Chronic dietary aflatoxins exposure in Kenya and emerging public health concerns of impaired growth and immune suppression in children

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ABSTRACT

Aflatoxins are toxic secondary metabolites produced by fungi and contaminate various agricultural commodities either before harvest or under post-harvest conditions. Acute aflatoxin poisoning leading to case-patients and deaths has continued to occur in several parts of Kenya. However, there is emerging evidence implicating chronic aflatoxins exposure as an important factor in infant growth stunting and immune suppression. The consumption of smaller dosages overtime produces no obvious symptoms as would happen with acute dosage. Thus, it has not attracted much attention in Kenya in terms of public health priorities. Aflatoxins have been detected mainly in the staple foods such as cereals and legumes commodities, which form the main gruel ingredients used to compose weaning foods in most rural households. This suggests that children may be more exposed to mycotoxins than the rest of the population and this could be the reason for increased cases of infant malnutrition and mortality in certain areas in Kenya. The extent to which stunted growth and immune suppression contribute to the overall burden of infectious disease merits consideration. Therefore, this paper discusses dietary chronic mycotoxins exposure in Kenya and emerging public health concerns of stunted growth and immune suppression as reported in various related animal and human studies. It also highlights several factors that may enhance the dietary mycotoxins exposure especially amongst children and further explores various localized control measures and research areas within the context of food scarcity and extreme poverty experienced in rural Kenya. This paper aims at reinforcing that presence of mycotoxins within the food system should be addressed as an urgent food safety issue as they place a significant hindrance towards the attainment of the Millennium Development Goals (MDGs) 4 and 6 on reduction of child mortality and combating of diseases, respectively.

Health indicators of children in Kenya

Child mortality still remains a critical problem in Kenya. The Kenya Demographic Health Survey (KDHS) 2008-2009 survey indicates that the national under-five and child mortality rates have declined from 115 per 1,000 live births and 41% in 2003 to 74 per 1,000 live births and 23% respectively in 2008-2009 mainly as a result of improved immunization of children (CBS, 2004). Nevertheless, the national child health indicators have not improved significantly

over the past years especially at the provincial level where the rates display considerable differentials (Kabubo-Mariara et al., 2006). The mortality rates have remained intolerably high in some regions such as Nyanza Province having 133 (infant) and 206 (child) deaths per 1,000 live births (CBS, 2004). The KDHS 2003 survey indicates that about 29% of child deaths occurring in the first five years of life take place within one month after birth (neonatal mortality), while 66% occur within the first one year and the remaining 34% in the remaining 1 - 4 years. The challenge therefore remains to understand and work on the causes of infant and child mortality especially within the first month after birth, if any progress is to be achieved in reducing child mortality. Amongst the leading causes of infant and child deaths in Kenya include malnutrition, respiratory infections especially pneumonia, diarrhea, malaria, measles, and Human Immunodeficiency virus (HIV/AIDS) (Ikamari, 2004; MPND, 2005).

Although dietary mycotoxins are not specifically mentioned, they may play a modulating role in a certain number of these factors. Fetal and early childhood environment is important for growth and disease risk in later life because it is the most critical time for the immune system development (Hendrickse, 1991). This implies that the causal associations between mycotoxin exposure and impaired growth; and immune suppression have significant effects on other aspects of child health, such as susceptibility to infectious diseases (Hendrickse et al., 1997; Terry and Susser, 2001). From this perspective, chronic dietary mycotoxin exposure amongst infants and children is a major concern in Kenya, particularly as a hindrance towards the attainment of the MDGs 4 and 6 on reduction of child mortality and combating of HIV/AIDs, malaria and other diseases (Williams et al., 2004). Therefore, there is urgent need to implement management strategies to reduce dietary mycotoxins exposure to levels below the regulatory limits.

Dietary mycotoxins exposure in Kenya

Mycotoxins are toxic secondary metabolites produced by fungi and contaminate various agricultural commodities either before harvest or under post-harvest conditions (Bhat et al., 2010). The most important mycotoxins of public health concern are aflatoxins, ochratoxins, deoxynivalenol (DON), zearalenone, fumonisin and trichothecenes. The main genera of fungi that produce mycotoxins in foods are *Aspergillus* spp, *Penicillium* spp and *Fusarium* spp. The toxins that are of greatest significance in tropical developing countries including Kenya are fumonisins and aflatoxins (Bankole et al., 2006; Wild, 2007).

