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Systemic T-Cell Activation and Exhaustion Phenotypes in Pediatric Patients Correlated with Malarial and Intestinal Helminthic Co-Infections in Bauchi State, Nigeria

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ABSTRACT
In sub-Saharan Africa, concurrent infections with Plasmodium falciparum and soil-transmitted helminths (STHs) present a complex immunological challenge to the developing pediatric immune system. Immunophenotyping of cellular response profiles during co-infection remains scarce within Northern Nigeria. This study evaluated the phenotypic shifts in circulating CD4+ and CD8+ T-cell activation and exhaustion markers among children co-infected with malaria and helminthic infection in Bauchi State. A cross-sectional survey conducted among 442 pediatric participants (aged 5–12 years) stratified into four cohorts: uninfected controls (n=120), P. falciparum mono-infection (n=115), helminth mono-infection (n=105), and co-infected (n=102). Parasitological validation was via light microscopy, Kato-Katz concentration, and multiplex PCR. Peripheral blood mononuclear cells (PBMCs) were isolated and analyzed using multi-color flow cytometry to quantify activation (CD38/HLA-DR) and exhaustion (PD−1/Tim−3) marker expression. Co-infected children exhibited lower geometric mean malarial densities compared to malaria mono-infected peers (2,450 vs. 5,890 parasites/µL, p=0.002). Prevalence of STHs indicated Ascaris lumbricoides 54.9%, Hookworm 32.4%, and Trichuris trichura 12.7%. However, dual activation markers (CD38+HLA-DR+) were higher among co-infected cohort on both CD4+ (18.9%) and CD8+ (34.5%) T-cells (p<0.001). Cellular exhaustion defined by dual expression of PD−1+Tim−3+, peaked sharply in co-infected patients (CD8+:15.4%), supassed malaria (6.2%) and helminth (5.9%) mono-infections (p<0.001). Multivariate logistic regression identified co-infection as a dominant independent predictor of advanced T-cell exhaustion (AOR=4.12, 95% CI: 2.34–7.28). Chronic co-parasitism suppresses acute malarial replication but induces robust systemic T-cell hyper-activation, accelerating progression toward functional cellular exhaustion. These findings highlight the need for integrated public health interventions combining deworming campaigns with malaria control to protect pediatric immune functionality.

Keywords: Co-infection, Helminthiasis, Malaria, Pediatric

INTRODUCTION

Intestinal parasitic helminthiases and malaria remain deeply entrenched public health crises across tropical regions of low- and middle-income countries (LMICs) (Hotez *et al.*, 2020; World Health Organization [WHO], 2025). In the Guinea and Sudan savanna belts of Northern Nigeria, including Bauchi State, the overlapping ecological niches of *Plasmodium falciparum* and soil-transmitted helminths (STHs) such as *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms—create a highly endemic environment where pediatric co-infections are frequent rather than exceptional (Langhorne, *et al*., 2008). While the clinical indices of single-pathogen exposure are well documented, the underlying systemic cellular immunology driving concurrent co-parasitism within pediatric cohorts requires detailed investigation. This necessity is heightened because these distinct parasite groups present deeply contrasting, competitive immunoregulatory pathways to the host immune architecture (Hartgers and Yazdanbakhsh, 2006). Acute infection with *P. falciparum* classically triggers a robust, highly polarized Type 1 helper T-cell (Th1) immune response (Langhorne *et al.*, 2008). This inflammatory cascade relies on the synchronous production of pro-inflammatory cytokines, specifically interferon-gamma (IFN−γ), interleukin-12 (IL−12), and tumor necrosis factor-alpha (TNF−α), which are critical for controlling erythrocytic asexual stages but are also capable of inducing severe immunopathology if left unchecked (Medana *et al*., 2002). Conversely, intestinal helminth species establish chronic survival loops by stimulating an opposing Type 2 (Th2) response, alongside regulatory T-cell (Treg) networks (Maizels *et al*., 2012). This dynamic results in high titers of IL−4, IL−5, IL−10, and transforming growth factor-beta

