control outcomes, we cannot fully rule out unmeasured or residual confounding. SMC campaigns which include community sensitization[42] may temporarily strengthen health-seeking behaviors and increase adherence to preventive practices,[43] such as increased bednet use and improved sanitation and hygiene, which may affect the risk of other infections. Furthermore, these indirect benefits of SMC were assessed in a setting where mass distribution of azithromycin was provided to some communities as part of a cluster-randomized trial. Additionally, the years included in the analyses (2020 and 2021) were during the COVID-19 pandemic, which may have affected clinic visits or regular patterns of care-seeking. Therefore, these findings may have limited generalizability to other periods or areas. Additionally, it is not clear whether non-malarial outcomes, such as pneumonia, diarrhea, and acute malnutrition, occurred independently or if some were concurrent with malaria. This distinction may influence how SMC affects the rates of these other infections in the weeks following administration. Future studies should evaluate this aspect to better understand the full impact of SMC on co-infections and overall health outcomes. Second, potential misclassification in diagnosing cases could affect our weekly count estimates. Additionally, surveillance data may be subject to underreporting or inconsistencies in data collection. Despite these limitations, it offers large-scale, real-time insights that are helpful for monitoring disease trends in populations and evaluating the need for and impact of interventions.[44] Lastly, the variability in indirect health benefits over the months may partly reflect chance findings, as only two years of data were available for analysis. Any differences

observed could also be mixed with seasonal changes in these outcomes that could mask effects during earlier administrations or be partially due to the waning of the seasonal epidemic of infections (e.g., respiratory pathogens) that could appear as enhanced benefit during particular cycles. Therefore, these results should be interpreted cautiously and confirmed by a study with a longer time frame with multiple years of data, which could provide a more accurate assessment of differences in effects across months and cycles.

Conclusion

We found modest reductions in non-malarial infectious outcomes following SMC administration, with reductions more pronounced in the last month of administration. Our findings suggest that SMC may have additional benefits beyond malaria prevention, particularly in contributing to reductions in common infectious diseases among children and routine antibiotic use. These findings indicate that SMC could have a broader utility in improving health and potentially lowering pressure on healthcare systems although further investigation is needed to fully assess its broader effects on health outcomes.

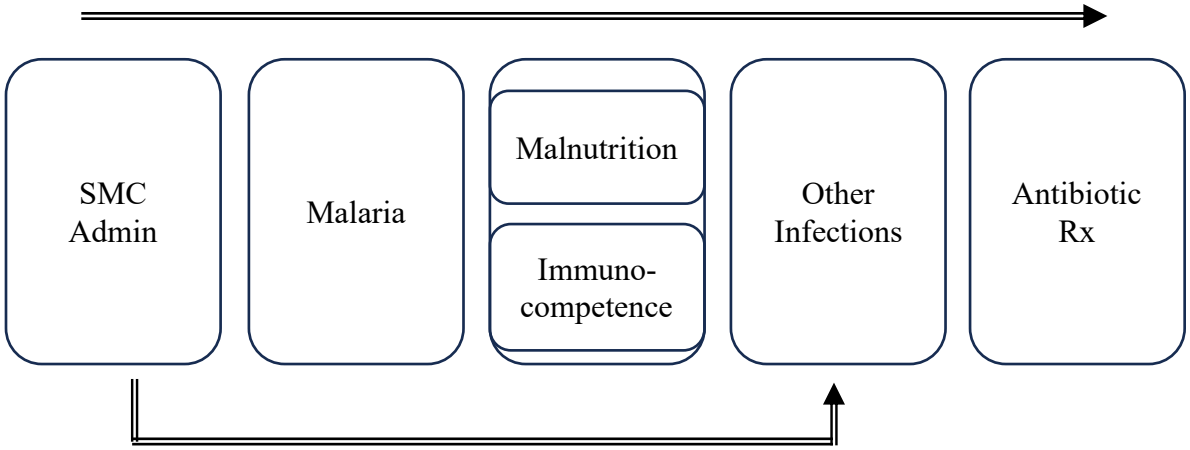


Figure 1.1- Conceptual Framework for SMC, Non-Malarial Outcomes, and Antibiotic Prescription Rates**.**
Note: This conceptual framework illustrates how SMC administration is hypothesized to affect non-malarial diagnoses and antibiotic prescriptions, though it does not depict every relationship between these factors/variables.

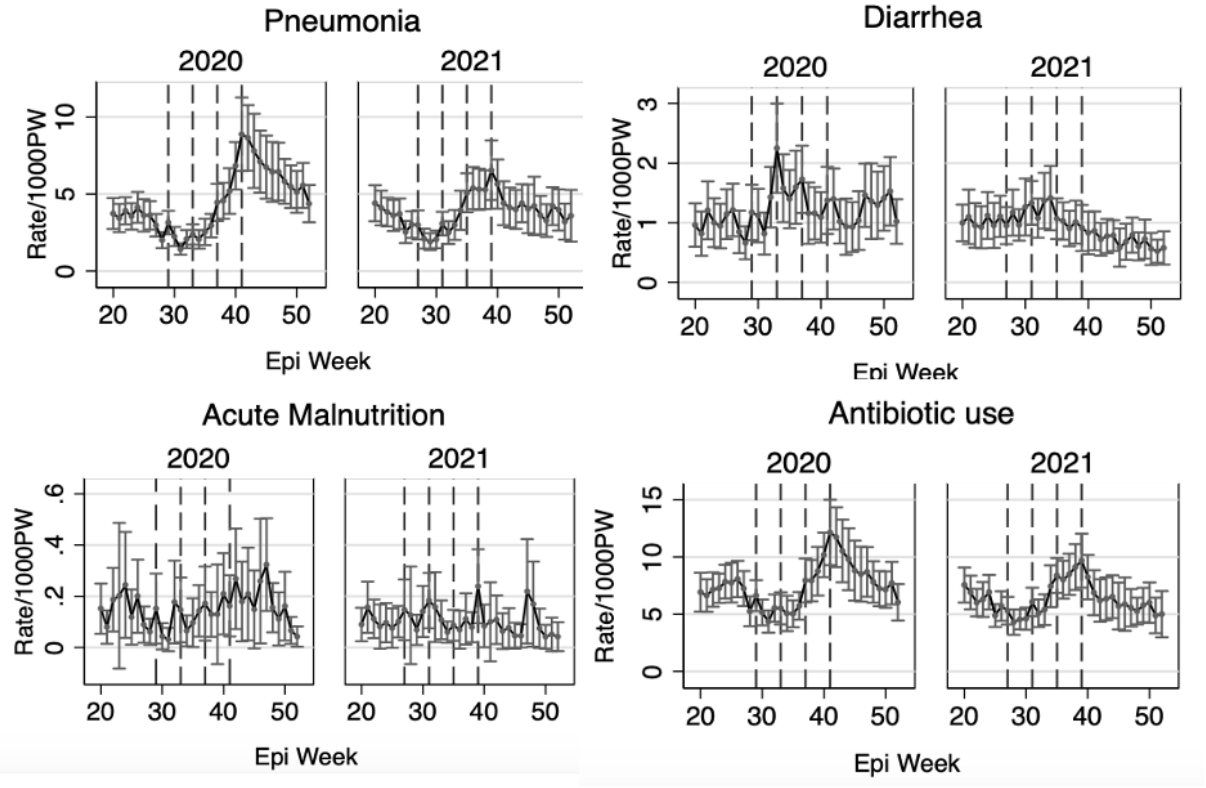


Figure 1.2- Diagnoses Rates and Treatment Prescription Rates in 2020 and 2021 in the Context of SMC Administration. Dashed vertical lines mark the four SMC administrations in each year of surveillance.

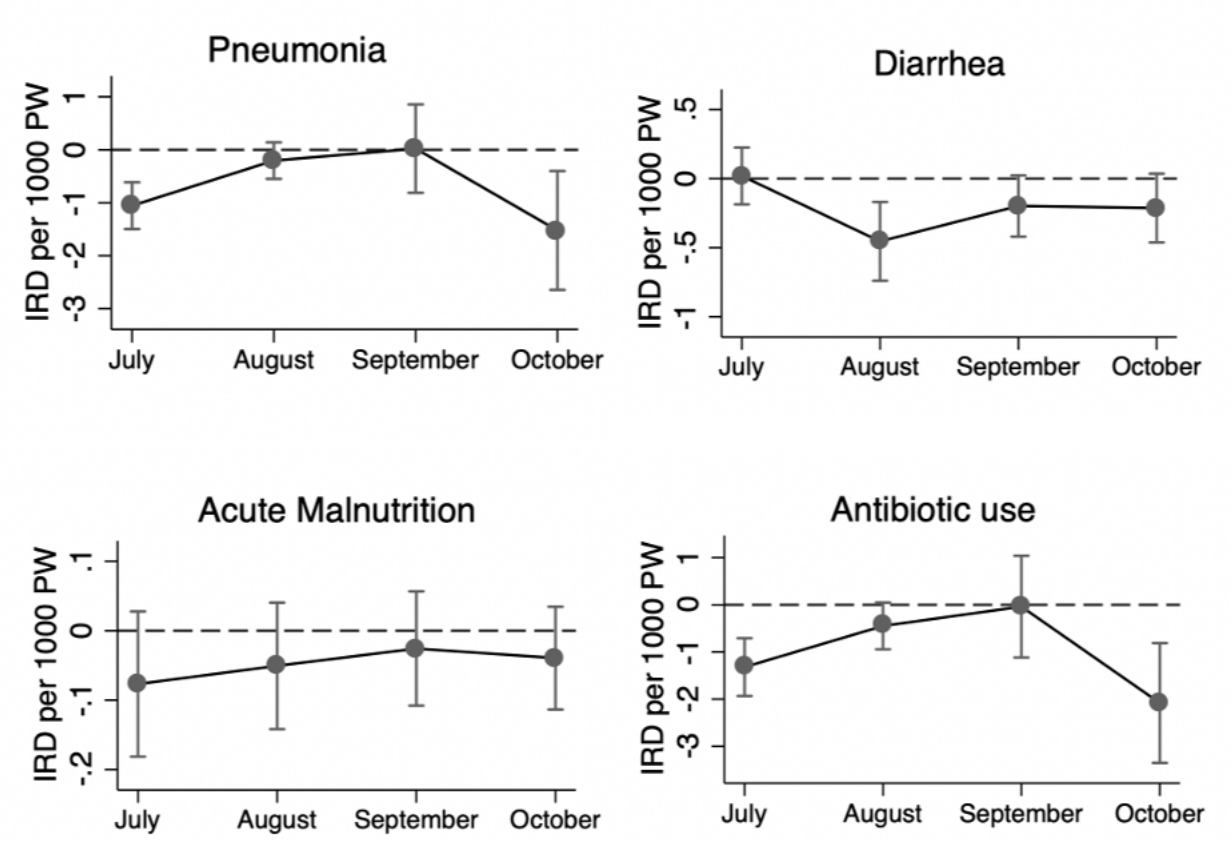
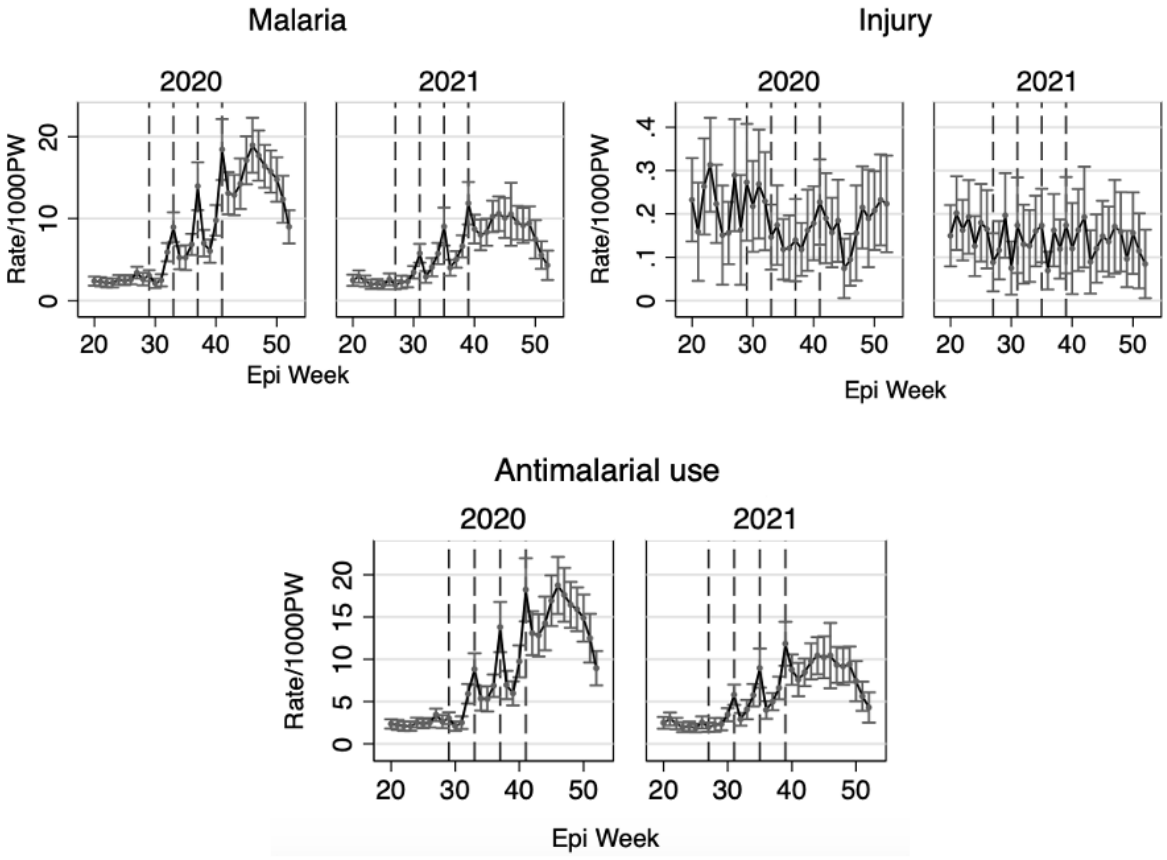
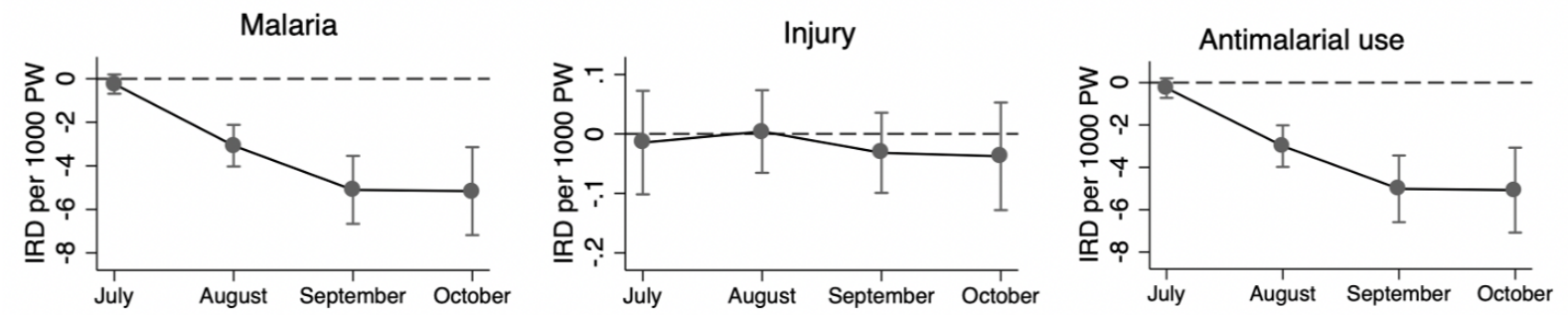