The presence of mycotoxins in food is often overlooked in Kenya, mainly due to the public ignorance about their existence and lack of effective regulatory mechanisms. Repetitive incidents of acute mycotoxicosis have re-occurred during periods 1981, 2001, 2004 and 2005 (CDC, 2004; Lewis et al., 2005). In 2004, 317 case-patients and 125 deaths were recorded in the eastern and central districts and were associated with aflatoxin poisoning, which arose from maize stored under damp conditions (Lewis et al., 2005). A similar outbreak occurred in the eastern districts of Kenya in 2005 resulting to 75 case-patients and 32 deaths. Survey of the affected region showed maize samples were contaminated with aflatoxin levels above 20 μgkg^{-1} legal limit (Azziz-Baumgartner et al., 2005; Muture and Ogana, 2005; Probst et al., 2007; Muthama et al., 2009). Smaller outbreaks have also been reported, resulting in 20, 12 and 9 deaths in 1981, 2001 and 2006, respectively (DN, 2001). Nevertheless, due to the remoteness of villages in the affected districts in Kenya and the large geographic area involved, the data on outbreak case findings have largely been limited to records from medical facilities. It is possible that some chronically affected persons might not have been able to reach health-care facilities for diagnosis and treatment; hence the true

magnitude of the outbreaks is likely to be considerably greater than reported.

Aflatoxins contamination of staple foods is prevalent within Kenya due to the prevailing hot and humid, tropical, or drought-like conditions that are ideal for the fungal growth and mycotoxin proliferation (Kabak et al., 2006). Aflatoxins are capable of accumulating in wide range of food commodities namely cereals, legumes, meat, dried fish, egg and milk products (Muriuki and Siboe , 1995; Egal et al., 2005; Bankole et al., 2006; Wagacha and Muthomi, 2008; Muthama et al., 2009). Most weaning foods in Kenya are derived from maize, groundnuts, sorghum, millet, dried fish, beans, cassava, rice and green grams. The *Aspergillus* spp and *Fusarium* spp, have been identified as the predominant fungi in weaning food gruel mixtures leading to contamination to as high as 82 μgkg^{-1} of aflatoxins (Okoth and Ohingo, 2004). Children of weaning age are, therefore, most susceptible to the mycotoxic risks because their diets are less varied, alternating between breast milk and weaning gruel.

Emerging public health concerns of dietary aflatoxins exposure
Impaired growth of children

Aflatoxins (types B_1, B_2, G_1, and G_2) are of particular public health importance because of their carcinogenic actions on human health (IARC, 1993). Ingestion of higher doses of aflatoxin can result in acute aflatoxicosis, which manifests as liver cancer and jaundice (Fung and Clark, 2004; Shephard, 2008; Lamplugh and Hendrickse, 1982). Chronic mycotoxic exposure, the consumption of smaller dosages overtime, is regarded as a 'silent killer' poison because the toxic chemicals are not detected by human antigens, hence produce no obvious symptoms as would happen with acute dosage. It has, therefore, not drawn much attention in Kenya in terms of public health priorities. Recently published reports indicate emerging evidence that both growth impairment and immune function are directly affected by cumulative

chronic mycotoxin exposure in developing countries. According to studies conducted in Benin and Togo by Gong et al. (2002), aflatoxin exposure increases at weaning stage and can lead directly to growth impairment and stunting of growth in infants. The AF-alb level increased with age up to 3 years, and within the 1–3 year age group was significantly related to weaning status; weaned children had approximately two fold higher mean AF-alb adduct levels (38 $pgmg^{-1}$) than those receiving a mixture of breast milk and solid foods. It was also observed that stunted children had 30–40% higher mean AF-alb levels than other children in the study. The authors also observed strong dose–response relationships between AF-alb levels and the extent of stunting and being underweight.

