Evidence-based strategies for reducing the health impacts of aflatoxin or fumonisin exposure in high exposure regions: An IARC expert panel.

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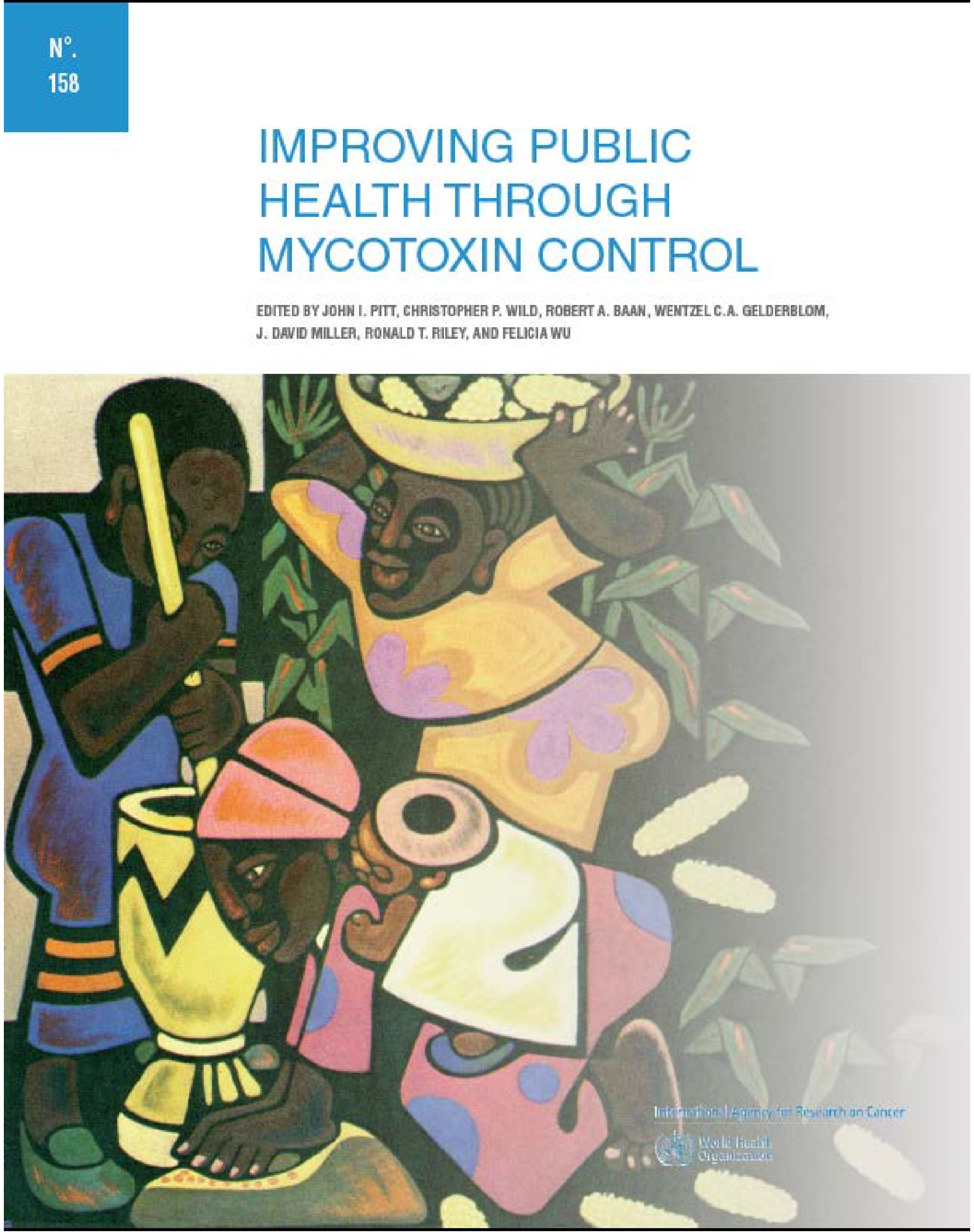
On behalf Prof. Chris Wild, Director IARC & Prof . J. David Miller, panel chair



In 2001, Dr. Jerry Rice was contacted by a country in Africa that had a lot of the groundnut crop was highly contaminated by aflatoxin

He was upset that he had no information that would be useful and began work on such a publication in 2003.

The project was restarted in 2008 by Prof. Wild and brought to completion.

