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Phillips, Erica

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Ethical considerations in the design and conduct of a cluster-randomised mycotoxin mitigation trial in Tanzania

E. Phillips^{1*}, P.C. Turner², F.M. Ngure³, N. Kassim⁴, E. Makule⁴, L.E. Smith⁵, R.J. Nelson⁶ and R.J. Stoltzfus⁷

¹Division of Nutritional Sciences, Cornell University, 244 Garden, Ithaca, NY 14853, USA; ²MIAEH, School of Public Health, University of Maryland, College Park, MD 20740, USA; ³Independent Research Consultant, Arusha, Tanzania and Nairobi, Kenya; ⁴Department of Food Biotechnology and Nutritional Sciences, (FBNS), School of Life Science and Bio-Engineering, The Nelson Mandela African Institution of Science and Technology (NM-AIST), P.O. Box 447, Arusha, Tanzania; ⁵Department of Population Medicine and Diagnostics, Cornell University, Ithaca, NY 14853, USA; ⁶School of Integrative Plant Science and Department of Global Development, Cornell University, Ithaca, NY 14853, USA; ⁷Goshen College, 1700 S. Main Street, Goshen, Indiana 46526, USA; elp28@cornell.edu

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Abstract

Aflatoxins are fungal metabolites that commonly contaminate staple food crops in tropical regions. Acute aflatoxin consumption in very high concentration causes aflatoxicosis and acute liver failure, while chronic, moderate levels of intake cause hepatocellular carcinoma. The effects of frequent moderate- to high-level exposure during infancy, however, is less clearly understood. Half a billion people in low- and middle-income countries continue to be exposed to aflatoxins through dietary consumption, in part because of lack of enforcement of regulatory limits and few feasible long-term mitigation options in these settings. Several epidemiologic studies have shown an association between aflatoxin exposure in infants and young children and growth failure, but strong experimental evidence is lacking. The Mycotoxin Mitigation Trial conducted in Tanzania was a cluster-randomised trial to assess the effect of a reduced aflatoxin diet on linear growth. Prior to the design and implementation of this trial, a group of multi-disciplinary and multi-national scientists reviewed literature in biomedical, public health, environmental health ethics. In this paper we outline the most salient ethical questions and dilemmas in the potential conduct of such a study and describe the ethical precedents and principles that informed our decision-making processes and ultimate study protocol.

Keywords: aflatoxin, bioethics, infant growth

1. Introduction

Research conducted with human subjects is informed and regulated by multiple guidelines, codes of practice and declarations including The Nuremberg Code, Declaration of Helsinki, Belmont Report, International Ethical Guidelines for Biomedical Research involving Human Subjects and Good Clinical Practice guidelines (Council for International Organizations of Medical Sciences (CIOMS), 2016; International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1997; Katz, 1996; The National Commission for the Protection of Human Subjects of

Biomedical and Behavioral Research, 1979; World Medical Association, 2013). Many of the basic principles described in these documents are codified into national laws. Relying on these guidelines and laws, national and institutional ethical review boards are empowered to determine the ethical acceptability and permissibility of specific research design, conduct and analysis.

Even with extensive guidance on the conduct of human subject research, debates and quandaries in research ethics arise. These debates often highlight the vastly divergent contexts in which research is carried out around the world. Researchers are challenged to know whether and

how to account for these contextual differences, especially when those differences generate the need for research. Different fields of study have divergent, possibly conflicting objectives. For example, clinicians have a duty to protect individual patients whereas public health researchers are concerned for the health of entire populations and communities. Debates also arise as researchers are pushing boundaries of conventional research methods to understand and find solutions to complex, multi-faceted problems including climate change, poverty, food security, and food safety in a globally integrated food system.