Figure 1.3- Difference in Incidence Rates of Diagnoses and Treatment During SMC Administration vs. Post-Administration Weeks, by Month of Administration
Note: P-values from the global test of interaction of SMC and month of administration were 0.000, 0.047, and 0.654 for pneumonia, diarrhea, and acute malnutrition, and 0.002 for antibiotic prescription rates.



Supplementary Figure 1.1- Diagnoses Rates and Treatment Prescription Rates for Control Outcomes in 2020 and 2021 in the Context of SMC Administration



Supplementary Figure 1.2- Difference in Incidence Rates of Diagnoses and Treatments During SMC Administration vs. Post-Administration Weeks, by Month of Administration for Control Outcomes

Note: P-values from the global test of interaction between SMC and month of administration were 0.000 and 0.861 for malaria
and injury, respectively, and 0.001 for antimalarial prescription rates

Table 1.1 Diagnoses and treatment rates in CSPS/Health Posts in Nouna, Burkina Faso included in the Analysis (n = 51), 2020 and 2021.

Rates per 1,000 person-week (95%CI)	Overall	Quarter 1 (Jan-Mar)	Quarter 2 (Apr-Jun)	Quarter 3 (July-Sept)	Quarter 4 (Oct-Dec)
Diagnoses					
Pneumonia	4.3 (3.5 to 5.2)	4.8 (3.9 to 5.7)	4.2 (3.4 to 5)	3.2 (2.7 to 3.8)	5.3 (4 to 6.5)
Diarrhea	1.1 (0.8 to 1.4)	1.2 (0.9 to 1.5)	1.0 (0.7 to 1.3)	1.2 (0.9 to 1.5)	0.95 (0.7 to 1.2)
Acute malnutrition	0.12 (0.1 to 0.2)	0.1 (0.06 to 0.15)	0.14 (0.1 to 0.2)	0.11 (0.1 to 0.2)	0.13 (0.1 to 0.2)
Malaria (positive control)	6.0 (5.2 to 6.9)	5.3 (4.4 to 6.1)	2.5 (2.1 to 3)	4.9 (4.1 to 5.7)	11.4 (9.8 to 13.1)
Injury (negative control)	0.16 (0.13 to 0.19)	0.15 (0.12 to 0.18)	0.18 (0.14 to 0.21)	0.16 (0.13 to 0.19)	0.16 (0.12 to 0.19)
Treatments					
Antibiotic prescription	6.9 (5.7 to 8.0)	6.7 (5.5 to 7.8)	7.1 (5.9 to 8.2)	6.3 (5.3 to 7.3)	7.4 (5.8 to 9.0)
Antimalarial prescription (positive control)	6.0 (5.1 to 6.9)	5.3 (4.5 to 6.1)	2.5 (2.0 to 2.9)	4.9 (4.1 to 5.8)	11.4 (9.7 to 13.1)

Table 1.2 Incidence rate, rate ratio and rate difference of outcomes on SMC administration weeks and the three weeks post administration.

Pre and Post SMC administration	Incidence rate per 1,000 person-week (95%CI)	Incidence rate ratio (95%CI)	Incidence Rate Difference per 1,000 person-week (95%CI)	P value	Romano-wolf adjusted p value
Pneumonia					
Admin weeks	4.7 (3.8 to 5.6)	Ref	Ref	-	-
Post admin weeks	4.1 (3.3 to 4.8)	0.86 (0.79 to 0.93)	-0.7 (-1.0 to -0.3)	0.000	0.003
Diarrhea					
Admin weeks	1.4 (1.0 to 1.7)	Ref	Ref		
Post admin weeks	1.1 (0.8 to 1.4)	0.83 (0.74 to 0.93)	-0.2 (-0.4 to -0.1)	0.002	0.003
Acute Malnutrition					
Admin weeks	0.17 (0.09 to 0.24)	Ref	Ref		
Post admin weeks	0.12 (0.05 to 0.18)	0.71 (0.51 to 0.97)	-0.05 (-0.09 to 0.0)	0.034	0.040
Control outcomes					
Malaria (Positive control)					
Admin weeks	9.8 (8.1 to 11.5)	Ref	Ref	-	-
Post admin weeks	6.1 (5.1 to 7)	0.62 (0.56 to 0.69)	-3.7 (-4.8 to -2.6)	0.000	0.003
Injury (Negative control)					
Admin weeks	0.17 (0.12 to 0.23)	Ref	Ref	-	-
Post admin weeks	0.15 (0.12 to 0.19)	0.89 (0.67 to 1.19)	-0.02 (-0.07 to 0.03)	0.422	0.232
Treatments					
Antibiotic use					
Admin weeks	7.9 (6.6 to 9.2)	Ref	Ref	-	-
Post admin weeks	6.9 (5.8 to 8.1)	0.88 (0.83 to 0.94)	-0.9 (-1.4 to -0.40)	0.000	0.003
Antimalarial use (Positive control)					
Admin weeks	9.7 (8 to 11.4)	Ref	Ref	-	-

Pre and Post SMC administration	Incidence rate per 1,000 person-week (95%CI)	Incidence rate ratio (95%CI)	Incidence Rate Difference per 1,000 person-week (95%CI)	P value	Romano-wolf adjusted p value
Post admin weeks	6.1 (5.1 to 7.1)	0.63 (0.56 to 0.69)	-3.6 (-4.7 to -2.5)	0.000	0.003

Supplementary Table 1.1 Changes in Diagnoses and Treatment rates following SMC by Month of SMC Administration and Overall (IRR, 95% CI).

Outcome	Overall	July	August	September	October	P value for global test of interaction
Pneumonia	0.86 (0.79 to 0.93)	0.66 (0.57 to 0.74)	0.92 (0.80 to 1.05)	1.0 (0.83 to 1.18)	0.81 (0.69 to 0.92)	0.000
Diarrhea	0.83 (0.74 to 0.93)	1.02 (0.82 to 1.22)	0.74 (0.61 to 0.88)	0.85 (0.70 to 1.0)	0.82 (0.67 to 0.97)	0.047
Acute malnutrition	0.71 (0.51 to 0.97)	0.49 (0.03 to 0.94)	0.69 (0.23 to 1.14)	0.81 (0.29 to 1.34)	0.80 (0.47 to 1.13)	0.654
Control outcomes						
Malaria (positive control)	0.62 (0.56 to 0.69)	0.90 (0.73 to 1.07)	0.59 (0.52 to 0.67)	0.54 (0.47 to 0.61)	0.67 (0.58 to 0.75)	0.000
Injury (negative control)	0.89 (0.67 to 1.19)	0.92 (0.46 to 1.37)	1.03 (0.57 to 1.48)	0.80 (0.44 to 1.16)	0.82 (0.43 to 1.20)	0.861
Treatments						
Antibiotic prescription	0.88 (0.83 to 0.94)	0.78 (0.70 to 0.86)	0.92 (0.84 to 1.0)	1.0 (0.86 to 1.13)	0.81 (0.72 to 0.91)	0.002
Antimalarial prescription (positive control)	0.63 (0.56 to 0.69)	0.90 (0.72 to 1.07)	0.60 (0.53 to 0.68)	0.54 (0.47 to 0.61)	0.67 (0.58 to 0.76)	0.000

Chapter 2: The role of Seasonal Malaria Chemoprevention in the effect of Azithromycin on Child Mortality: A Secondary Analysis of the CHAT Cluster Randomized Clinical Trial

INTRODUCTION

Many regions of sub-Saharan Africa have high child mortality rates.[45] Infectious diseases, in particular acute diarrheal and respiratory infections, and malaria, are the leading causes of illness and death in children in low- and middle-income countries.[1] Antimicrobial-based strategies such as mass drug administration of azithromycin (MDA AZ) and seasonal malaria chemoprevention (SMC) have been used to reduce child mortality in these settings.[11,46] Azithromycin (AZ) has been shown to reduce all-cause mortality as well as infectious morbidity due to diarrhea, pneumonia, and malaria.[46-48] The MORDOR study which randomized communities in Malawi, Niger, and Tanzania to four twice-yearly mass distributions of either oral AZ or placebo found that childhood mortality was lower in communities randomized to AZ, with the largest effect (a relative reduction in all-cause mortality of 18.1%) seen in Niger, where SMC was not being distributed.[46] The Community Health with Azithromycin Trial (CHAT) completed in 2023 and the AVENIR (Azithromycine pour la Vie des Enfants au Niger: Implementation et Recherche) trial in Niger also demonstrated that mass distribution of AZ remains effective at reducing child mortality in a setting receiving SMC.[22,49] The finding of these trials was consistent with MORDOR-Niger, showing a reduction in all-cause mortality overall in communities randomized to AZ compared to placebo.[22]

SMC involves monthly administration of a 3-day regimen of sulfadoxine-pyrimethamine and amodiaquine (SP-AQ) during the malaria season in regions with highly seasonal transmission, where there is no evidence of resistance to these drugs.[2] SMC treats current infection and

provides protection against future infections for up to 3-4 weeks.[50] As of 2020, following the WHO policy recommendation, 13 countries in Africa have adopted SMC with different scales of implementation.[3,51] Large-scale evaluations have found SMC effective at reducing malaria infection and all-cause mortality.[9,10] Despite the adoption of SMC, it is not clear how the antimalarial, antibacterial, anti-inflammatory and overall benefits of SP in SMC might affect the benefit of AZ for child mortality.[52] 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 chloroquinine[53,54] and SP alone.[55] 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.[12] 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.[56]

The potential heterogeneity in the effect of AZ calls for further studies before its widespread use can be recommended.[57] Studies are needed to refine key aspects of implementation, such as the optimal dose, frequency, timing,[58] and the populations to target or prioritize.[59,60] 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[22] 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.

METHODS

Study Design, Setting, Population and Data Collection

This was a secondary analysis of the CHAT trial and additionally included SMC data from NMCP. The methods and primary results have been reported previously.[20,22] In brief, CHAT was a cluster-randomized placebo-controlled trial designed to evaluate the efficacy of mass AZ strategies.[20] The trial enrolled children aged 1-59 months in Nouna District of Burkina Faso and covered both the Nouna Health and Demographic Surveillance Site (one third of Nouna District),[19] as well as the non-HDSS area in Nouna.[20] A map of the study area is included in the primary analysis of the trial.[22] Communities randomized to intervention received biannual mass oral AZ and communities randomized to placebo received biannual mass oral placebo for 3 years (2019-2023). 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.

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 1). Trial data were aggregated by cluster and these phases. 1,086 deaths over 119,139 person-years were observed.[22]

Four monthly cycles of SMC were administered per local standard-of-care to children aged 3 to 59 months during the malaria transmission season from July through October each year. SMC was administered to the study area over a 3-4 day period.[61] NMCP records were reviewed to obtain SMC coverage data, including number of children under 5 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 and the Comité National d'Ethique pour la Recherche (National Ethics Committee of Burkina Faso) in Ouagadougou, Burkina Faso.

Statistical Analysis

The primary outcome for these analyses was all-cause mortality. 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.[22] 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, [62] This method accounts for clustering by using a

randomization -unit level summary statistic.[62] 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 acyclic graph[63] shown in Figure 2 to visualize the relationship between SMC and effect of AZ on under 5 mortality examined in the interaction analyses.

For the analysis by season, the six phases were categorized as non-SMC (January-June) versus the SMC (July-December) seasons of the year, based on the timing of treatment and census. A Poisson regression model was used to analyze data at the cluster phase level with person-years included as an offset and robust standard errors clustered at the cluster level to account for repeating phases. This was used to estimate the mortality rate in AZ and placebo groups, their rate ratio by season, and their interaction on the multiplicative scale. The margins command in Stata was used to estimate incidence rate differences (IRDs) with 95% CIs using the delta method. Number needed to treat to avert one death was calculated using the rate differences.

