

Impact of Prenatal Nutrition Interventions on Infant Longitudinal Growth: A Secondary Analysis of the Mumta Pregnant Women Trial in Pakistan

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Abstract

Objective: To evaluate the effect of antenatal interventions on infant growth from birth till 12 months of age.

Patients and Methods: In the Mumta Pregnant Women (PW) trial conducted from July 22, 2019, to February 1, 2022, PW were randomly assigned (1:1:1:1) to one of 4 groups: control (standard antenatal care), balanced energy protein supplementation (BEP alone), BEP/azithromycin (AZ), or BEP/nicotinamide/choline. Infant growth trajectories were modeled using the broken stick method and k-means clustering for weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length z-scores. Random effect models assessed the impact of interventions and covariates (maternal age, height, parity, and mode of delivery) on growth outcomes.

Results: From 1884 PW randomized, 1678 infants were born alive and included in this analysis (control n=410, BEP only n=418, BEP/AZ n=428, and BEP/choline/nicotinamide n=422). The mean growth trajectories revealed that the BEP/AZ arm had higher mean WAZ, LAZ, and weight-for-length scores compared with control. BEP/AZ arm had the highest proportion of infants in the thriving cluster across WAZ (control 34.4 % and BEP/AZ 35.5 %), and LAZ (control 31.7%, BEP/AZ 33.4%) measures. The odds of membership to the faltering cluster were reduced in the BEP/AZ arm based on WAZ (control 22.3%, BEP/AZ 15.7%), and LAZ measures (control 22.1%, BEP/AZ 17.7%) as compared with control. Across all measures, faltering was 4-fold higher in small-for-gestational-age infants and 2-fold higher among infants born to undernourished mothers.

Conclusion: Antenatal interventions, such as BEP and prophylactic AZ, may have the potential to support and sustain infant growth outcomes in low-resource settings.

Trial Registration: Clinicaltrials.gov Identifier: NCT04012177.

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Maternal and childhood undernutrition is a leading risk factor for disability-adjusted life-years lost in low-income and middle-income countries.¹ In 2022, 22.3% of the world's children aged under 5 years were stunted and 6.8% were wasted, with Asia and Africa comprising 95% of stunting cases.² In Pakistan, the prevalence of stunting among children aged younger than 5 years is estimated at 40.2% and, the prevalence of wasting at 17.7%.³

Stunting and wasting are important to measure and monitor as they are associated with an increased risk of infection, mortality, reduced physical, neurodevelopmental, and economic capacity, and metabolic disease into adulthood.⁴ Growth patterns are assessed using weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) z-scores, standardized by age and sex using WHO references.⁵ Linear (height) and ponderal (weight) growth are also studied together



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because of their synergistic and cyclical interactions and overall development.⁶

Growth faltering arises from complex biological pathways, socioeconomic factors, and maternal determinants.⁷ The first 1000 days—from conception to age 2 years—are critical for child development, as 70% of the height deficit observed at age 2 years results from growth faltering during this period.⁸ Small-for-gestational-age (SGA) and low birth weight (LBW) are major contributors to child undernutrition, with SGA accounting for ~20% of stunting and 30% of wasting in low-income and middle-income countries; preterm birth (PTB) further increases the risk of stunting.⁹ About a fifth of the SGA births globally are attributable to maternal undernutrition during pregnancy.¹⁰ As a result, efforts to attenuate SGA risk aim to prevent undernutrition of mothers during pregnancy. Prophylactic antibiotics such as AZ, used to prevent maternal reproductive tract infections, along with micronutrient supplements and interventions such as balanced energy protein (BEP) during pregnancy, have shown potential in improving SGA and birth weight, with mixed results of impact on postnatal growth.¹¹⁻¹³ Nicotinamide (vitamin B3) and choline supplementation during pregnancy may influence fetal growth and developmental pathways relevant to childhood stunting.^{14,15}

Current WHO guidelines for pregnant women include at least 8 antenatal care visits, nutritional counseling, iron and folic acid supplementation, and tetanus toxoid vaccination. These interventions aim to prevent complications, improve maternal and fetal health outcomes, and ensure a healthy pregnancy journey.¹⁶ Understanding early growth patterns, the timing of growth faltering or recovery, and factors influencing infant growth are crucial for informing guidelines and designing effective interventions. This study aimed to assess whether the administration of nutritional supplements, with or without AZ and micronutrient fortification, influenced infant growth in the first year after birth in Pakistan. To do this, we analyzed growth trajectories of infants born to mothers receiving these nutritional supplements and tracked infant growth from birth to 12 months using clustering based on similar longitudinal growth patterns.

We sought to identify factors associated to each cluster group to better understand the patterns and determinants of growth during the first year of life, particularly in the faltering group.

METHODS

Study Population and Setting

The Mumta Pregnant Women (PW) trial was an open-label, superiority, assessor-blinded, randomized controlled trial in PW from a low-income squatter settlement in Karachi, Pakistan.¹⁷ The PW aged 13-49 years with a gestational age (GA) of 8-18.9 weeks were randomly assigned (1:1:1:1) to either the control arm (standard of care, which consisted of antenatal care and counseling), the BEP alone arm (BEP supplements, 2 sachets per day, containing 10.5 g protein, 400 kcal per sachet), the BEP plus AZ arm (AZ 2 g at weeks 20 and 28 of GA), or the BEP plus choline plus nicotinamide arm (daily oral tablets of choline 450 mg and nicotinamide 100 mg from enrollment till childbirth). All interventions arms received standard care. The primary outcome in the modified intention-to-treat population was birth weight of the live newborn assessed within 72 hours of birth (n=1678). Here, we present the results of a secondary objective of the trial, which was to evaluate the effect of interventions on infant anthropometric measures at extended follow-up timepoints from 0-12 months after birth. All mothers included in the study provided written informed consent. The Mumta PW study was approved by the institutional review board of VITAL Pakistan Trust, ethics review committee of the Aga Khan University, and the National Bioethics Committee of Pakistan. Approval for this secondary analysis was covered under the study's annual continuing ethical approval granted by the ethics review committee of Aga Khan University, Karachi (Reference: 2025-0772-39076).

Procedures

The cohort was followed up from birth with monthly follow-up visits until 7 months and then at 12 months (9 visits in total, including birth). Infant birth weight was measured in gm, recorded within 72 hours of delivery for all live-born infants. Cultural considerations

precluded birth weight assessments in cases of stillbirths and miscarriages. Infant weights were obtained using a SECA model 334 digital infant scale (SECA GmbH & Co). Secondary infant outcomes included birth length (cm), SGA, LBW, and PTB. Additional neonatal anthropometric indicators, such as head circumference (cm), mid-upper arm circumference (MUAC, cm), LAZ, WAZ, and WLZ, were calculated according to the WHO 2006 Child Growth Standards.¹⁸

All anthropometric measurements, including infant length, weight, head circumference, and MUAC, were obtained by trained field staff following standardized procedures adapted from the INTERGROWTH-21st protocol.¹⁹ To enhance measurement validity, 2 independent assessors recorded each measurement. Predefined thresholds for inter-observer agreement were set as ≤ 0.4 cm for infant length, MUAC, and head circumference, and ≤ 20 g for infant weight. For maternal assessments, the limits were ≤ 0.5 cm for MUAC and height and ≤ 0.2 kg for weight. A digital data capture system was used to log measurements, with automated alerts for discrepancies beyond these thresholds, prompting immediate repeat measurements. The final values for analysis were based on the average of 2 valid readings. Regular refresher training sessions were conducted every 3 months to uphold measurement fidelity, and all anthropometric equipment was routinely calibrated. Additionally, periodic inter-rater reliability checks were performed to ensure sustained measurement accuracy over the course of the study.