Research into mycotoxins and human health encompasses all of these challenges. Understanding and controlling hazardous substances in our food system is a critical goal for agricultural scientists, nutritionists, toxicologists and microbiologists. Dietary staples, such as grains and nuts, are frequently contaminated with secondary metabolites of fungal colonisation. When toxic these metabolites are called mycotoxins. Aflatoxins (AF) are an important family of mycotoxins that most commonly contaminate maize and groundnut, during both the growth of crops in the field and again during storage. In high-income countries, AF is well-regulated and managed throughout the value chain, although at high cost. In the United States, for example, the cost of control, surveillance and loss of food crops due to AF are estimated to be \$47 million for maize and groundnuts annually (Vardon *et al.*, 2003).

In the face of such costs, and lacking strong regulatory infrastructures and feasible interventions to mitigate toxins, around 500 million people remain at risk of being chronically exposed to dietary AF at high levels in low- and middle-income countries (LMICs) (Pitt *et al.*, 2012; Visser *et al.*, 2020; Wu *et al.*, 2014a). Low-resource and rural communities typically have restricted dietary diversity, and tend to be at greatest risk of contaminated food supplies (Pitt *et al.*, 2012; Wild *et al.*, 2015). Chronic AF consumption can lead to liver cancer and ingestion of very high levels causes acute toxicosis and possibly death (IARC, 2002; Lewis *et al.*, 2005; Williams *et al.*, 2004).

There is now a significant body of literature assessing the effect of AF consumption on infant growth. A 2019 systematic review identified two randomised controlled trials (RCT) and 29 observational and prospective cohort studies studying this relationship, but the authors concluded that the overall quality of evidence was low due to risk of bias and inconsistency in the reported outcomes, measurement method and exposure period, as well as failure to adjust for confounders (Tsfamariam *et al.*, 2019). Our internal review found that regions with the highest levels of AF contamination and intake, multiple studies have shown a positive association between AF exposure and growth faltering, suggesting a significant dose-response relationships and a possible threshold of effect (Gong *et*

al., 2002, 2003, 2004; Mahfuz *et al.*, 2020; Mitchell *et al.*, 2017; Turner *et al.*, 2007; Watson *et al.*, 2018). To generate strong causal evidence for the relationship between AF and stunting, we conducted a cluster-randomised trial (CRT) to assess the effect of AF on linear growth in infants and young children (Phillips *et al.*, 2020).

2. Unique ethical dilemmas in this study

As with any research on human subjects, we received ethical approval for the study through Cornell's Institutional Review Board and Tanzania's National Institute for Medical Research. Both bodies approved the research application following minor clarifications in study protocol. In accordance with Good Clinical Practices, we formed a Data Safety and Monitoring Board (DSMB), comprised of a Tanzanian biostatistician, nutritionist and paediatrician. We shared anthropometric data with the DSMB every six months during the trial, as well as immediate notice of any adverse events.

However, because this research involved exposure to toxins in a low-resource setting, we felt it was necessary to go beyond the typical ethical approvals at multiple points throughout the planning process. We initiated consultations with other researchers working in related fields and performed a literature review focused in biomedical, public health and environmental health ethics to identify the most salient ethical complexities and questions for this study. Below we describe four key questions pertinent to this research study and share our responses to them.

Question 1: Given what is already known about the health effects of AF, should a question about the relationship between AF and child growth be studied further in human subjects?

Human subject research must meet certain ethical criteria to be conducted. These include: (1) social and/or scientific value, (2) scientific validity, (3) risk minimisation and a favourable risk/benefit ratio, (4) respect for subjects, (5) informed consent, (6) independent review, (7) fair subject selection, (8) protection of confidentiality and privacy, and (9) protection of vulnerable subjects (US HHS, 2018; Emanuel *et al.*, 2000, 2004; ICH, 1997; Resnik, 2008a). The first four criteria have significant complexity and ultimately rely on value judgements. The latter five were less difficult to meet for this research question, with clear, published guidance and therefore we do not focus on these here.