Relative excess risk due to interaction (RERI) with bootstrap 95% confidence limits and 1000 repetitions was used to assess interaction on the additive scale.

For the analysis by coverage, we updated the SMC coverage for 2020 and 2021 originally reported by NMCP using 2006 denominators (estimates of total number of children), by the corresponding census denominators from CHAT to obtain more accurate coverage estimates for each CSPS. The SMC coverage for each cycle in each year for each CSPS was calculated as the number of children treated (obtained from NMCP) divided by the total number of children in the CSPS catchment area.

SMC coverage percentages for each cluster and each year (2019, 2020, 2021) were linked to the trial data by cluster. Since SMC coverage estimates for 2019 were not available and given the high correlation (>90%) in CSPS level coverage between 2020 and 2021, coverage estimates for 2020 were used for both 2019 and 2020. For the coverage estimate for each year, we used the average coverage level across the 4 cycles of SMC distributed during that year. Clusters with coverage estimates above 100% (~8%) were capped to 100%. SMC coverage was scaled for each unit increase to represent 10% increase in coverage. Given the short duration of protection of SMC,[64] 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.[65] 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,[63] as both may influence the level of SMC coverage and affect the benefit of AZ for mortality.[46,56,66]

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

Characteristics of communities included in the trial are presented in Table 1. Over 30% of the children in each arm were aged 12-23 months. The age and sex distributions were similar across arms. The SMC coverage estimates that were updated by recent denominators showed variability, with an overall average coverage of 79% (SD 0.59). The average SMC coverage across rounds was slightly higher in treatment versus placebo arm, 83% versus 74%, respectively. In both arms, SMC coverage level was slightly higher in the 4th cycle compared to other cycles.

For both arms, mortality rate was higher in the SMC seasons: 7.9 per 1000 person-years, 95% CI (6.9 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 second half of the year (Figure 3a) In both SMC and non-SMC seasons, mortality rate was higher in placebo arm (Table 2). The interaction between AZ and SMC season was not statistically significant on either the multiplicative or additive scale. The effect of AZ compared to placebo was 0.77, 95%CI (0.6 to 0.98) in SMC season vs 0.89 (0.68 to 1.15) in non-SMC season (Figure 3b).

Table 3 shows the mortality rates by arm and the effect of AZ at different SMC coverage levels. The interaction between AZ and SMC coverage (both on continuous scale and dichotomous at 80% coverage threshold) was not statistically significant on either the multiplicative or additive scale (P>0.05)., However, the benefit of AZ appeared to slightly lower with increasing SMC coverage (Figure 4b). The effect of AZ compared to placebo in clusters with <80% SMC

coverage was 0.73 95%CI (0.56 to 0.96) and in clusters with ≥80% SMC coverage, it was 1.0 95%CI (0.59 to 1.69).

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 5b).

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 ≥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.[67] Since AZ may provide short-term infection prevention and treatment by clearing infections,[47,68] 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.[68] Although other infectious diseases treated by AZ, such as pneumonia and diarrhea, may follow different seasonal patterns than malaria,[69,70] 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.[27] 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,[57,58] 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.

Although the interaction was not statistically significant, the slightly higher effect of AZ in clusters with lower SMC coverage may suggest that the benefit of AZ may be greater in areas with gaps in SMC coverage. A likely contributing factor could be that SMC coverage may be related to engagement with the healthcare system, with low-coverage areas likely facing obstacles to care.[66] AZ MDA has been found more effective for children who often have less access to preventive and curative care. [56] Therefore, the lower SMC coverage may reflect broader gaps in community and facility resources related to SMC administration. Previous studies have identified several barriers to SMC uptake, including local shortages, challenges reaching mobile populations and underserved areas, and issues related to community distributors' working conditions, such as workload and incentives.[66,71] Therefore regions with lower SMC coverage may also have other gaps in routine child health interventions and care, where AZ may be particularly helpful. Although it did not reach statistical significance, the higher benefit of AZ

in low SMC communities suggests that prioritizing AZ treatment in areas with inadequate SMC coverage might be beneficial.

The slightly reduced benefit of AZ in areas with high SMC coverage may also partly be due to reduction in malaria disease burden following SMC administration.[61] In regions with lower SMC coverage, important gaps in malaria prevention remain,[65] making AZ MDA likely beneficial as it may have some efficacy against both malaria and bacterial infections. Although the effect of AZ on malaria infections has been inconsistent,[72] analysis of causes of death from the MORDOR trial found that malaria was one of the primary causes of mortality against which AZ was beneficial.[48] With effective malaria interventions like SMC, the impact of AZ may be less apparent.[73] This is also consistent with the lack of observed benefit of AZ for mortality in the household randomized trial, where all enrolled children received SMC.[12]

This study has some limitations. First, it may have been underpowered to a detect significant interaction 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.[74] 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.

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.

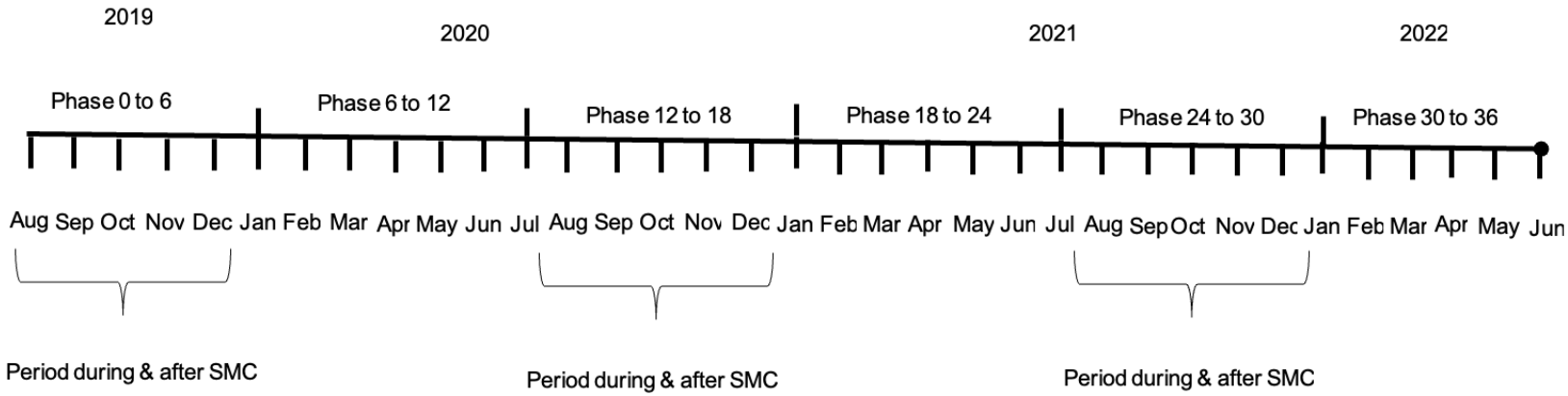


Figure 2.1- Timeline of census and AZ treatment phases in CHAT trial and SMC seasons

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

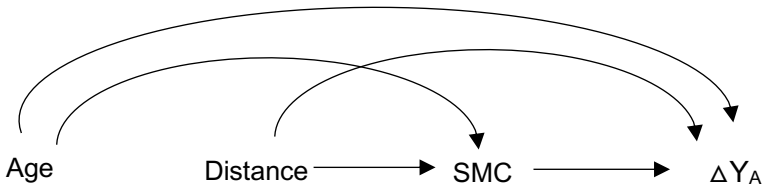


Figure 2.2- Interaction Directed Acyclic Graphs Illustrating the Interaction Between Mass AZ Treatment and SMC

Note: Age-age of children, Distance-distance to health facility, SMC-SMC coverage level, Y-under-five mortality, A- AZ treatment, ΔY_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

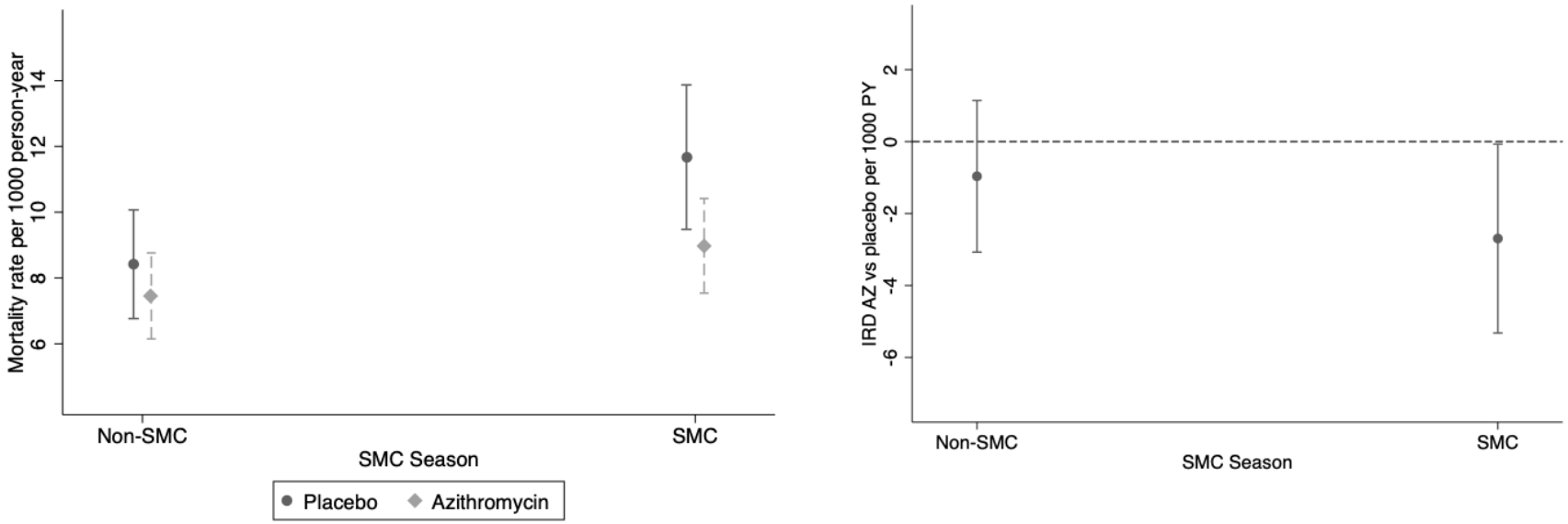


Figure 2.3- a) Mortality rate by treatment and SMC season and b) Mortality rate difference (AZ vs Placebo) by SMC season

Note: IRD- Incidence rate difference

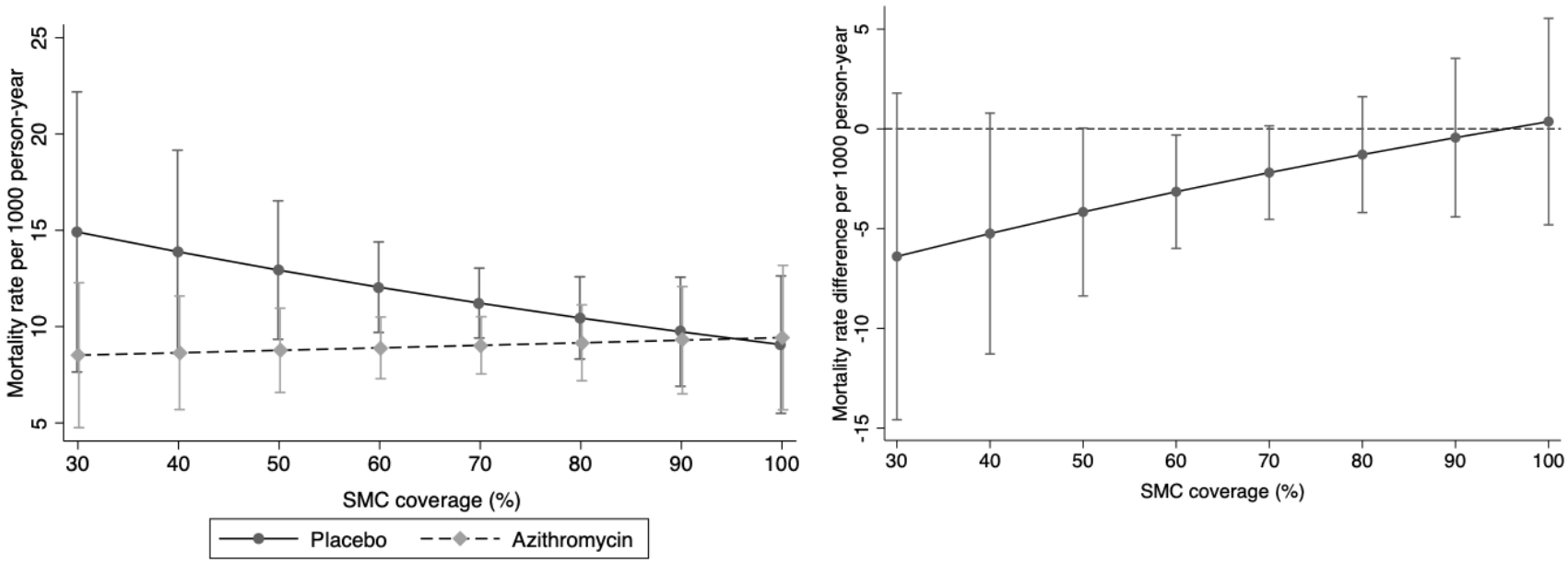


Figure 2.4- a) Mortality rate by treatment arm at each level of SMC coverage and b) difference in mortality rate (AZ vs Placebo) by SMC coverage

