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Health economic impacts and cost-effectiveness of aflatoxin reduction strategies in Africa: Case studies in biocontrol and postharvest interventions

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Abstract

Advances in health economics have proven useful in evaluating the cost-effectiveness of interventions, where the benefit usually takes the form of improved health outcomes rather than market outcomes. We perform health-based cost-effectiveness analyses of two potential aflatoxin control strategies in Africa: 1) pre-harvest biocontrol, using atoxigenic strains of *Aspergillus flavus* to competitively exclude toxigenic strains from colonizing maize in Nigeria, and 2) postharvest interventions in a package to reduce aflatoxin accumulation in groundnuts in Guinea. We describe how health benefits gained from each intervention, in terms of fewer aflatoxin-induced hepatocellular carcinoma (HCC) cases, can be compared with costs of implementing the interventions. We find that both interventions would be extremely cost-effective if applied widely in African agriculture. That is, the monetized value of lives saved and quality of life gained by reducing aflatoxin-induced HCC far exceeds the cost of either biocontrol or the postharvest intervention package to achieve those health benefits. The estimated cost-effectiveness ratio (CER; gross domestic product multiplied by disability-adjusted life years saved per unit cost) for biocontrol in Nigerian maize ranges from 5.10 to 24.8; while the estimated CER for the postharvest intervention package in Guinean groundnuts ranges from 0.21 to 2.08. Any intervention with a CER greater than 1 is considered by the World Health Organization to be “very cost-effective,” while an intervention with a CER greater than 0.33 is considered “cost-effective.” Aside from cost-effectiveness, public health interventions must be readily accepted by the public, and must have financial and infrastructural support to be feasible in the parts of the world where they are most needed.

Keywords

aflatoxin; health economics; cost effectiveness; risk assessment; hepatocellular carcinoma; biocontrol; postharvest control strategies; public health interventions

Introduction

The field of health economics has made great strides in the last several decades. Health economics strives to quantify health benefits or costs in such a way as to be comparable to monetary benefits or costs. Otherwise, it can be difficult to understand the extent to which a particular risk affects human society, especially if death is not a significant outcome; or,

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conversely, how much a public health intervention benefits human society, if there is not a direct market outcome. Putting monetary values on these health outcomes aids policymakers in understanding how important a risky agent or a disease is, how useful an intervention might be, and how to compare the relative importance of risks and the relative effectiveness of interventions.

Much of the literature in health economics focuses on medical treatments, with relatively fewer applications in food and agriculture. Examples of health economic assessments of food additives include a study of the potential cost-effectiveness of transgenic golden rice in reducing vitamin A deficiency (Stein et al. 2008), and a study of the cost-effectiveness of biofortifying foods to reduce micronutrient deficiency (Meenakshi et al. 2007). Havelaar (2007) provides a notable example of estimating the health-related costs of food contaminants: foodborne zoonoses (e.g., caused by *Campylobacter*, *Salmonella*, and *Cryptosporidium*) in Europe.

It is also important to consider the economic impacts of other food contaminants, such as mycotoxins (toxins of fungal origin). In particular, aflatoxin, the most toxic and carcinogenic of the known mycotoxins, imposes an enormous socioeconomic cost to human society. In industrial nations, it is relatively straightforward to estimate the cost of aflatoxin, because the costs are primarily market-related (Wu 2004; Wu et al. 2008). Namely, commodities that contain aflatoxin levels exceeding regulatory guidelines for human food or animal feed are discarded, or sold at a lower price for a different use. It is possible to estimate the cost of aflatoxin to a particular commodity group by estimating how much of the commodity must be discarded or discounted due to aflatoxin contamination.

In less developed countries (LDCs), however, estimating the total socioeconomic cost of aflatoxin is more complex. Health-related costs are almost certainly much higher than market-related costs (Williams 2008), and more difficult to value. One notable assessment of aflatoxin's social costs is that of Lubulwa and Davis (1994), in which both trade and health costs were estimated in Thailand, Indonesia, and the Philippines. Indeed, aflatoxin primarily affects food in tropic and subtropic regions of the world, and is especially a scourge in nations where agricultural systems are poorly equipped to handle food safety risks. Suboptimal field practices and poor storage conditions make the crops vulnerable to fungal infection and subsequent aflatoxin accumulation. Maize and groundnuts (peanuts), the two crops most conducive to aflatoxin contamination, are staples in the diets of many people worldwide, increasing aflatoxin exposure where dietary variety is difficult to achieve (Shephard 2008). Though nations suffering these risks have nominally established maximum allowable aflatoxin standards in food, there is very little enforcement of these standards. Subsistence farmers and local food traders sometimes have the luxury of discarding obviously moldy maize and groundnuts. But in drought seasons, or situations of food insecurity, oftentimes people have no choice but to eat moldy food or starve. For example, more than 125 people died due to acute aflatoxicosis in Kenya when food insecurity, caused by a variety of climatic and social reasons, led to widespread consumption of maize contaminated with high levels of aflatoxins (Lewis et al. 2005)

Thus, regulations do little to help reduce aflatoxin and its related health effects in less developed countries (Shephard 2008, Williams 2008). Rather, the focus should be on promoting the adoption of strategies that can control aflatoxin and its associated health risks, in the field, in postharvest conditions, or in the diet.

Health effects of aflatoxin

Aflatoxins are primarily produced by the fungi *Aspergillus flavus* and *A. parasiticus*, which colonize a wide variety of food commodities including maize, oilseeds, spices, groundnuts, tree nuts, milk, and dried fruit (Strosnider et al. 2006). Aflatoxin B₁, the most toxic of the aflatoxins, is the most potent naturally occurring chemical liver carcinogen known. Cytochrome P450 enzymes in the liver can metabolize aflatoxin into an epoxide (aflatoxin-8,9-epoxide), which can bind to proteins and cause acute toxicity (aflatoxicosis), or to DNA and induce hepatocellular carcinoma (HCC), a form of liver cancer.