To have scientific or social value, research should lead to improvements in health, well-being or increase knowledge (Emanuel *et al.*, 2000; World Medical Association, 2013). This research question is important because the majority of the pathways and contributors to stunting remain unexplained even though the negative effects of child

experimental (interrupted time series and controlled pre-post) and experimental designs (RCT, CRT and stepped-wedge design) (Bonell *et al.*, 2011; Cousens *et al.*, 2011; Kirkwood *et al.*, 1997; Sanson-Fisher *et al.*, 2014).

AF contamination in food is heterogeneous and variable within and between years. Therefore, to be scientifically valid, the design would have to control for temporal trends. Quasi-experimental designs could not sufficiently account for these. We strongly considered a stepped-wedge design, which is a one-way crossover cluster trial where all clusters eventually receive the intervention but the timing of when they receive it is randomly ordered. This design was appealing for equity reasons, as all participants would receive the same intervention. However, it would require a longer intervention period compared to an RCT or CRT, seasonality of AF exposure could remain confounding, and analysis and inference were more complicated (Hemming and Girling, 2013; Hussey and Hughes, 2007; Kotz *et al.*, 2012, 2013). Because we envisioned an intervention delivered through the existing health care infrastructure, we ultimately selected a CRT to generate the strongest causal inference in the shortest amount of time and with the fewest subjects.

A CRT can provide a convincing 'yes' or 'no' to our primary research question but not answer 'why' or 'why not'. We felt it would be irresponsible to invest resources into such a study with human subjects without further elucidating the 'impact pathways' of AF on growth (Kim *et al.*, 2011; Rawat *et al.*, 2013). Therefore, we designed a program impact pathway model and plan to link multiple data sources to these models, including survey data about infant feeding practices, blood and urine AF biomarkers and food contamination at five time points throughout the trial.

Question 3: What is the most ethical intervention to randomly allocate?

Unlike most biomedical and nutritional research that assess the efficacy of provided therapeutics, treatments and behavioural interventions, a toxin is not something that

can be given to a research participant. To understand the health impact of AF through an intervention, it needs to be reduced or removed from one's environment where it is pre-existing. Therefore, our operational strategy in intervention design was to reduce risk of toxin exposure to the most vulnerable member of the household (the infant), while not increasing risk exposure to others in the household or the community, to monitor infant health for signs of undernutrition, and inform all subjects about potential risks discovered in the study (described in Question 4) (Resnik *et al.*, 2005).

Early in our planning, the lead US-based research institution formed a collaborative partnership with a Tanzanian university and researchers who study AF exposure. Together, and with consultation of local government officials in potential research sites, we performed formative research to identify specific components of our intervention. We considered the use of (1) pre- and post-harvest interventions, including biocontrol, (2) sorbing using an enterosorbent, such as NovaSil, (3) hand sorting methods to remove contaminated maize and groundnut kernels, and (4) swapping household foods consumed by infants with low-AF version of the same foods. Similar to our process for evaluating study designs, we ranked each intervention based on available literature and our experiences as researchers, by (1) intervention safety, (2) feasibility of delivery, (3) evidence to reduce AF consumption or its effects after consumption (in the case of NovaSil) and (4) likelihood of effectiveness to reduce AF in infant-consumed foods (not only household foods) over one year's time (Table 2).

Pre-harvest interventions to reduce AF include biological control, such as Aflasafe, use of genetically resistant crop varieties, chemical control and good agricultural practices, such as timely harvest and removal of crops from fields (Wild *et al.*, 2015; Wu and Khlangwiset, 2010a). Post-harvest interventions to reduce AF include drying of crops prior to storage, improved storage practices to reduce moisture and application of insecticide, and sorting (Turner *et al.*, 2005; Wild *et al.*, 2015; Wu and Khlangwiset, 2010a).

Table 1. Strength of causal inference for potential study designs.

Study design	Has change occurred?	Are participants randomised?	Is there a control condition?	Likelihood that change is due to the intervention?
Randomised controlled trial	Strong	Yes	Yes	High
Cluster randomised controlled trial	Strong	Yes	Yes	High
Stepped wedge design	Strong	Yes	Yes	Moderate ¹
Interrupted time series	Moderate	No	No	Low ¹
Controlled pre/post	Moderate	No	Yes	Low ¹
Cohort or cross-sectional study	Moderate	No	No	Low ¹

¹ Can be subject to secular, temporal trends; Adapted from Sanson-Fisher *et al.* (2014).