Statistical Analyses

All statistical analyses were performed using STATA version 17.0 and R version 4.4.2 with relevant packages.²⁰ Normally distributed continuous variables were reported as mean $\pm$ SD, while non-normally distributed continuous variables were reported as median (IQR). Categorical variables were presented as frequencies and percentages. The normality of variables was assessed using the Shapiro-Wilk test.

Longitudinal growth trajectories were analyzed using a broken stick model, estimating piecewise linear segments with knots at different time points (3, 6, and 12 months).

K-means clustering was applied to identify distinct growth patterns, with infants grouped into clusters based on WAZ, LAZ, and WLZ trajectories.

To address missing data, infants with at least one valid anthropometric measurement at any follow-up visit were retained in the analysis and assigned to their respective study clusters. We assumed that missing data were missing at random and did not apply any imputation methods. To assess the plausibility of the missing at random assumption, baseline characteristics were compared between participants with and without anthropometric measurements at the final planned 12-month follow-up visit. For descriptive summaries and growth trajectory modeling, we used mixed-effects models to account for the hierarchical structure of the data and accommodate unbalanced observations due to intermittent missingness. This approach allowed us to include all available data without excluding infants with partial follow-up.

At univariate level mixed-effects logistic regression was performed to calculate odds ratios (ORs) with 95% CIs for potential factors (intervention, SGA, maternal body mass index [BMI], age, height, parity, and mode of delivery) associated with growth (WAZ, LAZ, and WLZ) faltering. All the factors with P values $< .20$ in univariate analyses were considered for multivariate analysis, a stepwise backward elimination approach was used to build the final multivariate model. A P value $< .05$ was considered statistically significant for all analyses.

RESULTS

Of 1884 randomized women, 1678 gave birth to infants who were born alive with anthropometric measures taken within the first 72 hours and included in the primary outcome analysis.¹⁷ For this secondary analysis, all infants born alive with anthropometric measurements were included ($n=1744$; 410 in the control arm, 418 in the BEP alone arm, 428 in the BEP plus AZ arm, and 422 in the BEP plus choline plus nicotinamide arm) (Figure 1).

The number of infants at each follow-up is shown in [Supplementary Table 1](#) (available online at <http://www.mcpiqjournal.org>). At

birth, 99.0% of the data were captured, while at 12 months, 68.8% of the data were available. Baseline characteristics by follow-up status are presented in [Supplementary Table 2](#) (available online at <http://www.mcpiqjournal.org>). Participants with incomplete follow-up (missing anthropometric measures the final 12-month follow-up) were more likely to be wasted at baseline (11.2% vs 6.4%; $P<.001$) and to have younger mothers (<25 years: 52.1% vs 41.7%; $P<.001$). As these characteristics were measured at baseline and included as covariates in the longitudinal models, these findings support the plausibility of the missing at random assumption. 829 (44.0%) of 1884 mothers with data were younger than 25 years ([Table 1](#)). Most infants (83.8%) were born at term (mean GA 37.8 ± 3.8 weeks), and 884 (50.7%) were boys and 860 (49.3%) were girls. The proportion of infants born SGA was 28.6% in the control arm, 28.3% in the

BEP-only arm, 24.1% in the BEP plus AZ arm, and 23.9% in the BEP plus choline plus nicotinamide arm. Similarly, the proportion of mothers who were underweight at delivery ($\text{BMI} < 18.5 \text{ kg/m}^2$) was 11.2% in the control arm, 8.2% in the BEP-only arm, 7.6% in the BEP plus AZ arm, and 6.5% in the BEP plus choline plus nicotinamide arm. The BEP plus choline plus nicotinamide arm had higher mean WAZ, LAZ, and WLZ scores at birth ([Supplementary Table 3](#), available online at <http://www.mcpiqjournal.org>). At 12 months, the proportion of infants who were underweight ($\text{WAZ} < -2$) was 39.0% in the control arm, 37.8% in the BEP-only arm, 36.9% in the BEP plus AZ arm, and 36.3% in the BEP plus choline plus nicotinamide arm ([Table 2](#)).

Trajectory plots showed a decline in WAZ and LAZ after birth, whereas WLZ showed an upward trend till the first month ([Figure 2](#)). Growth trajectories over infancy appeared