Acute aflatoxicosis, characterized by hemorrhage, acute liver damage, edema, and death, is associated with extremely high doses of aflatoxin. In recent years, hundreds of acute aflatoxicosis cases in Kenya have been associated with consumption of contaminated home-grown maize (Azziz-Baumgartner et al. 2005).

HCC as a result of chronic aflatoxin exposure has been well documented, presenting most often in persons with chronic hepatitis B virus (HBV) infection (Qian et al. 1994, Groopman et al. 2008). For individuals chronically infected with HBV, aflatoxin consumption raises by up to thirty-fold the risk of liver cancer compared with either exposure alone (Groopman et al. 2005). Unfortunately, these two risk factors – aflatoxin and HBV – are especially prevalent in poor nations worldwide.

Aflatoxin exposure is also associated with immune system disorders and diminished weight and height in children. Over three decades of animal studies have found that aflatoxin may have immunosuppressive impacts (Jolly et al. 2008). Aflatoxin and immunosuppression in humans has been relatively less well-characterized, but could in fact have enormous significance from a global health perspective (Williams et al. 2004). Several recent human studies have shown evidence of immunomodulation (Turner et al. 2003, Jiang et al. 2005, Jiang et al. 2008), though the actual outcomes of such immunomodulation have yet to be characterized in humans. Indeed, aflatoxin's immunotoxicity may be one explanation for the stunted growth in children that appears to follow a dose-response relationship with aflatoxin exposure (Gong et al. 2002, Turner et al. 2003). Another explanation may be altered intestinal integrity (Gong et al. 2008).

Aflatoxin control strategies

Multiple public health interventions exist by which to control aflatoxin or its burden in the human body, to prevent HCC (Strosnider et al. 2006). Several of these are listed in Table 1.

Interventions to reduce aflatoxin-induced illness can be roughly grouped into three categories: agricultural, dietary, and clinical. *Agricultural* interventions are methods or technologies that can be applied either in the field (“preharvest”) or in drying, storage and transportation (“postharvest”) to reduce aflatoxin levels in food. Agricultural interventions can thus be considered “primary” interventions, because they directly reduce aflatoxin in food. *Dietary* and *clinical* interventions can be considered “secondary” interventions. They cannot reduce actual aflatoxin levels in food, but they can reduce aflatoxin-related illness; either by reducing aflatoxin's bioavailability in the body (e.g., through enterosorption) or by ameliorating aflatoxin-induced damage (e.g., through induction of Phase II enzymes that detoxify the aflatoxin-8,9-epoxide).

Our case studies focus on the health economics and cost-effectiveness of two interventions to reduce aflatoxin: biocontrol in preharvest conditions, and a postharvest intervention package to reduce aflatoxin in storage.

Biocontrol through atoxigenic *Aspergillus* strains

Biocontrol broadly refers to the use of organisms to reduce the incidence of pests, diseases, or toxins (Pitt and Hocking 2006). The biocontrol strategy analyzed in this study refers to field application of atoxigenic strains of *Aspergillus flavus* that can competitively exclude toxigenic strains from colonizing crops and thereby reduce aflatoxin concentration (Cotty et al. 2007).

Biocontrol methods for aflatoxin reduction in corn, groundnuts, and pistachios have been demonstrated under field conditions; and are being used commercially in some parts of the United States, in select commodities. Cotty and Bhatnagar (1994) found multiple strains of atoxigenic *A. flavus* that could inhibit aflatoxin production of toxigenic strains *in vitro*, but one in particular, AF36, that also lowers aflatoxin concentration in cottonseed in the field, by out-competing the toxigenic strains. AF36 has a defective polyketide synthase gene (Ehrlich and Cotty 2004), which is required for aflatoxin biosynthesis. Dorner et al. (1999) achieved successful aflatoxin reduction in maize through use of atoxigenic *A. flavus* strains in preharvest field conditions. Inoculating corn with atoxigenic strains of *A. flavus* has been shown to reduce aflatoxin contamination (Abbas et al. 2006).

In AF36 applications, wheat seeds are coated with conidia of the AF36 atoxigenic strain, and these seeds are applied to cotton fields at a strategic time so that the atoxigenic strains competitively exclude toxigenic strains. Significant reductions in aflatoxin contamination in cottonseed have been achieved where AF36 has been approved for application to cotton (Arizona, Texas, and California) (Cotty et al. 2007). Afla-Guard™, another commercially available product for aflatoxin biocontrol in the US, is applied primarily to groundnut fields. Pearl barley grains are coated with conidia of an atoxigenic strain of *A. flavus*, and these grains are applied to groundnut fields to provide competitive exclusion of toxigenic strains. Similar to AF36, Afla-Guard™ achieved high levels of protection against aflatoxin contamination in peanuts.

Wu et al. (2008) evaluated the cost-effectiveness of AF36 in US cottonseed and Afla-Guard™ in US groundnuts, through an assessment of market benefits from commodities with reduced aflatoxin contamination compared with the cost of the products. Both of these aflatoxin biocontrol methods were shown to be cost-effective in most years under most conditions in the US (Wu et al. 2008), with AF36 having the greater margin of benefit because of the lower cost of product. However, these results are not directly generalizable to nations where aflatoxin losses are more related to health rather than to market deductions.