Table 2. Rating of dimensions for potential trial interventions.

Intervention	Safety	Feasibility of delivery	Level of evidence to reduce negative effects of aflatoxin/aflatoxin consumption in infants	Likelihood of effectiveness to reduce aflatoxin exposure in infant diets for duration of intervention period (one year)
Biocontrol	Uncertain	Not feasible	None	None – low (Pitt, 2019)
Sorbing	Limited data for infants	Low to moderate (Wu and Khlangwiset, 2010b)	High (Mitchell <i>et al.</i> , 2014)	Unknown for long term
Hand-sorting at household	High concern about management of toxic out-sorts	Limited evidence at large-scale	Low (Xu <i>et al.</i> , 2017)	Low
Food swapping at household	High	Moderate (complex exchange of tons of food)	Insufficient data	Low – not targeted to infants
IYCF education with provision and promotion of infant foods	High	Moderate (including a complex but more targeted food swap aimed at complementary food only)	Moderate (new intervention, but designed with effective pieces from other nutrition and food security interventions)	Moderate

There is evidence that many of these pre- and post-harvest interventions can be effective, but we believed them to lack the precision needed to control AF consumption for a long-term research intervention targeting infant dietary intake. Additionally, Aflasafe had not been authorised for use in Tanzania at that time. Pilot studies of community hand-sorting of groundnuts to reduce AF in communities have shown promising results, however, sustainability of the intervention in food-insecure regions and safety of the most toxic ‘out-sorts’ was a critical concern, as these could pose high risk to humans and animals (Filbert and Brown, 2012; Xu *et al.*, 2017). If these out-sorts were consumed or sold, a sorting intervention may do greater harm than not sorting at all because the out-sorts concentrate the most toxic kernels. Additionally, out-sorts may be fed to and cause toxicosis to household owned livestock, to the detriment of the family’s food and/or socio-economic status. We did not believe the research project or local partners could have the capacity to adequately monitor and dispose of the out-sorts from households across a district.

Sorbing has been shown to be effective in adults in short-term studies (up to three months), but we ruled it out due to limited evidence about its safety, including micronutrient bioavailability, in infants for longer durations (Mitchell *et al.*, 2014; Phillips *et al.*, 2008; Wu and Khlangwiset, 2010a). As mentioned above, a separate component of our overall research project was to develop a scalable and long-term sorting technology that could be used in local mills to remove toxins in maize and groundnut kernels. However, at the start of the trial this technology was not ready for implementation. Swapping of household foods was the safest option, but for a 12-month intervention period would

have been costly and perhaps not sufficiently targeted to infant diets.

We therefore developed an intervention drawing upon effective public health nutrition and food security interventions. We designed an infant and young child feeding (IYCF) educational intervention with provision (intervention arm) or promotion (control arm) of commonly consumed blended porridge flours. This IYCF intervention was created to meet multiple objectives: (1) promote a nutritionally diverse and adequate diet for all infants in the study, including exclusive breastfeeding through six months of age, (2) minimise dietary differences between intervention arms, and (3) generate strong causal evidence.

A nutritionally diverse diet, exclusive breastfeeding to six months and continued breast-feeding beyond six months are protective behaviours against moderate and high AF exposure in infants and young children (Gong *et al.*, 2003, 2004; Wu *et al.*, 2014b). We used these elements to design an intervention that would reduce the risk of malnutrition and AF exposure in all participants. To generate strong causal inference about AF exposure, we needed to create a contrast of AF consumption between the control and intervention groups, without creating differential macro- or micro-nutrient intake, nor differences in feeding and care practices that could affect stunting between arms. To reduce the risk of introducing these biases, we designed the intervention to include: (1) education to improve infant feeding and care practices using Tanzania Food and Nutrition Center’s materials, and (2) behaviour change communication on the use of blended infant porridge (Table 3). Therefore, our control group condition is ‘enhanced IYCF education,’

as the content and frequency of education is beyond the 'standard of care' for IYCF in the location of the study.

