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Early life adversity, biological adaptation, and human capital: evidence from an interrupted malaria control program in Zambia

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ABSTRACT

Growing evidence from evolutionary biology demonstrates how early life shocks trigger physiological changes designed to be adaptive in challenging environments. We examine the implications of one type of physiological adaptation – immunity formation - for human capital accumulation. Using variation in early life malaria risk generated by an interrupted disease control program in Zambia, we show that exposure to infectious diseases during the first two years of life can reduce the harmful effects of malaria exposure on cognitive development during the preschool years. These findings suggest a non-linear and trajectory-dependent relationship between early life adversity and human capital formation.

I. Introduction

A growing body of work illustrates the importance of the *in utero* and early childhood developmental periods for human capital development (Black et al., 2016; Grantham-McGregor et al., 2007). Adverse early life experiences, particularly those affecting early childhood health, have been shown to undermine early skill formation and result in persistent disadvantage over the life course (Almond et al., 2018).

Economists have increasingly become interested in the dynamics of human capital formation, focusing in particular on whether investments in human capital across developmental periods are complements or substitutes (Aizer and Cunha, 2012; Attanasio et al., 2020; Attanasio et al., 2017a; Cunha et al., 2010; Johnson and Jackson, 2019). While existing human capital production models highlight interactions between different shocks and potential responses by parents or policy makers, they typically do not account for the potential *biological adaptation* to these shocks.[1] Unless parents overcompensate for early shocks (Cunha and Heckman, 2007; Heckman, 2007), or positive early life shocks and investments increase the opportunity cost of schooling relative to labor (Bau et al., 2020), contemporary human capital models predict that exposure to early adversity should always have negative implications for human capital accumulation.

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[1] Two exceptions of studies in the economics literature that incorporate insights from biological theories of adaptive responses are Hoynes et al. (2016) and Schneider (2017).

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In this paper, we argue that these predictions may not hold in settings where early exposure to adverse shocks leads to beneficial biological adaptations to the environment. We first develop a stylized model of human capital formation that considers both the immediate negative impacts of an adverse early life shock and the consequences of resulting biological responses. The model conceptualizes insights from evolutionary biology, which highlight the myriad of evolutionarily-selected physiologic changes made by organisms to increase their chances of survival in complex environments (Bateson et al., 2014; Gluckman and Hanson, 2006). Physiological adaptations to challenging environments seem obvious and necessary from an evolutionary perspective, but are likely costly from a developmental perspective as they limit nutritional resources available for other processes. Whether these biological responses are optimal for human capital accumulation in the long run likely depends to the ex-post returns to the adaptive changes made.[2]

In order to assess this question empirically, we explore spatial and temporal variation in early life exposure to malaria in Zambia. Malaria is an ideal condition to examine the role of biological adaptation in human capital formation for three reasons. First, exposure to malaria, like other common infectious diseases, results in one very well-understood form of physiological adaptation: immunity formation. Developing immunity is costly - as it requires disease exposure - but can result in significant benefits in the event of subsequent re-exposure to the disease (Doolan et al., 2009; Reves et al., 1989; Yang and Rubin, 1995). The first two years of life are widely considered the most critical period for immunity formation, characterized by unmatched rates of immune system learning (Holt and Jones, 2000; M'Rabet et al., 2008). Failure to form early immunity to a given disease is inconsequential if children are permanently protected from this disease. However, in environments where exposure to the same infections occurs repeatedly throughout the life course, this is likely not the case. Even though immune system learning continues at older ages, declining ability to adapt to new infectious agents, means that lack of early immunity can potentially result in increased vulnerability and reduced health status in all subsequent periods. Second, the formation of adaptive immunity in endemic settings is relatively well understood. A substantial body of evidence shows that individuals not previously exposed to malaria have more severe disease than individuals who have had past exposures, due to the formation of protective partial immunity (Goncalves et al., 2014; Gupta et al., 1999). Third, malaria has also been well-studied in the economics literature, with a number of studies demonstrating large, positive long-run health and human capital impacts from *sustained* reductions in the risk of contracting disease from the *in utero* years onward (Barofsky et al., 2015; Barreca, 2010; Bleakley, 2010; Chang et al., 2014; Cutler et al., 2010; Hong, 2007; Kuecken et al., 2020; Lucas, 2010; Venkataramani, 2012).

The Zambia malaria program we explore was highly successful in reducing malaria risk during its early years (Ashraf et al., 2010). However, the disease rebounded in several areas of the country after 2009, due to disruptions in external funding that brought program efforts to a temporary stop. These swings in disease risk resulted in variation in exposure to malaria across different developmental periods by birth cohort and area of residence. We use this variation to assess the human capital impacts of malaria exposure in the first two years of life in a setting where immunity formation is likely to be beneficial. To do so, we combine detailed child development data collected specifically for this study with locally- and nationally- representative data on malaria infection rates. Between 2006 and 2012, the government of Zambia collected nationally representative data on fever, anemia and malaria parasite prevalence every two years. In each of these Malaria Indicator Surveys (MIS), approximately 20 children were assessed per enumeration area (i.e., villages or urban areas of about 250 households each as defined in the 2010 Census).

We selected 53 of the enumeration areas surveyed in the 2006 MIS for two rounds of detailed child development assessments in 2010 and 2012. The focus of the first round conducted in 2010 were children born in 2004, who were either 1 or 2 years old when the 2006 MIS was conducted in their village, and 5-6 years old at the time of the 2010 assessment. In 2012, we came back to the same 53 areas, and assessed a matching set of 5-6-year-olds (children born in 2006) from the same communities.

If the Zambian malaria campaign had been as successful as planned, our theoretical prediction would be straightforward: on average, children born after campaign commencement would have experienced much lower malaria exposure, and would thus be expected to have better developmental outcomes by ages 5-6. However, given that malaria resurged rapidly after 2009, the predicted impacts of reduced early life malaria impacts are ambiguous. Leveraging within village-cohort variation in malaria risk over the course of childhood, along with village-level variation in the initial malaria disease burden for identification, we find that children exposed to reduced malaria in the first two years of the program – but re-exposed to higher rates of malaria in the pre-school years – had *poorer* cognitive development at ages 5-6 than children from the same areas more exposed to malaria in the first two years of their life. The estimated effect sizes are substantial: each standard deviation decrease in early life malaria exposure is associated with roughly 0.16 standard deviation decrease in cognitive development. We also find negative, though imprecisely estimated, effects on performance on a test of attention (our measure of non-cognitive skills), while estimates for physical development are sensitive to specification.

Comparing children living in areas that experienced resurgent diseases versus those that did not, we find that the negative effects accrue only among children experiencing resurgence. In areas where RBM-led declines in malaria were sustained, reduced early life exposure was associated with substantial (but imprecisely estimated) improvements in cognition at age six, consistent with prior

[2] The recent theory of "predictive adaptive responses," developed to explain rising chronic disease rates, formalizes this intuition. The critical mechanism in this theory is that periods of hardship or abundance stimulate physiological changes (for example, epigenetic modification - the change by which genes are expressed) that favor physiologic pathways that are advantageous for this early environment. However, if this early environment changes, these physiologic changes may either confer no benefit, or may become maladaptive. A well-known set of examples are the physiologic changes stimulated by early exposure to nutritional scarcity. These changes may be advantageous when faced with nutrition-poor environments later in life, but may lead to chronic diseases such as obesity or diabetes thereafter. The theory also applies to the inverse situation where the early shock is beneficial, but the later life environment is challenging. This is the situation we examine in this paper.

work examining the impacts of sustained declines in malaria and other infectious diseases on measures of cognition and achievement (Chen et al., 2020; Kremer and Miguel, 2004; Kuecken et al., 2020; Venkataramani, 2012). We also show that our core findings are unlikely to be explained by omitted area and time-varying shocks, selection, access to health services, reduced supply (crowd-out) or demand for non-malaria related health services, and changes in parental investments.

We conduct two tests to more directly examine the role of partial immunity formation as key mechanism behind these patterns. First, in descriptive models of cognitive development that control for early (ages 0-2) and late exposure (ages 3-5) to malaria as well as the interaction between these two age-specific exposures, we find that the interaction term is positive, significant and more predictive of the outcomes than the age-specific terms, suggesting that earlier exposures offset the negative effects of later malaria exposures. This also implies that our core finding of poorer developmental outcomes for the post-RBM cohort likely cannot be explained alone by higher malaria exposure at ages 3-5 (i.e., the preschool years being a critical period). Effects of pre-school malaria exposure are decreasing with higher rates of early life exposure - consistent with the importance of adaptive immunity. Second, we use data on malaria infections and morbidity for children under age 5 over the period 2006-2010 to assess how measures of disease risk and severity vary as a result of different early life exposures. We find that cohorts with higher exposure to malaria infection risk in the first two years of life were substantially less likely to be anemic and to suffer from fever – two key symptoms of malaria – at ages 3-5 than cohorts with lower early exposure in early life in similar disease environments. This finding, which suggests that early exposure can increase children's ability to cope with disease exposure later, is consistent with biomedical work on partial immunity formation (Aponte et al., 2007; Gupta et al., 1999) showing that adaptive immunity formation can reduce the risk of severe disease upon (re)infection.

Our findings have several implications. First, the results demonstrate that the relationship between early life shocks and subsequent development may be more complex than previously portrayed in the economics literature. In particular, in settings where repeated exposure to pathogens or other stressors is high, early exposure to adverse shocks may blunt the longer-run harms of disease exposure, via realization of adaptive biological responses. While our specific case-study involves malaria, they concord with the observations in the biomedical literature on putative long-run impacts of adaptive responses to adverse early life shocks more generally (Wells 2012, Bateson, Gluckman et al. 2014). These results are also consistent with recent evidence from Sweden, which shows that earlier entrance into the public daycare system increases morbidity initially, but yields substantial increases in child health in the medium to long run (Siflinger and van den Berg, 2018). The direction and magnitude of our estimates should compel researchers to consider biological adaptation in human capital models, and investigate the consequences of adaptations to a variety of different shocks, such as other infectious diseases or dramatic changes in access to nutrition or nurturing care.

Our results also highlight the importance of distinct sub-periods in the first years of children's lives. As highlighted in several recent studies (Attanasio et al., 2020; Attanasio et al., 2017a; Gunnsteinsson et al., 2019; Rossin-Slater and Wüst, 2016), models of human capital formation that consider the under-5 age range as a single developmental period - or focus on the first two years of life only - may not be a good approximation of early life developmental processes, as they abstract away from the complex interplay between experiences in the first, second, as well as all subsequent years of childhood.

Finally, our results also highlight programmatic implications that pose challenges to disease eradication or control campaigns. Interventions that seek to ameliorate infectious disease can threaten both population health and child development if these efforts are not sustained. This contention is particularly relevant in the context of malaria control, which has been characterized by a long history of disease resurgence in the face of inconsistent funding, program implementation, and changes in disease ecology (Cohen et al., 2012). Given that major local investments in public goods like malaria control seem unlikely in the short run (Kremer and Miguel, 2007; Maskin et al., 2019), continued global support will likely be needed to prevent major relapses in the future. Moreover, our results may also be relevant to modern vaccine campaigns. For example, recently developed malaria vaccines have shown promising efficacy, but their durability may depend on doses administered up to more than a year after an initial series of shots (Datoo et al., 2021). Lack of uptake of this final dose may have consequences that extend beyond increased disease risk.

The rest of the paper is structured as follows. We introduce a stylized model of human capital formation which incorporates adaptive biological responses in Section 2. Section 3 tests the predictions of this model using the temporarily halted Zambian malaria control effort as a case study. Section 4 discusses – and rules out – alternate explanations for our findings. Section 5 reports descriptive evidence in support of the immunity formation mechanism. Section 6 concludes.