Importantly, atoxigenic *A. flavus* strains have been found in sub-Saharan Africa, which show promise for controlling aflatoxin in African crops (Bandyopadhyay et al. 2005, Atehnkeng et al. 2008). In field trials involving inoculation of maize with toxigenic vs. atoxigenic isolates of *A. flavus*, naturally occurring atoxigenic isolates found in Nigerian soils showed a 70.1% to 99.9% reduction in aflatoxin levels, compared with the toxigenic isolates (Atehnkeng et al. 2008).

Selecting appropriate atoxigenic *Aspergillus* strains for application is a complex task (Bandyopadhyay et al. 2005, Pitt and Hocking 2006). Pitt and Hocking (2006) describe five criteria for the choice of strains: 1) they should be unable to produce toxins; 2) they should be unlikely to revert or incapable of reverting to toxicity; i.e., they should be genetically stable; 3) they must be competitive with naturally occurring toxigenic strains under field conditions; 4) they should be naturally occurring rather than mutated or genetically modified; and 5) they should be produced and applied in such a way as to ensure operational safety, as *A. flavus* is a known human pathogen, particularly to immunocompromised

individuals. Bandyopadhyay et al. (2005) further note that the strains' propensity to multiply, colonize and survive are other selection criteria, to minimize the necessary number of applications after the atoxigenic strains have been introduced into the environment.

Postharvest intervention package to reduce aflatoxin

Suboptimal postharvest conditions may be responsible for the greatest part of aflatoxin accumulation in food crops in LDCs. Improper drying, poor storage conditions such as excessive heat and moisture, insects and other pests, and consumption of food that has remained in storage for months (if not years; Hell et al. 2000) all contribute to dangerous aflatoxin exposures. Indeed, much aflatoxin contamination of food takes place during postharvest storage, as opposed to in preharvest conditions (Wild and Hall 2000). Hence, controlling aflatoxin in postharvest settings is crucial.

Turner et al. (2005) described a postharvest intervention package to reduce aflatoxin in groundnuts, tested in Guinea. The package consisted of six components: education on hand-sorting nuts, natural-fiber mats for drying the nuts, education on proper sun drying, natural-fiber bags for storage, wooden pallets on which to store bags, and insecticides applied on the floor of the storage facility under the wooden pallets.

After five months in the Guinea intervention study, individuals who had received the postharvest intervention package had on average 57.2% lower aflatoxin-albumin concentrations in the blood (8 pg/mg), compared with individuals in the control group (18.7 pg/mg; Turner et al. 2005). Indeed, the adduct levels in the intervention group after five months was similar to the adduct levels in both groups immediately postharvest. Because this biomarker (the aflatoxin-albumin adduct) can be directly correlated with aflatoxin exposure in the diet (Shephard 2008), the results of the Guinea study imply that the postharvest intervention package could essentially prevent aflatoxin from accumulating beyond its immediate postharvest level, even after five months of storage.

Any one of these six strategies in the intervention package, or any combination thereof, is useful in at least partially reducing aflatoxin contamination; because the strategies serve to control two of the major problems associated with storage: moisture, and insect pest damage and fungal spore vectoring. We evaluate the entire package in this study, because of its proven efficacy and information regarding cost.

Materials and Methods

We assessed the cost-effectiveness of biocontrol and postharvest interventions in reducing aflatoxin-induced HCC, using a combination of health-economic formulae and quantitative cancer risk assessment. Specifically, we focus on cost-effectiveness of biocontrol in maize in Nigeria, and cost-effectiveness of postharvest aflatoxin-reduction interventions for groundnuts in Guinea. Two scenarios are used in our cost-effectiveness analyses for biocontrol: (1) only maize grown for human consumption is treated with biocontrol, and (2) biocontrol is applied to all maize fields in Nigeria, even for uses other than human consumption. Likewise, our cost-effectiveness assessment of the postharvest intervention package accounts for two scenarios: (1) the postharvest intervention package is applied only to groundnuts used for food purposes, and (2) the package is applied to all groundnuts grown in Guinea. We recognize that it may not be possible, practically speaking, to segregate food production practices for human consumption vs. for other purposes in these two nations. Therefore, we use these scenarios as upper and lower bounds of what the actual cost-effectiveness is of these two interventions.

Aflatoxin exposure is not limited to maize consumption in Nigeria, nor to groundnut consumption in Guinea. People in these nations are exposed to aflatoxin from many food sources including maize, groundnuts, cassava, and yams; and potentially other foods through cross-contamination in storage. However, we focus on aflatoxin reduction using the above-stated interventions in just one crop per nation, to see how liver cancer rates can change as a result of implementing the interventions.

In this section, we first describe the methodologies and calculations used that are relevant to both interventions. Then we describe the particular methodologies used to evaluate cost-effectiveness for each individual intervention.

Health economics: criteria for cost-effectiveness of interventions

How can the cost-effectiveness of a health intervention be determined, if there are no direct market benefits? The World Health Organization (WHO) Commission for Macroeconomics and Health (WHO 2001) has provided the following guideline for thresholds of cost-effectiveness:

1. An intervention is considered very cost-effective, if the monetary amount spent on the intervention per disability-adjusted life year (DALY) saved is less than the *per capita* gross domestic product (GDP) for the nation in which the intervention is applied.
2. An intervention is considered (moderately) cost-effective, if the monetary amount spent on the intervention per DALY saved is less than three times the *per capita* GDP.
3. An intervention is not cost-effective if, per DALY saved, its cost is greater than three times the *per capita* GDP.