We carefully considered if the standard intervention should include groundnut as an infant food, as this is a potential source of AF. Some regional projects and government agencies in Tanzania have promoted groundnut as a nutritious infant food while others have recommended against its consumption because of potential for AF exposure. In more than one year of formative research in the research region we found that infants consume a monotonous, cereal-based diet with limited animal-source foods. Groundnuts are commonly consumed and culturally acceptable, with two-thirds of mothers in the region reported feeding groundnuts to their infants (E. Phillips *et al.*, unpublished data). In this region groundnuts are one of the few sources of available and accessible protein, monounsaturated fats, fibre, several B vitamins, vitamin E and antioxidants (Mupunga *et al.*, 2017). If we recommended against feeding groundnut, we could harm infants by creating nutritional deficiencies. Without an equally nutritionally-dense alternative to groundnuts, and after consultation with local District Nutrition Officer, we decided to include groundnuts in our intervention food and our feeding recommendations.

Question 4: What is the best approach to sharing biological and food sample results with research subjects?

A fourth major consideration of conducting this trial was if, how and when to share results of biological and food sample analyses with research participants. While there is a strong ethical imperative to share these results, there is no consistent guidance about when and how to do so. The National Bioethics Advisory Committee (NBAC) in

the United States advises sharing results 'only when (a) the findings are scientifically valid and confirmed, (b) the findings have significant implications for the subject's health concerns, and (c) a course of action to ameliorate or treat those concerns is readily available.' When applying these standards to AF testing in foods and biomarkers, each of these proves challenging given current knowledge and available technologies for LMICs. Additionally, according to Tanzanian guidelines all data must be presented to government authorities first and approval sought before sharing with research participants.

Human AF biomarkers are not clinical measures with determined cut-offs to distinguish between safe or potentially unsafe levels. Without established clinical cut-offs, there is no clear scientific or health justification to flag or report results except at the levels observed in cases of acute aflatoxicosis (IARC, 2002; Williams *et al.*, 2004). Outside of the range of acute illness, the research will undoubtedly find results that are in the upper ranges compared to other research subjects or other reported data. However, there are no established recommended actions or interventions in this putative 'grey zone'.

Secondly, there is no available technology that will allow rapid analysis of blood or urine samples in the field, so samples must be taken to a laboratory. Analysis of AF-alb requires equipment that is not available in Tanzania, so samples were to be exported for analysis, creating a time lag between sample collection and analysis. We considered working with a local laboratory to build local capacity for AF-alb, but the assays require a high level of investment and it was deemed not possible to accomplish in our budget and time frame. We did, however, build local capacity for analysis of urine biomarkers using ELISA. Even so, because

Table 3. Description of trial intervention by arm (Modified from Phillips *et al.*, 2020).

Enhanced IYCF Education Plus Porridge Flour Provision Group (Intervention)	Enhanced IYCF Education Group Plus Porridge Flour Promotion Group (Control)
Infant feeding education: <ul style="list-style-type: none"> • Breastfeeding (exclusive through 6 months and continued through 2 years) • Dietary diversity • Feeding frequency • Hand washing 	Infant feeding education: <ul style="list-style-type: none"> • Breastfeeding (exclusive through 6 months and continued through 2 years) • Dietary diversity • Feeding frequency • Hand washing
Behaviour change communication on the use of pre-blended porridge flours <ul style="list-style-type: none"> • Timing of introduction, frequency of feeding, density and composition of porridge • Provision of 4:1 ratio of maize meal to groundnut powder made from low-aflatoxin ingredients • Provision of low-aflatoxin groundnut flour 	Behaviour change communication on the use of pre-blended porridge flours <ul style="list-style-type: none"> • Timing of introduction, frequency of feeding, density and composition of porridge • Promotion of 4:1 ratio of maize meal to groundnut powder made from household ingredients • Promotion of groundnut flour

the dynamics of AF exposure are highly variable, by the time sample outliers would be identified, the properties of food consumed by the individual would undoubtedly differ from those consumed when the sample was taken. The results of the analysed samples would not be relevant by the time it could be reported.