2. Human Capital Formation with Adaptive Biological Responses - A Stylized Model

We consider a standard model of human capital formation, where childhood is divided into multiple developmental periods $t \in \{1, 2, ..., T\}$ and adult outcomes are determined by cognitive, socio-emotional, and physical skills children achieve at the end of childhood. In each period, children get exposed to shocks. In our empirical section, we focus on infectious disease shocks (exposure to malaria) and the resulting biological response of immunity formation. However, the model applies to other forms of adversity as well, such as poor nutrition, accidents, or exposure to violence - all which may offer only limited time frame for physiologic adaptation. The dynamics of *ISC* and *H* essentially describe the physiologic changes underlying the theory of predictive adaptive responses, a framework from evolutionary and developmental biology which posits that early life health and nutritional shocks serve as cues that generate epigenetic responses that help ensure short-run survival and reproductive success, but may lead to harm if they are "mismatched" with subsequent changes in the environment (Bateson et al., 2014; Gluckman and Hanson, 2006). The model is also aligned with the well-known "hygiene hypothesis," which posits that declining exposure to early life infections may lead to inflammatory conditions, such as asthma and allergies, and autoimmune conditions, such as Type 1 diabetes (Vanaten et al., 2016; Yazdanbaksh et al., 2002).

Skill formation in period t and state s depends on preexisting skills (θ), investments (I), parental skills and efforts (P), health (H), and unobserved skill shocks ϵ_t

$$\theta_{t+1} = f_{t,s}(\theta_t, P_t, I_t, H_t, \epsilon_t) \tag{1}$$

As in Cunha and Heckman (2007), we assume that the human capital production function f is twice differentiable and monotonically increasing in its arguments. The inclusion of health stock or status (H) in our model follows recent extensions of the original model in Conti and Heckman (2014). Period-specific health is a function of exposure to health shocks η, previous health H_{t-1} as well as well as immune system capacity ISC. Specifically, the health stock in period t is given by:

$$H_t = H(H_{t-1}, ISC_t, \eta_t) \tag{2}$$

with $\frac{\partial H}{\partial \eta} < 0$.

The human immune system comprises an innate and an adaptive component. The former includes physical barriers (such as skin), chemical barriers (substances released by mucosal cells which are toxic to infectious pathogens), and immediate cellular responses to a broad class of agents foreign to the body. Adaptive immunity is the cellular response to infections that generates memory. With subsequent exposure to the same disease agent, memory cells recognize the agent and initiate an immune response that either reduces the burden of disease or prevents symptomatic infection entirely. Thus, immune system capacity to fight disease – or in a more general model, the sum of changes from adaptive biological responses – develops over time through exposure to health shocks:

$$\frac{\partial ISC_t}{\partial n_{t-1}} \geq 0 \tag{3}$$

and enters the health production function by moderating the impact of negative health shocks:

$$\frac{\partial H_t}{\partial n_t} \partial ISC_t \geq 0 \tag{4}$$

Consistent with biomedical evidence, we allow for immunity to be partial or complete. Partial immunity occurs where there is repeated exposure to an evolving pathogen (which can be parasites, viruses, or bacteria) or a pathogen with large (bio-)diversity around a set of core characteristics. With partial immunity, exposure to the infectious agent will still result in morbidity. However, the immune system response is more rapid and the symptoms will be less severe. Complete immunity is possible when a host has a subsequent encounter with an identical pathogen. In this case, the individual will not experience an acute health shock and will often experience no symptoms. If the child gets exposed to strictly different virus, bacteria, or parasites over time, (3) can be assumed to be zero.

In the context of infectious diseases such as malaria, diarrhea, or pneumonia, complete immunity is rare as the pathogens that cause these diseases are numerous and constantly evolving. With malaria, however, partial immunity after disease exposure is a well-documented phenomenon (Aponte et al., 2007; Gupta et al., 1999). In particular, the breastfeeding period is a privileged time for the formation of adaptive partial immunity, as infants are protected from severe malarial infections because of protective protein components of breast milk (Doolan et al., 2009; Snow et al., 1997). The dynamics of immune system responses to malaria and direct protection from breastmilk proteins are thought to explain the unique epidemiologic profile of the disease in endemic regions among children under the age of 5: while exposure to parasites (and bloodstream presence of parasites) remains constant, the risk of severe disease increases initially after weaning and then declines sharply thereafter (Goncalves et al., 2014). In addition, some health shocks can be so severe that the immune system cannot adapt. An extreme case of this is death; a less extreme case is where health shocks lead to a severe nutrient imbalance that reduces the available energy for the formation of adaptive immunity (Chandra, 1997). These cases are not trivial in the context of malaria, which both has a high probability of resulting in death and may also result in permanent cognitive impairment (i.e., cerebral malaria) (Boivin et al., 2007).[3]

With this general setup, our stylized model generates the following predictions:

1 Exposure to infectious diseases reduces health and developmental outcomes.
2 Temporary reductions in early-life exposure will improve developmental outcomes in the short-run, but may make children worse off in the medium- to long-run if the returns to immunity formation are sufficiently large.

Prediction (1) follows directly from our modeling setup: early life health shocks η_t lower early life health status H_t and, through reduced health, lower subsequent developmental outcomes (e.g., θ_{t+1} and subsequent periods). This direct and immediate health effect has been the focus of much of the published literature linking health adversity to developmental outcomes (Almond et al., 2018).

Prediction (2) is the primary prediction of interest of this paper, as well as its main conceptual contribution. Given that early exposure to health adversity increases subsequent resilience, the net impact of early life exposure to infectious disease depends on the magnitude of the immediate developmental losses compared to the magnitude of the reductions in the subsequent losses due to improved immune system development. This is most easily illustrated in a three-period model, where the first period corresponds to the first two years (highlighted as the most critical window in the literature), the second period is ages 3 and 4, which represents

[3] In most settings, these extreme cases are relatively rare, such that most children are exposed to more limited adversity.

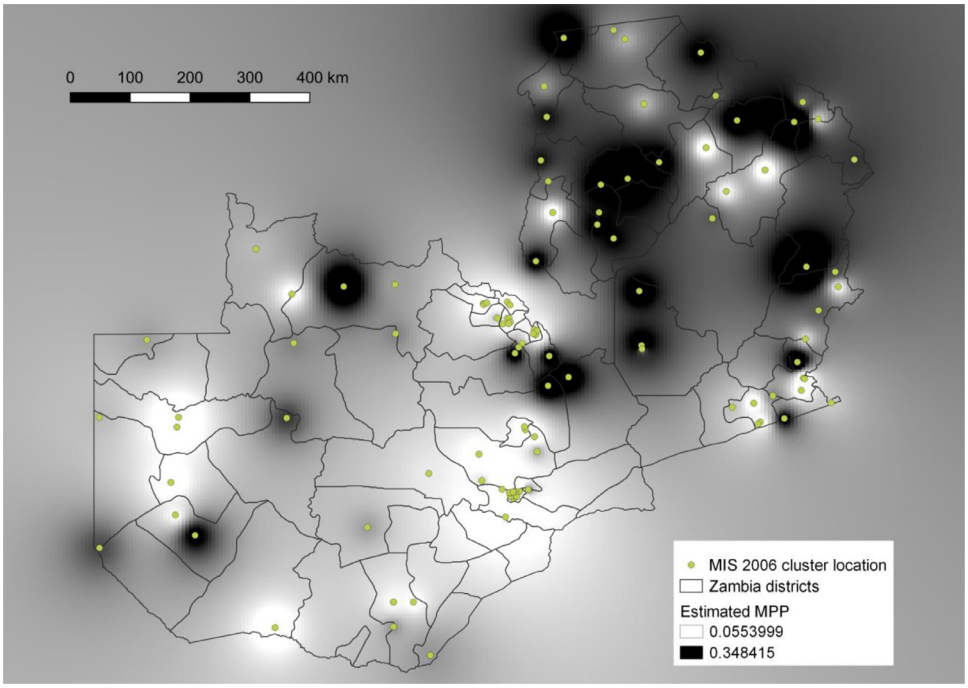

Fig. 1. – Malaria Endemicity among Children under Age 5
Notes: Data from Zambia Malaria Indicator Survey, 2006. We used inverse-distance weighted spatial interpolation of survey clusters to predict local malaria parasite positivity (MPP) rates among children 5 and under. Completely white areas correspond to an MPP rate of zero; the darkest areas correspond to an MPP of 0.5 (i.e., 50% of surveyed children tested positive for parasites in the bloodstream by a rapid diagnostic test).

post-weaning and the pre-school years (period 2), and the third period is ages 5 and up, which is when we observe our developmental and human capital outcomes. In this setup, human capital in period 3 will be given by:

$$\theta_3 = f\left(\theta_2,\ P_2,\ I_2,\ H_2,\ \epsilon_2\right) \tag{5}$$

Assuming investment does not change in response to health shocks, the partial derivative of this expression with respect to early life adversity is given by:

$$\frac{\partial \theta_3}{\partial n_1} = \frac{\partial f()}{\partial \theta_2}\frac{\partial \theta_2}{\partial H_1}\frac{\partial H_1}{\partial n_1} + \frac{\partial f()}{\partial H_2}\frac{\partial H_2}{\partial H_1}\frac{\partial H_1}{\partial n_1} + \frac{\partial f()}{\partial H_2}\frac{\partial H_2}{\partial ISC_2}\frac{\partial ISC_2}{\partial n_1} \tag{6}$$

The first term captures the developmental delays generated by early health adversity through lower health status in the first period, which we posit will be unambiguously negative. The second captures the long-run health consequences of early life adversity. These can be assumed to be zero if infections are minor, but could be significantly negative for severe infections like cerebral malaria, which may alter a child's health status permanently. The third term captures the benefits of increased immunity: early exposure to infectious disease lowers the health impact that future exposure has, so that children with poorer initial health will have better health in all subsequent periods. If these returns – which are likely to differ across domains such as cognitive or non-cognitive development and physical growth - are large enough, children with early exposure may be better off than children without such exposure in settings where both groups are exposed to equivalent disease risks later in life.

3. Zambia's rollback malaria program, research strategy and results

3.1. Background

Malaria is endemic in all parts of Zambia. As seen in Fig. 1, exposure to malaria (measured in terms of the fraction of under 5 with evidence of parasites in blood samples, hereafter malaria parasite positivity - MPP) in the year prior to Roll Back Malaria (RBM) varied substantially across the country, with highest rates in the Northeast and the lowest rates in the Southwest region of the country. Between 2000 and 2005, malaria accounted on average for 48% of all under-5 inpatient visits, and for 30% of all under-5 mortality registered at inpatient facilities (Ashraf et al., 2010).