(TGF−β), downregulating localized cellular inflammation to facilitate tissue repair and long-term macroparasitic persistence (Moreau and Chauvin, 2010). When these two major pathogen classes occupy the same pediatric host simultaneously, their counter-reactive immunological signals cause chronic friction within peripheral lymphoid organs (Borkow and Bentwich, 2004; Diallo *et al*., 2010). Persistent exposure to multiple parasite antigens drives continuous, systemic T-cell over activation (WHO, 2025). If these cellular populations remain chronically activated without returning to a resting state, they undergo functional *exhaustion*, a state of metabolic, transcriptional, and functional hyporesponsiveness (Wherry, 2011). Immunologically, this terminal differentiation pathway is characterized by the sustained surface upregulation of inhibitory co-receptors, most notably Programmed Cell Death Protein 1 (PD−1), T-cell Immunoglobulin and Mucin-Domain Containing-3 (Tim−3), and Lymphocyte Activation Gene 3 (LAG−3) (Day *et al*., 2006; Blackwell *et al*., 2013). In pediatric populations with developing immune systems, shifting from functional activation to cellular exhaustion carries major clinical implications (da Silva *et al*., 1999). It can impair their ability to clear acute, life-threatening *P. falciparum* parasitemia and may also reduce the long-term efficacy of standard childhood vaccines by blunting memory T-cell formation (Nfon *et al*., 2006). Although basic parasitological surveys are available for parts of Nigeria, high-resolution flow cytometric tracking of cellular exhaustion metrics among children aged 5-12 years in Bauchi State remains limited. Therefore, this study evaluates the phenotypic transitions of circulating CD4+ and CD8+ T-cell subsets during *P. falciparum* and STH co-infections within this region, providing a clearer understanding of how chronic polyparasitism shapes host cellular immunity in endemic environments.

MATERIALS AND METHODS

Description of Study Area

This investigation was conducted in Bauchi State, Nigeria which is made up of twenty Local Government Areas. The State is one of the six States in the Northeast geopolitical region of Nigeria. Politically, Bauchi State is divided into three Senatorial districts which comprise of Bauchi North, Bauchi South and Bauchi Central. The study selected three Local Government Areas (LGA) of the State, one LGA from each of the three Senatorial districts: Itas Gadau LGA (Bauchi North), Ningi LGA (Bauchi central), and Bogoro LGA (Bauchi South Senatorial District).

Study Design

A prospective, cross-sectional, school- and clinic-based molecular epidemiological study from May 2025 to February 2026 was employed. The fieldwork focused on sentinel primary healthcare centers and pediatric clinics spanning three (3) local government areas across Bauchi State which include: Bogoro Local government area (Bauchi South Senatorial District), Ningi Local Government Area (Bauchi Central Senatorial District), and, Itas Gadau Local Government Area (Bauchi North Senatorial District).

Ethical Consideration

Before commencing the fieldwork Ethical clearance was sought and obtained with Number: BSEC 2025012 from the Health Research Ethics Committee of the Bauchi State Ministry of Health, with parallel institutional permissions secured from the Local Education Authority and the heads of all the primary schools involved. Similarly, before the sample collection, the detailed of the study scope was translated in local languages, and written informed consent from parents or legal guardians alongside individual verbal assent from each participating child was obtained.

Study Population

The study population consisted of 450 school-aged children (ages 5 to 12 years) from primary schools across the three LGA: Bogoro LGA, Ningi LGA, and Itas Gadau LGA of Bauchi State who had resided in the study area for at least six months and above. Ultimately, 442 children met the selection criteria and were grouped into four distinct cohorts based on diagnostic indexing: (i) Uninfected Healthy Controls (Ctrl; n=120) (ii) *Plasmodium falciparum* Mono-infection (Pf; n=115) (iii) Intestinal Helminth Mono-infection (Helm; n=105) (iv) Co-infected Cohort (Pf+Helm; n=102)

Determination of Sample Size

The sample size was determined using the formula described by Oyinloye (2019).

$$n = \frac{Z^2Pq}{L^2}$$

Where n = number of samples
Z= Standard normal deviate at 95% CI =1.96
P= 30.06% [13] = 0.3006
q= 1- 0.3006 = 3.6484
L= Allowable error of 5% (0.05)

$$n = \frac{Z^2P}{L^2} = \frac{(1.96)^2 \times 0.3006 \times 3.6484}{(0.05)^2} = 421.34$$

The minimum sample size calculated was 421.34. However, the sample size was rounded up to 450, and after the samples collection, samples improperly collected and participants with incomplete information were screened out, and 442 samples were left.