Other authors have also reported on kwashiorkor (usually attributed to protein energy malnutrition) and chronic aflatoxin exposure (Hendrickse et al., 1982; 1984; 1991; Coulter et al., 1986; Katere et al., 2008). A study conducted in Kisumu district, Kenya, by Okoth and Ohingo (2004), observed that 31% of the young children were malnourished and the correlation between the number of children who were wasting and were being fed on flour contaminated with mycotoxins was highly significant. Clinical studies performed in Embu and Kakamega districts, Kenya, have also reported on the association between aflatoxin exposure and incidence of kwashiorkor (De Vries et al., 1990). Studies conducted in Sudan have indicated detection of aflatoxins in liver biopsies obtained from kwashiorkor children but none in biopsies from marasmus children (Hendrickse et al., 1983; Coulter et al., 1986). The correlation between occurrence liver cancer and kwashiorkor with aflatoxin exposure has also been reported in Ghana by Apeagyei et al., (1986). According to Adhikari et al. (1994), children with kwashiorkor who had tested positive for aflatoxin in blood and urine had statistically significant longer hospital stay and suffered more infections.

Immune suppression effect of aflatoxins exposure

The immunosuppressive properties of AFB_1, particularly on cell mediated immunity, have been demonstrated in various animal models (Bondy and Pestka, 2000). Studies on the immunotoxic effect of aflatoxin using animal models have shown that exposure to aflatoxin impaired macrophage and neutrophil effector functions in developing animals (Silvotti et al., 1997), suppressed natural killer (NK) cell-mediated cytolysis (Reddy and Sharma, 1989), decreased T or B lymphocyte activity (Reddy et al., 1987), modified synthesis of inflammatory cytokines (Moon et al., 1999), decreased immunity to vaccination (Gabal and Azam, 1998; Meissonier et al., 2008), and decreased resistance to infectious diseases (Joens et al., 1981).

There are limited studies on the immune effects of aflatoxin in humans exposed to low levels of aflatoxin in contaminated foods. In Gambia, Turner et al. (2003) studied modification of immune function through exposure to dietary aflatoxin in children and reported detection of aflatoxin albumin (AF-alb) adducts in 93% of the children (range 5 – 456 $pgmg^{-1}$). Immunoglobulin A (sIgA) was markedly lower in children with detectable AF-alb compared with those with non-detectable AF-alb adduct levels. The sIgA provides an important component of the mucosal barrier in saliva, breast milk, tears, and mucus of the bronchial, genitourinary, and digestive tracts by binding to bacterial and viral surface antigens. In a separate study in Ghana (Jiang et al., 2005), the authors investigated the relationship between the cellular immune status and the levels of aflatoxin AF-alb adducts in plasma and reported AF-alb adducts levels ranged from 0.3325 to 2.2703 $pmol\ mg^{-1}$ albumin. In the same study, the differential subset distributions and functional alterations of specific lymphocyte subsets between study participants with high and low levels of AF-alb adducts, showed decrease in activated T cells and B cells and significantly

lower levels of perforin- and granzyme A-expressing CD8+ cytotoxic T cells in those with high AF-alb adducts compared with those with low AF-alb adducts.

A study on aflatoxin-related immune dysfunction in health and in Human Immunodeficiency Virus (HIV) disease in Ghana (Jiang et al., 2008), observed that HIV-infected people are chronically exposed to aflatoxin in their diets. The following observations were also reported after cross-sectional comparisons between HIV positive and aged-matched HIV negative Ghanaians with high (≥ 0.91 pmol mg^{-1} albumin) and low (< 0.91 pmol mg^{-1} albumin) AF-alb levels. First, among both HIV positive and negative participants, high AF-alb was associated with lower perforin expression on CD8+ T-cells. These results may indicate that CD8+ T-cells synthesizing perforin are impaired in individuals with high AF-alb. Secondly, HIV positive participants with high AF-alb had significantly lower percentages of CD4+ T regulatory cells (Tregs) and naive CD4+ T cells compared to HIV positive participants with low AF-alb. The loss of Tregs in HIV positive participants with high AF-alb may facilitate HIV associated immune hyperactivation and lead to more severe disease. Third, HIV positive participants with high AF-alb had a significantly reduced percentage of B-cells compared to those with low AF-alb. These alterations in immunological parameters in participants with high AFB1 levels could result in impairments in cellular immunity that could decrease host resistance to infections. The underlying physiological mechanisms on the association between aflatoxin exposure, growth stunting and immune suppression, remain unclear and hence are important to investigate. According to Luster et al. (1987), the immunotoxicity effect is thought to result from various mechanisms such as decreased protein and, or DNA synthesis, changes or loss in enzymatic activity and changes in metabolism or cell cycles, which may result in apoptosis or necrosis