Interventions discussed in the book

- Education leading to improved awareness of mycotoxins across different sectors of society
- Better description of the prevalence and level of mycotoxin exposure in the most affected regions
- Development of accurate and applicable mycotoxin testing kits, sampling equipment, and training models for use in low-income countries
- Conduct of epidemiological studies to assess the acute and chronic health effects of mycotoxin exposure; priorities include the impact of mycotoxins on child growth and immune status

Interventions discussed in the book…

- Identification of individuals and groups who are particularly susceptible to mycotoxins to ensure focused attention
- Development and evaluation of cost-effective, simple, and sustainable intervention methods suited to low-income countries
- Detailed economic assessments of interventions, in terms of either improved markets or improved human health

This information provided for each intervention discussed.

- **Description**: A description of the intervention
- **Stage of development**: How well developed and tested is the intervention in terms of controlling the mycotoxin?
- **Efficacy**: By how much can the intervention reduce mycotoxin risk, compared to conditions where there is no intervention?
- **Geographic regions**: Where has this intervention been tested or adopted around the world?
- **Simplicity/Complexity**: How simple or complex is the intervention as far as usage characteristics

This information provided for each intervention discussed…

- **Population/Individual**: Is the intervention tailored with a population approach or does the intervention rely on individuals for implementation?
- **Utility in emergencies**: Is this intervention suitable for use in a time of emergency; e.g., when mycotoxin levels are known to be high in available foods, or in the event of acute poisoning?
- **Locality of resources**: Can the intervention be manufactured using local resources, or does it require importation of resources and/or trained operators?
- **Accessibility**: Is the intervention applicable in low income countries and among subsistence farmers in relation to access, cost, etc.?

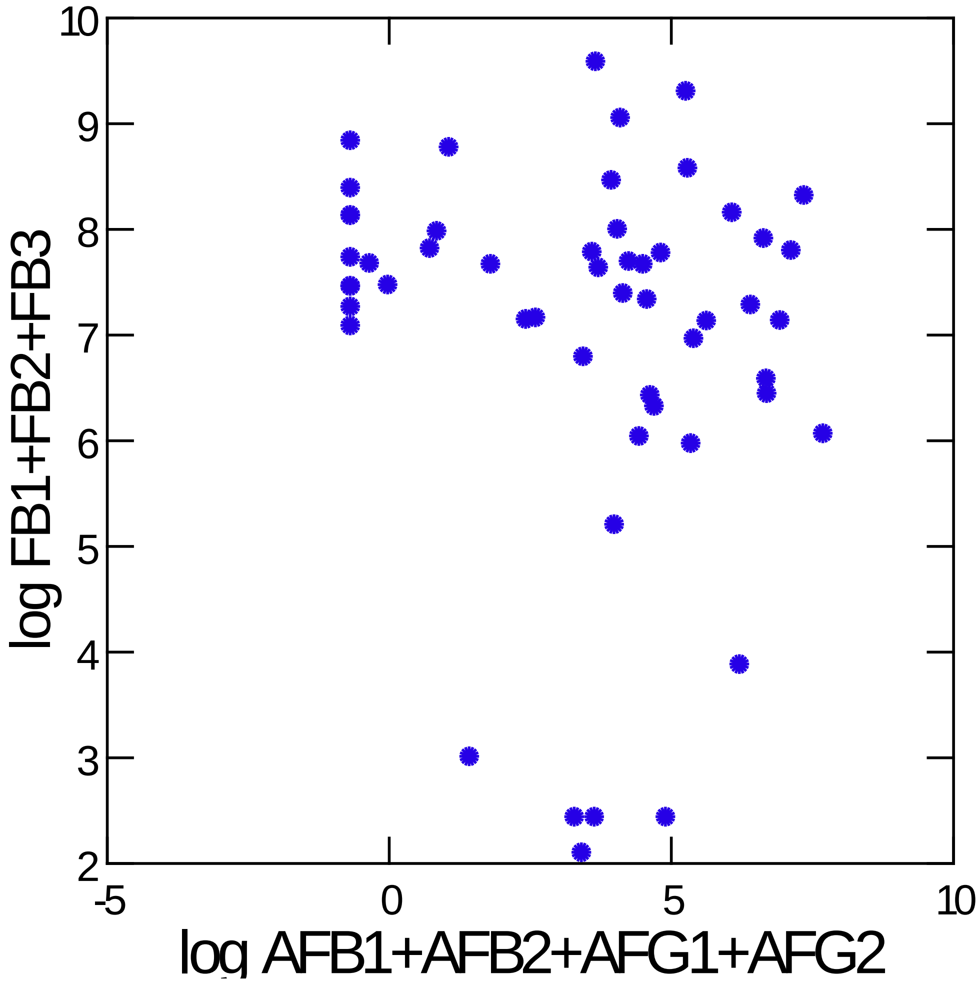
Aflatoxin and fumonisin where there are important co-exposures.
ca. 100 pages of text accessible to policy makers

IARC panel covered a number of key areas:

1. Epidemiology of stunting and wasting and interventions for prevention or treatment
2. Prevalence, regulatory status for mycotoxin control and mycotoxin exposure globally
3. Human studies of acute (aflatoxicosis) and chronic disease
4. Studies in children and impact of aflatoxin/fumonisin on growth and development
5. Aflatoxin-related immune modulation
6. Experimental studies of acute and chronic toxicity
7. In utero exposure to fumonisins and child health

In maize, where aflatoxin is present, almost always, fumonisin is also present -all over Africa.