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

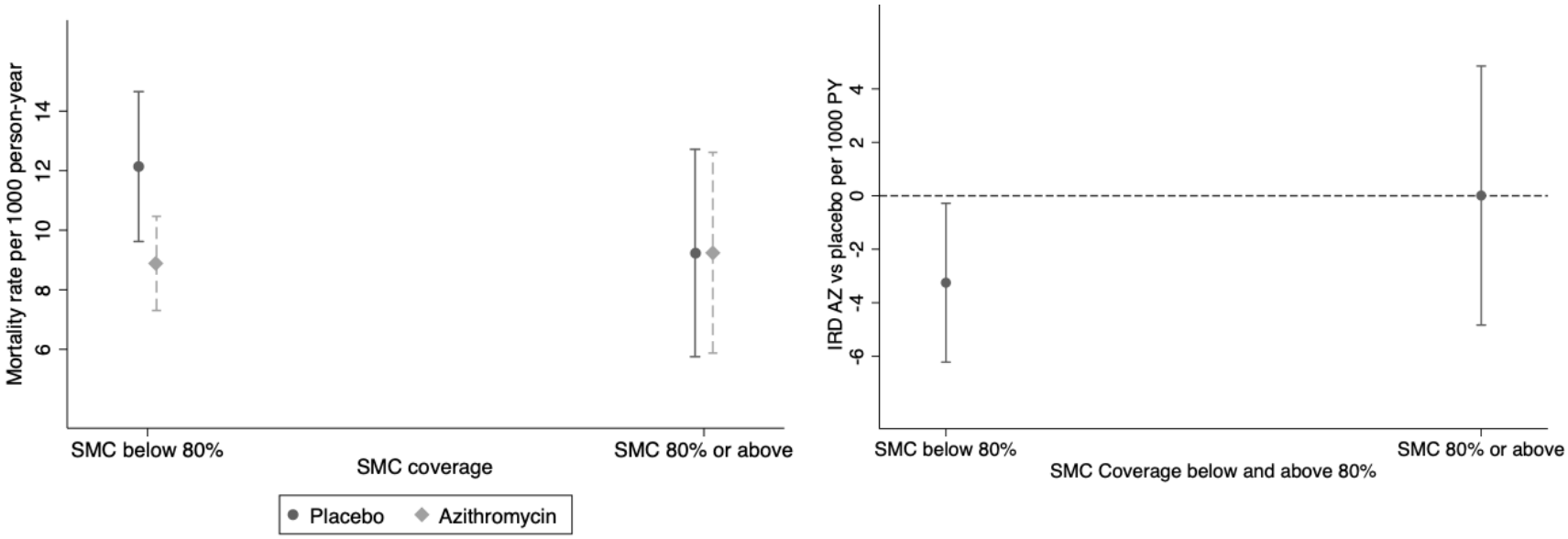
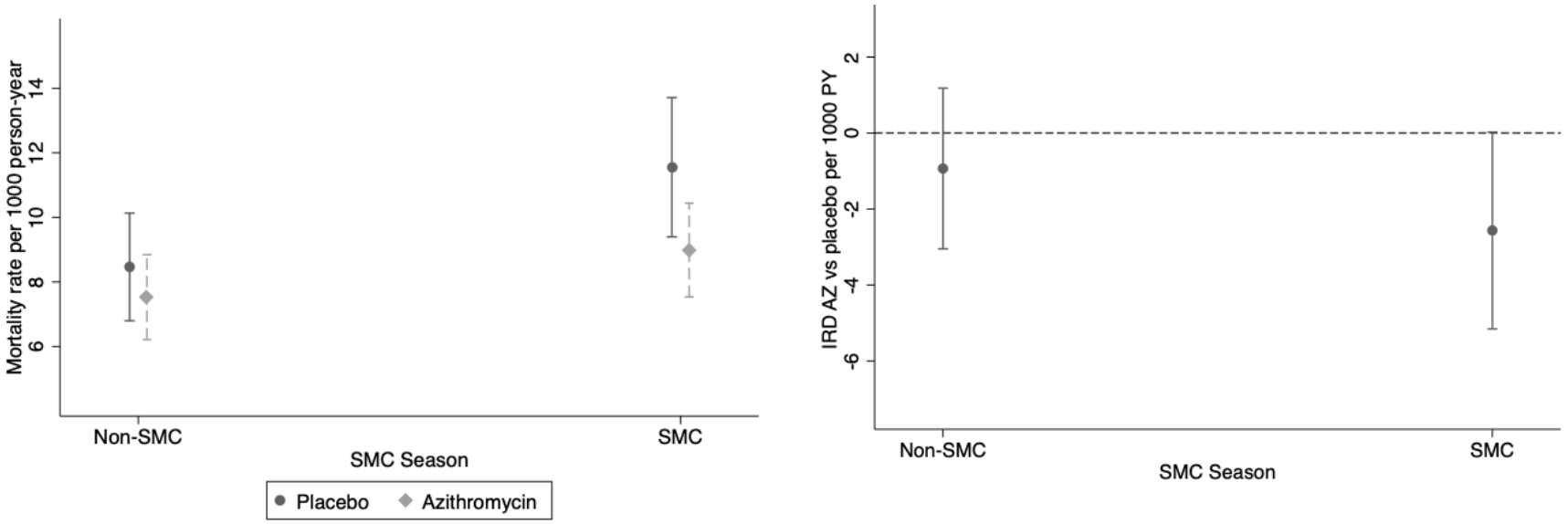
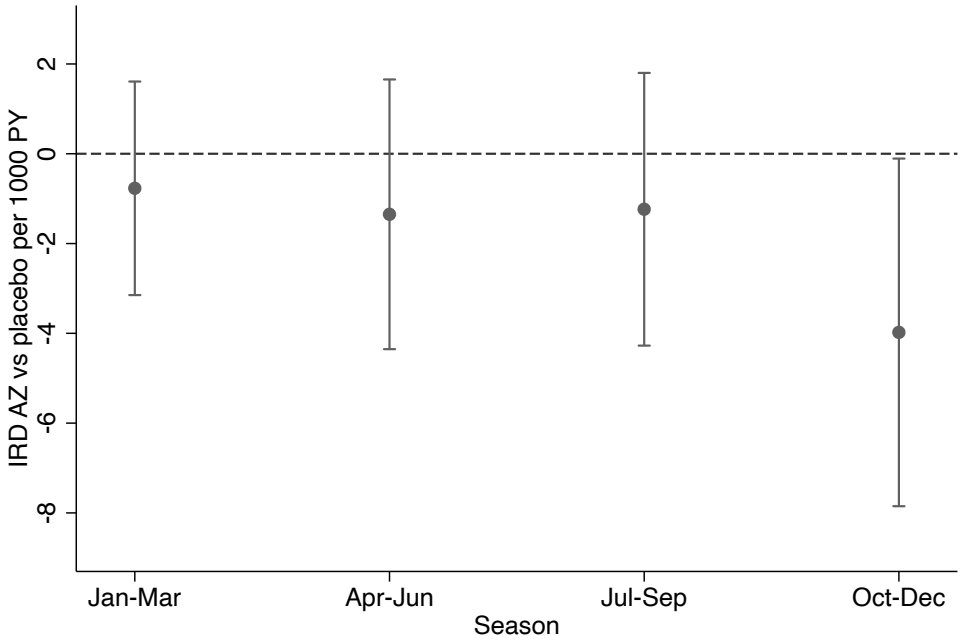


Figure 2.5- a) Mortality rate by treatment and SMC coverage and b) Mortality rate difference (AZ vs placebo) by SMC coverage threshold of 80%

Note: IRD- Incidence rate difference

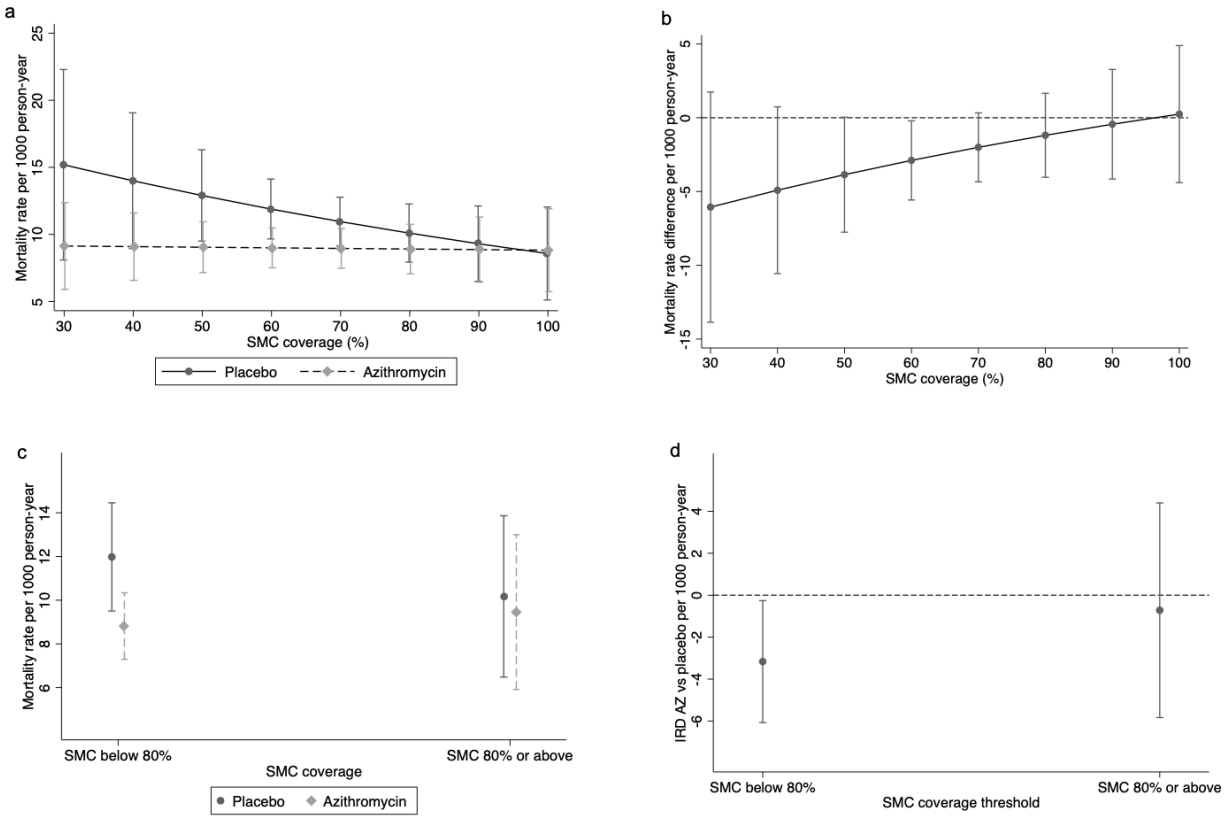


Supplementary Figure 2.1- a) Mortality rate by treatment and SMC season and b) Mortality rate difference (AZ vs Placebo) by season adjusting for SMC coverage level



Supplementary Figure 2.2- 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 2.3- 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

Table 2.1 Characteristics of communities in CHAT trial.

	Azithromycin group (152 communities)	**Placebo group (145 communities)**
Number of Children (mean number, SD)	265 (148)	280 (149)
	Age groups (mean %, SD)	
1–11 months	19.5% (5.0)	18.7% (4.0)
12–23 months	33.0% (5.4)	32.7% (4.8)
24–35 months	16.4% (3.1)	16.8% (3.4)
36–47 months	15.8% (4.3)	15.5% (3.1)
48–59 months	15.4% (3.8)	16.3% (4.3)
Male sex (mean %, SD)	50.2% (4.2)	50% (4.0)
SMC coverage (mean %, SD)	83% (0.67)	74% (0.49)
Cycle 1 (July)	81% (0.65)	72% (0.47)
Cycle 2 (August)	82% (0.66)	73% (0.5)
Cycle 3 (September)	84% (0.67)	75% (0.5)
Cycle 4 (October)	86% (0.69)	76% (0.51)

Table 2.2 Effect of Azithromycin vs Placebo Distribution on Child Mortality by overall and by SMC season.

	Overall (Jan-Dec)	**Non-SMC (Jan-Jun)**	**During/post-SMC (Jul-Dec)**
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)	9.0 (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 2.3 Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC coverage level

SMC coverage	Mortality rate per 1000 PY (all clusters)	Mortality rate per 1000 PY in AZ	Mortality rate per 1000 PY in Placebo	IRR (AZ vs placebo)	IRD (AZ vs Placebo) per 1000 PY	Number needed to treat
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 (9.0 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)	9.0 (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 2.4 Effect of Azithromycin vs Placebo Distribution on Child Mortality by SMC coverage threshold of 80%

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.

	Across all clusters (N=285)	**Coverage below 80% (N=222)**	**Coverage 80% or above (N=86)**
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		

Chapter 3: Exploring Heterogeneity in Treatment Effects: The Impact and Interaction of Asset-Based Wealth and Mass Azithromycin Distribution on Child Mortality

INTRODUCTION

The Sustainable Development Goals aim to end preventable deaths of children under 5 by 2030.[75] Although significant progress has been made in reducing global child mortality, improving child survival remains an international priority.[76] As of 2022, the global under-five mortality rate was 37 deaths per 1000 live births, a significant decline from the 93 deaths per 1,000 live births in 1990.[76] However, there is considerable variability in mortality rates and improvements across regions,[45] with substantial inequalities observed in sub-Saharan Africa.[77] For instance, in 2019, two regions accounted for the majority of under-5 deaths: sub-Saharan Africa with 55% (53–57) of global under-5 deaths, and south Asia with 26% (26–27) of the total.[78] Considering such disparities, assessing local and regional trends can help identify areas for improvement despite overall progress, and help prioritize child survival interventions for those who need them most.[45] Understanding context-specific differences is essential for evaluating health equity, informing policy decisions, and effectively addressing local health disparities and their specific challenges.