Determinants of chronic mycotoxin exposure in Kenya

Socioeconomic factors

High incidences of poverty levels coupled with limited education, especially amongst mothers, are some of the factors that contribute to dietary mycotoxin exposure and precipitation of malnutrition (Mustafa and Odimegwu, 2008). Due to the recurrent widespread drought, most households in rural Kenya face an acute food shortage and are vulnerable to food insecurity. It is, therefore, difficult to prioritize the issue of mycotoxin control in those communities in which food sufficiency has not been attained. Most families have no choice but consume the available food without regard to safety. The children and mothers bear the greatest burden of food insecurity in the rural communities. In a study by Okoth and Ohingo (2004), on the link between aflatoxin exposure and growth impairment amongst children, none of the mothers was aware of mycotoxins. However, 20% of the mothers appreciated that their flour would deteriorate with time and therefore had spoilage signs. The rest of the mothers used the flour as long as it lasted.

Regulatory capacity

There is lack of regulatory mechanism to routinely monitor food samples from the farms, distribution and market points. The ability of the regulators to enforce the mycotoxin standards requires that they must be capable of testing food for contamination. In Kenya, laboratories that are capable of analyzing foods for mycotoxin are limited, whereas the analytical procedures are very expensive (Moturi, 2008). Inspections are mostly done after outbreaks and are not used accordingly as pre-warning tools for the rural communities on impending mycotoxic risks. Furthermore, these samples are mostly obtained from local market centers, therefore excluding on-farm samples, which are consumed directly due to the subsistence nature of rural households. The contaminated maize is always destroyed but no further action is taken. Most of the food sampling by inspectors and researchers have focused on maize and ignored other important staple foods such as legumes, fish and meat commodities which could also have the potential to pose mycotoxic risks if contaminated by toxic fungi.

Infant exposure due to dietary mycotoxins carry-over

Several authors have reported the presence of mycotoxins, especially aflatoxins in the milk of farm animals, when they consume contaminated feeds (Bhat et al., 2010). This activity is common in the rural areas, especially when substandard farm produce are not discarded but instead fed to farm animals. A study by Jonsyn, (1999) in Sierra Leone, indicated that some local foodstuffs were contaminated with aflatoxins B_1 and G_2, Ochratoxin A and reported that the major source of mycotoxin ingestion by infants was breast milk. The detection of aflatoxins and Ochratoxin A was observed in 88% and 35% of the milk samples contaminated respectively. In a study by Wild et al. (2006), it was reported that 11% of breast milk samples collected from women in rural villages in Zimbabwe, were found to be positive with aflatoxin levels up to 50 μgml^{-1} of breast milk. Aflatoxin M1, which is a derivative of aflatoxin B_1, has also been reported in human breast milk from Gambia (Zarba et al., 1992). These observations suggest that if the mother is exposed to dietary mycotoxicoses, there's likelihood of the mycotoxins being carried-over to the infants during breast feeding. Due to limited data in Kenya, there is need for further research into exposure of newborn children to aflatoxins through human breast milk and the interaction between aflatoxins exposure and infection during early life.

Weaning status of the infants

Weaning of infants onto family foods represents a period of increasing mycotoxin exposure. In a study by Gong et al. (2003) in Benin and Togo, aflatoxin exposure in young children was significantly related to weaning status in children 1-3 years of age, with mean

aflatoxin-albumin (AF-alb) levels approximately 2-fold higher in fully weaned children compared with those receiving a mixture of breast milk and solid foods. Furthermore, the level of AF-alb was strongly associated with growth stunting. The most likely sources of mycotoxin exposure during the weaning periods are dietary staples frequently contaminated with mycotoxins such as maize or groundnuts (Setamou et al., 1997; Hell et al., 2000a, 2000b). According to Okoth and Ohingo (2004), 29% of weaning food samples obtained from Kisumu district of Kenya, were positive for aflatoxins at ranges 2 – 82 μgkg^{-1} when compared with the regulatory upper limit of 20 μgkg^{-1} (KEBS, 1988).