The DALY is a measure of the burden of disease. It extends the concept of potential years of life lost due to premature death to include equivalent years of “healthy” life lost in states of less than full health, broadly termed *disability* (Havelaar 2007). One DALY can thus be thought of as one lost year of healthy life. The total number of DALYs associated with a disease is the sum of the years of life lost due to mortality from the disease (YLL) and the number of years lived with a disability multiplied by a weighting factor between 0 and 1, depending on the severity of the disability (YLD):

$$\text{DALY} = \text{YLL} + \text{YLD} \quad \text{Equation (1)}$$

For this study, we chose the health endpoint of aflatoxin-induced HCC. DALYs for any given disease are estimated separately for high-income, middle-income, and low-income nations, based on assumptions about how many years individuals will live with a disability in different parts of the world, and what resources are available to alleviate disability. Because we are focusing on aflatoxin reduction in Nigeria and Guinea, we used DALY estimates for HCC in low-income nations.

Quantitative cancer risk assessment

Quantitative risk assessment primarily requires data for two measures: 1) a dose-response relationship between a risky agent and a particular health outcome, and 2) exposure to the risky agent for an individual or population of interest. For cancer risk assessment specifically, it is traditionally assumed that there is no threshold of exposure to a carcinogen below which there is no observable adverse effect (NRC 2008). Cancer potency factors are

calculated based on the slope of the linearized dose-response curve of the relationship between the carcinogen and the incidence of cancer in a population. Hence, to estimate both number of aflatoxin-induced HCC cases in Nigeria and Guinea, and reduction in these cases attributable to the interventions biocontrol and postharvest strategies, we collected data on the following variables:

- HCC potency factors for aflatoxin in HBV+/HBV- populations
- Average daily aflatoxin exposure through maize in Nigeria, and groundnuts in Guinea
- HBV prevalence in Nigeria and Guinea
- Population sizes of Nigeria and Guinea
- Percent reduction in aflatoxin afforded by biocontrol and the postharvest intervention package

The seminal aflatoxin-induced HCC risk assessment study was performed by the Joint Food and Agriculture Organization (FAO) / WHO Expert Committee on Food Additives (JECFA 1998; summarized in Henry et al. 1999). The JECFA panel used two different cancer potency factors for aflatoxin: **0.01** cases per 100,000 per year for every ng/kg bw/day aflatoxin exposure for individuals without chronic HBV infection, and **0.30** corresponding cases for individuals with chronic HBV infection.

We used these same potency factors to estimate the number of aflatoxin-induced HCC cases in both Nigeria and Guinea. We collected data on estimated HBV prevalence in these two nations, as well as data on aflatoxin exposure through maize in Nigeria and groundnuts in Guinea. To estimate aflatoxin-induced HCC cases per 100,000 in the population, we multiplied the potency factors by the exposure estimates. Then we multiplied these values by the nations' population sizes divided by 100,000 to derive the total number of aflatoxin-induced HCC cases in each nation.

To calculate the number of HCC cases averted due to aflatoxin control strategies: similar to the JECFA (1998) evaluation, we assumed that there was a linear dose-response relationship between *reduction* in aflatoxin exposure and reduction in aflatoxin-induced HCC cases in a given population. Assuming 100% adoption of the interventions in each nation, we calculated reduction in HCC cases by multiplying the percent reduction in aflatoxin exposure associated with each intervention by the total number of HCC cases in each nation.

Biocontrol applied to maize in Nigeria

The aforementioned methods enabled us to estimate the number of aflatoxin-induced HCC cases averted by biocontrol. Then, to translate this into cost-effectiveness terms, we needed to transform biocontrol's cost data into metrics that could be directly comparable with the effects.

Biocontrol costs are usually presented in a monetary cost per unit land. There are many categories of cost in the full life cycle of biocontrol, from production to use. These include:

- The cost of maintaining the cultures used, including professionals needed to maintain them
- Manufacturing costs for the large numbers of spores needed for application to the substrate (the grains used to convey the spores in the field)
- The cost of the substrate itself

- The cost of sterilizing the substrate on a large scale
- The cost of mixing the spores and the substrate with a binder, such as oil or molasses
- The cost of application – on small farms using hand application, this cost may be minimal

At a lower estimate, we took the cost of biocontrol per hectare to be \$10 (Dr. Ranajit Bandyopadhyay, personal communication). This estimate also matches with costs of biocontrol in cottonseed in the US (Wu et al. 2008). However, accounting for the additional costs described above, we estimated that at an upper estimate, the total cost could be as high as \$20. Therefore we estimated the range of biocontrol costs in Nigeria to be \$10 to \$20 per hectare. We transformed this into a monetary cost per human life affected in the following way:

Scenario 1: Biocontrol is applied only to maize grown for human consumption

- Obtained data on the cost per hectare of biocontrol, per year
- Obtained data on maize yield per hectare in Nigeria
- Obtained data on maize consumption *per capita* per day in Nigeria, and transformed to yearly consumption.
- Obtained estimated total Nigerian population in 2009
- Multiplied maize consumption *per capita* by maize yield per hectare and Nigerian population, to estimate how many hectares of maize are required to supply annual human demand per year.
- Multiplied this value by the cost of biocontrol per hectare, to estimate the cost of biocontrol for maize grown for human consumption in Nigeria per year.