RBM was initiated in 2006 as national control effort coordinated by the National Malaria Control Center and supported by a large group of international donors, including the Global Fund, World Bank, the Bill and Melinda Gates Foundation, and the President's Malaria Initiative. The goal of the RBM program was to reduce malaria by two-thirds within five years (Zambia Ministry of Health, 2006). To date, the program remains one of the largest infectious disease treatment and prevention plans in per-capita-terms

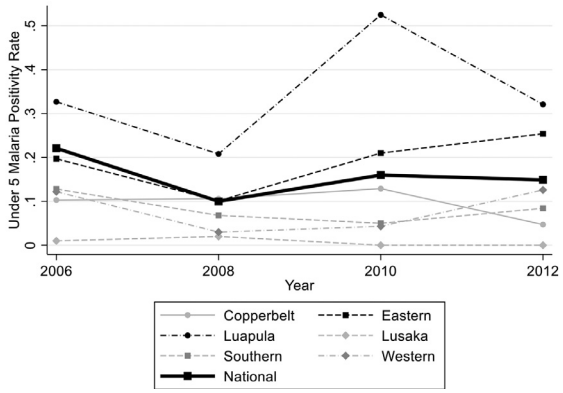

Fig. 2. – Trends in Malaria Infection Rates, 2006-2012.
Notes: Aggregate data from Zambia Malaria Indicator Surveys, 2006-2012. Provinces displayed are those represented in our child development sample. The national trend line. shows a drop in under-5 malaria rates by 50% between 2006 and 2008, with resurgence in 2010. In the high prevalence Eastern and Luapala provinces, parasite positivity rates in 2010 exceeded those in 2006. Estimates present regionally and nationally weighted averages as reported in the MIS reports 2006-2012.

in the region, with an estimated annual budget of approximately US $10-15 per person/year. Between 2003 and 2010, the program received close to US $200 million in foreign contributions (Mouzin et al., 2011). Following World Health Organization guidelines, the program's four principal strategies were: (1) administration of intermittent preventive treatment for pregnant women; (2) distribution of insecticide treated nets to households; (3) indoor residual spraying; and (4) case management, including the systematic diagnosis of fever patients through Rapid Diagnostic Tests and their treatment with artemisinin-based combination therapies. Large reductions in malaria incidence and prevalence were noted by 2008 (Ashraf et al., 2010; NMCC, 2009).

However, these impacts were short-lived. In the wake of a corruption scandal at the Ministry of Health, Global Fund grants were suspended (Usher, 2010, 2015) and program funding dropped markedly in 2009 (see **Appendix Fig. B1** for details), leading to pronounced reductions in program efforts (**Appendix Fig. B2**), and an almost immediate resurgence of malaria. This resurgence is illustrated in Fig. 2 which shows the regional and national prevalence estimates of under-5 malaria between 2006-2012 from the Zambia Malaria Indicator Surveys (MIS; see Section 4 and **Appendix A**). MPP declines substantially between 2006 and 2008, and then increases again in 2010. This resurgence was particularly pronounced in Eastern Province and Luapula, where MPP rates rose above 0.50 (meaning that half of children under-5 had malaria parasites at the time of the survey), while MPP rates remained relatively low in Lusaka, Northwestern, and Southern Province. Nationwide, MPP was substantially higher in 2010 and 2012 than in 2008, with 2012 levels only slightly below the (pre-program) 2006 levels.[4]

3.2. Research Strategy

To assess the impact of early disease environments on human capital, we conducted two rounds of original data collection on children's developmental outcomes at age six (prior to school entry in Zambia) in 2010 and 2012. Working closely with a local expert team, we developed a new assessment battery - the Zambian Child Assessment Test (ZamCAT) - designed to comprehensively measure development (cognitive, non-cognitive, and physical skills prior to school entry) in the local context (Fink et al., 2012). A first cohort of children – children born in 2004 – was assessed in 2010, across 73 clusters originally selected for, and surveyed in the 2006 MIS. We returned to 53 of these clusters in 2012 to conduct assessments for children born in 2006.

We purposefully conducted our assessments for both cohorts during the low transmission season for malaria (July-October), to avoid picking up contemporaneous impacts of active or recent malaria infection on measures of child development (Boivin et al., 2007; Thuilliez et al., 2017). Table 1 shows descriptive statistics for the sample. On average, children were a little over six years old at the time of the assessment. While 50% of the sample were female in the 2004 cohort, this proportion was slightly smaller (44%) in the 2006 cohort, who on average also appear to live in larger households.[5] Other household and community characteristics were similar across the two cohorts. Further details on data sources are provided in Appendix A.

Our empirical strategy assesses the (net) consequences of reduced exposure to early malaria and its symptoms at ages 0-2 on three key developmental domains at age 6. The ZamCAT contains multiple tasks and assessments in each domain – we used principal

[4] The exact reasons for the persistent reversal in trends in the most malaria exposed regions are not well understood. The funding freeze in 2009 is likely only a partial explanation given that it was temporary. It is possible that partial (i.e., un-sustained) program efforts led to the natural selection of hardier mosquitos and parasites and, therefore, reduced efficacy of spraying and bed net coverage in these areas (Cohen et al., 2012). Both of these phenomena have been implicated in failures of control efforts in other contexts, as well (Alonso et al., 2011).

[5] Data on household size across the two rounds is unfortunately not directly comparable: while households were asked to list all members for the 2004 cohort, only total household size numbers were reported in 2010 – this likely explains some of the size differences observed.

Table 1
Descriptive Statistics: Zambia Early Childhood Development Project Data.

	Cohort 2004			Cohort 2006		
Child characteristics	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*
Female	1,109	0.51	0.50	849	0.44	0.50
Age in months	1,109	75.79	4.06	849	72.00	0.00
Household size	1,109	5.45	1.85	845	7.04	2.54
Wealth quintile	1,109	2.86	1.40	849	2.77	1.36
Caregiver education	1,109	8.93	3.22	849	8.96	3.11
Number of child books	1,109	0.28	0.45	849	0.32	0.47
Adult reading time	1,109	0.46	0.50	849	0.55	0.50
Other books	1,109	0.67	0.47	849	0.63	0.48
Height-for-age z-score	1,096	-0.96	1.26	844	-1.00	1.20
Weight-for-age z-score	1,097	-0.90	1.08	847	-0.82	1.00
BMI z-score	1,084	-0.36	1.06	844	-0.25	0.96
Cognition Z-score	1,109	0.05	1.00	849	-0.06	0.99
Physical Z-score	1,084	-0.03	1.01	844	0.02	0.98
Attention Z-score	1,104	0.09	0.95	839	0.01	1.12
Cluster characteristics						
Cluster is urban	1,109	0.50	0.50	849	0.46	0.50
MPP 2006[a)]	1,109	0.13	0.19	849	0.15	0.20
Mean rainfall[b)]	1,109	676.04	126.72	849	657.33	107.23
Mean temperature[c)]	1,109	72.21	3.25	849	71.86	2.47
Constituency characteristics						
Literacy	1,086	0.81	0.13	833	0.80	0.12
Asset score	1,086	-0.16	0.81	833	-0.26	0.80
Sewage access	1,086	0.16	0.22	833	0.15	0.21

Notes: a) MPP malaria parasitemia prevalence based on Malaria Indicator Survey 2006. b) Rainfall in mm; c) temperature in degrees Fahrenheit.

component analysis to synthesize these subdomain-specific scores within each domain into a single summary score to reduce multiple hypothesis testing concerns, and show subdomain results in the Appendix. Some children did not complete all of the assessments – we imputed missing scores in these subdomains using data from available scores from the same domains. Within each cluster, we compare developmental outcomes for the 2006 birth cohort – who faced reduced malaria risk in the first years of life and thereby were less likely to form partial immunity when faced with disease resurgence – to those of the 2004 birth cohort, who only benefitted from RBM-led reductions in malaria risk at ages 3-5. We begin by estimating versions of the following continuous difference-in-differences model, which has commonly been used in the economics literature to assess the impacts of malaria control on human capital outcomes (Bleakley, 2010; Cutler et al., 2010; Kuecken et al., 2020; Lucas, 2013; Venkataramani, 2012):

$$y_{icdt} = \alpha_0 + \alpha_1 1\left(Post_t\right) \times MPP2006_c + X_{icdt}\beta + \theta_c + \gamma_t + \omega_d \times \pi_t + \varepsilon_{icdt} \tag{7}$$

where y is the developmental outome of interest, and i indexes the individual; c indexes the cluster of residence at time of the interview; d the district in which the cluster was situated; and t the birth cohort. The 2004 cohort – fully exposed to malaria up to 2006 – is our main reference group; the cohort fixed effects π_t capture the developmental differences between the 2004 and the 2006 cohorts in areas without malaria, *MPP* denotes cluster-specific malaria parasite prevalence rates among children under-5 at baseline, and the interaction between *Post* and *MPP* captures the additional difference in areas with high malaria - our primary parameter of interest (with the main effects for *Post* and *MPP* subsumed by cohort and cluster fixed effects, respectively). The vector X_{icdt} denotes child demographic covariates (age and gender). The cluster fixed effects (θ_c) adjust for time-invariant village level characteristics, including size, location and pre-intervention malaria burden, and restrict our analysis to a comparison of children growing up in the same villages within two years.

The main coefficient of interest is α_1, which recovers the effect of reduced early life exposure to malaria as a result of RBM. In prior work focusing on sustained reductions in malaria risk, estimates of α_1 are positive, indicating beneficial effects of reduced early life exposure to malaria. However, our case study is different. Given that the disease resurged (on average) across Zambia, estimates of α_1 may be negative, if prior immunity formation from exposures at ages 0-2 are critical for protecting children from (severe) disease during their pre-school years.

Because we only have two cohorts, we are unable to conduct standard tests for violations of the parallel-trends assumption. We initially address this limitation by estimating specifications with increasingly stringent controls. We first account for parent and household characteristics (e.g., parental education and household wealth). We then adjust for regional trends by introducing province-cohort fixed effects. We thereafter add district-cohort fixed effects in our model (denoted by $\omega_d \times \pi_t$ in Equation (7)), which capture all changes within a district over time, aand cluster-level measures of average rainfall and temperatures during the birth year. Because districts are relatively small (on average, the size of a U.S. county), these fixed effects tightly capture a number of potential local cohort *and* period-specific confounds, such as variation in the rollout of key health and social programming, as well as small-area economic and environmental shocks that may have affected the two cohorts differentially. For example, antiretroviral therapy (ART) for HIV was rolled out at the district level starting in 2004 (Lucas and Wilson, 2013; Wilson, 2014). ART is associated with improved

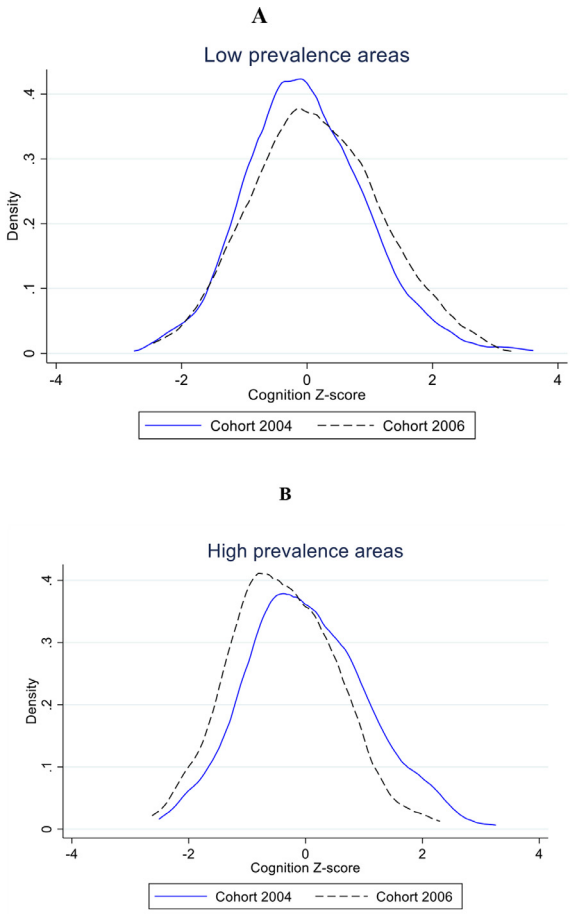

Fig. 3. – Density Plot of Developmental Outcomes.
Notes: Figs. plot densities of cognitive z-scores for each of the two ZECDP birth cohort. Plots stratify data by residence in a cluster with low (Panel A) versus high (Panel B) under-5 malaria prevalence at baseline, which is determined based on MPP above or below the sample median of 0.2 (20% of children with positive parasitemia test).

survival and anthropometric outcomes among children in Zambia, and higher child human capital investment elsewhere (Baranov and Kohler, 2012), though HIV prevalence historically has been higher in areas where malaria prevalence is generally low. Similarly, the Zambian Child Grant program was also rolled out starting in 2010 on a district-level basis (Handa et al., 2016).