The leading causes of child mortality, particularly in sub-Saharan Africa, include infections such as malaria, diarrhea, and pneumonia.[79] Addressing these issues involve strengthening health systems, implementing nutritional interventions, improving water, sanitation, and hygiene services, and preventing infections.[80] Antibiotic-based strategies, such as mass distribution of azithromycin (AZ), have also been used to reduce child mortality in these settings. Previous randomized controlled trials, such as the MORDOR study, conducted in Malawi, Niger, and

Tanzania, as well as the recent community-randomized CHAT trial in Burkina Faso, and the AVENIR trial in Niger have shown that childhood mortality was lower in communities that received mass distributions of oral AZ.[22,46,49]

Previous evidence suggests that AZ is not only effective in reducing child mortality but can also help buffer against disparities in child mortality by potentially addressing gaps in treatment.[56] A secondary analysis of the MORDOR trial found that the effect of MDA with AZ was larger in communities farther from clinics.[56] Since distance from health facilities is a barrier to accessing routine and life-saving interventions,[21,81] hard-to-reach and rural communities, which often lack resources, [21,82] may benefit more from mass AZ treatment. Another key determinant of access to treatment and care is socioeconomic status (SES).[83] Socioeconomic factors are known to be important determinants of child mortality, by which disparities in health outcomes have been previously noted.[77,84]Individuals in poorer communities often have less access to quality care, services and information,[83] and may therefore also benefit more from mass AZ treatment. However, despite its suggested effect in addressing gaps in treatment, there is no clear evidence whether MDA of AZ interacts with wealth status to help reduce wealth-related inequalities in child mortality.

Additionally, poorer communities may have greater exposure to infectious diseases due to crowding, poorer housing structures, and limited access to clean water and sanitation.[85] Consequently, the poorest communities may experience a higher infection burden and benefit more (have more harm averted) from treatment.[86] For instance, previous research shows that

reducing childhood infections, particularly in families with lower SES, may more substantially reduce the burden of cardiovascular disease in adults compared to families with higher SES.[87] Therefore, examining whether the effect of AZ varies by wealth level may help determine whether AZ MDA is more beneficial for households and communities with lower SES, which typically have reduced access to resources, healthcare, and antibiotics, and aid in resource prioritization and the development of targeted approaches.

Evaluating these effects at both the household and cluster/community levels may provide a comprehensive understanding of how MDA interventions could affect wealth-related inequalities. Since socioeconomic determinants operate at multiple levels such as individual, household, and community,[88] this approach may provide insights into effects within individual households, as well as broader patterns and resource gaps at the community level, enabling more targeted strategies.

Using data from a cluster randomized trial of 278 villages in Burkina Faso[22] (CHAT) and data on household characteristics, we examined whether there is an asset-based wealth gradient in under-five mortality in these communities and whether there is an interaction between mass AZ distribution and wealth status on child mortality.

METHODS

Study Design, Setting, and Population

This was a secondary analysis that utilized data from the CHAT trial and a pre-census survey data collected prior to the first CHAT census, before the trial began. The CHAT trial was a

cluster-randomized study aimed at assessing the effectiveness of mass AZ distribution for prevention of mortality in children aged 1-59 months.[20] It involved children under-five in the Nouna District of Burkina Faso, in both the Nouna Health and Demographic Surveillance Site (HDSS) and the surrounding non-HDSS area.[20] Under-five mortality in Burkina Faso declined substantially,[89] from 184 per 1,000 live births in 2003 to 48 per 1,000 live births in 2021, largely due to improvements in prevention and care.[75] Malaria, pneumonia, and diarrhea were the leading causes of child death.[90] A previous study found that the median rate of visits to government-run primary healthcare facilities for children under five in the villages was 6.7 per 100 child-months, with the majority due to pneumonia (37.5%), malaria (25.1%), and diarrhea (9.1%).[21] The median distance from healthcare facilities for a child was approximately 5 km.[21] Over 40% of the population of Burkina Faso lives below the poverty line,[91] with poverty concentrated in rural areas.[92]

Data Collection

In the CHAT trial, mass drug administration (MDA) of AZ or placebo was assigned at the cluster, specifically at the community level. Eligible children in treatment clusters received twice yearly doses of oral AZ, while those in placebo clusters received twice yearly doses of oral placebo over a period of 3 years (2019-2023; 6 treatment distributions in total).[20] A census was conducted every 6 months to record births, deaths, pregnancies, and migrations. The study employed an open cohort design, with varying person-time contributions from enrolled children as children could age in or out of the cohort or could move in or away or die. Vital status updates for each child, along with their household and community identifiers, were recorded during each 6-month census phase. Throughout the study, six rounds of census and

treatment were performed, and a total of 1,086 deaths were observed across 119,139 person-years.[22] Detailed methods of the CHAT trial have been described previously.[20,22] The CHAT trial was reviewed and approved by the Institutional Review Boards at the University of California, San Francisco, and the Comité National d'Ethique pour la Recherche in Ouagadougou, Burkina Faso. Written informed consent was obtained from the caregiver of each enrolled child.

Before the study began, the study team conducted a pre-census survey in study communities, collecting data on household-level wealth indicators in regions outside of the HDSS. These data included habitat type (e.g.simple detached house, villa, multiple dwelling building, apartment building), ownership status (e.g., owner, tenant, housed by employer/parents/friends, other), and housing structure, such as the construction material used for walls (hard, semi-hard, banco, straw), floors (tiles, cement, clay, sand), and roofs (concrete, tiles, sheets, straw/leaf, crammed earth). It also included the main source of cooking energy (electricity, gas, coal/wood, petroleum stove) and access to clean water and toilets (e.g., type of toilet such as flush toilet, latrines, unconfined latrines, no toilet) and the main source of drinking water (faucet, well, drilling, river). Data on asset ownership was also collected, including items such as radio, television, video/DVD player, telephone, freezer, gas cooker, generator, computer, car, motor, and tricycle. The pre-census data covered 15,291 households in 170 clusters involved in the CHAT trial, while 12,872 households in CHAT were not included in the pre-census.

Statistical Analysis Methods

We conducted three steps: 1) generated the wealth index score for each household, 2) assessed how child mortality rates change with the asset-based wealth index, and 3) evaluated the interaction between the azithromycin MDA intervention and wealth on all-cause mortality. The latter two analyses were conducted at both the household and cluster levels. Descriptive analyses were used to describe the characteristics of households from the pre-census, by treatment arm. While the overall sample size was based on childhood mortality for the AZ versus placebo comparison in CHAT trial,[22] only households present in both the pre-census and the trial were included in the household-level analyses, while clusters with at least one household in the pre-census were included in the cluster level analyses.

Principal Component Analysis (PCA)

The wealth index score for each household was created using PCA, which is a data reduction technique that reduces dimensionality by replacing many correlated variables with a smaller set of uncorrelated 'principal components' that explain most of the variance.[93,94] To prepare variables for PCA, household characteristics were recoded as either improved or unimproved based on DHS categorization.[95] Ownership of assets was recorded as binary. We assessed household characteristics, their correlations, eigenvalues and the factors that explained majority of the variability.

Of these characteristics/assets, 14 were selected for inclusion in the PCA based on higher prevalence, component loading, and their positive association with wealth status. These included improved wall, floor, roof, and toilet, as well as ownership of radio, TV, video/DVD,

mobile, freezer, solar plate, solar lamp, motorcycle, bicycle and cart. We used the first component that explained the largest proportion of the total variance to create the wealth score, with higher scores representing wealthier households.

We categorized the wealth index into quintiles, dividing households into five groups from the least wealthy 20% to the wealthiest 20% based on this relative measure of poverty.[96]

Wealth status and Mortality

The wealth index score for each household was merged with the mortality data, which included the number of deaths, person-time at risk (aggregated by household), and the corresponding treatment value (AZ vs placebo) for the cluster in which each household was located. We examined whether mortality rate in children under five changes with increase in each quintile of the wealth index. Quintiles were analyzed both as a linear ordinal predictor and as categorical variables (with the least wealthy group as the reference), following tests for linear trends across categories.

We used a Poisson regression model with person-years as an offset, a log link, and robust standard errors clustered at the cluster level to account for the cluster-level treatment in the household-level analysis. The margins command in Stata was used to estimate incidence rate differences (IRDs) with 95% CIs using the delta method. In the adjusted analysis, we included distance to facility as a covariate, since it has been previously identified as strong predictor of child mortality in this setting,[97] and is often associated with wealth.[98]

We also assessed wealth-related inequalities in mortality by calculating the Relative Index of Inequality (RII) and the Slope Index of Inequality (SII) which are key measures used in epidemiologic studies to quantify and compare health inequalities across populations.[99] The RII represents the ratio of predicted outcomes between the wealthiest and poorest quintiles in the wealth distribution of the population, whereas the SII reflects the absolute difference between these groups. [99] RII and SII values of 1 and 0 indicate no inequality, respectively, while higher values indicate worse outcomes for the most disadvantaged group. We used bootstrapping with 1,000 replicates, resampling clusters with replacement, to calculate the 95% confidence limits for these estimates. Additionally, we used the Gini index and the concentration index. The Gini index, commonly used to measure income inequality, is also used to measure health inequality by providing estimates that capture the distribution of health or health risks.[100,101] We used the Gini index to assess the overall distribution and degree of inequality in child mortality across households and communities. The Gini index ranges from 0 to 1, where a value of 0 represents perfect equality and a value of 1 indicates perfect inequality.[101] The concentration index captures the extent to which health outcomes differ across individuals or communities ranked by an indicator of socioeconomic status, and is commonly used to measure socioeconomic related health inequality.[102] The concentration index was used to measure how child mortality is concentrated among different wealth groups. It is defined as twice the area between the concentration curve and the 45° line, which represents equality, and ranges from -1 to 1. For an ill-health outcome (such as child mortality), a negative concentration index indicates that ill health is higher among the poor. A value of -1 represents maximal pro-rich inequality (disproportionate burden on the poor), 0 indicates no inequality, and 1 represents maximal pro-poor inequality (disproportionate burden on the wealthy).[102,103]

Wealth-AZ Interaction

We examined whether the effect of AZ on child mortality varies by asset-based wealth and whether the relationship between wealth and mortality varies by treatment arm. We used the interaction directed acyclic graph (DAG)[63] shown in Figure 1A and 1B to determine and visualize the relationships between variables relevant for the interaction analyses. We used Poisson regression models similar to those described above, including both the main effects of wealth and AZ, as well as their interaction term to assess interaction on a multiplicative scale. To evaluate interaction on an additive scale, we calculated the relative excess risk due to interaction (RERI) with bootstrap 95% confidence intervals, resampling clusters with replacement, using 1000 repetitions. Based on the interaction DAG, distance to facility was included as a covariate in adjusted models.

In addition to household-level analyses, we conducted these analyses at the cluster level by aggregating deaths and person-time by cluster and averaging household wealth scores to determine wealth quintiles for each cluster. This approach provided insights into community-level relationships and allowed the use of pre-census household wealth data to calculate the wealth index for clusters with at least one household in the pre-census. As a result, clusters with at least one household in the pre-census were included in the cluster-level analysis, enabling the inclusion of mortality data from clusters missing households in the pre-census data.

Sensitivity Analyses

We conducted several sensitivity analyses. First, since the first 4 principal components explained a much larger proportion of the total variance than just the first component, we combined them

(using weighted sum) to create the wealth score, which was then used in analyses similar to those conducted for the wealth index constructed from the first component.[93] Second, because households not included in the pre-census were excluded from the household-level analysis, we examined whether the effect of AZ on mortality varied by selection/inclusion into the analysis (Figure 1C). Third, we assessed whether selection/inclusion into the household-level analyses varied by treatment arm to determine if changes in mortality by wealth could be related to selection through treatment (Figure 1D)**.** The latter two sensitivity analyses were conducted to assess potential selection bias and determine whether the results from the selected population can be generalized to the full sample and target population.[63]

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

There were 15,291 households in 170 clusters included in the analysis. About 53% of these households were in communities randomized to receive AZ (Table 1). Over 97% of participants in both arms lived in self-owned habitats, and over 75% resided in simple detached houses or villas. Housing materials varied: while three-quarters of households had relatively improved roof materials (concrete, tiles, or sheets), less than 40% had improved floor materials (tiles or cement), and fewer than 10% had houses with improved wall materials (hard or semi-hard walls). 5.3% of households in the AZ group and 4.5% in the placebo group had access to flush

toilets or latrines. In both arms, less than 1% had access to clean drinking water, and similarly low percentages used electricity or gas for cooking. The most commonly owned assets, with over 70% prevalence in both groups, included mobile phones, bicycles, and solar lamps. The largest differences between the groups were in the ownership of radios and solar plates, with 44.6% and 57.5% in the AZ group compared to 49.3% and 61.5% in the placebo group, respectively.

PCA

In the PCA, the first four components had eigenvalues greater than 1, explaining 46% of the variability, with the first component accounting for the largest portion at 20.5%. The Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy was 0.78, indicating that the data was suitable for PCA.[104]

Ownership of solar plates, motorbikes, radios, and TVs, as well as having an improved floor, had component loadings greater than 0.3, indicating a larger contribution to the asset score. Approximately 99% of the standardized asset score values ranged from -3.5 to 4.2, with a maximum score of 6.2, and a mean of 2.6. Based on the asset score rankings, the wealth index had five levels, with the least wealthy 20% of households in the 1st quintile and the wealthiest 20% in the 5th quintile.