Scenario 2: Biocontrol is applied to all maize grown in Nigeria

- Obtained data on the cost per hectare of biocontrol, per year
- Projected data on 2009 agricultural area devoted to maize in Nigeria using 2003–2007 data
- Multiplied area devoted to maize by the cost of biocontrol per hectare, to estimate the cost of biocontrol if there were 100% adoption of biocontrol in maize

Then, to estimate cost-effectiveness, we obtained the average *per capita* GDP in Nigeria (adjusted for purchasing power parity), and multiplied the GDP by the total number of DALYs saved as calculated by the number of averted HCC cases multiplied by the number of DALYs associated with each case. In order to estimate number of averted HCC cases, we found estimates for the percentage reduction in aflatoxin afforded by biocontrol, even after six months' storage. We applied an appropriate discount rate to this benefit, to account for the fact that liver cancer cases do not decrease instantaneously upon application of the intervention: we assumed benefits realized after 5 years, with a discount rate of 3%. We then compared this result with the total extrapolated cost of biocontrol across Nigeria.

Postharvest intervention package applied to maize and groundnuts in Guinea

Our calculation methods for cost-effectiveness of the postharvest interventions differ from those in the case of biocontrol, because the data available are in terms of cost per household

(Turner et al. 2005), rather than cost per unit land. We transformed the cost data in the following way:

Scenario 1: The postharvest intervention package is applied only to groundnuts for human consumption

- Obtained data on the cost for storing 500-1,250 kg groundnuts according to postharvest intervention package
- Obtained data on groundnut consumption *per capita* per year in Guinea (FAOSTAT 2009)
- Obtained data on population of Guinea in 2009
- Multiplied groundnut consumption per capita per year by population to estimate total human groundnut consumption in Guinea.
- Divided this value by minimum and maximum quantity of groundnuts (500 to 1,250) which were used in the study of Turner et al. (2005), to obtain minimum and maximum number of postharvest intervention packages required
- Multiplied this value by the cost of the postharvest intervention package, to obtain the total cost of the postharvest intervention package if it is applied to groundnuts used for food purpose

Scenario 2: The postharvest intervention package is applied to all groundnuts grown in Guinea

- Obtained data on the cost for storing 500 kg to 1,250 kg groundnuts in 50 kg- bag
- Projected total 2009 groundnut production in Guinea, using 2003–2007 data (FAOSTAT 2009)
- Divided total groundnut production by the minimum and maximum quantity of groundnuts (500 to 1,250), which were used in the study of Turner et al. (2005), to obtain minimum and maximum number of postharvest intervention packages required throughout Guinea
- Multiplied these values by the cost of the postharvest intervention package, to obtain total cost of the intervention package if there were 100% adoption for groundnuts

Then, as with biocontrol, we obtained the average *per capita* GDP in Guinea, and multiplied the GDP by the total number of DALYs saved as calculated by the number of averted HCC cases multiplied by the number of DALYs associated with each case. We applied the appropriate discount rate as described above, then compared this result with the total extrapolated cost of the postharvest intervention package across Guinea.

Results

Cost-effectiveness of biocontrol

Tables 2a and 2b contain the values found in the literature or calculated for each relevant parameter to assess the cost-effectiveness of using biocontrol to control aflatoxin-induced liver cancer in Nigeria. The cost of biocontrol is estimated to be \$10 to \$20 per hectare (Wu et al. 2008; Dr. Ranajit Bandyopadhyay, personal communication). Table 2a presents parameters and calculations regarding the first scenario's cost-effectiveness analysis. In this case, the total cost would be estimated to be \$15.7 million to \$ 18.8 million per year if

biocontrol were applied only to maize grown for human consumption. In the second scenario, if biocontrol were applied to all maize fields in Nigeria, the estimated total cost would be \$42.3 million to \$50.7 million per year (assuming that applications would take place every year, which may not be necessary after establishment of atoxigenic strains in the environment).

In the absence of biocontrol, given a HBV prevalence of about 15% the estimated number of HCC cases due to aflatoxin in Nigeria is 0.054 per 100,000 individuals. The 2009 population of Nigeria is approximately 150 million (CIA 2009). If we assume that biocontrol application can reduce aflatoxin by 50% to 90% even after six months postharvest, that virtually all maize is consumed within this time period, and use JECFA (1998) aflatoxin exposure data from African maize, then the expected number of HCC cases prevented by a theoretical 100% adoption of biocontrol methods is 7,900 to 14,200 per year. This estimate takes into account a 3% discount rate for the benefits, as described earlier. The estimated DALYs associated with each HCC case in a relatively poor nation is 13 (WHO 2008). Hence, the number of DALYs saved in Nigeria per year from biocontrol to reduce aflatoxin-induced HCC ranges from 103,000 to 184,000.

According to WHO (2001) guidelines for cost-effectiveness, an intervention can be considered “very cost-effective” if its cost-effectiveness ratio – the *per capita* GDP multiplied by total DALYs saved divided by the cost of the intervention – is greater than 1. The average *per capita* GDP in Nigeria is \$2,290 (Economy Watch 2009^b). Therefore, the cost-effectiveness ratio for biocontrol in reducing aflatoxin-induced liver cancer, accounting for the variation in costs and benefits, is 13.8 to 24.8 in the first scenario (biocontrol applied only to maize for human consumption) and 5.10 to 9.18 in the second scenario (biocontrol applied to all maize). This means that the monetized health benefits from biocontrol's reduction of aflatoxin-induced HCC is significantly greater – roughly 5 to 25 times greater – than the costs of biocontrol to achieve that health benefit. However, in practical situations, it can be difficult to selectively apply biocontrol only to maize grown for human food purposes. Therefore, the second scenario in which biocontrol is applied to all maize fields may provide more realistic cost-effectiveness ratios. Even these ratios show biocontrol to be extremely cost-effective, by WHO standards, in reducing aflatoxin-induced liver cancer.