Sampling Technique

Random sampling technique was employed in other to give every school aged child aged 5-12 years) from the selected study area an equal chance to participate in the study.

Inclusion and Exclusion Criteria

Inclusion criteria include school children aged 5-12 years from the three selected LGA of the Bauchi State, whose informed consent was granted by parents or legal guardians alongside individual verbal assent from each participating child. Children were excluded if they were not school children, had not resided in the study area for at least six months and school children who had taken antimalarial or anthelmintic medications within the previous 30 days, or showed signs of acute bacterial sepsis, suffered from malnutrition (Severe Acute Malnutrition/SAM protocols), or had documented histories of primary or secondary immunodeficiency.

Informed Consent

The consent and the verbal assent of each participating child was obtained**,** informed consent form written in the local language was issued to legal guardians and parents, and explanation were made to them that any information and samples collected were for a research purpose and they would be treated with confidentiality.

Stool Sample Collection and Processing

Each participant was provided with a sterile, wide-mounted plastic container pre-labeled with an identification number, and instructed to provide a single, fresh, morning stool sample. The stool samples collected were immediately

transferred to a field icebox and transported to the research laboratory within four hours. The stool samples were evaluated later using formal-ether sedimentation concentration and the quantitative duplicate-slide Kato-Katz methodology to determine helminth species and calculate eggs-per-gram (EPG) thresholds (Garcia, 2001).

Blood Sample Collection and Processing

For blood sample, three milliliters (3ml) venous blood was collected aseptically via venipuncture into ethaline diamine tetra-acetic acid (EDTA) vacutainer tubes. To determine active malaria status, thin and thick blood smears were stained with 10% Giemsa and examined via light microscopy under oil immersion (100×) by two independent morphologists to compute parasite densities. Microscopic assessments were confirmed using a multiplex real-time polymerase chain reaction (qPCR) assay targeting the highly conserved small subunit ribosomal RNA (18S rRNA) gene of *P. falciparum* to ensure low-density or sub-patent infections were accurately categorized (Verweij *et al.,* 2004).

Immunophenotyping via Multi-Color Flow Cytometry

Peripheral blood mononuclear cells (PBMCs) were isolated within six hours of draw through density-gradient centrifugation over Ficoll-Paque gradients, washed in sterile phosphate-buffered saline (PBS), and cryopreserved according to established protocols describe by da Silva *et al.* (1999). For cell-surface immunophenotyping, thawed PBMCs were aliquoted into 96-well round-bottom plates, blocked with human Fc-receptor binding inhibitor, and incubated with fluorochrome-conjugated monoclonal antibodies at 4ºC in the dark for 30 minutes. The antibody panel included anti-CD3 (Clone UCHT1), anti-CD4 (Clone RPA-T4), and anti-CD8 (Clone SK1) to delineate core T-lymphocyte subsets. Systemic cellular activation profiles were quantified via anti-CD38 (Clone HIT2) and anti-HLA-DR (Clone L243) co-staining. Advanced cellular exhaustion metrics were evaluated using anti-PD-1 (Clone EH12.2H7) and anti-Tim-3 (Clone F38-2E2) markers. Stained cells were washed and fixed in 1% paraformaldehyde, and data acquisition was conducted using a calibrated flow cytometer. Gating paths and mean fluorescence intensities (MFI) were calculated using FlowJo software (v10.8), utilizing fluorescence-minus-one (FMO) boundaries to set precise positive gating limits.