Co-occurrence of dietary mycotoxins

In most tropical and humid developing countries such as Kenya, it is reported that various mycotoxins commonly occur at the same time as mixtures in the staple foods such as maize meal (Muriuki and Siboe, 1995; Kenji et al., 2000; Muture and Ogana, 2005; Mwihia et al., 2008; Mutegi et al., 2009; Muthama et al., 2009). Despite of the recognized human health effects of other toxins namely ochratoxins, deoxynivalenol, zearalenone, fumonisin and trichothecenes, most of the studies in Kenya are, however, still focused on aflatoxins poisoning. Mycotoxin poisoning may be compounded by the co-occurrence of aflatoxins with other mycotoxins (Bhat et al., 2010). The role of possible interactions between these co-contaminants and the underlying mechanisms of growth impairment is of public health interest. Some authors have suggested synergistic effect between various toxins while others have reported antagonistic interactions (Bankole, 2006).

Pre-harvest and post-harvest practices

Poor harvesting methods, improper transportation, marketing, processing and storage conditions can also contribute to fungal growth and increase the risk of mycotoxin production (Williams et al., 2004; Turner et al., 2005). Conditions such as unseasonal rains during harvest can lead to fungal proliferation and production of mycotoxins. These conditions were implicated in the 2004 aflatoxicosis outbreak in Kenya, which involved maize harvested during off-season, early rains (Lewis et al., 2005; Probst et al., 2007). Insect damage, cracking or breaking of maize kernels or groundnut shell during manual harvesting and presence of excessive chaff in the harvested grains also promote mould infection (Hell et al., 2000b). The practice of spreading crops on bare ground to sundry brings them in direct contact with soil fungal inoculums. There's need for awareness promotion on removal and destruction of debris of the previous harvest and cleaning of stores before loading new produce in order to reduce aflatoxin levels (Hell et al., 2000a).

According to Muthama et al. (2009), semi processed grains have lower isolation frequency of *Fusarium* spp and *Aspergillus* spp compared to the whole grain. It has also been found that commercial maize processing reduces mycotoxin levels, especially aflatoxins, which are concentrated in bran and germ. The traditional home processing of maize flour involves milling of the whole grain including the pericarp and the germ, which could imply inclusion of fungi and the associated mycotoxins. Most of the storage systems in use such as storing grains on the floors offer little protection against insect and mould deterioration (Naresh and Aldred, 2007).

Possible intervention strategies to alleviate dietary aflatoxins exposure

Given the potential adverse public health effects of the dietary mycotoxins, it is important to evaluate intervention strategies appropriate to rural populations in Kenya.

Awareness strategies

The strategies to mitigate the mycotoxin problem should include education of the rural population, especially the mothers on the prevalence and danger of mycotoxins in staple foods. In Kenya, there's need for fact

sheets on the occurrence of mycotoxins to be developed for dissemination using simplified methods through community colleges (Kabak et al., 2006). Key part of the strategy should include awareness on preventive measures during pre- and post-harvest management of the farm produce. Mouldy grains and other foods suspected of being contaminated with mycotoxin should be discarded by burning. Dietary interventions should include the target areas with high mycotoxins exposure levels. This can be achieved through reduction of the frequent consumption of high risk foods and adoption of different methods that have less risk to prepare such staple foods. There should be targeted approaches for different stakeholders including community opinion leaders, farmers, consumers, policy makers, researchers, extension workers, non-government organizations (NGOs), donors, media, traders, processors, health workers and school children.

Pre-harvest strategies

Precautions should be taken during cultivation of crops to prevent fungal spores from being established during the growing period. The factors that influence potential for pre-harvest fungi to develop include physiological, morphological state of plant and climatic conditions (Setamou et al., 1997). Farmers should ensure that the seeds used for planting are certified and ensure they are free from pests and diseases while stored in the homesteads. Drought stress caused by lack of water facilitates attack by moulds by allowing the plant to crack resulting to open passage ways through which fungal spores can enter the crop stem or head (FAO, 2007). Where irrigation system is functional, farmers should always try to supplement local rainfall to avoid drought stress. If it is not possible to irrigate, they should plant and harvest as early as possible. Plant stress also occurs when nutrients are not available and leading to exposure of internal tissues which may be exposed to fungal attack. This can be overcome by appropriate application of organic and inorganic fertilizers.