Cost-effectiveness of postharvest interventions

Tables 3a and 3b contain the values found in the literature or calculated for each relevant parameter to assess postharvest intervention packages' cost-effectiveness in Guinea. Similar to the biocontrol case study, we proposed two scenarios of postharvest intervention package application. In the first scenario, the postharvest intervention packages were applied to groundnuts grown for human consumption only (assuming it would be possible to segregate groundnuts for different purposes); while in the second scenario, the packages were applied to all groundnuts grown in Guinea.

The cost of the postharvest intervention package was about \$50 in 2005 (Turner et al. 2005). This cost was estimated from the package (as described in the study) including the drying and storing of 10 to 25 bags, each containing 50 kg of groundnuts, for a total of 500-1,250 kg groundnuts dried and stored per package. It is assumed that these particular interventions – mats, natural-fiber bags, wooden pallets, and a 10-kg bag of insecticide – could be used for up to five years; so the per-year cost is averaged by dividing the one-time cost by five. Hence, the total cost of the postharvest interventions in the first scenario is \$0.62 million to \$1.55 million per year, and in the second scenario is \$3.33 million to \$8.32 million per year.

The HBV prevalence in Guinea is assumed to be 18.2% (Ivanov et al. 1987), and we use JECFA (1998) exposure data from groundnuts in Africa. Thus, the expected number of HCC cases due to aflatoxin from groundnuts per year is 0.062 per 100,000 individuals. In the Turner et al. (2005) study, the mean aflatoxin B1 levels in the intervention and the control groundnuts after five months were 55 ng g⁻¹ and 17 ng g⁻¹, respectively. Therefore, the expected efficacy of the postharvest interventions in reducing aflatoxin B1 is 69%. Assuming a linear extrapolation between aflatoxin reduction and liver cancer risk reduction, and including the 3% discount rate on liver cancer risk reduction benefits as described above, the expected number of HCC cases prevented assuming 100% adoption of the package to groundnuts in Guinea is about 86 per year. Again, we assume that DALYs per HCC case is 13, leading to a total number of DALYs saved by the postharvest intervention package of 1,121.

The average *per capita* GDP in Guinea was \$1,100 in 2005 (Turner et al. 2005). Hence, in the first scenario, the estimated cost-effectiveness ratio of the postharvest intervention package in reducing liver cancer ranges from 0.82 to 2.08: on average, “very cost-effective” by WHO standards. In the second scenario (in which the postharvest package is applied to all groundnuts in Guinea), the cost-effectiveness ratio ranges from 0.21 to 0.55: on average, “cost-effective” by WHO standards (CER > 0.33).

Discussion and conclusions

Liver cancer is the third leading cause of cancer deaths worldwide (WHO 2008). Aflatoxin exposure in the diet – a significant risk factor for liver cancer – can be controlled by introducing interventions that can dramatically reduce cancer burden. Yet many parts of the world where the risk is particularly high do not have either the technologies or the infrastructures to reduce aflatoxin exposure. Aflatoxin risks are high in sub-Saharan Africa due to a combination of conditions. Much agricultural land in these areas lies in climatic regions that are favorable for *A. flavus* and *A. parasiticus* growth and proliferation. Suboptimal field practices and poor storage conditions make the crops vulnerable to fungal infection and subsequent aflatoxin accumulation (Williams et al. 2008). Maize and groundnuts, two crops susceptible to *Aspergillus* infection, are staples in the diets of many Africans. Therefore, interventions should focus on reducing aflatoxin in simple and cost-effective ways in these staple foods. Health economics, combined with cancer risk assessment, sheds light on how useful interventions can be in nations that cannot afford complicated technologies to reduce aflatoxin.

We have shown that two simple interventions, biocontrol and postharvest intervention packages, are cost-effective from a health-economic standpoint in reducing aflatoxin-induced liver cancer. Indeed, for biocontrol used in Nigerian maize fields, the cost-effectiveness ratios (monetized health benefits gained divided by costs to implement the intervention) are substantially higher than what is considered to be “very cost-effective” by WHO standards. Even so, these agricultural strategies' cost-effectiveness ratios are underestimated in this study, because the only endpoint measured was reduction in aflatoxin-induced liver cancer. At the moment, there is not enough information to monetize the risk reduction associated with aflatoxin-induced immunotoxicity or growth retardation in early life. Williams et al. (2004) and Shephard (2008) surmised that the inhibitory impact of aflatoxins on child growth and immune suppression is likely to be much more than HCC. Therefore, it is safe to assume that the cost-effectiveness ratio of aflatoxin intervention would be several times higher than described for HCC. Currently, sufficient data is not available on the outcomes aflatoxin induced immune suppression and growth retardation of children to estimate the monetized value of overall health benefits of biocontrol and

postharvest intervention. If future toxicological and risk assessment studies informed this area more thoroughly, the benefits of these aflatoxin control strategies would show themselves to be even higher. Moreover, improving food quality can also result in improved market outcomes, which, to evaluate, would require a separate study.

Yet cost-effectiveness of a strategy, however large, is not enough for widescale global adoption. To assess the feasibility of interventions to reduce aflatoxin from a global perspective, we must also consider the following questions:

1. Are there any countervailing health or ecological risks associated with each of these interventions?
2. What would the delivery mechanism of the intervention be?
3. Can the intervention be manufactured locally, or must it be imported?
4. Can farmers or consumers afford the upfront costs, and if not, who will pay for the intervention?
5. Is the intervention culturally appropriate?
6. Would people comply with the intervention? Related to this: How often does it need to be implemented, and how many people need to implement it?
7. How easy or difficult is it to apply the intervention effectively, so as to reduce aflatoxin or its adverse effects? Are there risks associated with applying it improperly?