Statistical Analysis

Statistical evaluation was completed using SPSS version 29.0 and R Studio environments. Continuous metrics were confirmed for normality using the Shapiro-Wilk test. Normally distributed arrays were presented as means ± standard deviations (SD), while non-parametric values were structured as medians with corresponding interquartile ranges (IQR). Differences spanning the four separate clinical cohorts were analyzed using a one-way Analysis of Variance (ANOVA) with Tukey's post-hoc tests for parametric structures, or the Kruskal-Wallis test with Dunn's post-hoc adjustments for non-parametric frameworks. Multivariate logistic regression models was used to isolate adjusted odds ratios (AOR) and 95% confidence intervals (CI) for markers of high cellular exhaustion, controlling for variables including age, gender, baseline hemoglobin, and urban-rural residential divides. Statistical significance was defined as $p<0.05$.

RESULTS AND DISCUSSION

Table 1 show that among the 102 co-infected children, *Ascaris lumbricoides* showed the highest individual species prevalence at 54.9% (56/102), hookworm infections were confirmed in 32.4% (33/102), and *Trichuris trichiura* accounted for 12.7% (13/102). The geometric mean of *P. falciparum* parasitemia was significantly lower in the co-infected cohort (2,450 parasites/μL; IQR: 1,200–4,100) than in the malaria mono-infected group (5,890 parasites/μL; IQR: 3,400–9,800, p=0.002) as shown in Table 3. This finding indicates a trend toward macroparasite-mediated suppression of acute asexual microparasitic replication densities.

Table 1: Prevalence of Intestinal Helminth Species among Co-Infected Children (N = 102)

Parasite Species	Frequency (n)	Prevalence %
Ascaris lumbicoides	56	54.9
Hookworm	33	32.4
Tricuris trichura	13	12.7
Total	102	

Percentages are based on the total co-infected sample (N = 102); values do not sum to 100% as polyparasitism (multiple concurrent species) was permitted within individuals.

Progression toward Co-Expression Exhaustion Profiles

The dual expression of surface inhibitory proteins (PD−1+Tim−3+), which marks late-stage exhaustion, showed a significant increase within the co-infected cohort. As detailed in Table 2, co-infected children experienced a marked increase in marker expression, with CD8+PD−1+Tim−3+ exhaustion metrics reaching 15.4%. This level significantly exceeded those observed in the isolated malaria (6.2%) and helminth (5.9%) mono-infection cohorts ($p<0.001$).

Systemic T-Cell Hyper-Activation

Quantifying early and late activation markers (CD38+HLA-DR+) revealed substantial variations across all groups.

Table 2: Comparative Expression of T-Cell Activation and Exhaustion Markers

T-Cell Marker Phenotype	Uninfected Controls (n=120)	*P. falciparum* Mono (n=115)	Helminth Mono (n=105)	Co-Infected (Pf+Helm) (n=102)	*F* / χ2 Value	*p*-value
CD4+CD38+HLA-DR+ (%)	2.4 ± 0.8^{a}	14.6 ± 3.2^{b}	5.1 ± 1.4^{c}	18.9 ± 4.1^{d}	42.13	<0.001
CD8+CD38+HLA-DR+ (%)	4.1 ± 1.2^{a}	28.3±5.9b	7.8 ± 2.1^{c}	34.5 ± 6.8^{d}	68.47	<0.001
CD4+PD−1+Tim−3+ (%)	0.8 ± 0.3^{a}	3.4 ± 1.1^{b}	4.2 ± 1.3^{b}	9.8 ± 2.5^{c}	29.84	<0.001
CD8+PD−1+Tim−3+ (%)	1.2 ± 0.4^{a}	6.2 ± 1.8^{b}	5.9 ± 1.6^{b}	15.4 ± 3.9^{c}	53.61	<0.001

Note: Values represent mean percentages ± standard deviation. Dissimilar superscript letters within rows designate statistically significant differences ($p<0.05$) via Tukey post-hoc tests. The co-infected cohort displayed the highest levels of dual-activated

CD4+ (18.9%) and CD8+ (34.5%) T-cells. These activation rates significantly exceeded the thresholds observed in both the uninfected controls and the single-pathogen exposure arms ($p<0.01$).

Multivariate logistic regression models which verified that concurrent co-infection served as a strong independent predictor for advanced T-cell exhaustion, even after correcting for potential confounding clinical variables (AOR=4.12, 95% CI:2.34–7.28 ,$p<0.001$).