Wealth and Mortality

The mortality rate across all households was 9.7 per 1,000 person-years, 95% CI: 8.3 to 11.2 (Table 2). Mortality rates varied by wealth, with households in the first quintile experiencing the highest rate (12.3 per 1,000 person-years, 95% CI: 9.4 to 15.2) and those in the fifth quintile

having the lowest rate (7.0 per 1,000 person-years, 95% CI: 5.3 to 8.6). There was a 11% decrease in mortality rate for each one-level increase in wealth quintile (IRR = 0.89, 95% CI: 0.83 to 0.95). With measures of inequality, on the relative scale (RII), children in households in the lowest wealth quintile were 1.12 times (95% CI: 1.05 to 1.19) more likely to die than those in the wealthiest households. On the absolute scale, households in the lowest socioeconomic status experienced approximately 1.5 additional child deaths per 1,000 person-years (95% CI: 0.5 to 2.5) compared to the wealthiest households (Table 3). The Gini index was 0.59 (95% CI: 0.56 to 0.62) at the household level and 0.40 (95% CI: 0.37 to 0.43) at the community level, indicating high inequality in child mortality within households, with some households experiencing much higher child mortality rates than others, and moderate inequality across communities (Table 3). The Concentration Index was -0.14 (95% CI: -0.25 to -0.04) at the household level and -0.15 (95% CI: -0.24 to -0.06) at the community level, reflecting modest but statistically significant inequality in child mortality by wealth, disadvantaging the poor (Figure 3).

Mortality rates decreased with increasing wealth quintiles at both the household and cluster levels, with the greater reductions occurring from the first to the second and the fourth to the fifth quintile (Figure 2). Although the trend was similar, the change in mortality rate by wealth was slightly more pronounced at cluster level, with a 15% reduction for each increase in quintile level (IRR = 0.85, 95% CI: 0.77 to 0.94).

The wealth related inequalities in mortality were also slightly larger at the community level with RII of 1.17, 95%CI (1.05 to 1.29) and SII: 2.3 per 1000-person year, 95%CI (0.2 to 4.4). These

disparities, though small, were statistically significant. The observed changes in mortality by wealth quintiles remained consistent when adjusting for distance to the facility (Table 2).

Wealth-AZ Interaction

Mortality rates decreased with increasing wealth quintiles for both AZ and placebo clusters (IRR for AZ = 0.87, 95% CI: 0.80 to 0.95; IRR for placebo = 0.90, 95% CI: 0.82 to 0.99). Across all quintiles, the mortality rate was lower in the AZ group compared to the placebo group (IRR = 0.83, 95% CI: 0.63 to 1.1). The effect of AZ compared to placebo did not change significantly with the wealth index, and the change in mortality rate by wealth did not vary significantly between the arms (Table 4, Figure 4). Although there was a slight difference in the pattern of change at the household versus cluster level (Figure 4), there was no significant interaction between AZ and wealth on either the multiplicative or additive scale at both the household and cluster levels (Table 4). Differences in RII and SII by arm were also minimal (Table 5).

Sensitivity Analyses

In the sensitivity analysis using the first 4 components, the results were similar (Supplementary Figure 1 and 2). We found that that the probability of households being included in the pre-census (selected) did not vary significantly by study arm (RR= 1.14, 95%CI (0.9 to 1.44). Furthermore, the effect of AZ on mortality did not vary substantially between households included in pre-census (selected) and missing households (P value for AZ*selection interaction=0.862, Supplementary Table 1).

DISCUSSION

We found a wealth gradient in child mortality at both household and community levels, with more pronounced disparities at the community level. At both levels, those in the least wealthy quintile had the highest mortality rates. These wealth-related disparities were similar in both AZ and placebo groups. Although AZ-treated groups consistently had lower mortality rates, the effect of AZ compared to placebo did not vary significantly across wealth quintiles. There was no significant interaction between AZ and wealth status on either a multiplicative or additive scale at the household or cluster levels.

Wealth and Mortality

We found that mortality rates declined substantially with increasing wealth, consistent with previous studies that identified wealth as a key factor in under-5 mortality variability.[77,105] Wealth may influence child mortality in several ways. At the community level, factors such as ecological settings (e.g., local environment), political economy (e.g., economic conditions and governance), and health systems (e.g., access to healthcare services) can all influence child mortality.[88] At the household level, factors linked to a family's income and wealth can influence access to goods and services—such as housing, food, transportation, and healthcare.[88,106] These factors can individually and collectively affect mortality through more proximal factors like poorer living conditions, higher susceptibility to infections, and reduced access to quality care,[88,107,108] likely contributing to the higher child mortality observed among the poorest households and communities. Additional barriers include limited access to routine services, such as timely childhood vaccination, which are often lower among the most disadvantaged populations in Sub-Saharan Africa.[109] Distance to facilities and the inability to afford care—

factors commonly associated with poverty—have been noted as reasons for such disparities and as general barriers to care.[21,110,111] However, in our study, adjusting for distance to facilities did not change the disparities in mortality observed by wealth.

Over the years, Burkina Faso has made notable progress in reducing childhood mortality by increasing access to free care, adopting seasonal malaria chemoprevention, expanding services, and improving the quality of care.[112] While free healthcare for children under 5 has improved healthcare utilization and helped reduce inequalities,[113] some disparities remain, with the least wealthy households and communities experiencing the highest mortality rates. The modest change in mortality rates for those in the 40th to 80th percentiles suggests that the wealth impacts on under 5 mortality may be most pronounced in the wealthiest and poorest 20%. A closer examination of how wealth translates to health outcomes at the extremes of the wealth spectrum could be helpful. Although the Gini index showed higher variability in child mortality across households than communities, disparities by wealth appeared to be higher at the community level, as seen with the relative and slope inequality indices, as well as the concentration index. The more pronounced community-level disparities (than the household level) may suggest that aggregate factors—such as healthcare accessibility, environmental conditions, and community resources—may play a larger role, especially in the context of residential segregation by wealth. Targeted approaches addressing the specific challenges of vulnerable populations,[114] including enhancing community resilience,[115] may further reduce differential mortality.

Wealth-AZ Interaction

We did not find evidence of an interaction between AZ and wealth on mortality rates. The wealth gradient in child mortality was similar in both AZ and placebo-treated clusters. Previous research indicated that AZ could help reduce health disparities by being particularly beneficial for distant communities with reduced access to healthcare and antibiotics.[56] Although the mechanism of action is not clear, AZ may improve short-term health outcomes by clearing infections,[48] which is critical given that many infectious diseases can worsen rapidly without treatment. This can make AZ particularly effective at reducing mortality and morbidity in populations that are geographically disadvantaged, where treatment access is limited. While distance to facilities is a significant barrier to accessing routine and life-saving interventions,[21,81] it often represents one of many obstacles to care. Thus, while mass AZ distribution may also help address some of the wealth-related disparities due to barriers to treatment and care, its effectiveness in addressing broader disparities influenced by factors such as economic inequality, nutrition, and living conditions may be more limited.

Regardless of its impact on wealth-related disparities, AZ remains effective in reducing child mortality,[22,46,49] as reflected with the lower mortality rates in AZ treated communities. Therefore, using AZ with comprehensive approaches that strengthen health systems and services in poor communities, improve living conditions and nutritional status of disadvantaged children, increase awareness and coverage of interventions, and enhance the quality and equity of care may better help address wealth-related disparities.[114]

The consistent effect of AZ across different wealth levels may imply that it provides similar

benefits across economically diverse communities, with no evidence suggesting enhanced benefits for disadvantaged communities or for prioritizing treatment based on wealth status. Previous studies exploring the heterogeneity of AZ's effect by underlying mortality rate[116] or by nutritional status[117] did not find strong evidence of effect modification. While concerns about resistance call for targeted approaches,[60] AZ appears beneficial for a broad range of populations. Findings from the AVENIR trial also showed that nontargeted intervention for all children aged 1 to 59 months yielded a greater benefit against mortality compared to restricting treatment to infants 1-11 months.[118] While it is important to explore whether certain populations benefit more from MDA with AZ and prioritize them accordingly, continuing to treat all children who can benefit from it remains crucial in the absence of evidence for a targeted approach or better alternatives.[119] A study weighing the risks and benefits of MDA AZ found that the short term benefits outweigh the risks, as AZ is an effective short-term strategy for reducing mortality that can be used along with larger-scale structural and systemic changes.[120]

This study has some limitations. The first is reduced statistical power due to relatively low mortality rates. The need to restrict the analysis to households included in the pre-census—i.e., the exclusion of missing households—further lowered our sample size. Analyzing data at the cluster level partly mitigated this issue by averaging household wealth scores and aggregating mortality by cluster, allowing us to incorporate mortality information from households missing wealth scores. This, however, relied on the assumption that the households with non-missing scores can adequately represent those with missing scores. Additionally, our sensitivity analyses suggest that the missingness of households in the pre-census appears to be a random process and does not differ systematically by study arm. The scenario shown in Figure 1D indicates that

selection can be a threat to generalizability of findings to target population if S (selection) for inclusion in the analysis is associated with changes in mortality by wealth (ΔY_W).[63] Our sensitivity analysis shows that treatment (A) is not associated with selection (S), thereby breaking the link between these variables. Additionally, the effect of AZ on mortality in the selected and missing households was also similar. This suggests that the threat to validity shown in Figure 1C may not apply, since there is no association between selection into the sample (S) (selection) and the effect of AZ on mortality (ΔY_A) in our data. This implies that the observed effects in the selected population can be generalized to the full sample and target population.[63]

Second, there is a potential for misclassification or measurement error, as the asset-based wealth index may not fully capture the complexity of wealth within households. Although this limitation could affect the accuracy of our analyses, it would likely impact all communities similarly and would not be differential by mortality levels. The extent to which these scores adequately represent wealth can also be affected by the PCA. Although the proportion of variability explained by the first component was not large, the combination of the first 4 components, which explained a much larger proportion of variability, generated similar findings. Additionally, a summary of household characteristics by wealth index quintile shows that asset ownership increases with wealth, as expected. This trend further strengthens our confidence in using the scores generated from PCA to represent wealth status (Supplementary table 1). Lastly, since we did not have additional data on clusters and households, we could not adjust for other potential confounders of the wealth-mortality association, such as bed net access. Therefore, the objective was to examine how mortality rates vary with wealth in these communities and examine how it

interacts with AZ, rather than to estimate the causal effect of asset-based wealth on child mortality.

Conclusion

Our results suggest that while wealth-related disparities in child mortality were observed at both the household and community levels, mass AZ treatment did not appear to mitigate these disparities, highlighting the need for other targeted approaches that could address this differential mortality. We did not find evidence of an enhanced benefit of AZ for disadvantaged communities or for prioritizing treatment based on wealth status. Therefore, it may be beneficial for MDA AZ programs to continue providing treatment to all children who could benefit. Further work is needed to address the underlying factors contributing to disparities in child mortality in these communities.

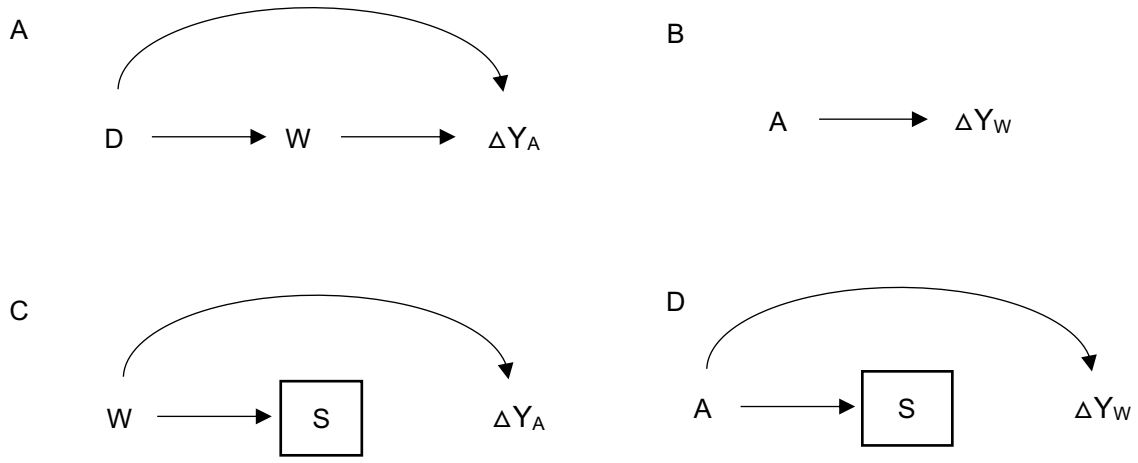


Figure 3.1- Interaction Directed Acyclic Graphs Illustrating the Interaction Between Mass AZ Treatment and Asset-Based Wealth.
Note: W- Wealth, A- AZ treatment, S-Selection (household being included in pre-census), D-Distance to health facility, Y-under-five mortality, ΔYA-effect of AZ on mortality, ΔYW-change in mortality by wealth. Figure 1A-how wealth may modify the effect of AZ on mortality with distance to health facility as a potential confounder; Figure 1B-how AZ may influence the change in mortality by wealth; Figure 1C- selection as a threat to generalizability to target population -sensitivity analysis examined association between selection (S) and effect of AZ on mortality (ΔYA). Figure 1D- selection as a threat to generalizability to target population, sensitivity analysis examined association between S (selection) and A (AZ)