Regarding the first question: Because of the potential risk of invasive aspergillosis from *A. flavus* exposure among immunocompromised individuals (as highlighted in Krishnan et al. 2009 and Hedayati et al. 2007), it is important to ensure that the biocontrol material is applied in such a way as to minimize direct inhalation of spores. The biocontrol methods used commercially and in field trials in various parts of the world, in which the atoxigenic *Aspergillus* spores are applied in an oil or molasses mixture to seeds (Cotty et al. 2007, Pitt and Hocking 2006) that are then applied to fields, minimizes potential inhalation risks.

There are several limitations to our study. The first is that DALYs can be a controversial measure. For example, how is a weighting factor calculated for years lived with the burden of a disability? In the case of HCC, a patient usually does not live more than a few months after the disease is diagnosed; so the uncertainty in this variable is relatively lower, but still exists. Second, we assumed that there was a linear dose-response relationship between the amount of aflatoxin reduction afforded by each intervention and the reduction of aflatoxin-induced liver cancer cases in the population. This assumption has been used in previous risk assessments (e.g., JECFA 1998), but the true relationship between aflatoxin exposure and liver cancer may possibly be non-linear at lower doses. Third, and perhaps most importantly, cost-effectiveness is but one component of the feasibility of aflatoxin-reduction strategies in less developed countries. There are many other important factors, some of which are suggested in the questions above.

Nevertheless, evaluation of cost-effectiveness of interventions fills a critical gap in the literature on aflatoxin control. Most studies on aflatoxin risk reduction strategies have focused primarily on efficacy, with little or no mention of cost. Several studies describe costs of interventions (e.g., Turner et al. 2005) and suggest that benefits could significantly outweigh costs, but do not include a quantitative analysis of this. Our results lend credence to those previous statements: Certain aflatoxin control strategies can be enormously cost-effective from a health-economic standpoint in the countries where they are most needed.

While it is impossible to completely eliminate aflatoxin in food worldwide, it is possible to significantly reduce levels and thus dramatically reduce liver cancer incidence – as well as other adverse effects of aflatoxin. The challenge remains to deliver these interventions to places of the world where they are most needed.

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Table 1

A sampling of interventions to reduce aflatoxin risk in field, dietary, and clinical settings.

Setting		Intervention
Agricultural	Preharvest	<ul style="list-style-type: none"> • Choice of suitable cultivars • Transgenic or conventional breeding for resistance • Biocontrol • Chemical control (insecticides, fungicides) • Good agricultural practices • Antioxidants (e.g., caffeic acid, gallic acid)
	Postharvest	<ul style="list-style-type: none"> • Cleaning • Sorting and segregation • Improved storage / drying / transportation conditions • Ammoniation • Chemical control (insecticides, fungicides)
Dietary		<ul style="list-style-type: none"> • Enterosorbents (e.g., calcium aluminosilicates, chlorophyllin) • Chemopreventive agents (e.g., Oltipraz, isothiocyanates, triterpenoids) • COX-2 inhibitors • Green tea polyphenols
Clinical		<ul style="list-style-type: none"> • HBV vaccination

Table 2

Table 2a. Cost-effectiveness of biocontrol in Nigerian maize: parameters and calculations. Scenario 1: Only maize intended for human consumption is treated with biocontrol, assuming in-field segregation is possible.		
Parameter	Value (all monetary values in USD)	Source
Biocontrol cost / ha	\$10–\$20	Wu et al. (2008); Dr. Ranajit Bandyopadhyay, personal communication
Maize yield / ha (Projected to year 2009 from 2003–2007 data)	1.9 t (1,900 kg)	FAOSTAT (2009) ^b
Average maize consumption per year in Nigeria (data in 2003)	20.0 kg	FAOSTAT (2009) ^a
Population of Nigeria, 2009	149,229,090	CIA (2009)
Area required to produce maize for annual consumption	1,570,832 ha	
Biocontrol cost in Nigeria	\$15.7 million – \$18.8 million	
Nigeria GDP <i>per capita</i> , 2009 (adjusted for PPP)	\$2,290	Economy Watch (2009) ^b
Effectiveness of biocontrol in reducing aflatoxin in maize, up to 6 months postharvest	50%–90%	Dr. Ranajit Bandyopadhyay, personal communication
HBV prevalence	15%	Averaged from various sources (Forbi et al. 2008, Iwalokun et al. 2006, Mabayoje et al. 2007, Onakewhor et al. 2001, Uneke et al. 2005)
Expected number of HCC cases due to aflatoxin per year, per 100,000 pop.	0.054	Calculated through risk assessment
Aflatoxin exposure per person per day (ng/kg bw/day)	226.8	Bandyopadhyay et al. (2007)
Expected number of HCC cases prevented due to 100% adoption of biocontrol in maize (assuming 50–90% efficacy), applying discount rate of 3% and assuming 5-year lag time for benefits	7,900–14,200	Calculated through risk assessment
DALYs per HCC case	13	WHO (2008)
DALYs saved in Nigeria from biocontrol to reduce aflatoxin-induced HCC	103,000–184,000	
Cost-effectiveness ratio (CER) (GDP * DALYs saved / cost of biocontrol)	13.8–24.8	
Is biocontrol “very cost-effective” (CER > 1)?	Yes	
Table 2b. Cost-effectiveness of biocontrol in Nigerian maize: parameters and calculations. Scenario 2: All maize grown in Nigeria is treated with biocontrol.		
Parameter	Value (all monetary values in USD)	Source
Biocontrol cost / ha	\$10–\$20	Wu et al. (2008); Dr. Ranajit Bandyopadhyay, personal communication
Maize agricultural area (Projected to year 2009 from 2003–2007 data)	4,227,600 ha	FAOSTAT (2009) ^b
Biocontrol cost	\$ 42.3 million – \$ 50.7 million	
Population of Nigeria, 2009	150 million	CIA (2009)
Nigeria GDP <i>per capita</i> , 2009 (adjusted for PPP)	\$2,290	Economy Watch (2009) ^b
Effectiveness of biocontrol in reducing aflatoxin in maize, up to 6 months postharvest	50%–90%	Dr. Ranajit Bandyopadhyay, personal communication
HBV prevalence	15%	Averaged from various sources (Forbi et al. 2008, Iwalokun et al. 2006, Mabayoje et al. 2007, Onakewhor et al. 2001, Uneke et al. 2005)