Good plant husbandry is important in prevention of fungal invasion (Bhat et al., 2010). Even though minimal tillage is common amongst farmers due to savings on time and money, it is important to consider the possible negative effects. Without tillage, crop residues remain on the soil surface and eventually will harbour soil borne fungal spores, allowing them to infect the next crop (FAO, 1985). Other good plant husbandry measures include keeping the farm plots weed-free, control of insects by use of commercial insecticides applicants and other recommended methods of control such as botanical pesticides. Timing of the production cycle is also important and planting should be done at recommended time to avoid too early or too late maturity during periods of prolonged rainfall. Farmers should be encouraged to plant seed varieties that are pest and fungal resistant (FAO, 2007).

Harvesting strategies

The most important factors that influence mould growth once the plant is mature are water activity and physical damage. It is essential to dry the produce to safe moisture content as quickly as possible without causing any damage (FAO, 1985). Rapid drying requires that harvesting should be done as quickly and the crop transported to the homestead as soon as possible. The rate of drying will depend on the harvesting practices and crop involved. If the weather is dry and hot, the crops can be left standing in the field, but there is a risk of unexpected rainfall occurring during this period leading to mould growth. The common practice of cutting cereals at the base of stalk and pile stalks with cobs into conical bundles may inhibit ventilation and slow the drying process (FAO, 2007). Some farmers spread bundles of stalks especially legumes on the soil, which creates an opportunity for fungal spores in the soil to invade the grain. This can be avoided by

placing a barrier between the crop and the soil or use of platform above the ground.

Post-harvest strategies

Drying begins before harvest and further drying is necessary until the crop is put in store (Turner et al., 2005). The crops can be spread on polythene preferably black or empty sacks laid on the ground or concrete floor. Unthreshed crop should be laid on platform or cobs can be tied and suspended from vertical frame to dry. Threshing, shelling and winnowing should be done carefully to avoid damaged grains. Farmers should avoid beating the crop with sticks which result in grain damage, eventually leading to mould development unless the grain is to be used quickly and not stored (FAO, 2007). Farm produce should be stored in suitable containers which are raised above ground level. If it has to be stored on the ground, farmers should use suitable water-proof barriers. However, if stored for more than two months, the grains should be treated with suitable grain protectants against insect damage. Further protection of the crop against damage by rodents is also necessary.

Food processing strategies

Various techniques are critical in mycotoxin removal or reduction. These include cleaning through sorting whether manual or mechanical, winnowing, sieving to remove screenings, washing through floatation or density segregation (Williams et al., 2004). Steeping is effective for fumonisins reduction; however there's need to change steep water often during a 48-hour steep period and use as much water as possible to steep maize. Dehulling and degerming are also effective for aflatoxins and fumonisins reduction (Muthama et al., 2009), while cooking and boiling is effective for aflatoxins and citrinin reduction in foods though the moisture content and cooking times are critical. The combined use of elevated temperature and pressure (extrusion cooking) has shown that fumonisins are effectively reduced. However, more information is needed to establish whether aflatoxins and citrinin are metabolized into other toxic compounds with heat treatment.

Conclusion

The occurrence of mycotoxins in the food chain is a serious problem that tropical developing countries such as Kenya are facing. Chronic exposure is particularly of great clinical importance due to the emerging evidence in their role in growth impairment and immune suppression. Given the high burden of infection-related mortality in Kenya, further investigation of the stunted growth and immune effects of aflatoxin exposure in children is merited. Comprehensive food safety program remains an important opportunity for addressing current mycotoxicosis problems in Kenya, particularly with regard to the achievement of the MDG 4 and 6 goals. These interventions must target all stakeholders including the market vendors, local farmers and rural households. Efforts should focus on the prevention of mycotoxin exposure by developing framework on strengthened surveillance and local education. The prioritization of other interventions will be largely guided by the availability of technology that can be applied in the short, medium and long term; and the impact of an intervention upon implementation.

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