The advantage of the continuous difference-in-differences specification in Equation (7) is that it helps connect our results to the prior economics literature on malaria and affords greater purchase on causal inference. However, it does not take advantage of the varying trajectories in malaria exposures across different study areas (Fig. 2). To address this heterogeneity, we estimate versions of Equation (7) separately for children living in clusters experiencing disease resurgence (defined as similar or higher parasitemia rates in 2010 versus prior to RBM in 2006) and children living in clusters with sustained declines in malaria (defined as lower district-level parasitemia rates in 2010 versus 2006). We also explore age-specific exposures in section 5 of the paper where we try to identify the key mechanisms underlying the changes observed.

3.3. Results

Fig. 3 previews our main findings showing densities for an index of cognitive test scores, stratified by birth cohort and pre-intervention malaria prevalence (high versus low). For the lower prevalence clusters – clusters with malaria parasitemia prevalence below the median, shown in panel (A) - we find a small, rightward shifts in the distribution of cognitive z-scores, suggesting higher average scores for the 2006 than for the 2004 birth cohort. In contrast, for clusters with high baseline prevalence of malaria (B) – which benefitted more from the initial RBM efforts - the post intervention cohorts appear to have substantially *poorer* outcomes, illustrated by notable leftward shifts in the densities.

Table 2 presents the regression estimates for Equation (7). Estimates for each of the component measures are provided in Appendix **Table C1**. In specifications that only include cluster, cohort, and child age and gender, we find large, negative estimates of the effect of reduced early life exposure as a result of RBM on all three developmental domains, even though estimates for the physical development

Table 2
– Impact on Developmental Indices

Panel A: Cognitive Development Index					
	(1)	(2)	(3)	(4)	(5)
*1(Post)*MPP*	-0.864*	-0.961*	-0.672*	-0.834*	-0.853*
	(0.504)	(0.531)	(0.390)	(0.458)	(0.453)
Observations	1,958	1,958	1,958	1,958	1,958
Panel B: Physical Development Index					
	(1)	(2)	(3)	(4)	(5)
*1(Post)*MPP*	-1.055*	-1.070**	-0.699*	0.0550	0.0438
	(0.543)	(0.531)	(0.393)	(0.246)	(0.247)
Observations	1,928	1,928	1,928	1,928	1,928
Panel C: Attention Z-score					
	(1)	(2)	(3)	(4)	(5)
*1(Post)*MPP*	-1.518***	-1.594***	-0.468	-0.666	-0.689
	(0.516)	(0.515)	(0.403)	(0.564)	(0.561)
Observations	1,943	1,943	1,943	1,943	1,943
Cluster FE	X	X	X	X	X
Child controls	X	X	X	X	X
Household controls		X	X	X	X
Province-cohort fixed effects			X		
District-cohort fixed effects				X	X
Climate controls					X

Notes. OLS estimates of the continuous DID model (equation 7). All outcome variables are normalized to mean 0 and standard deviation 1 within the ZECDP sample. All models include cluster and birth cohort fixed effects. Model (1) also controls for child age and child gender. Model (2) additionally controls for parental education and household assets. Model (3) includes additional controls for province-cohort fixed effects. Model (4) includes district-cohort fixed effects as well. Model (5) further includes cohort-year temperature and rainfall measures. The temperature controls comprise of a vector of indicators denoting 5 10-degree bins for the maximum temperature in individual's cluster and cohort of birth. Rainfall includes a linear term for the interpolated cluster level of rainfall in the birth year. Robust standard errors correcting for clustering at the survey cluster level in parenthesis are shown in parentheses. Coefficients represent cohort differences for a hypothetical 100% differences in baseline parasitemia. Mean (SD) of baseline MPP were 0.12 (0.18).

*** p<0.01,
** p<0.05,
* p<0.1.

index are imprecise. The inclusion of province-cohort and, as per our preferred specification, district-cohort fixed effects, attenuate estimates for the tests of attention or inhibitory control and physical development. With province-cohort and district-cohort fixed effects, estimates for the anthropometric index are close to zero, which suggests that increased morbidity during the pre-school age does not harm physical growth as much, or that such effects can be compensated by children later on(i.e., that there is potential for catch-up growth). While much of the traditional nutrition literature suggests that growth trajectories are largely determined by age 2 (Victora et al., 2010), our null-findings on physical growth suggest that both early and late exposure to malaria-induced morbidity have negative growth consequences, which is consistent with the high degree of later-life growth variability documented in the more recent growth literature (Fink and Rockers, 2014). These findings are also consistent with some of the prior economics literature on malaria, in which large impacts on cognition have been found, without any impacts on height (see, for example, Venkataramani 2012).

The estimates for the cognitive index are large, negative, relatively precisely estimated (with p<0.10), and remain largely unchanged regardless of covariates. We focus on these findings in the remainder of the paper. Focusing on the results from our preferred specification (column 5), the estimated coefficient of -0.85 implies that 1 s.d. decrease in baseline MPP (19 percentage points - similar to the mean decline in MPP during the RBM era) results in a 0.16 s.d. decrease in cognition. On average, children from the 2006 cohort growing up in clusters with high MPP had substantially *worse* cognitive outcomes than children from the 2004 cohorts from the same clusters even though the latter had substantially higher exposure to malaria in their first two years of life.

Given that the malaria trajectories varied substantially over time, we estimate separate models for clusters with declining and clusters with resurgent malaria. The results presented in Table 3 show that the large, negative impacts on cognition are driven by children living in areas experience malaria resurgence, with a precisely-estimated 1 s.d. decrease in baseline MPP resulting in a 0.21 s.d. decrease in cognition in clusters where MPP was higher in 2010 than in 2006 (column 1). By contrast, children living in areas with consistently declining malaria experienced a 0.08 s.d. *increase* in cognition from the same 1 s.d. decrease in early exposure (column 2). This means that with sustained malaria control, substantial improvements were seen in endemic areas, a finding which

Table 3
– Impact in Resurgent and Non-Resurgent Areas

	Outcome: Cognitive Development Index			
	(1)	(2)	(3)	(4)
Cluster restriction	MPP 2010 > MPP 2006	MPP 2010 <= MPP 2006	Moving in and out of high MPP	Always high or always low
***1**(Post)*MPP*	-1.149**	0.453*	-1.331***	0.872
	(0.409)	(0.249)	(0.377)	(0.728)
Observations	901	1,057	940	897
R-squared	0.312	0.389	0.331	0.312

Notes. OLS estimates of the continuous DID model (equation 7). All outcome variables are normalized to mean 0 and standard deviation 1 within the ZECDP sample. All models include a full set of controls including child and household characteristics, cluster and birth cohort fixed effects, climate controls, and district-cohort fixed effects . Columns 3 and 4 compare clusters moving in an out of high transmission to clusters with always high or always low parasitemia. Coefficients represent cohort differences for a hypothetical 100% differences in baseline parasitemia. Mean (SD) of baseline MPP were 0.12 (0.18).
*** p<0.01,
** p<0.05,
* p<0.1.

Table 4
– Robustness Checks

	Outcome: Cognitive Development Index			
	(1)	(2)	(3)	(4)
Model used	Constituency controls	Year of assessment disease controls	Excluding Luapula	MPP categories
***1**(Post)*MPP*	-0.738**	-0.836	-1.301***	
	(0.342)	(0.578)	(0.377)	
***1**(Post)*Intermediate*				-0.107
				(0.115)
***1**(Post)*High*				-0.220**
				(0.104)
Observations	1,919	1,958	1,562	1,958
R-squared	0.352	0.351	0.362	0.350

Notes. OLS estimates of the continuous DID model (equation 7). All outcome variables are normalized to mean 0 and standard deviation 1 within the ZECDP sample. All models include a full set of controls including child and household characteristics, cluster and birth cohort fixed effects, climate controls, and district-cohort fixed effects. Column 1 includes constituency-level covariates interacted with post. Column 3 also controls for cluster-level parasitemia (MAP estimate) in the year of the developmental assessment (2010 for the pre-RBM cohort and 2012 for the post-RBM cohort). Column 3 excludes Luapula as the region with the highest parasitemia. Column 4 discretizes baseline cluster parasitemia prevalence into three categories < 0.10 (reference group), 0.10-0.27 (intermediate), > 0.27 (high).
*** p<0.01,
** p<0.05,
* p<0.1.

aligns with the economics literature on the human capital effects of malaria eradication (Cutler et al., 2010; Kuecken et al., 2020). Similar patterns can be seen when we split the sample into clusters experiencing pronounced changes over time (going from high to low transmission and back) and clusters that have relatively constant exposure profiles (columns 3 and 4). Once again, we see large declines in cognition in clusters exposed to changing exposures, and moderate improvements in clusters with flat (and generally low) exposure profiles.

3.4. Robustness checks

We undertake a number of additional checks to assess whether our findings for the human capital outcomes are driven by potential confounders. We note that any relevant unobservables would have to be operative at the *sub-district-year* level, since our specification includes district-year fixed effects (which account for cohort- and period-level time varying shocks for land areas the size of U.S. counties).

We first test the robustness of our findings to the inclusion of constituency characteristics, interacted with **1**(*Post*). Constituencies are parliamentary subdivisions that are smaller than district (there are over 156 such constituencies in Zambia - or about two in each of the 72 districts). We use pre-intervention constituency-level data from the 2000 Zambian census on household assets scores (a measure of socioeconomic status), adult literacy rates, and fraction of households with access to sewage. The inclusion of these characteristics changes the main results only marginally (Table 4, column 1).

Table 5
– Impact on Households' Socioeconomic Status

	Household Size	Wealth Quintile	Household in bottom 2 quintiles	Caregiver Schooling (Years)
*1(Post) * MPP*	0.456	0.208	-0.0611	-0.368
	(0.684)	(0.573)	(0.229)	(1.709)
Sample mean	6.13	2.82	0.46	8.98
Observations	1,958	1,958	1,958	1,958
R-squared	0.248	0.558	0.454	0.340

Notes: Estimates of identical model as in column 5 of Table 2 (with sample restricted to observations in clusters surveyed in both rounds of the ZECDP), except here parental characteristics serve as the dependent variable. Household Asset Score is a normalized Filmer-Pritchett Index based on household ownership of a number of durable and consumer goods. Robust cluster corrected standard errors are in parenthesis. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

To address concerns that the observed patterns may be driven by exposure to malaria in the year of the assessment, we also estimate a model additionally controlling for estimated malaria risks in 2010 (for the 2004 cohort) and 2012 (for the 2012 cohort). The estimated coefficient on the main interaction term is larger in magnitude than our core estimates, but also less precise[6] (Table 4, column 2). We also examined the sensitivity of our findings to outliers. Given that malaria in Zambia is particularly high in specific regions, it is possible that marked swings in malaria prevalence or unobserved adverse disease or macroeconomic shocks in a few highly endemic areas could drive our main negative findings. To address this possibility, we re-estimated our main models removing observations from the Luapala province, where malaria resurgence was most pronounced as shown in Fig. 2. The estimated coefficient increases in magnitude after doing so (Table 4, column 3). We also explore a less parametric specification, where we divide MPP into low (<10%), intermediate (10-27%) and high (< 27%) initial levels (Table 4, column 4). We find an average decline of 0.1 s.d. in the intermediate group, and an average decline of 0.22 s.d. in cognition in the high exposure group – both of which align with the average magnitudes seen in Table 2 and 3.