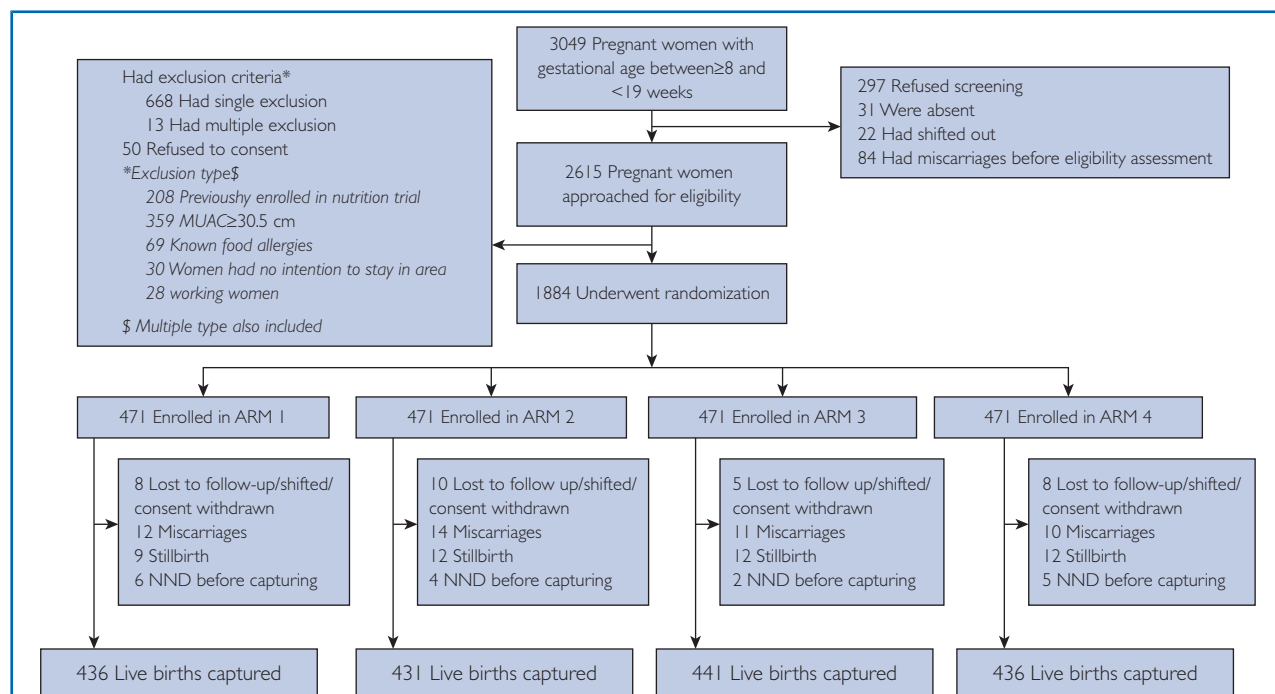


FIGURE 1. CONSORT Flow Diagram. A total of 3049 pregnant women underwent routine ultrasound for screening and 434 were excluded as they did not meet the gestational age criteria. Of the remaining 2615, 731 women were excluded as they did not meet further criteria for inclusion. A total of 1884 participants were randomized to 1 of 4 groups (control, BEP alone, BEP plus azithromycin, or BEP plus choline and nicotinamide). Lost to follow-up, miscarriages, stillbirths, neonatal deaths before data capture, were not included in the 1 year follow-up analysis. This analysis included 1744 infants who were born alive and had anthropometric measurements.

TABLE 1. Baseline Characteristics of Mothers and Infants in this Study^a

All Live Births Captured	Control Arm	BEP-Only Arm	BEP + Azithromycin Arm	BEP + Choline + Nicotinamide Arm	Total
Child characteristics	n=436	n=431	n=441	n=436	N=1744
Growth indicators at birth					
Underweight (WAZ<-2)	93/429 (21.7%)	102/427 (23.9%)	69/437 (15.8%)	69/429 (16.1%)	333/1722 (19.3%)
Stunted (LAZ<-2)	79/424 (18.6%)	82/421 (19.5%)	67/435 (15.4%)	69/427 (16.2%)	297/1707 (17.4%)
Wasted (WLZ<-2)	33/385 (8.6%)	30/377 (8.0%)	27/406 (6.7%)	31/403 (7.7%)	121/1571 (7.7%)
Small for gestational age ^b					
No	307/430 (71.4%)	306/427 (71.7%)	333/439 (75.9%)	328/431 (76.1%)	1274/1727 (73.8%)
Yes	123/430 (28.6%)	121/427 (28.3%)	106/439 (24.1%)	103/431 (23.9%)	453/1727 (26.2%)
Sex					
Male	232/436 (53.2%)	220/431 (51.0%)	224/441 (50.8%)	208/436 (47.7%)	884/1744 (50.7%)
Female	204/436 (46.8%)	211/431 (49.0%)	217/441 (49.2%)	228/436 (52.3%)	860/1744 (49.3%)
Preterm birth					
No	365/436 (83.7%)	355/431 (82.4%)	378/441 (85.7%)	363/436 (83.3%)	1461/1744 (83.8%)
Yes	71/436 (16.3%)	76/431 (17.6%)	63/441 (14.3%)	73/436 (16.7%)	283/1744 (16.2%)
Maternal characteristics	n=471	n=471	n=471	n=471	N=1884
Age					
<25 y	205/471 (43.5%)	209/471 (44.4%)	206/471 (43.7%)	209/471 (44.4%)	829/1884 (44.0%)
25-35 y	235/471 (49.9%)	229/471 (48.6%)	242/471 (51.4%)	222/471 (47.1%)	928/1884 (49.3%)
>35 y	31/471 (6.6%)	33/471 (7.0%)	23/471 (4.9%)	40/471 (8.5%)	127/1884 (6.7%)
Height, cm					
Number of mothers with height data	465	464	466	467	1862
Mean height ± SD	153.8 ± 6.0	153.2 ± 5.1	153.2 ± 5.6	153.3 ± 5.6	153.3 ± 5.6
Weight, kg					
Number of mothers with weight data	444	442	452	446	1784
Mean weight ± SD	54.6 ± 9.3	54.4 ± 8.8	55.5 ± 9.1	54.9 ± 8.7	54.8 ± 9.0
BMI at delivery					
Not underweight (BMI ≥ 18.5 kg/m ²)	390/439 (88.8%)	401/437 (91.8%)	414/448 (92.4%)	414/443 (93.5%)	1619/1767 (91.6%)
Underweight (BMI < 18.5 kg/m ²)	49/439 (11.2%)	36/437 (8.2%)	34/448 (7.6%)	29/443 (6.5%)	148/1767 (8.4%)
Gestational age at the time of outcome, weeks					
Number of mothers with data	457	457	464	458	1836
Mean gestational age (±SD)	37.8 ± 3.9	37.7 ± 4.0	38.0 ± 3.9	37.8 ± 3.5	37.8 ± 3.8
MUAC, cm					
Malnourished (MUAC < 21 cm)	57/444 (12.8%)	47/442 (10.6%)	44/452 (9.7%)	35/446 (7.8%)	183/1784 (10.3%)
Normal (21 ≤ MUAC < 23 cm)	63/444 (14.2%)	92/442 (20.8%)	73/452 (16.2%)	81/446 (18.2%)	309/1784 (17.3%)
Well nourished (MUAC ≥ 23 cm)	324/444 (73.0%)	303/442 (68.6%)	335/452 (74.1%)	330/446 (74.0%)	1292/1784 (72.4%)
Parity					
No previous birth	18/342 (5.3%)	22/324 (6.8%)	23/329 (7.0%)	28/332 (8.4%)	91/1327 (6.9%)
1-2 births	177/342 (51.8%)	169/324 (52.2%)	171/329 (52.0%)	171/332 (51.5%)	688/1327 (51.8%)
3-5 births	121/342 (35.4%)	112/324 (34.6%)	115/329 (35.0%)	112/332 (33.7%)	460/1327 (34.7%)
>5 births	26/342 (7.6%)	21/324 (6.5%)	20/329 (6.1%)	21/332 (6.3%)	88/1327 (6.6%)
Gravidity					
1	122/464 (26.3%)	139/463 (30.0%)	135/464 (29.1%)	134/466 (28.8%)	530/1857 (28.5%)
2	89/464 (19.2%)	90/463 (19.4%)	93/464 (20.0%)	92/466 (19.7%)	364/1857 (19.6%)
3	79/464 (17.0%)	79/463 (17.1%)	75/464 (16.2%)	75/466 (16.1%)	308/1857 (16.6%)
4	62/464 (13.4%)	61/463 (13.2%)	52/464 (11.2%)	58/466 (12.4%)	233/1857 (12.5%)

Continued on next page

TABLE 1. Continued

All Live Births Captured	Control Arm	BEP-Only Arm	BEP + Azithromycin Arm	BEP + Choline + Nicotinamide Arm	Total
Gravidity, continued					
5 and above	112/464 (24.1%)	94/463 (20.3%)	109/464 (23.5%)	107/466 (23.0%)	422/1857 (22.7%)
Mode of delivery					
Vaginal delivery	328/445 (73.7%)	333/443 (75.2%)	322/453 (71.1%)	315/448 (70.3%)	1298/1789 (72.6%)
Cesarean section	117/445 (26.3%)	110/443 (24.8%)	131/453 (28.9%)	133/448 (29.7%)	491/1789 (27.4%)

^aData are n/N (%) unless otherwise indicated.