Given that AF biomarker and food testing fail to meet the criteria for sharing results described by the NBAC and needing to first consult with the Tanzanian authorities, we designed protocols for sharing results in the case of outlying values for food and biomarker specimens. These are described in detail in our trial protocol ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03940547) identifier: NCT03940547). Briefly, for blood and urinary biomarker reporting, we decided to report the percent of samples above 1000 pg/mg to local authorities. We subjectively chose this cut-off because these are these are levels usually found in the highest quintile in other high-risk countries and we believed that this threshold represented our best estimate to identify this as a reporting concern. For urinary aflatoxin M₁ data, there is no evidence to determine a cut point, so we were unable to take any action based on those analyses.

The legal limit for total AF allowed in foods at the point of sale in Tanzania is 10 µg/kg (Anonymous, 2004). There are no set standards for AF in IYC foods in Tanzania or East Africa. We chose a limit of 5 µg/kg for total AF as a more stringent cut off for IYC foods in our research project. Given the documented AF problem in the region of the research site and our formative research in this location, and the significant amount of food grown and sold outside of regulated markets, we decided to respond to exceptionally high levels of AF in for food samples. We decided to report the percent AF >1000 µg/kg in maize or >5,000 µg/kg in groundnut to the local authorities. We subjectively chose these cut-offs because these are these are levels usually found in the highest quintile in other high-risk countries and we estimate that maize is consumed five times as much as groundnut. If a second food sample from the same household were above these cut-offs we would make a home visit to the family to assess the health of the infant and understand more the food security and food quality issues in the household, particularly as they pertain to the infant and possibly refer the infants to health and agricultural authorities.

3. Discussion and conclusions

As researchers attempt to understand and find solutions to complex, multi-faceted problems that affect people in low-resource contexts, they must grapple with ethical questions that are unique to the type of research and the conditions and inequities of those settings. We have made our planning and decision-making processes transparent to assist other

researchers when the nuances of their ethical questions are not addressed by guidelines or statements.

We can very broadly share the lessons learned through our planning experiences. Research conducted with teams of multi-disciplinary and multi-national professionals brings a wide variety of perspectives and viewpoints. The process of considering ethical aspects of this study was enhanced by having a diverse team of experts from multiple research backgrounds, and intentionally establishing a structure of multi-national leadership and oversight positions. With such a diverse group, throughout our planning process there were some areas that required multiple conversations to come to consensus. For example, we faced disagreement around if and when to report food, blood and urine results to participants given the lack of precision about their implications and limited options to sustainably remove toxins. To structure and guide our decision-making in these cases, we explored the literature about recommendations and precedents for reporting results in similar instances. Then we jointly and iteratively reviewed and discussed our protocols until there was accord.

Our funder, The Bill & Melinda Gates Foundation, initiated this research and agreed to fund us to perform an ethical review prior to developing a full research proposal, and further conducted an external review of the final research proposal prior to its acceptance. We benefited by having a multi-year planning process to explore these decisions and flexibility in all trial and intervention design decisions. These factors allowed us to help ensure open discussions, sharing of beliefs and opinions, and building of trust among stakeholders. This approach provided transparency and objectivity in developing, running and reporting of the study.

Given the importance of stunting as a problem of global child health and the vulnerability of many families and children to chronic consumption of AF-contaminated food systems, we were strongly motivated to conduct this research. We recognise that there are no definitive answers to these questions and others might come to different conclusions. Yet we believe this research is valuable, not only to better understand the problem, but to motivate action to improve it.

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Conflict of interest

The authors declare no conflict of interest.

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