Table 2a. Cost-effectiveness of biocontrol in Nigerian maize: parameters and calculations. Scenario 1: Only maize intended for human consumption is treated with biocontrol, assuming in-field segregation is possible.		
Parameter	Value (all monetary values in USD)	Source
Expected number of HCC cases due to aflatoxin per year, per 100,000 pop.	0.054	Calculated through risk assessment
Aflatoxin exposure per person per day (ng/kg bw/day)	226.8	Bandyopadhyay et al. (2007)
Expected number of HCC cases prevented due to 100% adoption of biocontrol in maize (assuming 50–90% efficacy), applying discount rate of 3% and assuming 5-year lag time for benefits	7,900-14,200	Calculated through risk assessment
DALYs per HCC case	13	WHO (2008)
DALYs saved in Nigeria from biocontrol to reduce aflatoxin-induced HCC	103,000-184,000	
Aflatoxin exposure per person per day (ng/kg bw/day)	226.8	Bandyopadhyay et al. (2007)
Cost-effectiveness ratio (CER)	5.10-9.18	
Is biocontrol “very cost-effective” (CER > 1)?	Yes	

Table 3

Table 3a. Cost-effectiveness of postharvest intervention package in Guinean groundnuts: parameters and calculations. Scenario 1: The package is applied only to groundnuts for human consumption, assuming segregation is possible. Scenario III: The postharvest intervention were applied only to groundnuts used for food purpose		
Parameter	Value (all monetary values in USD 2009)	Source
Postharvest intervention package cost to dry/store 10-25 bags of 50 kg groundnuts per bag)	\$50 in USD 2005	Turner et al. (2005)
Groundnuts consumption per year <i>per capita</i> in 2009 (in shell Eq) Projected from 1994–2003 data)	6.3 kg	FAOSTAT (2009) ^a
Population of Guinea, 2009	10,057,975	CIA (2009)
Groundnuts annual consumption demand	63,365,242 kg	
Postharvest intervention package cost if the package were applied only to groundnuts used for food purpose	\$ 0.62 million/yr to \$1.55 million/yr, assuming package can be reused over 5 yrs	
Guinea GDP <i>per capita</i> , 2009 (adjusted for PPP)	\$1,100	Turner et al. (2005)
Effectiveness of package in reducing aflatoxin levels in groundnuts	69%	Turner et al. (2005)
HBV prevalence	18.2%	Ivanov et al. (1987)
Aflatoxin levels in groundnuts (ng g ⁻¹)	55	Turner et al. (2005)
Expected number of HCC cases due to aflatoxin per year, per 100,000 pop.	0.062	Calculated through risk assessment
Expected number of HCC cases prevented due to 100% adoption of package, applying discount rate of 3% and assuming 5-year lag time for benefits	86	
DALYs per HCC case	13	WHO. (2008)
DALYs saved in Guinea from package to reduce aflatoxin-induced HCC	1,121	
CER	0.82-2.08	
Is package “very cost-effective” (CER > 1)?	Yes, on average	
Table 3b. Cost-effectiveness of postharvest intervention package in Guinean groundnuts: parameters and calculations. Scenario 2: The package is applied to all groundnuts harvested in Guinea.		
Parameter	Value (all monetary values in USD 2009)	Source
Postharvest intervention package cost to dry/store 10-25 bags of 50 kg groundnuts per bag)	\$50 in USD 2005	Turner et al. (2005)
Groundnut production in Guinea	250,000,000 kg	University of Georgia (2003)
Postharvest intervention package cost if 100% adoption in Guinea	\$ 3.33 million/yr to \$ 8.32 million/yr, assuming package can be reused over 5 yrs	
Population of Guinea, 2009	10,057,975	CIA (2009)
Guinea GDP <i>per capita</i> , 2009 (adjusted for PPP)	\$1,038	Economy Watch (2009) ^a
Effectiveness of package in reducing aflatoxin levels in groundnuts	69%	Turner et al. (2005)
HBV prevalence	18.2%	Ivanov et al. (1987)
Aflatoxin levels in groundnuts (ng g ⁻¹)	55	Turner et al. (2005)
Expected number of HCC cases due to aflatoxin per year, per 100,000 pop.	0.062	Calculated through risk assessment

Table 3a. Cost-effectiveness of postharvest intervention package in Guinean groundnuts: parameters and calculations. Scenario 1: The package is applied only to groundnuts for human consumption, assuming segregation is possible. Scenario III: The postharvest intervention were applied only to groundnuts used for food purpose

Parameter	Value (all monetary values in USD 2009)	Source
Expected number of HCC cases prevented due to 100% adoption of package, applying discount rate of 3% and assuming 5-year lag time for benefits	86	
DALYs per HCC case	13	WHO (2008)
DALYs saved in Guinea from package to reduce aflatoxin-induced HCC	1,121	
CER	0.21-0.55	
Is package “very cost-effective” (CER > 1)?	No	
Is package “cost-effective” (CER > 0.34)?	Yes, on average	