^bSmall for Gestational Age (SGA) = birth weight <10th percentile for gestational age and sex.

similar between the BEP-only and control groups, with no consistent separation observed at birth or during follow-up. Compared with infants in the control group, those in the BEP plus AZ arm appeared to have higher mean WAZ scores from birth until 1-2 months and beyond 6 months; higher mean LAZ scores from birth until 6 months and beyond 11 months; and higher mean WLZ scores from birth until 1-2 months and beyond 7 months. Although infants in the BEP plus choline plus nicotinamide arm also had higher mean WAZ, LAZ, and WLZ scores than infants in the control arm at birth, these effects were not apparently sustained beyond the 1-month timepoint.

K-means clustering identified 3 groups (A, B and C) as the optimal number of clusters in our dataset, in which group C exhibited poorer growth (henceforth termed faltering cluster), group A exhibited better growth patterns (henceforth termed thriving cluster), and group B exhibited stable growth (Figure 3). In the WAZ category, the faltering cluster was composed of 22.3% (95% CI, 20.6-24.1) of infants from the control arm, 21.2% (95% CI, 19.6-22.9) from the BEP-only arm, 15.7% (95% CI, 14.2-17.2) from the BEP plus AZ arm, and 19.3% (95% CI, 17.8-21.0) from the BEP plus choline plus nicotinamide arm. In the WAZ category, the thriving cluster was composed of 34.4% (95% CI, 34.2-36.4) of infants from the control arm, 30.1% (95% CI, 28.3-32.0) from the BEP-only arm, 35.5% (95% CI, 33.6-37.4) from the BEP plus AZ arm, and 32.6% (95% CI, 30.7-34.5) from the BEP plus choline plus nicotinamide arm. While the 3 clusters were fairly separated at birth, there

are some infants whose trajectories moved from one cluster to another. In the LAZ category, the faltering cluster was composed of 22.1% (95% CI, 20.4-23.9) of infants from the control arm, 24.3% (95% CI, 22.6-26.1) from the BEP-only arm, 17.7% (95% CI, 16.3-19.3) from the BEP plus AZ arm, and 19.1% (95% CI, 17.6-20.8) from the BEP plus choline plus nicotinamide arm. In the LAZ category, the thriving cluster was composed of 31.7% (95% CI, 29.8-33.7) of infants from the control arm, 27.9% (95% CI, 26.1-29.8) from the BEP-only arm, 33.4% (95% CI, 32.5-36.3) from the BEP plus AZ arm, and 31.0% (95% CI, 29.2-32.9) from the BEP plus choline plus nicotinamide arm.

In the WLZ category, the faltering cluster was composed of 45.2% (95% CI, 43.1-47.3) of infants from the control arm, 49.3% (95% CI, 47.3-51.4) from the BEP-only arm, 48.3% (95% CI, 46.3-50.4) from the BEP plus AZ arm, and 49.2% (95% CI, 47.1-51.2) from the BEP plus choline plus nicotinamide arm. The thriving cluster was composed of 25.4% (95% CI, 23.6-27.3) of infants from the control arm, 23.2% (95% CI, 21.5-25.0) from the BEP-only arm, 22.4% (95% CI, 20.8-24.1) from the BEP plus AZ arm, and 23.0% (95% CI, 21.3-24.7) from the BEP plus choline plus nicotinamide arm.

To investigate factors associated with cluster membership, we performed a mixed-effects model with the use of the control arm as the referent (Table 3). Infants in the BEP plus AZ arm had 17% decreased odds of being in the faltering WAZ cluster (adjusted OR, aOR, 0.83; 95% CI, 0.72-0.96) and 17% decreased odds of being in

TABLE 2. Growth Indicators at Birth and at 12 Months After Birth^a

	Control Arm		BEP-Only Arm		BEP + Azithromycin Arm		BEP + Choline + Nicotinamide Arm		Total	
	At birth	At 12 mo	At birth	At 12 mo	At birth	At 12 mo	At birth	At 12 mo	At birth	At 12 mo
WAZ	93/429 (21.7%)	108/277 (39.0%)	102/427 (23.9%)	113/299 (37.8%)	69/437 (15.8%)	113/306 (36.9%)	69/429 (16.1%)	106/292 (36.3%)	333/1722 (19.3%)	440/1174 (37.5%)
LAZ	79/424 (18.6%)	123/277 (44.4%)	82/421 (19.5%)	139/302 (46.0%)	67/435 (15.4%)	127/315 (40.3%)	69/427 (16.2%)	120/296 (40.5%)	297/1707 (17.4%)	509/1190 (42.8%)
WLZ	33/385 (8.6%)	56/275 (20.4%)	30/377 (8.0%)	51/296 (17.2%)	27/406 (6.7%)	56/306 (18.3%)	31/403 (7.7%)	58/293 (19.8%)	121/1571 (7.7%)	221/1170 (18.9%)

^aData are n (%).

the faltering LAZ cluster (0.83; 0.69-0.90) compared with infants in the control arm. The SGA was associated with higher odds of being in the faltering WAZ cluster (4.27; 3.82-4.77), being in the faltering LAZ faltering (3.44; 3.08-3.85), and being in the faltering WLZ cluster (1.92; 1.67-2.20). Each 1-cm increase in maternal height was associated with 4% decreased odds of being in the faltering WAZ cluster (0.96; 0.95-0.97), and 6% decreased odds of being in the faltering LAZ cluster (0.94; 0.93-0.95). Maternal BMI at delivery was strongly associated with cluster membership, with infants of mothers who were underweight having higher odds of being in the faltering WAZ cluster (2.27; 1.91-2.70), the faltering LAZ cluster (1.33; 1.11-1.59), and the faltering WLZ cluster (1.99; 1.62-2.43). Maternal age, parity, and mode of delivery were not associated with any cluster membership.

DISCUSSION

In this longitudinal cohort of infants from the MUMTA trial in Pakistan, the antenatal interventions of BEP plus AZ and BEP with choline and nicotinamide outperformed the control arm in birth outcomes and growth trajectories. We identified 3 linear growth trajectory clusters over the 1-year follow-up period that were influenced by the AZ intervention, maternal height, BMI, and infant size at birth.