To ensure our estimates are not affected by household level shocks, all of our models also adjust for household wealth and caregiver education. Following recent work suggesting that mis-measured covariates may be better used in balancing tests rather than as controls (Pei et al., 2018), we also re-estimate our main specification using the household socioeconomic measures as dependent variables. We find no substantive association between RBM exposure and any of these outcomes (Table 5). Specifically, we find that a 1 s.d. change in baseline malaria prevalence (a 0.19 decrease in MPP, which roughly represents mean decline nationwide in the RBM era) is associated with a 0.18 increase in household size (0.08 standard deviations); a 0.01 s.d. decrease in household asset scores; a 0.02 increase in wealth (a 1-5 scale representing quintiles); and a -0.05 year decrease in caregiver schooling (a -0.02 s.d. decrease).

Finally, while are unable to directly assess for violations of the parallel-trends assumption in the ZECDP data (as we only have measures for one pre- and one post- intervention cohort), we do try to do so using an alternate data source, the Zambia Demographic and Health Surveys (DHS). Specifically, we use data from the 2007 DHS (see Appendix A for descriptive statistics). We regress anthropometric and morbidity measures (cognitive and non-cognitive development measures are not collected in the DHS) against district-level MPP interacted with birth cohort for the 2003-2005 (pre-intervention) birth cohorts. We find no evidence in any substantive or statistically significant pre-trends for these variables (Appendix **Table C2**). We view these results as only suggestive, as they are conducted in a different dataset, do not cover the range of outcomes that we explore in the ZEDCP, and focus on district-level, rather than cluster-level, variation in the exposure. Importantly, district-level trends are fully adjusted for in our preferred specification.

4. Alternative explanations

Mortality and fertility selection: A standard concern in the early childhood literature is that reduced mortality from positive health shocks may increase the odds of survival of less developed or less resilient children, who may perform poorly on developmental assessments and bias the overall results. This is a concern given that malaria remains a primary cause of child mortality in sub-Saharan Africa.

A simple bounding exercise, however, demonstrates that mortality selection unlikely to explain our findings: under-five mortality in 2007 was just below 100 deaths per 1000 live births (Zambia Central Statistic Office et al., 2009). With an estimated 20-25% of these deaths attributable to malaria (GBD Collaborators, 2014), reducing malaria mortality by 50% - the initial impact of the program - would thus have increased the percentage of children surviving from each cohort from 90% to 91.25%. Even if this surviving

[6] We used data from the Malaria Atlas Project (MAP) to estimate cluster-level malaria risks in 2010 and 2012, since these data are not available from the MIS. The MAP data use MIS data, along with area-level socioeconomic characteristics, to construct spatially- and temporally-smoothed measures of local malaria risk. Because these measures are modelled and smoothed in this fashion, they are not appropriate for our main analysis (since they may incorporate trends in developmental outcomes by socioeconomic characteristics and not just malaria risk and since they would not reliably distinguish year-to-year trends in exposure). In addition, the temporal smoothing used to construct the MAP data introduce substantial collinearity across periods. The higher standard errors obtained after including year of assessment MAP measures is not surprising

Table 6
– Impact on Caregiver Behavior.

	Adults Reads to Child	HH Has Children's Books	HH Has Other Books	ECD Program (Years)	BCG Vaccine	Polio Vaccine	Length of Breastfeeding
*1(Post)*MPP*	0.489	-0.262	-0.119	0.0831	0.133	0.153	2.849
	(0.303)	(0.211)	(0.185)	(0.624)	(0.120)	(0.115)	(2.650)
Sample mean	0.30	0.65	0.50	0.77	0.92	0.93	14.65
Observations	1,958	1,958	1,958	1,923	2,416	2,416	2,587

Notes: Estimates of models examining parental investments. Robust cluster corrected standard errors are in parenthesis. Adult Reads to Child, Household (HH)Has Children's Books, HH Has Other Books, and ECD Program (which denotes the number of years a given child spent in preschool or an early childhood program) are all derived from the ZECDP. For these variables, MPP is defined at the cluster level and all models include the controls listed in column 5 of Table 2. BCG Vaccine, Polio Vaccine, and Length of Breastfeeding (in months) are derived from the 2007 DHS. The DHS sample is restricted to the two main study cohorts, i.e. children born in 2004 and 2006. Polio is coded as one if the child got at least one polio vaccination. Breastfeeding is measured as total number of months the child was (exclusively or non-exclusively) breastfed. Columns 5-7 include cluster fixed effects as well as province-cohort fixed effects. Parasitemia levels are computed at the district level using the 2006 MIS. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

group had an average cognitive z-score of -3 (i.e. they were all in the bottom 1% of the skill distribution), the maximum plausible shift in population average outcomes would have been smaller than 0.04 SD, which is an order of magnitude below the estimates reported in Table 2–4**.** In practice, national estimates actually suggest that malaria mortality did not increase much after 2008 despite increased morbidity, which is likely at least partially explained by the increased availability of artemisinin-based therapies after 2006 (World Health Organization, 2017).

The extent to which fertility selection plays a role depends on the extent to which the price of child quality fell relative to that of quantity and whether the fertility response differed across families in the ability distribution. If the quantity price effect is dominant, then an increase in the number of less endowed children may explain the negative findings (Lucas, 2013). However, again, this effect must be large to explain our profoundly negative findings, which is not consistent with overall observed trends in fertility.[7] In addition, the null association between cohort program exposure and caregiver and household socioeconomic characteristics (Table 5) as dependent variables helps rule out a shift towards lower socioeconomic status households.

Compensating parental investments: It is possible that pre-RBM infants received greater human capital or health investments by virtue of being sicker early in life. The literature on whether parental investments compensate or reinforce adverse early life shocks is mixed (Almond and Mazumder, 2013; Attanasio et al., 2017b; Fan and Porter, 2020; Yi et al., 2015). However, the potential of compensating investments explaining the negative findings in this study seems unlikely as it would suggest compensation of pre-eradication cohorts to a degree that goes above and beyond what seems expected in the literature. Nevertheless, we tested the relevance of this channel by estimating our core model using data on parental effort and investments – specifically time spent reading to children, whether the household has books or other reading material, and attendance in (costly) early childhood development centers - from the ZECDP. We find no substantive association between exposure to RBM and any of these indicators (Table 6**,** columns 1-4**)**.

Crowd out of health services: Malaria eradication programs may have reduced the demand for, or crowded out the supply of, preventative services such as vaccines, thus worsening health and, consequently, developmental outcomes. A recent line of work in the economics literature documents the potential importance of this mechanism. For example, Bennett (2012) demonstrates an increase in diarrheal disease rates after the provision of piped water due to over-compensatory behavioral responses in sanitation disposal. Keskin et al. (Forthcoming) use data from Bangladesh to demonstrate a reduction in breastfeeding by parents in response to improvements in groundwater arsenic content, potentially leading to increases in infant mortality. Grepin (2012) and Wilson (2015) provide suggestive evidence of crowd out of child vaccination with scale-up of HIV treatment services -the only global health program larger in scope than Rollback Malaria - in sub-Saharan Africa., t.

To test this hypothesis, we estimate our core model using data from the 2007 DHS. The data include measures of breastfeeding duration and parental vaccination behaviors, which capture both health investment and resource crowd-out.[8] We find no substantive or statistically significant evidence of crowd out (Table 6**,** columns 5-7).

Disease-related income shocks: One may also argue that the findings could be driven by negative income shocks from severe episodes of child or adult malaria during the resurgence years. However, for this explanation to hold, the marginal effect of household income on endowment formation and developmental outcomes would need to be higher for preschoolers rather than infants or toddlers. The literature on whether this is possible is mixed (Banerjee et al., 2010; Carneiro et al., 2021; Maccini and Yang, 2009).

[7] According to the 2013 Demographic and Health Surveys (DHS), total fertility rates declined only marginally at the country level from 6.2 in 2007 to 5.2 in 2013, with no consistent differences across provinces.

[8] While a number of vaccines are reported in the DHS, we focus on BCG and polio. Both of these vaccines are administered in the first six months of life, which means that we can more readily compare children from the 2004 cohort to children from the 2006 cohort, who were on average only 12 months old when the 2007 DHS was conducted.

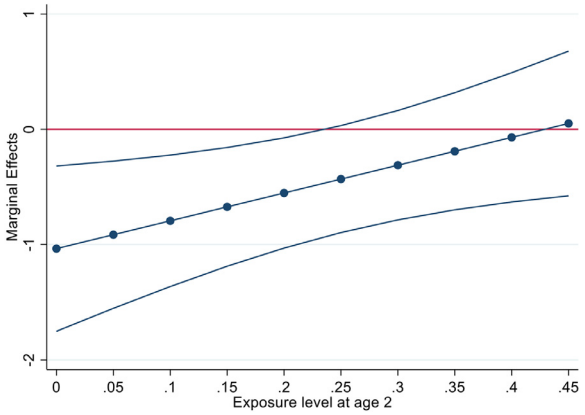

Fig. 4. – Marginal Effect of Age 3-5 Exposure on Cognition at age 6, by Level of 0-2 Exposure.
Notes: Figure plots marginal effects (dotted line with 95% confidence intervals) from Equation (8), which regresses cognition on malaria exposure at ages 0-2, ages 3-5, and their interaction. All exposures are measured at the district level, the smallest geographic unit followed serially in the MIS. Models adjusting for child age, gender, parental education, household wealth, and cluster and cohort fixed effects. The specific marginal effect we focus on is the association between cognition and malaria exposure ages 3-5, as it varies by exposure at ages 0-2. The slope (the estimated interaction effect) is large and statistically significant, and shows that the detrimental consequences of malaria at ages 3-5 are decreasing with higher ages 0-2 exposure.

However, we anticipate that this explanation is unlikely to play a large role in our context. In a recent experimental study conducted in Zambia, provision of effective malaria prevention technologies did have positive impacts on productivity and income among small-scale cotton farmers, but the income effects were small (Fink and Masiye, 2015).

Programmatic changes: Changes in malaria control activities could theoretically explain our findings, if cohorts affected by RBM in the first years of life were exposed to reduced prevention and treatment efforts later in childhood. This seems unlikely because the resumption of RBM programmatic spending after the temporary halt would have likely increased access to these services in affected districts at the time of survey. Using data from the 2006-2010 Malaria Indicator Surveys (described in Appendix A), we find increases in the likelihood that households of 3-5-year-olds who were exposed to Rollback Malaria in the first two years of life owned an insecticide treated bed net and received spraying, though the coefficients are imprecisely estimated (Appendix **Table B1**). We also do not find any negative impacts on the availability of anti-malarial drugs.

Development of drug resistance: If early RBM efforts lead to overtreatment in endemic areas, then it is possible that appropriate treatment in the same areas may have led to fewer health benefits during resurgence, because of the selection of resistant parasites (Bloland, 2001; Mita and Tanabe, 2012; White, 2004). However, this explanation is unlikely for two reasons. First, RBM efforts led to increasing use of more accurate tests to diagnose malaria. As such, the scope for misdiagnosis and inappropriate treatment was limited. Second, resistance to artemisinin-based therapies, the main agents used to treat malaria, has not been reported in Zambia during the study period (Mita and Tanabe, 2012; Zhao and Wang, 2014).