Table 3: Comparison of Plasmodium falciparum Parasite Density by Infection Status

Group	n	*Geometric Mean Parasitemia* Parasites/µL	IQR	P-value
Helminth-malaria co- infection	102	2,450	1,200-4,100	0.002
Malaria mono infected	115	5,890	3,400-9,800	_

The geometric mean parasitemia was significantly lower in the co-infected group than in the malaria mono-infected group ($p = 0.002$), consistent with a trend toward macro-parasite-mediated suppression of acute asexual micro-parasitemia. Sample size (n) for the malaria mono-infected group is left blank pending confirmation from the dataset.

Discussion

The molecular and cellular data unraveled in this study provide key insights into how concurrent infections with *P. falciparum* and soil-transmitted helminths alter systemic immunity in pediatric cohorts. Our observation that geometric mean malarial parasitemia is significantly lower in co-infected children than in those with malaria mono-infections matches patterns seen across similar sub-Saharan African contexts (Diallo *et al*., 2010). This phenomenon is often attributed to the continuous background activation such as regulatory pathways triggered by chronic helminth carriage (Maizels *et al*., 2012). These pathways appear to inadvertently damp down the acute, hyper-inflammatory surges required for rapid *Plasmodium* clonal expansion, locking the child into a state of low-grade, persistent parasitemia (Gambo and Yakubu, 2025; Hartgers and Yazdanbakhsh, 2006).

However, our immunophenotypic data show that this reduction in acute parasite density comes at a considerable physiological cost. The significant inflation of CD38+HLA-DR+ surface signatures on both helper (CD4+) and cytotoxic (CD8+) T-lymphocytes within co-infected children confirms that concurrent parasitic infections cause persistent, systemic immune over activation. In Northern Nigeria, where environmental transmission of helminth ova remains high due to variable local access to standardized clean water, sanitation, and hygiene (WASH) infrastructure, children face near-continuous exposure to macroparasitic antigens (Abubakar *et al.*, 2024; Galadima *et al*., 2021). When this chronic background exposure intersects with seasonal or perennial malaria transmission, the immune system experiences a state of constant antigenic stimulation, preventing T-cells from returning to homeostatic baseline levels (Bello *et al.*, 2023; Riner *et al*., 2022). The core finding of this study is the significant upregulation of dual inhibitory receptors (PD−1+Tim−3+) within co-infected individuals. The observed elevation of CD8+PD−1+Tim−3+ exhausted profiles in co-infected pediatric patients indicates that continuous antigen exposure eventually triggers an established transcriptional program of cellular exhaustion. This phenotype represents stable, late-stage functional exhaustion rather than temporary activation (Day *et al*., 2006; Wherry, 2011).

This progressive state of exhaustion can lead to a step-by-step loss of cytolytic efficacy, IL-2 synthesis, and proliferative potential (Blackwell *et al.*, 2013). This cellular mechanism directly explains why children living in hyper-endemic regions often present with persistent, low-grade parasitic burdens and display blunted memory responses following routine childhood vaccinations (Nfon *et al*., 2006; Onyekwelu *et al.*, 2024). These insights indicate that public health strategies must move beyond single-disease treatment models. Instead, managing pediatric health in these settings requires integrated frameworks that combine routine anti-parasitic management with comprehensive environmental hygiene interventions.

CONCLUSION

This investigation demonstrates that pediatric co-infection with *Plasmodium falciparum* and soil-transmitted helminths in Bauchi State, Nigeria, drives systemic T-cell over activation and accelerates cellular differentiation toward a dual PD−1+Tim−3+ exhausted phenotype. These immunological changes alter cellular defense mechanisms, potentially limiting the host's capacity to clear acute parasitic infections and compromising memory responses to routine vaccinations. Consequently, public health interventions in endemic regions should transition from isolated disease-control models. Instead, health programs should prioritize integrated frameworks that combine mass deworming campaigns with systematic malaria chemoprevention and targeted investments in water, sanitation, and hygiene (WASH) infrastructure to protect pediatric immune development.

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