Consistent with previous evidence that nutritional interventions alone often produce modest gains in birth size and early growth trajectories, BEP supplementation alone in our study did not improve infant birth weight or 12 month growth trajectories.^{21,22} Maternal small quantity lipid-based nutrition supplementation given at preconception and prenatally from the women first trial (with participants from Democratic Republic of Congo, Guatemala, India, and Pakistan) has shown persistence of benefit in longitudinal growth models in infants from birth to 6 months of age.²² Prenatal BEP supplementation in the MISAME-III trial was associated with a considerable higher LAZ scores and lower stunting prevalence at 6 months of age but no difference in growth trajectories over the first year of life.²³

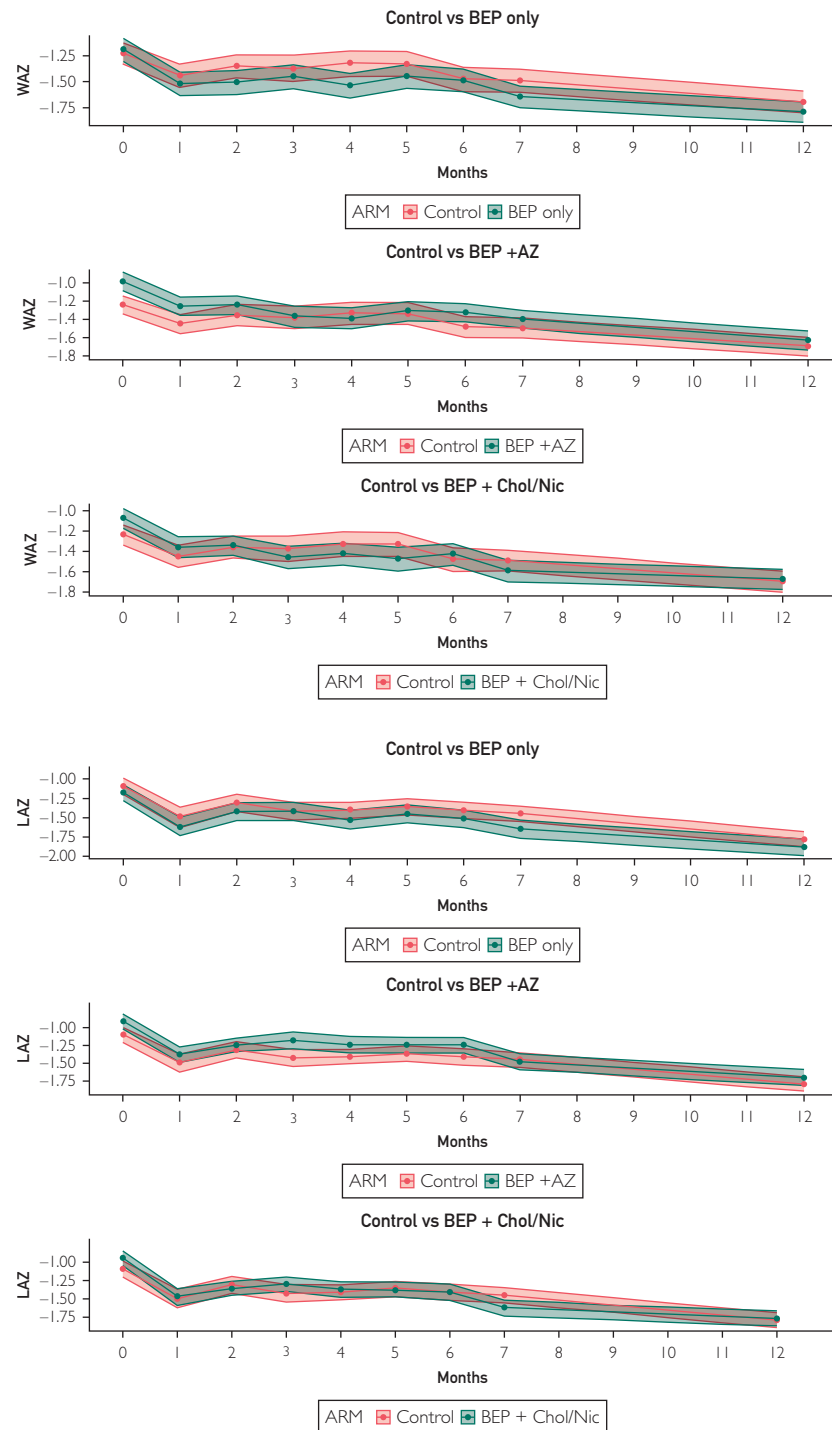


FIGURE 2. Trajectory analysis of mean WAZ, LAZ, and WLZ scores with 95% CIs from birth until 12 months. The 3 intervention groups (green line) are compared with the control arm (red line). Overlapping 95% CIs suggest no statistical significance. Trends are noted on the basis of separate visible lines whose 95% CIs do not overlap. LAZ, length-for-age z-scores; WAZ, weight-for-age z-scores; WLZ, weight-for-length z-scores.

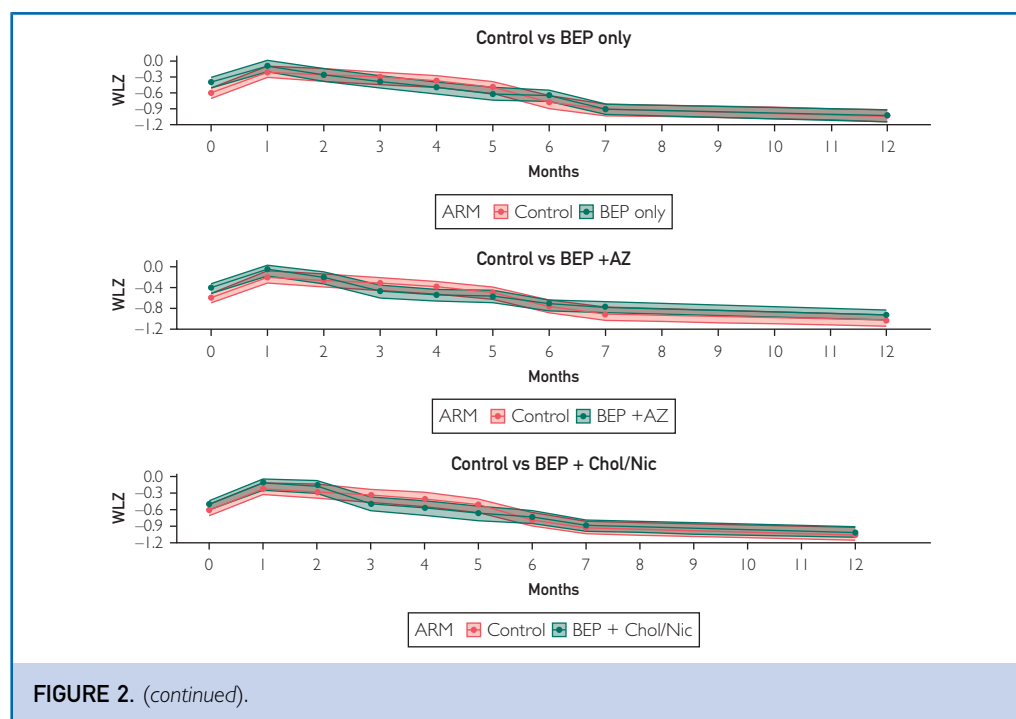


FIGURE 2. (continued).