5. Evidence in support immunity formation as a mechanism

5.1. Interactions between early and late malaria exposure

We directly assess whether early life exposure to malaria is protective when faced with sustained disease, by estimating the following model:

$$y_{icdt} = \gamma_0 + \gamma_1 MPPUnder2_{dt} + \gamma_2 MPP3to5_{dt} + \gamma_3 \left(MPPUnder2_{dt} \times MPP3to5_{dt}\right) + X_{icdt}\beta + \pi_t + \theta_d + \epsilon_{icdt} \quad (8)$$

Here, $MPPUnder2_{dt}$ and $MPP3to5_{dt}$ represent average malaria parasitemia rates at ages 0-2 and ages 3-5, respectively, for each child. These exposures are defined at district-level (rather than the cluster-level as in our main results), because this is the smallest geography that is consistently followed in the MIS. π_t and θ_d represent cohort and district fixed effects. The coefficients γ_1 and γ_2 recover the associations between malaria exposure at ages 0-2 and 3-5, respectively, on developmental outcomes assessed at age 6; we expect these estimates to be negative. The term, γ_3, is of primary interest: a positive estimate would be consistent with our model of adaptive immunity, in that the negative association between malaria at ages 3-5 with developmental outcomes should primarily be seen for children with reduced levels of exposure at ages 0-2 (i.e. later impacts become less negative with higher earlier exposure). Importantly, given that age-specific exposures are only available at the district level over time and thus potentially correlated to district-level changes, we interpret the results here as descriptive rather than causal.

Fig. 4 presents marginal effects estimated from this model. While malaria exposure at ages 3-5 displays a highly negative association with cognition at age six in areas where children had reduced early exposure, the same is not true for areas with continued

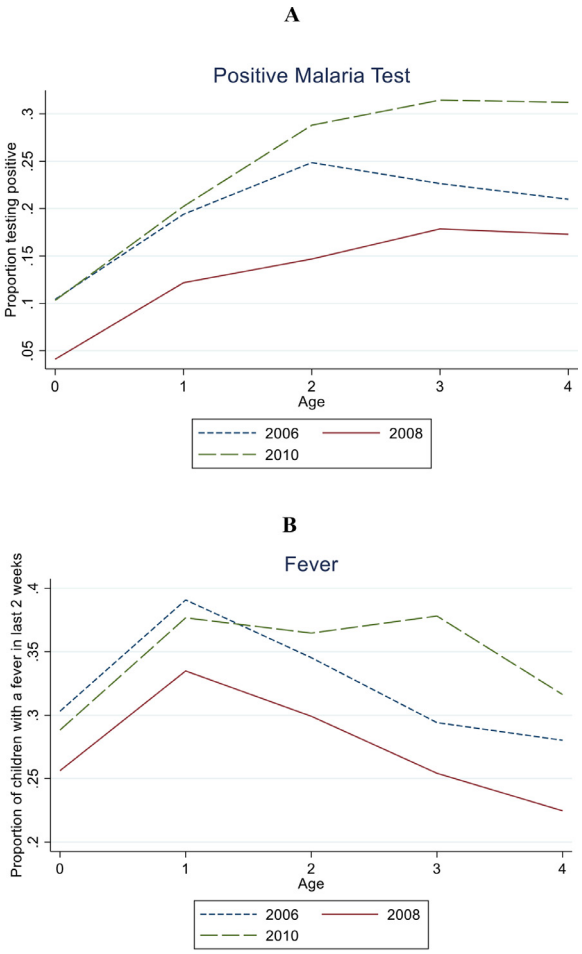

Fig. 5. – Age-Specific Morbidity 2006-2010.
Notes: Figs. shows age and cohort averages as reported in the Zambia Malaria Indicator Surveys (MIS), individual level data from 2006, 2008, and 2010. Panel A shows the proportion of children ages 0, 1, 2, 3 and 4 with a positive rapid diagnostic test. Panel B shows the proportion of children in each age group with a reported fever in the two weeks preceding the survey. Children age 3 in the 2006 MIS correspond to birth cohorts 2002 and 2003; children age 3 in the 2008 MIS to birth cohort 2004 and 2005; children age 3 in the 2010 MIS correspond to birth cohorts 2006 and 2007.

high exposure. Both age 0-2 and age 3-5 malaria exposure are, as expected, negatively associated with cognition, though the coefficients for the latter are larger and more precisely estimated (-.02 (0.37) vs. -1.03 (0.37)). The coefficient on the interaction is 2.4 (1.10).Specifically, we find that a unit increase in age 3-5 exposure reduces cognition by 1 s.d. (beta = -1.03, p-value < 0.01) if early life exposure is close to zero; for baseline MPP > 0.4, this effect is close to zero and not statistically significant. This finding is consistent with the protective benefits of early malaria exposure with subsequent reexposure. In addition, it also suggests that the main findings are unlikely to be solely driven by higher disease exposure in the pre-school years (as with this latter explanation, we would see no gradient in the effect of pre-school years malaria risk by prior exposure histories).

5.2. RBM impacts on health measures

Examining measures of disease risk and morbidity provides complementary evidence supporting the importance of adaptive immunity in driving our findings. While there are currently no biomarkers available to measure immune system formation in field settings, we can test immune system performance by looking at malaria-specific health outcomes across age groups over time. As discussed in Section 2, failure to form partial immunity should result in greater morbidity from malaria upon exposure to the disease. We can explicitly test this prediction using data from the 2006, 2008, and 2010 MIS, which collected detailed child-level information on malaria infections (using rapid diagnostic tests with laboratory confirmation of positive rapid diagnostic tests) and parent-reported disease symptoms (Appendix A).

As an initial illustration, we plot malaria parasite prevalence by age and survey round (Fig. 5, Panel A). Average parasitemia prevalence is almost identical for children under age 2 in 2006 and in 2010, which suggests similar overall disease environments in

these two years (consistent with initial impacts of RBM, children under 2 in the 2008 MIS had far lower parasitemia rates). The same is not true for older children in these environments: infection and morbidity rates of 3- and 4-year-olds in 2010 were almost twice as high as the corresponding rates among younger children. The 3- and 4-year-olds observed in 2010 directly correspond to children born in 2006 and 2007, who were most protected from malaria in the first two years of life due to early RBM efforts. In comparison, the 3- and 4-year-olds observed in 2006 were born in 2002 and 2003 and, thus, exposed to a continuously high malaria burden up to the time of the 2006 survey. The patterns are generally similar for fever – the main difference is that fever prevalence peaks at age 1, and then declines for older ages. Similar to malaria infection rates, we once again see however that the 3- and 4-year-olds from the 2006 and 2007 cohorts display much higher morbidity than the same age cohorts observed in earlier rounds.

Overall, these figures suggest that children exposed to less malaria in the first two years of life were more likely to subsequently experience malaria-related morbidity. To formally assess the impacts of early exposure to RBM on malaria-related outcomes, we estimate the following continuous difference-in-differences model using the MIS data:

$$y_{idpt} = \delta_0 + \delta_1 1(Post_t) \times MPP2006_d + X_{idt}\beta + \omega_d + \lambda_p \times \pi_t \quad \varepsilon_{icdt} \tag{9}$$

This equation follows the same form as the model estimated for the human capital outcomes (Equation 7) - *i* indexes the individual; *d* and *p* the district and province of residence at time of the interview, respectively; and *t* the birth cohort (reflecting the interval 2003-2007). Measures of malarial infection and morbidity are denoted by *y*. These include malaria test positivity (based on a rapid diagnostic tests and identification of parasites on blood smears); fever in the last two weeks; severe anemia (based on measured hemoglobin), a common consequence of malaria infection (though is also related to nutritional intake and other comorbid conditions, such as hookworm infection); and having both biomarker evidence of severe anemia and self-reporting fever, which we use as a marker of severe infection.[9] The $\mathbf{1}(Post_t)$ indicator here marks the 2006 and 2007 cohorts, who were exposed to reduced malaria risk due to RBM during the first 2 years of life, and is interacted with initial local malaria parasitemia prevalence. Unlike Equation 7, we use the *district-level* malaria prevalence given that this is the smallest sub-region that is consistently followed through each MIS wave. The vector $\boldsymbol{X}$ denotes child characteristics such as age (in months) and gender and also includes survey round fixed effects to adjust for potential measurement differences across rounds. The terms π_t, and ω_d refer to birth cohort and district fixed effects, respectively, and the term $\lambda_p \times \pi_t$ denotes province-cohort fixed effects. The cohort fixed effects absorb all general differences across cohorts in areas without malaria (as well as the generic 1(Post) term); the district fixed effects control for all time-invariant factors at the district level such as pre-intervention development or parasitemia. The term $\lambda_p \times \pi_t$.

We again are interested in the coefficient on the interaction term δ_1, which denotes the difference in health outcomes across birth cohorts and areas with different pre-intervention malaria burdens. To estimate program impacts during the first two years of RBM, we first use data from the 2006 and 2008 MIS - just before and just after the program started – and focus on children under the age of 2. In these models, we would expect post-intervention cohorts to show better health outcomes given that the intervention was clearly effective in reducing malaria rates (as illustrated in Fig. 2) in the short run. We then estimate the model for children 3 years and above (using the 2008 and 2010 MIS). This model captures the period of malaria resurgence; if the partial immunity hypothesis holds, we would expect α_1 to be negative.

As with the analysis in Section 3, a key threat to inference is the presence of omitted time-varying processes that may influence malaria exposure and child health. Unlike the analysis of human capital outcomes, we do not have sub-district variation in malaria burdens, and so this specification is prone district-year omitted characteristics. To at least partially address this issue, we include province-birth year and province-survey year fixed effects, recognizing that we are unlikely to fully adjust for confounding in these analyses.

Table 7 presents the main results of this analysis. Columns (1) and (2) show malaria-related health outcomes among children under 2 years old in the 2006 and 2008 MIS. We find positive estimates (morbidity reductions) for all outcomes, which confirms that RBM reduced malaria test positivity and clinical consequences of diseases such as fever and anemia. The results presented in Table 1 suggest that moving from the top to the bottom quintile of baseline parasitemia (a change in parasitemia of 0.43) was associated with a 10% point decrease (0.43*coefficient estimate; nearly 25% of the pre-intervention mean in high prevalence areas) in the probability of testing positive for malaria by rapid diagnostic test; a 10% point decrease in the probability of reporting a fever in the prior two weeks; a 21% point decrease in the probability of severe anemia; and a 16% point decrease in the probability of having both fever and anemia. The estimates remain similar in magnitude with the inclusion of province-year fixed effects though precision of the estimates declines in some cases.

Columns (3) and (4) present the health outcomes for the same birth cohorts during the ages of 3-5, when children in resurgent areas were exposed to a high malaria burden. The results are exactly the opposite as those in columns (1) and (2). Consistent with our partial immunity interpretation, we find that the risk of malaria test positivity is now *larger* (by a similar order of magnitude) for cohorts born during RBM, though less precisely estimated. Children exposed to RBM had much significantly higher risk of having severe anemia, as well as concurrent fevers and anemia at ages 3 and 4. Moreover, the age-specific coefficients shown in Table 7 imply that program impacts on malaria related outcomes at age 3-5 were of similar magnitude as the initial benefits of a disease-free environment.[10] Collectively, these findings are consistent with biomedical models of immunity formation mentioned in the introduction that shows higher risk of (mild and severe) malaria without previous exposure (Aponte et al., 2007; Doolan et al., 2009; Goncalves et al., 2014; Gupta et al., 1999; Snow et al., 1997).

[9] We follow the World Health Organization convention in defining age specific thresholds for severe anemia.

[10] For example, the results from Table 5 imply that a 1 s.d. temporary decrease in birth cohort MPP was associated with a decrease in severe anemia equivalent to 64% of the age 0-2 mean, but a 75% increase relative to the age 3-5 mean.