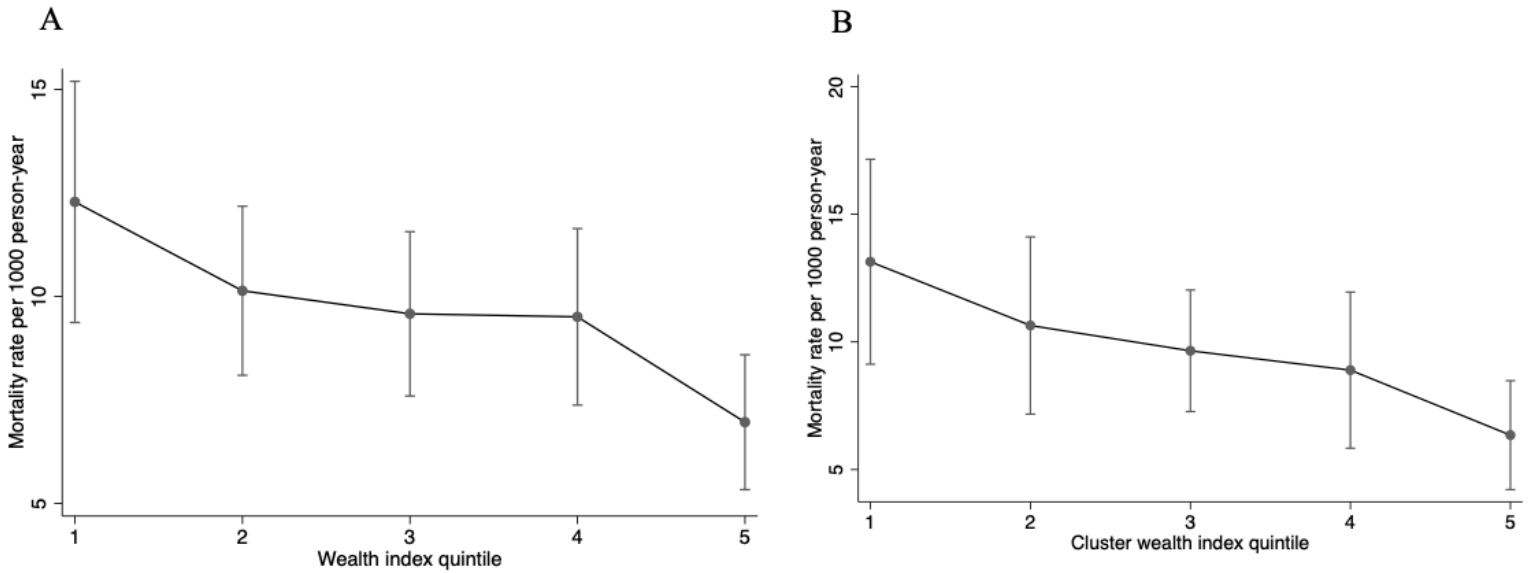


Figure 3.2- Mortality rate by a) Household wealth index quintile and b) wealth at cluster level.
Note: Wealth index quintile 1 represents the 20% with the lowest wealth, while quintile 5 represents the 20% with the highest wealth.

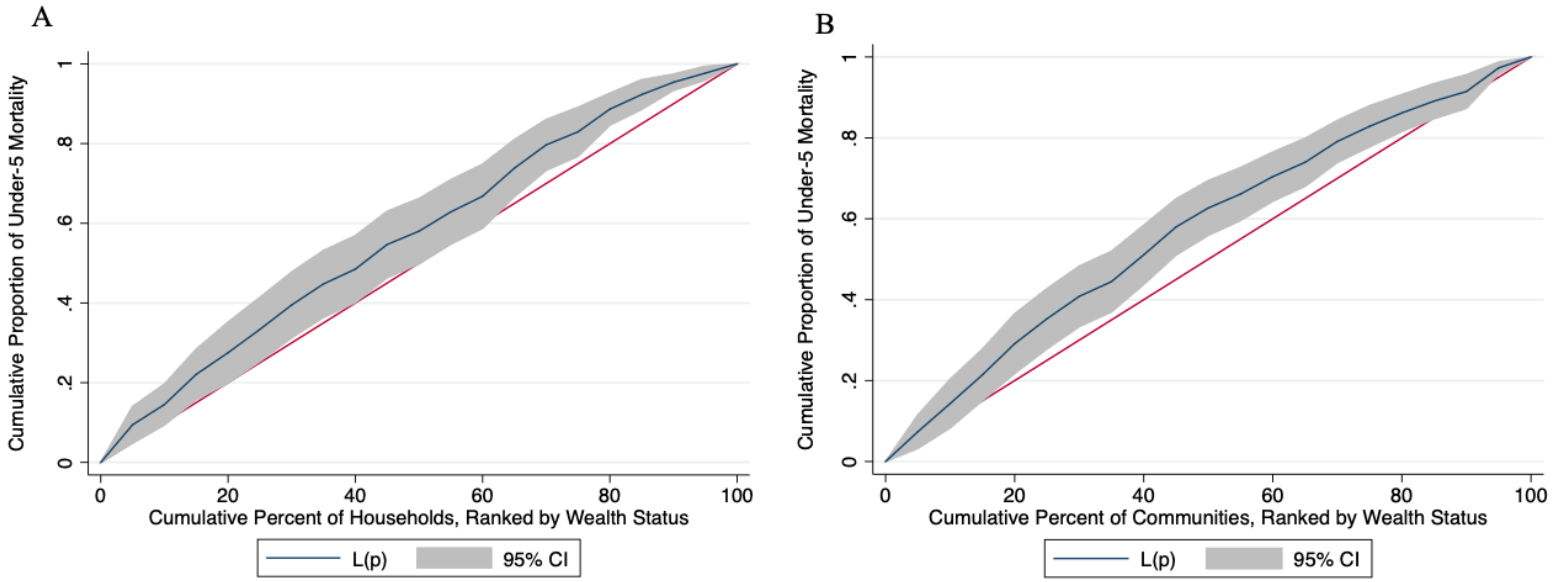


Figure 3.3- Concentration Index of Child Mortality by Wealth Status at a) Household and b) Community Levels
Note: L(P)- Cumulative Proportion of Under-5 Mortality at Wealth Percentile p. A concentration curve above the 45° line indicates inequality disfavoring the poor and corresponds to negative concentration index values.

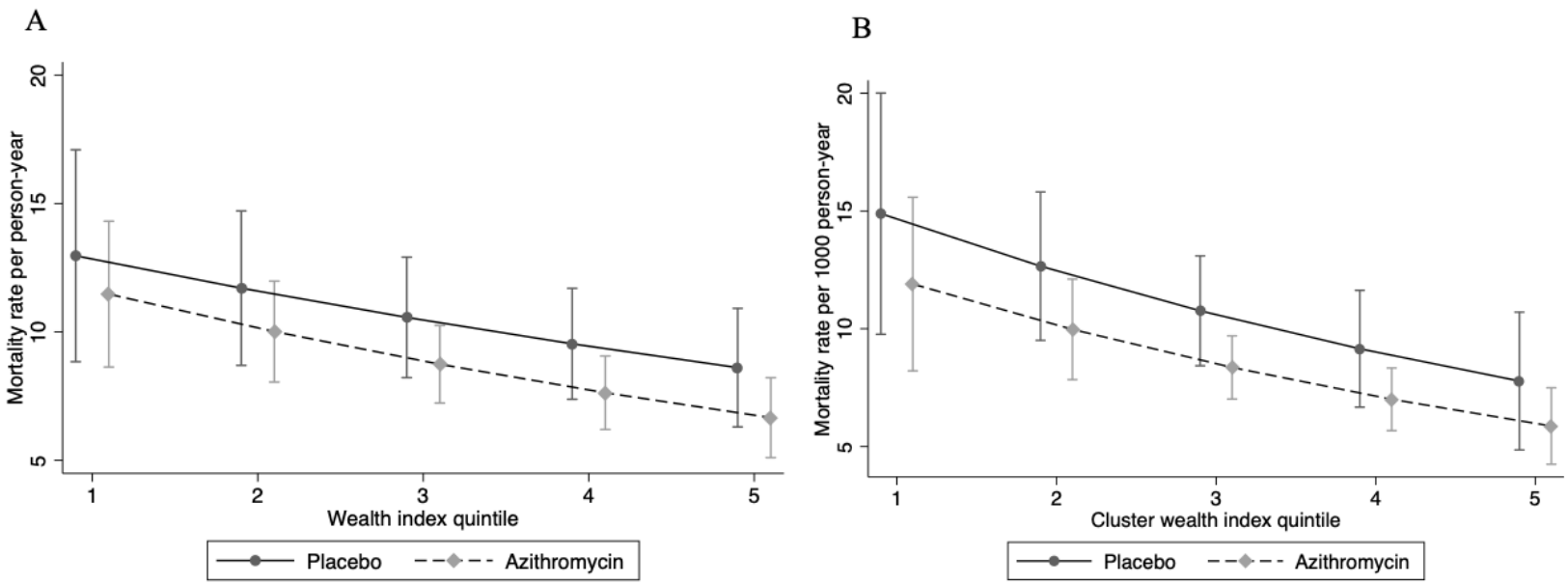
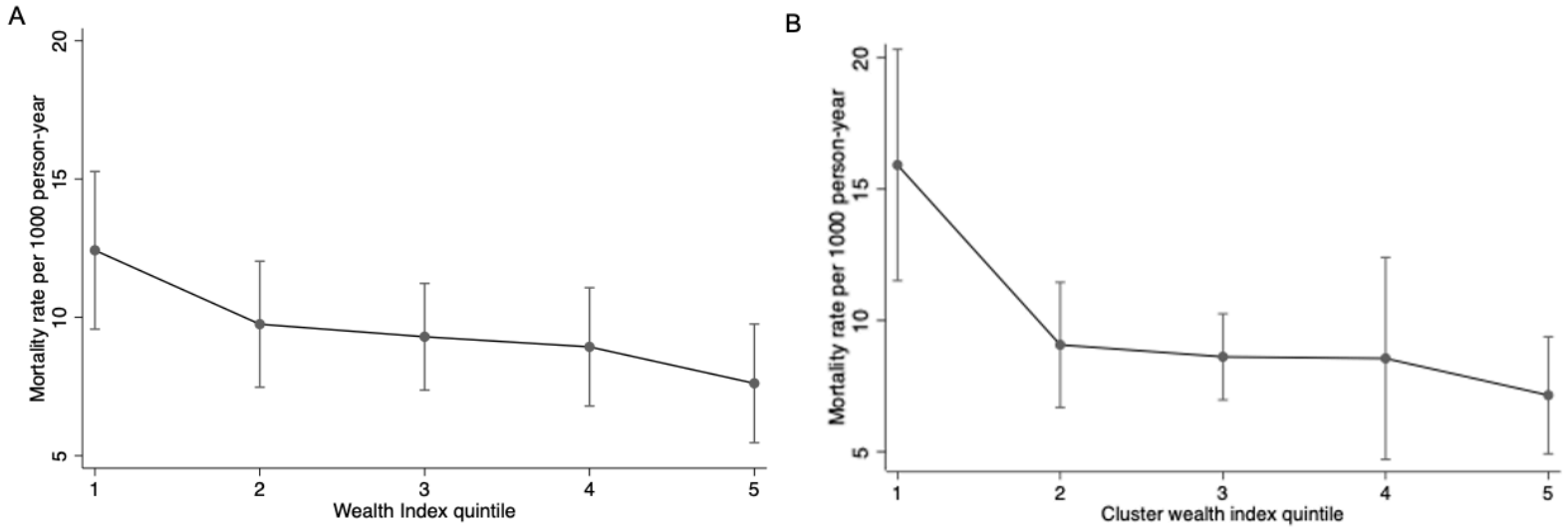
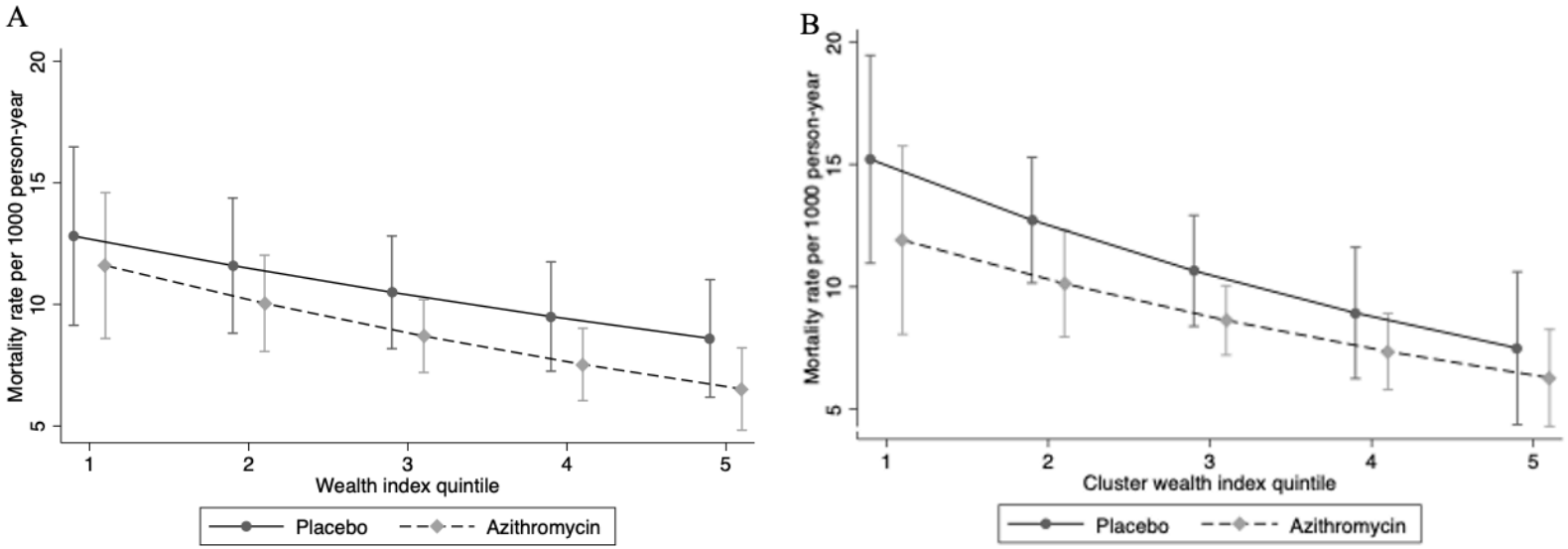


Figure 3.4- Mortality rate by treatment and wealth index quintile at a) household level and b) cluster level
Note: models included distance to facility as covariate.