Infants born to mothers in the BEP plus AZ arm had a higher mean WAZ scores from birth to 2 months and beyond 6 months, a higher mean LAZ scores from birth to 6 months and beyond 11 months, and a higher mean WLZ scores from birth to 2 months and beyond 7 months. Our cluster analysis indicated that infants in the BEP plus AZ arm had the highest membership in the thriving cluster across WAZ, WLZ, and LAZ measures. Moreover, faltering growth, based on WAZ and LAZ trajectories, was lowest in the BEP plus AZ arm, and infants in that arm had a 17% reduced risk of being underweight and 17% reduced risk of stunting compared with the control arm. In terms of using prophylactic antibiotics for maternal antenatal infection control, trials from Papua New Guinea²⁴ and Sierra Leone²⁵ report positive effects on birth size, and the Sierra Leone study showed positive effects up to 6 months of age. A trial in Malawi investigated the impact of adding 2 doses of AZ to antenatal monthly sulfadoxine-pyrimethamine (SP) on maternal PCR-diagnosed malaria parasitemia, fetal biparietal diameter, and femur length growth velocity in the second and third trimesters of

pregnancy.²⁶ Findings showed a reduction in the incidence of PTB, LBW, and stunting during the first 5 years of life in the AZ with SP arm. The AZ with SP arm showed significant benefits over the control group (SP only) in child growth outcomes. Specifically, it showed improved height-for-age z-scores up to 12 months, a lower prevalence of stunting up to 36 months, and a reduced incidence of stunting persisting through 60 months.²⁷ The authors interpreted this pattern as suggesting that AZ's impact on fetal growth and PTB may operate through antibacterial and anti-inflammatory pathways rather than primarily by reducing malaria parasitemia. Consistent with this hypothesis, PW receiving SP plus AZ have been shown to have considerable lower levels of the inflammatory biomarkers α -1-acid glycoprotein and c-reactive protein at delivery.²⁸

Our findings bring further evidence on the potential role of AZ in improving child growth trajectories both at birth and during infancy. We postulate that this effect may occur through the broader actions of macro-lides, including immunomodulatory effects that enhance epithelial barrier function,

contributing to therapeutic benefits in chronic inflammatory conditions such as malnutrition, while simultaneously reducing the burden of infection. Such modulation of maternal gut physiology could potentially improve absorption of nutritional supplements, leading to survival and growth benefit.^{29,30} This may also explain the lack of effect seen in the BEP-only arm, in which inflammation, dysbiosis, or altered maternal physiology prevents the uptake of nutrients from diet.

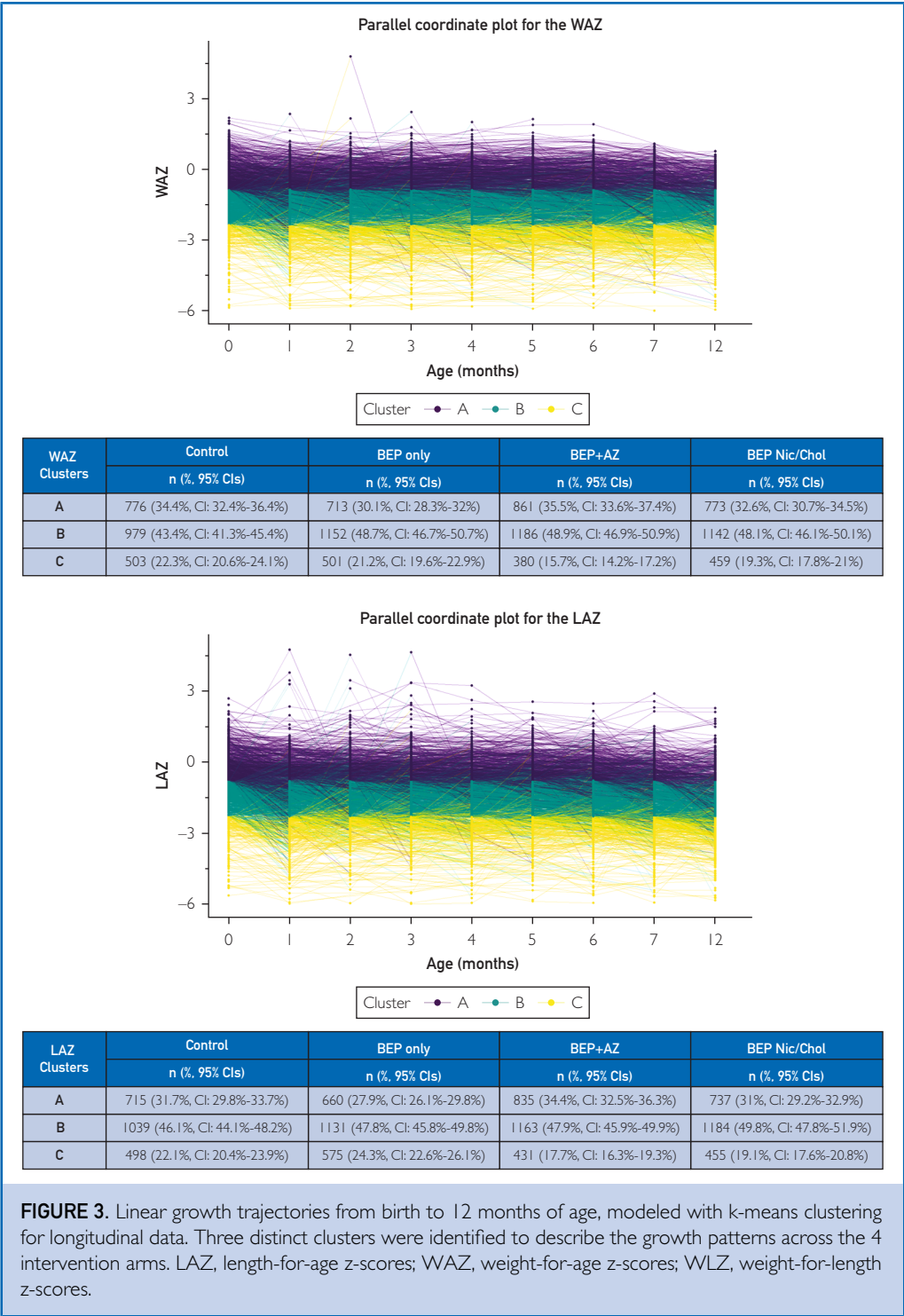
Given concerns regarding antimicrobial resistance following AZ exposure, we also evaluated carriage of the *mph(A)* gene, which confers resistance to macrolides. We found no evidence of a difference in *mph(A)* carriage between study arms from birth to 12 months of age.¹⁷ This suggests that, within the duration of follow-up, the intervention was not associated with a detectable increase in macrolide resistance, although longer-term effects and broader resistance patterns warrant further study. Nicotinamide and choline both play critical roles in supporting fetal growth. It is known that nicotinamide or niacin (B3) and other B complex vitamins are crucial cofactors for generating and releasing energy in cells, as well as for the metabolism of all macronutrients.³¹ Nicotinamide improves maternal conditions and fetal development through multiple mechanisms, including reducing oxidative stress and inflammation in the placenta via FoxO3 activation,³² normalizing ATP synthesis to prevent fetal growth restriction in preeclampsia models,³³ and prolonging pregnancies while mitigating adverse effects such as hypertension and placental dysfunction.³³ Only a limited number of studies; however, have thoroughly investigated the connection between nicotinamide and fetal growth. A nutritional investigation among mothers in Brazil found that antenatal vitamin B3 and C intake was considerably associated with increased birth weight.³⁴ Similarly, a study in Iran showed a weak positive correlation between maternal intake of some micronutrients, among them vitamin B3, and infant birth weight ($P < .05$),³⁵ but other studies found no association between nicotinamide intake and infant birth weight.³⁶⁻³⁸