Table 7
– Age-specific Changes in Malaria Morbidity

	Ages 0-2		Ages 3-5	
	(1)	(2)	(3)	(4)
Positive RDT (=1)	-0.294***	-0.233*	0.342*	0.244
	(0.108)	(0.132)	(0.184)	(0.198)
Sample mean	0.11	0.11	0.28	0.28
N	1,819	1,819	2,197	2,197
Slide Positivity (=1)	-0.726***	-0.802***	0.413**	0.285
	(0.109)	(0.115)	(0.167)	(0.201)
Sample mean	0.11	0.11	0.18	0.18
N	1,820	1,820	2,185	2,185
Fever = 1	-0.249*	-0.174	0.235	0.246
	(0.136)	(0.162)	(0.145)	(0.148)
Sample mean	0.33	0.33	0.29	0.29
N	1,479	1,479	1,806	1,806
Hemoglobin (mg/dl)	2.620***	2.580***	-1.328**	-1.277
	(0.566)	(0.526)	(0.660)	(0.764)
Sample mean	10.09	10.09	10.99	10.99
N	1,780	1,780	2,192	2,192
Severe Anemia (=1)	-0.437***	-0.480***	0.107**	0.108**
	(0.0960)	(0.0922)	(0.0432)	(0.0468)
Sample mean	0.06	0.06	0.02	0.02
N	1,780	1,780	2,192	2,192
Fever + Anemia (=1)	-0.381**	-0.379**	0.342**	0.381***
	(0.161)	(0.178)	(0.136)	(0.113)
Sample mean	0.68	0.68	0.38	0.38
N	1,370	1,370	1,698	1,698
Controls				
District-cohort fixed effects	X	X	X	X
Province-cohort fixed effects		X		X

Notes: Estimates of continuous DID model (equation 7) in main text. Columns (1) and (2) use data from the 2006 and 2008 Malaria Indicator Surveys. Columns (3) and (4) use data from the 2008 and 2010 MIS rounds. All models control for age and sex of child and the controls denoted at the bottom of the table. Robust standard errors, corrected for clustering at the district level, in parenthesis. Sample includes all children under the age of 2 who were born between 2004 and 2007. The key difference is that cohorts are ages 3-5 at the time of survey in columns (3) and (4), instead of 0-2, and are captured during a time of program interruption and malaria resurgence (Fig. 2).The coefficients reported are those on Post*MPP. Post, which is equal to 1 for the 2006 and 2007 birth cohorts and 0 otherwise, denotes cohort exposure to Rollback Malaria, which was initiated in 2006. MPP reflects the district specific under-5 malaria test positivity rate in 2006. ** $p < 0.01$ ** $p < 0.05$ * $p < 0.1$. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

6. Discussion – Implications for human capital theory and public health programs

Nearly 250 million children worldwide are currently estimated to be at risk of not meeting their developmental potential (Black et al., 2016; McCoy et al., 2016). Many of these children reside in sub-Saharan Africa, where infectious diseases such as malaria and malnutrition remain common challenges to optimal skill formation (Li et al., 2016). While a large literature has highlighted the human capital benefits of lowering exposure to infectious diseases in early childhood, we show that exposure to reduced early life exposure to disease may actually confer a disadvantage if improvements in children's environment are not sustained. These results support a broader model of human capital formation where adaptive biological responses play a critical role in shaping the returns to early life investments and exposure when the surrounding environment changes.

Our findings have several important implications for the literature on human capital production. First, the observed inter-temporal trade-offs between health exposures and skill formation suggest a human capital production function whose properties may transcend simple cross-period substitution and dynamic complementarity. Models incorporating adaptive biological responses suggest that the human capital impact of early exposures is non-linear and trajectory-dependent, in ways that are not captured by standard stylized models of health and human capital formation. While our paper focuses primarily on malaria, the findings presented here could plausibly extend to other common childhood infectious diseases as well as health and nutritional investments. Exploring the broader relevance of adaptive responses in these other cases – and their implications for skill formation - is an important area for future research. A challenge to such research – which led us in the present paper to consider the case of malaria - will be finding plausible exogenous variation and high-resolution data.

Second, our findings suggest an alternate rationale for follow-on or continued investments beyond dynamic complementarity. In addition to raising the marginal returns to initial investment, follow-on investments – in our case, continued successful interventions to keep malaria at bay – may be necessary to ensure concordance between initial biological responses and the subsequent environment to avoid harm.

Finally, our results also highlight the importance of understanding the dynamics within the broad period of what constitutes "early childhood." Our findings suggest that being healthy in the first two years (the first 1000 days) of life might be a necessary, but not a sufficient condition for optimal early development and human capital formation. An increased focus on later periods of childhood, as well as an increased focus on understanding the interactions between period-specific exposures and long-run outcomes seems thus desirable.

Author Statement

Günther Fink. Funding acquisition. Project administration, Conceptualization, Methodology, Formal analysis Writing- Original draft preparation. Writing- Reviewing and Editing,

Atheendar S. Venkataramani. Conceptualization, Methodology, Formal analysis, Visualization. Original draft preparation. Writing- Reviewing and Editing.

Arianna Zanolini. Data Acquisition, Methodology, Formal analysis Writing- Original draft preparation. Writing- Reviewing and Editing.

Data Availability Statement

The data used in this article will be made available online through the journal's webpage.

Disclosure Statement, Günther Fink

I hereby declare that I have no relevant or material financial interests that relate to the research described in this paper. I received no funding for this project other than the funding obtained for the original ZECDP data collection (UNICEF Zambia, Julie Henry, and the Özyegin Family–AÇEV Global Early Childhood Research Fund). The ZECDP project was approved by the IRB at the Harvard School of Public Health as well as the University of Zambia IRB.

Disclosure Statement, Atheendar S. Venkataramani

I hereby declare that I have no relevant or material financial interests that relate to the research described in this paper. I received no funding for this project.

The ZECDP project was approved by the IRB at the Harvard School of Public Health as well as the University of Zambia IRB.

Disclosure Statement, Arianna Zanolini

I hereby declare that I have no relevant or material financial interests that relate to the research described in this paper. I received no funding for this project. I have worked on the project in my personal capacity rather than as an employee of the UK Foreign, Commonwealth and Development Office (FCDO). This research has been done independently, and does not reflect or represent official FCDO views.

The ZECDP project was approved by the IRB at the Harvard School of Public Health as well as the University of Zambia IRB.

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Supplementary materials

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References

Aizer, A, Cunha, F., 2012. The Production of Human Capital: Endowments, Investments and Fertility. Natl. Bureau Econ. Res. Working Paper Series No. 18429.

Almond, D, Currie, J, Duque, V., 2018. Childhood circumstances and adult outcomes: act II. J. Econ. Lit. 56, 1360–1446.

Almond, D, Mazumder, B., 2013. Fetal Origins and Parental Responses. Annu. Rev. Econ. 5, 37–56.

Alonso, PL, Brown, G, Arevalo-Herrera, M, Binka, F, Chitnis, C, Collins, F, Doumbo, OK, Greenwood, B, Hall, BF, Levine, MM, Mendis, K, Newman, RD, Plowe, CV, Rodríguez, MH, Sinden, R, Slutsker, L, Tanner, M., 2011. A Research Agenda to Underpin Malaria Eradication. PLoS Med. 8, e1000406.

Aponte, JJ, Menendez, C, Schellenberg, D, Kahigwa, E, Mshinda, H, Vountasou, P, Tanner, M, Alonso, PL., 2007. Age interactions in the development of naturally acquired immunity to Plasmodium falciparum and its clinical presentation. PLoS Med. 4, e242.

Ashraf, N, Fink, G, Weil, DN., 2010. Evaluating the effects of large scale health interventions in developing countries. In: The Zambian Malaria Initiative. National Bureau of Economic Research, Cambridge, Ma, p. 2010 (Ed)ˆ(Eds), NBER Working Paper, vol. 16069.

Attanasio, O, Cattan, S, Fitzsimons, E, Meghir, C, Rubio-Codina, M., 2020. Estimating the Production Function for Human Capital: Results from a Randomized Controlled Trial in Colombia. Am. Econ. Rev. 110, 48–85.

Attanasio, O, Meghir, C, Nix, E, Salvati, F., 2017a. Human capital growth and poverty: Evidence from Ethiopia and Peru. Rev. Econ. Dyn. 25, 234–259.

Attanasio, O, Meghir, C, Nix, E, Salvati, F., 2017b. Human capital growth and poverty: Evidence from Ethiopia and Peru. Rev. Econ. Dyn. 25, 234–259.

Banerjee, A, Duflo, E, Postel-Vinay, G, Watts, T., 2010. Long-Run Health Impacts of Income Shocks: Wine and Phylloxera in Nineteenth-Century France. Rev. Econ. Stat. 92, 714–728.

Baranov, V, Kohler, H-P., 2012. The indirect impact of antiretroviral therapy on savings and human capital investment in Malawi. Mimeo. Univ. Melbourne.

Barofsky, J, Anekwe, T, Chase, C., 2015. Malaria eradication and economic outcomes in sub-Saharan Africa: evidence from Uganda. J. Health Econ. 44, 118–136.

Barreca, AI., 2010. The Long-Term Economic Impact of In Utero and Postnatal Exposure to Malaria. J. Hum. Resour. 45, 865–892.

Bateson, P, Gluckman, P, Hanson, M., 2014. The biology of developmental plasticity and the Predictive Adaptive Response hypothesis. J. Physiol. 592, 2357–2368.

Bau, N, Rotemberg, M, Shah, M, Steinberg, B., 2020. Human Capital Investment in the Presence of Child Labor. Natl. Bureau Econ. Res. Working Paper Series 27241. http://www.nber.org/papers/w27241.

Bennett, D., 2012. Does Clean Water Make You Dirty?: Water Supply and Sanitation in the Philippines. J. Hum. Resour. 47, 146–173.

Black, MM, Walker, SP, Fernald, LC, Andersen, CT, DiGirolamo, AM, Lu, C, McCoy, DC, Fink, G, Shawar, YR, Shiffman, J, Devercelli, AE, Wodon, QT, Vargas-Baron, E, Grantham-McGregor, S., 2016. Early childhood development coming of age: science through the life course. Lancet North Am. Ed. DOI. doi:10.1016/S0140-6736(1016)31389-31387, Epub Before Printhttp://dx.doi.org/.

Bleakley, H., 2010. Malaria Eradication in the Americas: A Retrospective Analysis of Childhood Exposure. Am. Econ. J.: Appl. Econ. 2, 1–45.

Bloland, PB., 2001. Drug resistance in malaria. World Health Organization, Geneva, Switzerland, p. 2001 (Ed)ˆ(Eds).

Boivin, MJ, Bangirana, P, Byarugaba, J, Opoka, RO, Idro, R, Jurek, AM, John, CC., 2007. Cognitive impairment after cerebral malaria in children: a prospective study. Pediatrics 119, e360–e366.

Carneiro, P, Kraftman, L, Mason, G, Moore, L, Rasul, I, Scott, M., 2021. The Impacts of a Multifaceted Pre-natal Intervention on Human Capital Accumulation in Early Life. Am. Econ. Rev. forthcoming.

Chandra, RK., 1997. Nutrition and the immune system: an introduction. Am. J. Clin. Nutr. 66, 460S–463S.

Chang, S, Fleisher, B, Kim, S, Liu, S-y., 2014. Long-Term Health Effects of Malaria Exposure around Birth: Evidence from Colonial Taiwan. Econ. Dev. Cultural Change 62, 519–536.

Chen, YJ, Li, L, Xiao, Y., 2020. Early-Life Exposure to Tap Water and the Development of Cognitive Skills. J. Hum. Resour..