Supplementary Figure 3.1- Mortality rate by a) Household wealth index quintile and b) wealth at cluster level with wealth score generated from 4 principal components.



Supplementary Figure 3.2- Mortality rate by treatment and wealth index quintile at a) household level and b) cluster level with wealth score generated from 4 principal components.

Table 3.1 Characteristics of households from the pre-census (n= 15, 291 households in 170 clusters).
Note: †Characteristics included in principal component analysis

	Azithromycin (n=8,157 households)	**Placebo (n=7,134 households)**
Persons per household (mean, SD)	7.24 (4.86)	7.17 (4.86)
Children per household (mean, SD)	1.59 (1.39)	1.56 (1.37)
Household characteristics (n, %)		
Improved housing (case, simple detached house, villa)	6254 (76.7%)	5522 (77.4%)
Ownership of habitat (own)	7983 (97.9%)	7027 (98.5%)
Improved wall material (hard, semi-hard)†	535 (6.6%)	594 (8.3%)
Improved floor material (tiles, cement) †	2917 (35.8%)	2573 (36.1%)
Improved roof material (concrete, tiles, sheets) †	6201 (76%)	5343 (74.9%)
Source of cooking energy (electricity, gas)	43 (0.5%)	18 (0.3%)
Access to toilet (flush toilet, latrines) †	430 (5.3%)	329 (4.6%)
Access to clean drinking water (source-faucet, well)	52 (0.6%)	41 (0.6%)
Ownership of assets		
Radio†	3593 (44.6%)	3503 (49.3%)
TV†	991 (12.6%)	884 (12.7%)
Video / CD / DVD Player†	262 (3.4%)	250 (3.6%)
Fixed telephone	11 (0.1%)	14 (0.2%)
Mobile telephone†	6113 (75.4%)	5559 (78.4%)
Freezer†	27 (0.3%)	5 (0.1%)
Solar plate†	4645 (57.5%)	4362 (61.5%)
Generator	7 (0.1%)	4 (0.1%)
Solar lamp†	5951 (73.9%)	5426 (77.4%)
Petroleum lamp	8 (0.1%)	16 (0.2%)
Car	14 (0.2%)	8 (0.1%)
Motorbike†	3254 (40.9%)	3066 (43.7%)
Tricycle	87 (1.1%)	70 (1%)
Bicycle†	5792 (71.6%)	5288 (74.6%)
Cart†	4695 (58.2%)	4415 (62.4%)
Computer office	3 (0%)	0 (0%)
Laptop computer	14 (0.2%)	8 (0.1%)

Table 3.2 Mortality Rates, Rate Ratios, and Rate Differences by Asset-Based Wealth Quintiles. Note: IRR-Incidence Rate Ratio, IRD-Incidence Rate Difference, P=0.0004 and P= 0.0018 for test of linear trend in categories for household and cluster level respectively

		Unadjusted		**Adjusted for distance to facility**	
	Mortality Rate per 1000 PY	**IRR**	**IRD per 1000 PY**	**IRR**	**IRD per 1000 PY**
Household level	Across quintiles				
Wealth index quintile linear	9.7 (8.3 to 11.2)	0.89 (0.83 to 0.95)	-1.1 (-1.8 to -0.5)	0.89 (0.83 to 0.95)	-1.2 (-1.8 to -0.5)
Wealth index quintile	In each quintile				
1st (least wealthy)	12.3 (9.4 to 15.2)	ref	ref	ref	ref
2nd	10.1 (8.1 to 12.2)	0.83 (0.65 to 1.05)	-2.1 (-4.9 to 0.6)	0.82 (0.65 to 1.05)	-2.2 (-5.0 to 0.6)
3rd	9.6 (7.6 to 11.6)	0.78 (0.6 to 1.01)	-2.7 (-5.7 to 0.3)	0.78 (0.6 to 1.01)	-2.8 (-5.7 to 0.2)
4th	9.5 (7.4 to 11.6)	0.77 (0.6 to 0.99)	-2.8 (-5.6 to 0.0)	0.77 (0.6 to 0.98)	-2.9 (-5.6 to -0.1)
5th (wealthiest)	7.0 (5.3 to 8.6)	0.57 (0.42 to 0.77)	-5.3 (-8.4 to -2.3)	0.56 (0.42 to 0.76)	-5.4 (-8.4 to -2.3)
Cluster level	Across quintiles				
Wealth index quintile continuous	9.9 (8.5 to 11.2)	0.85 (0.77 to 0.94)	-1.6 (-2.6 to -0.5)	0.85 (0.77 to 0.94)	-1.5 (-2.6 to -0.5)
Wealth Index quintile	In each quintile				
1st (least wealthy)	13.1 (9.1 to 17.2)	ref	ref	ref	ref
2nd	10.6 (7.2 to 14.1)	0.81 (0.52 to 1.27)	-2.5 (-7.8 to 2.8)	0.85 (0.54 to 1.32)	-2.0 (-7.2 to 3.3)
3rd	9.7 (7.3 to 12.0)	0.73 (0.5 to 1.09)	-3.5 (-8.2 to 1.2)	0.77 (0.52 to 1.15)	-2.9 (-7.6 to 1.7)
4th	8.9 (5.8 to 12.0)	0.68 (0.43 to 1.07)	-4.2 (-9.3 to 0.8)	0.69 (0.44 to 1.09)	-4.0 (-8.9 to 1.0)
5th (wealthiest)	6.3 (4.2 to 8.5)	0.48 (0.31 to 0.76)	-6.8 (-11.3 to -2.2)	0.49 (0.31 to 0.77)	-6.5 (-10.9 to -2.1)

Table 3.3 Estimates of Inequality Indices: Relative Index, Slope Index, and Concentration Index at household and cluster level.

	Point Estimate (95%CI)
Household level	
Relative Index of Inequality (RII)	1.12 (1.05 to 1.19), P=0.00
Slope Index of Inequality (SII): average difference in mortality per 1000 PY	1.50 (0.5 to 2.5), P=0.004
Gini Index	0.59 (0.56 to 0.62), P=0.000
Concentration Index	-0.14 (-0.25 to -0.04), P=0.007
Cluster level	
Relative Index of Inequality (RII)	1.17 (1.05 to 1.29), P=0.00
Slope Index of Inequality (SII): average difference in mortality per 1000 PY	2.30 (0.2 to 4.4), P=0.034
Gini Index	0.40 (0.37 to 0.43), P=0.00
Concentration index	-0.15 (-0.24 to -0.06), P=0.002

Table 3.4 Interaction between wealth and treatment on under-5 mortality at household and cluster level.
Note: IRR-Incidence Rate Ratio, IRD-Incidence Rate Difference. Wealth quintiles were used as linear form in estimating effect of wealth on mortality by treatment arm. Distance to facility was included as covariate. Slope Index of Inequality (SII) showing average difference in mortality per 1000 PY

Household level	**Azithromycin**	**Placebo**	**IRR (AZ vs placebo)**	**IRD (AZ vs placebo) per 1000PY**
Mortality rate per 1000 PY				
Across quintiles	8.9 (7.3 to 10.5)	10.7 (8.3 to 13.1)	0.83 (0.63 to 1.1)	-1.8 (-4.7 to 1.1)
By wealth index quintile				
1st	11.5 (8.6 to 14.3)	13.0 (8.8 to 17.1)	0.88 (0.53 to 1.24)	-1.5 (-6.5 to 3.5)
2nd	10.0 (8.0 to 12.0)	11.7 (8.7 to 14.7)	0.86 (0.58 to 1.13)	-1.7 (-5.3 to 1.9)
3rd	8.7 (7.2 to 10.2)	10.6 (8.2 to 12.9)	0.83 (0.59 to 1.06)	-1.8 (-4.6 to 1.0)
4th	7.6 (6.2 to 9.1)	9.5 (7.4 to 11.7)	0.80 (0.56 to 1.04)	-1.9 (-4.5 to 0.7)
5th	6.7 (5.1 to 8.2)	8.6 (6.3 to 10.9)	0.77 (0.5 to 1.05)	-2.0 (-4.7 to 0.8)
Interaction Coeff multiplicative scale		0.97 (0.85 to 1.1), P=0.607		
Interaction Coeff additive scale (RERI)		-0.02 (-0.19 to 0.15), P= 0.823		
Cluster level				
Mortality rate per 1000 PY				
Across quintiles	8.9 (7.3 to 10.5)	10.7 (8.3 to 13.1)	0.83 (0.63 to 1.1)	-1.8 (-4.7 to 1.1)
By wealth index quintile				
1st	11.9 (8.2 to 15.6)	14.9 (9.8 to 20)	0.80 (0.43 to 1.17)	-3.0 (-9.3 to 3.3)
2nd	10.0 (7.8 to 12.1)	12.7 (9.5 to 15.8)	0.79 (0.53 to 1.05)	-2.7 (-6.5 to 1.1)
3rd	8.4 (7 to 9.7)	10.8 (8.4 to 13.1)	0.78 (0.57 to 0.99)	-2.4 (-5.1 to 0.3)
4th	7.0 (5.7 to 8.3)	9.2 (6.7 to 11.6)	0.77 (0.51 to 1.02)	-2.1 (-5.0 to 0.7)
5th	5.9 (4.2 to 7.5)	7.8 (4.9 to 10.7)	0.75 (0.4 to 1.11)	-1.9 (-5.3 to 1.4)
Interaction Coeff multiplicative scale		0.99 (0.82 to 1.19), P=0.881		
Interaction Coeff additive scale (RERI)		0.02 (-0.23 to 0.27), P= 0.884		

Table 3.5 Estimates of Inequality Indices by treatment arm at household and cluster level

Household level	**Azithromycin**	**Placebo**
IRR (wealth-> mortality)	0.87 (0.8 to 0.95)	0.90 (0.82 to 0.99)
IRD (wealth-> mortality) per 1000 PY	-1.20 (-2.0 to -0.4)	-1.10 (-2.2 to 0.0)
Relative Index of Inequality (RII)	1.15 (1.05 to 1.24), P=0.00	1.11 (1.01 to 1.2), P=0.00
Slope Index of Inequality (SII)	1.70 (0.30 to 3.10), P=0.019	1.40 (-0.10 to 2.90), P=0.072
Gini Index	0.59 (0.54 to 0.63), P=0.00	0.58 (0.54 to 0.62), P=0.00
Concentration index	-0.20 (-0.32 to -0.08), P=0.002	-0.09 (-0.26 to 0.08), P=0.289
Cluster level		
IRR (wealth-> mortality)	0.84 (0.74 to 0.95)	0.85 (0.74 to 0.98)
IRD (wealth-> mortality) per 1000 PY	-1.50 (-2.70 to -0.3)	-1.80 (-3.5 to -0.1)
Relative Index of Inequality (RII)	1.19 (1.04 to 1.34), P=0.00	1.18 (1.0 to 1.35), P=0.00
Slope Index of Inequality (SII)	2.30 (-0.30 to 4.9), P=0.084	2.60 (-0.8 to 6.1), P=0.134
Gini Index	0.41 (0.37 to 0.46), P=0.00	0.38 (0.34 to 0.41), P=0.00
Concentration index	-0.17 (-0.31 to -0.03), P=0.021	-0.13 (-0.25 to -0.01), P=0.032

Supplementary Table 3.1 Sensitivity Analyses Assessing the Role of Selection into Analysis Note: HH-household, [a] Sensitivity analysis corresponding to Figure 1D representing relative risk; [b] sensitivity analyses corresponding to Figure 1C representing rate ratios

	Relative risk (95%CI)
Association between AZ and HH being observed[a]	1.14 (0.9 to 1.44)
Effect of AZ on mortality overall	0.82 (0.66 to 1.01)
Effect of AZ on mortality among pre-census HHs (selected)[b]	0.82 (0.62 to 1.09)
Effect of AZ on mortality among missing HHs[b]	0.79 (0.58 to 1.08)
Interaction Coeff for AZ* HH being observed[b]	1.04 (0.69 to 1.56), P=0.862

Supplementary Table 3.2 Summary of household characteristic by wealth index quintiles

	Wealth Index quintile					
Household characteristics (Proportion)	**1 (n=2,925)**	**2 (n=2,759)**	**3 (n=2,840)**	**4 (n=3,014)**	**5 (n=2,638)**	**Component loading**
Improved wall material (hard, semi-hard)	0.02	0.04	0.04	0.06	0.24	0.281
Improved floor material (tiles, cement)	0.05	0.18	0.33	0.44	0.82	0.524
Improved roof material (concrete, tiles, sheets)	0.40	0.70	0.80	0.92	0.97	0.464
Access to toilet (flush toilet, latrines)	0.04	0.05	0.05	0.03	0.09	0.064
Ownership of assets						
Radio	0.08	0.26	0.46	0.69	0.88	0.564
TV	0.0003	0.004	0.03	0.05	0.58	0.576
Video / CD / DVD Player	0	0	0	0.01	0.18	0.387
Mobile telephone	0.41	0.76	0.85	0.92	0.97	0.465
Freezer	0	0	0	0.0007	0.011	0.092
Solar plate	0.06	0.37	0.69	0.93	0.96	0.661
Solar lamp	0.62	0.79	0.73	0.88	0.82	0.155
Motorbike	0.04	0.17	0.39	0.65	0.90	0.629
Bicycle	0.42	0.69	0.77	0.91	0.91	0.417
Cart	0.26	0.42	0.67	0.85	0.85	0.490

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