Choline is known to be essential for fetal development, particularly for brain

development and the formation of cell membranes, an effect mediated through the provision of methyl groups for epigenetic modifications.^{39,40} This influence on gene expression could potentially impact growth. Research on maternal choline supplementation during pregnancy has shown cognitive benefits for offspring, such as improved information processing speed⁴⁰ and sustained attention.⁴¹ Although these studies highlight the importance of choline during pregnancy, they do not specifically address the impact of antenatal choline on linear growth. Few studies have investigated dietary choline supplementation in PW and its impact on infant linear growth. One study conducted in South Africa assessed the effect of choline (2 g per day) with a placebo administered to heavy-drinking PW from mid-pregnancy to delivery. Its findings showed no difference in birth weights between the study groups, but the children born to the mothers in the choline group showed a higher catch-up growth in weight and head circumference at 6.5 and 12 months.⁴²

There are some studies that have investigated postnatal serum choline levels and their association with linear growth in children. A study done in Malawi showed that low serum choline concentrations in infants aged 12-50 months are associated with linear growth failure in young children, possibly because of the role of choline in the linear growth of long bones by endochondral ossification.⁴³ The KOALA group in The Netherlands found that higher levels of choline in the mother's blood during the third trimester of pregnancy were associated with babies gaining slightly more weight in their first year and having a slightly higher BMI in early childhood (1-2 years).⁴⁴

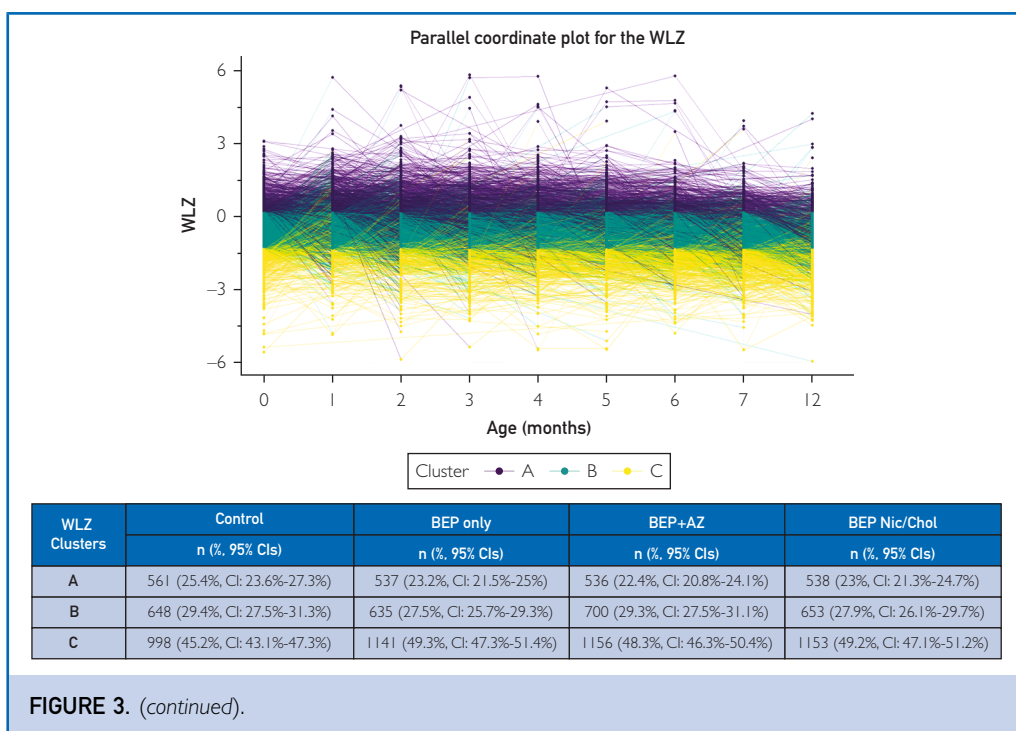
Our findings from the BEP plus choline plus nicotinamide arm add important evidence to a limited body of outcomes research evaluating these micronutrients in pregnancy. We found that the BEP plus choline plus nicotinamide arm had higher mean WAZ, LAZ, and WLZ scores at birth. The unadjusted difference in birth weight between the BEP plus choline plus nicotinamide group and the control group was 58 g (95% CI, -26 to 142; $P = .07$),¹⁷ These findings are consistent with literature in suggesting a positive impact of the micronutrient on birth



outcomes. In terms of the postnatal growth trajectory of our cohort, the effect on higher WAZ, LAZ, and WLZ at birth in infants in the BEP plus choline plus nicotinamide arm

was not sustained in the postnatal period up to 12 months.

The difference observed between the BEP plus AZ arm and the BEP plus choline plus



nicotinamide arm in their effects on infant growth during the first year of life highlights the potential importance of continued postnatal nutritional interventions to support child growth. The divergence in postnatal growth trajectories in our study raises the question of whether extending micronutrient supplementation, either through maternal supplementation during lactation or direct neonatal supplementation, may help prevent growth faltering and promote sustained linear growth through later infancy. These findings underscore the need to consider linking antenatal and postnatal interventions, such as those evaluated in this study and in the Mumta Lactating Women trial,⁴⁵ to provide comprehensive nutritional support across the continuum of pregnancy and lactation, particularly in malnourished settings.

The strengths of this longitudinal analysis lie in the robust methodology used to model growth trajectories, whereby all infants, regardless of the number of follow-up visits, were assigned to a trajectory cluster. This inclusive approach retains the full sample and reduces bias that could result from excluding participants with incomplete data. The identification

of distinct linear growth clusters, influenced not only by the intervention but also by maternal height, BMI, and infant size at birth, provides novel insight into the multifactorial determinants of early childhood growth. If these findings are corroborated in other settings, they could have important implications for maternal and child health guidelines, particularly in regions with high rates of undernutrition and growth faltering. Notably, safety and antimicrobial resistance profiles were systematically recorded and analyzed throughout the entire duration of follow-up. The interventions tested are simple, scalable, and potentially cost-effective, offering a practical strategy to support healthy growth in infancy and reduce the burden of stunting. This underscores the potential for targeted maternal nutrition programs during pregnancy to yield long-term benefits for child health in similar low-resource settings.