Cohen, JM, Smith, DL, Cotter, C, Ward, A, Yamey, G, Sabot, OJ, Moonen, B., 2012. Malaria resurgence: a systematic review and assessment of its causes. Malar. J. 11, 122.

Conti, G, Heckman, JJ., 2014. The economics of child well-being. In: Ben-Arieh, A, Casas, F, Frones, I, Korbin, JE (Eds.), Handbook of Child Well-Being: Theories, Methods, and Policies in Global Perspective. Springer, Dordrecht, p. 2014.

Cunha, F, Heckman, JJ., 2007. The technology of skill formation. Am. Econ. Rev. 97, 31–47.

Cunha, F, Heckman, JJ, Schennach, SM., 2010. Estimating the Technology of Cognitive and Noncognitive Skill Formation. Econometrica 78, 883–931.

Cutler, D, Fung, W, Kremer, M, Singhal, M, Vogl, T., 2010. Early-Life Malaria Exposure and Adult Outcomes: Evidence from Malaria Eradication in India. Am. Econ. J.: Appl. Econ. 2, 72–94.

Datoo, MS, Natama, MH, Somé, A, Traoré, O, Rouamba, T, Bellamy, D, Yameogo, P, Valia, D, Tegneri, M, Ouedraogo, F, Soma, R, Sawadogo, S, Sorgho, F, Derra, K, Rouamba, E, Orindi, B, Ramos Lopez, F, Flaxman, A, Cappuccini, F, Kailath, R, Elias, S, Mukhopadhyay, E, Noe, A, Cairns, M, Lawrie, A, Roberts, R, Valéa, I, Sorgho, H, Williams, N, Glenn, G, Fries, L, Reimer, J, Ewer, KJ, Shaligram, U, Hill, AVS, Tinto, H, 2021. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet North Am. Ed. 397, 1809–1818.

Doolan, DL, Dobaño, C, Baird, JK., 2009. Acquired immunity to malaria. Clin. Microbiol. Rev. 22, 13–36 Table of Contents.

Fan, W, Porter, C., 2020. Reinforcement or compensation? parental responses to children's revealed human capital levels. J. Popul. Econ. 33, 233–270.

Fink, G, Masiye, F., 2015. Health and agricultural productivity: Evidence from Zambia. J. Health Econ. 42, 151–164.

Fink, G, Matafwali, B, Moucheraud, C, Simmons-Zuilkowski, S., 2012. The Zambian Early Childhood Development Project: Round I Final Reports. Harvard Center on the Developing Child: Cambridge;.

Fink, G, Rockers, PC., 2014. Childhood growth, schooling, and cognitive development: further evidence from the Young Lives study–. Am. J. Clin. Nutr. 100, 182–188.

Collaborators, GBD, 2014. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet.

Gluckman, P, Hanson, M., 2006. Mismatch: Why Our World No Longer Fits Our Bodiess. Oxford University Press, Oxford, UK.

Goncalves, BP, Fried, M, Duffy, PE., 2014. Parasite burden and severity of malaria in Tanzanian children. N. Engl. J. Med. 371, 482.

Grantham-McGregor, S, Cheung, YB, Cueto, S, Glewwe, P, Richter, L, Strupp, B, 2007. International Child Development Steering Group. Developmental potential in the first 5 years for children in developing countries. Lancet 369, 60–70.

Grepin, K., 2012. HIV donor funding has both boosted and curbed the delivery of different non-HIV health services in sub-Saharan Africa. Health Aff. (Millwood) 31, 1406–1414.

Gunnsteinsson, S, Adhvaryu, A, Christian, P, Labrique, A, Sugimoto, J, Shamim, AA, Keith, P., West, J., 2019. Protecting Infants from Natural Disasters: The Case of Vitamin A Supplementation and a Tornado in Bangladesh. NBER Working Paper 25969.

Gupta, S, Snow, RW, Donnelly, CA, Marsh, K, Newbold, C., 1999. Immunity to non-cerebral severe malaria is acquired after one or two infections. Nat. Med. 5, 340–343.

Handa, S, Peterman, A, Seidenfeld, D, Tembo, G., 2016. Income transfers and maternal health: evidence from a national randomized social cash transfer program in Zambia. Health Econ. 25, 225–236.

Heckman, JJ., 2007. The Economics, Technology, and Neuroscience of Human Capability Formation. Proc. Natl. Acad. Sci. 104, 13250–13255.

Holt, PG, Jones, CA., 2000. The development of the immune system during pregnancy and early life. Allergy 55, 688–697.

Hong, SC., 2007. The Burden of Early Exposure to Malaria in the United States, 1850-1860: Malnutrition and Immune Disorders. J. Econ. History 67, 1001–1035.

Hoynes, H, Whitmore Schanzenbach, D, Almond, D, 2016. Long-run impacts of childhood access to the safety net. Am. Econ. Rev. 106, 903–934.

Johnson, RC, Jackson, CK., 2019. Reducing inequality through dynamic complementarity: evidence from Head Start and public school spending. Am. Econ. J.: Econ. Policy 11, 310–349.

Keskin, P, Shastry, GK, Willis, H., 2020. Water quality awareness and breastfeeding: evidence of health behavior change in Bangladesh. Rev. Econ. Statistics Forthcoming.

Kremer, M, Miguel, E, 2004. Worms: Identifying Impacts on Education and Health in the Presence of. Treat. Externalities Econometrica 72, 159–217.

Kremer, M, Miguel, E, 2007. The Illusion of Sustainability. Q. J. Econ. 122, 1007–1065.

Kuecken, M, Thuilliez, J, Valfort, M-A., 2020. Disease and Human Capital Accumulation: Evidence from the Roll Back Malaria Partnership in Africa. Econ. J..
Li, C, Black, MM, Richter, L., 2016. Risk of poor development in young children in low-income and middle-income countries: an estimation and analysis at the global, regional, and country level. Lancet North Am. Ed. doi:10.1016/S2214-1109X(1016)30266-30262, http://dx.doi.org/.
Lucas, A., 2010. Malaria Eradication and Educational Attainment: Evidence from Paraguay and Sri Lanka. Am. Econ. J.: Appl. Econ. 2, 46–71.
Lucas, A., 2013. The Impact of Malaria Eradication on Fertility. Econ. Dev. Cultural Change 61, 607–631.
Lucas, AM, Wilson, NL., 2013. Adult Antiretroviral Therapy and Child Health: Evidence from Scale-Up in Zambia. Am. Econ. Rev. Papers Proc. 103, 456–461.
M'Rabet, L, Vos, AP, Boehm, G, Garssen, J, 2008. Breast-feeding and its role in early development of the immune system in infants: consequences for health later in life. J. Nutr. 138, 1782S–1790S.
Maccini, S, Yang, D., 2009. Under the Weather: Health, Schooling, and Economic Consequences of Early-Life Rainfall. Am. Econ. Rev. 99, 1006–1026.
Maskin, E, Monga, C, Thuilliez, J, Berthélemy, J-C., 2019. The economics of malaria control in an age of declining aid. Nat. Commun. 10, 2269.
McCoy, DC, Peet, ED, Ezzati, M, Danaei, G, Black, MM, Sudfeld, CR, Fawzi, W, Fink, G., 2016. Early Childhood Developmental Status in Low- and Middle-Income Countries: National, Regional, and Global Prevalence Estimates Using Predictive Modeling. PLoS Med. 13, e1002034.
Mita, T, Tanabe, K., 2012. Evolution of Plasmodium falciparum drug resistance: implications for the development and containment of artemisinin resistance. Jpn. J. Infect. Dis. 65, 465–475.
Mouzin E, Mukonka V, Kamuliwo M, Hamainza B, Mwanza M, Wamalume P, Jennings T, Miller JM. Focus on Zambia. 2011.
, 2009. Zambia Malaria Indicator Survey 2008. (Ed)ˆ(Eds). Zambia Ministry of Health, Lusaka, Zambia, p. 2009.
Pei, Z, Pischke, J-S, Schwandt, H., 2018. Poorly measured confounders are most useful on the left than on the right. J. Bus. Econ. Stat. Forthcoming.
Reves, RR, Hossain, MM, Midthun, K, Kapikian, AZ, Naguib, T, Zaki, AM, DuPont, HL., 1989. An observational study of naturally acquired immunity to rotaviral diarrhea in a cohort of 363 Egyptian children. Calculation of risk for second episodes using age-specific person-years of observation. Am. J. Epidemiol. 130, 981–988.
Rossin-Slater, M, Wüst, M., 2016. Are Different Early Investments Complements or Substitutes? Long-Run and Intergenerational Evidence from Denmark∗. Mimeo.
Schneider, EB., 2017. Children's growth in an adaptive framework: explaining the growth patterns of American slaves and other historical populations. Econ. Hist. Rev. 70, 3–29.
Siflinger, B, van den Berg, G., 2018. The effects of public day care on health during childhood: Evidence by age. IZA Discussion Paper No. 11447.
Snow, RW, Omumbo, JA, Lowe, B, Molyneux, CS, Obiero, J-O, Palmer, A, Weber, MW, Pinder, M, Nahlen, B, Obonyo, C, Newboldb, C, Gupta, S, Marsh, K., 1997. Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. Lancet 349, 1650–1654.
Thuilliez, J, d'Albis, H, Niangaly, H, Doumbo, OK., 2017. Malaria and education: evidence from Mali. J. African Econ. 26, 443–469.
Usher, AD., 2010. Donors lose faith in Zambian Health Ministry. Lancet North Am. Ed. 376, 403–404.
Vanaten, T, Kostic, AD, d'Hennezel, E, Siljander, H, Franzosa, EA, Yassour, M, Kolde, R, Vlamakis, H, Arthur, TD, Hamalainen, A-M, Peet, A, Tillman, V, Uibo, R, Mokurov, S, Dorshakova, N, Ilonen, J, Virtanen, SM, Szabo, S, Porter, JA, Lahdesmaki, H, Huttenhower, C, Gevers, D, Cullen, TW, Knip, M, Xavier, R., 2016. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. Cell 165, 842–853.
Venkataramani, A., 2012. Early life exposure to malaria and cognition in adulthood: evidence from Mexico. J. Health Econ. 31, 767–780.
Victora, CG, Md, Onis, Hallal, PC, Blössner, M, Shrimpton, R., 2010. Worldwide timing of growth faltering: revisiting implications for interventions. Pediatrics 125, e473–e480.
White, NJ., 2004. Antimalarial drug resistance. J. Clin. Invest. 113, 1084–1092.
Wilson, N., 2014. Prevention of Mother-to-Child Transmission of HIV and Reproductive Behavior in Zambia. In: Edwards, S, Johnson, S, Weil, DN (Eds.), African Successes: Human Capital. University of Chicago Press, p. 2014 Volume 2.
Wilson, N., 2015. Can disease specific funding harm health? In the shadow of HIV/AIDS service expansion. Demography 52, 1671–1700.
World Health Organization, 2017. World Malaria Report 2017s. WHO, Genevia.
Yang, E, Rubin, BK., 1995. Childhood" viruses as a cause of pneumonia in adults. Semin. Respir. Infect. 10, 232–243.
Yazdanbaksh, M, Kremsner, PG, van Ree, R., 2002. Allergy, parasites, and hygiene hypothesis. Science 296, 490–494.
Yi, J, Heckman, JJ, Zhang, J, Conti, G., 2015. Early Health Shocks, Intra-Household Resource Allocation and Child Outcomes. Econ. J. 125, F347–F371.
Zambia Ministry of Health, 2006. A 6-year Strategic Plan A Road Map for Impact on Malaria in Zambia 2006-2011s. NMCC, Lusaka.
Zhao, SM, Wang, MY., 2014. [Artemisinin resistance in Plasmodium falciparum: global status and basic research]. Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi 32, 380–384.