Despite the strengths of this study, several limitations warrant consideration. First, while the longitudinal design enabled the assessment of growth trajectories over the first year of life, some infants had missing anthropometric measurements at intermediate time points (Supplementary Table 1). Second, the study

TABLE 3. Unadjusted and Adjusted Mixed-Effects Modeling for Membership to WAZ, LAZ, and WLZ Faltering Cluster From Birth to 12 Months^{a,b,c,d}

	Faltering WAZ				Faltering LAZ				Faltering WLZ			
	OR (95% CI)	P	aOR (95% CI)	P	OR (95% CI)	P	aOR (95% CI)	P	OR (95% CI)	P	aOR (95% CI)	P
Arm												
Control	Ref		Ref		Ref		Ref		Ref		Ref	
BEP only	0.99 (0.87-1.13)	.86	0.99 (0.86-1.14)	.94	1.15 (1.01-1.32)	.03	1.18 (1.02-1.36)	.02	0.93 (0.78-1.12)	.47	0.95 (0.79-1.15)	.61
BEP + azithromycin	0.77 (0.67-0.88)	<.001	0.83 (0.72-0.96)	.01	0.79 (0.69-0.90)	.001	0.83 (0.72-0.96)	.01	0.91 (0.76-1.09)	.30	0.97 (0.80-1.16)	.72
BEP + choline + nicotinamide	0.85 (0.75-0.97)	.02	0.94 (0.81-1.08)	.36	0.88 (0.77-1.01)	.06	0.92 (0.80-1.06)	.27	0.98 (0.82-1.17)	.81	1.05 (0.87-1.26)	.62
Small-for-gestational-age												
Yes	4.82 (4.32-5.37)	<.001	4.27 (3.82-4.77)	<.001	3.85 (3.45-4.29)	<.001	3.44 (3.08-3.85)	<.001	2.02 (1.76-2.31)	<.001	1.92 (1.67-2.20)	<.001
No	Ref		Ref		Ref		Ref		Ref		Ref	
Maternal characteristics												
Age												
<25 y	Ref				Ref				Ref		Ref	
25-35 y	1.04 (0.94-1.14)	.49			0.97 (0.88-1.07)	.52			1.16 (1.02-1.33)	.03	1.21 (1.05-1.39)	.007
>35 y	1.10 (0.91-1.32)	.32			1.05 (0.87-1.27)	.63			1.03 (0.79-1.35)	.80	1.08 (0.83-1.41)	.57
Height (per cm increase)	0.95 (0.95-0.96)	<.001	0.96 (0.95-0.97)	<.001	0.93 (0.93-0.94)	<.001	0.94 (0.93-0.95)	<.001	1.00 (0.99-1.02)	.48		
BMI at delivery ^c												
Underweight	2.68 (2.28-3.15)	<.001	2.27 (1.91-2.70)	<.001	1.53 (1.3-1.82)	<.001	1.33 (1.11-1.59)	.002	2.25 (1.85-2.75)	<.001	1.99 (1.62-2.43)	<.001
Not Underweight	Ref		Ref		Ref		Ref		Ref		Ref	
Parity												
No previous birth	Ref				Ref				Ref			
1-2 births	0.94 (0.75-1.18)	.60			0.92 (0.73-1.15)	.46			1.09 (0.79-1.50)	.61		
3-5 births	0.94 (0.75-1.19)	.62			0.83 (0.66-1.06)	.13			1.15 (0.82-1.60)	.42		
>5 births	0.95 (0.69-1.29)	.73			0.86 (0.63-1.18)	.35			1.26 (0.83-1.92)	.28		
Mode of delivery												
Vaginal delivery	Ref				Ref				Ref			
Cesarean section	1.04 (0.94-1.16)	.46			0.96 (0.86-1.07)	.49			0.99 (0.85-1.15)	.89		

^aThe WAZ and LAZ models were adjusted for arm, SGA, maternal height, and BMI category at delivery. The WLZ model was adjusted for arm, SGA, maternal age, and BMI category at delivery.

^bVariables not significant in univariate analysis (maternal age, parity, mode of delivery) were excluded from the multivariable mixed-effects model.

^cMaternal underweight (BMI<18.5 kg/m²)/ Not underweight (BMI≥18.5 kg/m²).

^dAbbreviations: aOR, adjusted odds ratio; OR, odds ratio.

was conducted in a single peri-urban setting in Pakistan, which may limit the generalizability of the findings to rural populations or other low to middle income countries contexts with different patterns of malnutrition, infection, and health care access. Third, although we collected data on potential confounders such as maternal anthropometry and socioeconomic status, residual confounding from unmeasured variables (eg, dietary diversity, household food insecurity, infection, and caregiver care-seeking practices) cannot be ruled out. Infection burden may play an important role, as recurrent or subclinical infections can adversely affect infant growth while also influencing exposure to antibiotics. Additionally, care-seeking behavior may differ across participants, potentially affecting both access to treatment and underlying health status. These factors could contribute to the observed associations and may not be fully captured in our analysis. Finally, while this study focused primarily on linear growth outcomes, additional developmental domains such as cognitive, immune, and metabolic outcomes were not explored here. However, these are the focus of ongoing analyses and forthcoming manuscripts, which aim to provide a more comprehensive understanding of the impact of antenatal interventions on child development.

CONCLUSION

In summary, we report 1-year follow-up of growth trajectories for infants from the Mutma PW trial. We found no effect of BEP alone, when compared with control, on any anthropometric measure. The combined effect of BEP and AZ on growth trajectories was seen at birth, throughout the postnatal period, and into late infancy. In contrast, the effect of BEP with choline and nicotinamide was evident at birth but decreased by the 1-year follow-up. Antenatal interventions such as BEP supplementation with prophylactic AZ could help support and sustain infant growth outcomes in low-resource settings. Elucidating the antimicrobial and nonantimicrobial mechanisms of AZ in malnourished women and infants is critical for addressing the global malnutrition crisis.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

ETHICS STATEMENT

The Mumta PW trial was a community-based, open-label, assessor-blinded randomized controlled superiority trial. The full trial protocol is published and registered at clinicaltrials.gov (NCT04012177). The study was overseen by a technical committee and an independent data and safety monitoring board (DSMB). Ethics approval of the trial was obtained from the institution review board of VITAL Pakistan Trust (Reference: 004-VPT-IRB-18 on Date: September 11, 2018), ethics review committee of Aga Khan University (Reference: 2019-0772-2783 on Date: March 11, 2019), and National Bioethics Committee of Pakistan (Reference: 4-87/NBC-409/19/303 on Date: November 19, 2019). This secondary analysis was covered under the study's annual continuing ethical approval granted by the ethical review committee of Aga Khan University, Karachi (Reference: 2025-0772-39076). Informed consent will be obtained from all participants. The trial was performed in accordance with the principles of the Declaration of Helsinki. All the authors vouch for the completeness and accuracy of the reported data and the fidelity of the trial to the protocol.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

Generative artificial intelligence tools were used to assist with language editing and clarity. All content was reviewed, verified, and approved by the authors, who take full responsibility for the accuracy and integrity of the work.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mcpiqojournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AZ**, azithromycin; **BMI**, body mass index; **BEP**, balanced energy protein; **LAZ**, length-for-age Z-score; **LBW**, low birth weight; **MUAC**, mid-upper arm circumference; **PW**, pregnant women; **PTB**, preterm birth; **SP**, sulfadoxine-pyrimethamine; **SGA**, small-for-gestational-age; **WAZ**, weight-for-age Z-score; **WLZ**, weight-for-length Z-score

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