Alfatoxins and fumonisins in stored maize five agro-ecological zones of Nigeria



Maize samples where aflatoxins were >30 ppb for or fumonisins were > 1ppm.

Mycotoxin Res 30:89; raw data provided by authors

Constraints to Monitoring of aflatoxins and fumonisins exposures

- There is no immediate prospect of enabling uniform information collection in many developing countries
- Increasing the availability of mycotoxin biomonitoring including an improved biomarker for fumonisins exposure seems to be the sensible course
- Availability of reagents, analytical costs and absence of high throughput technology remains a restriction

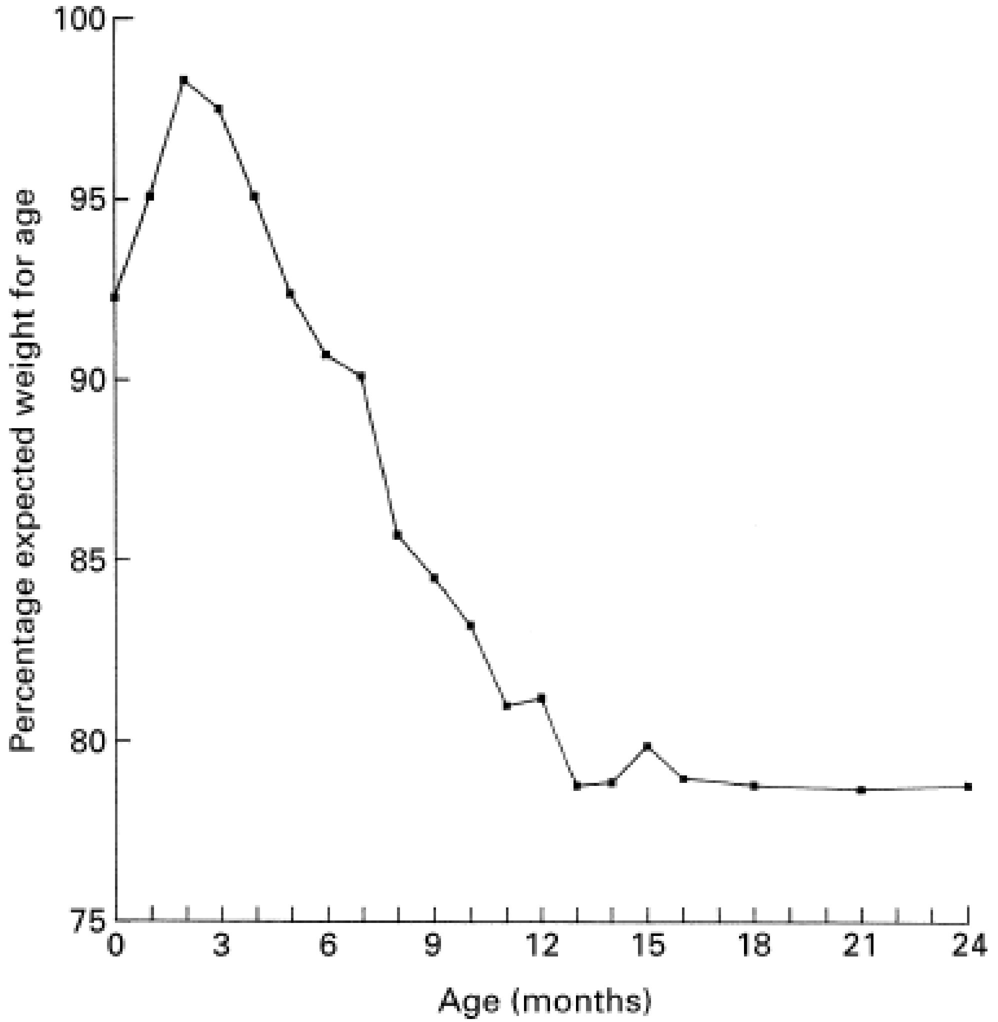


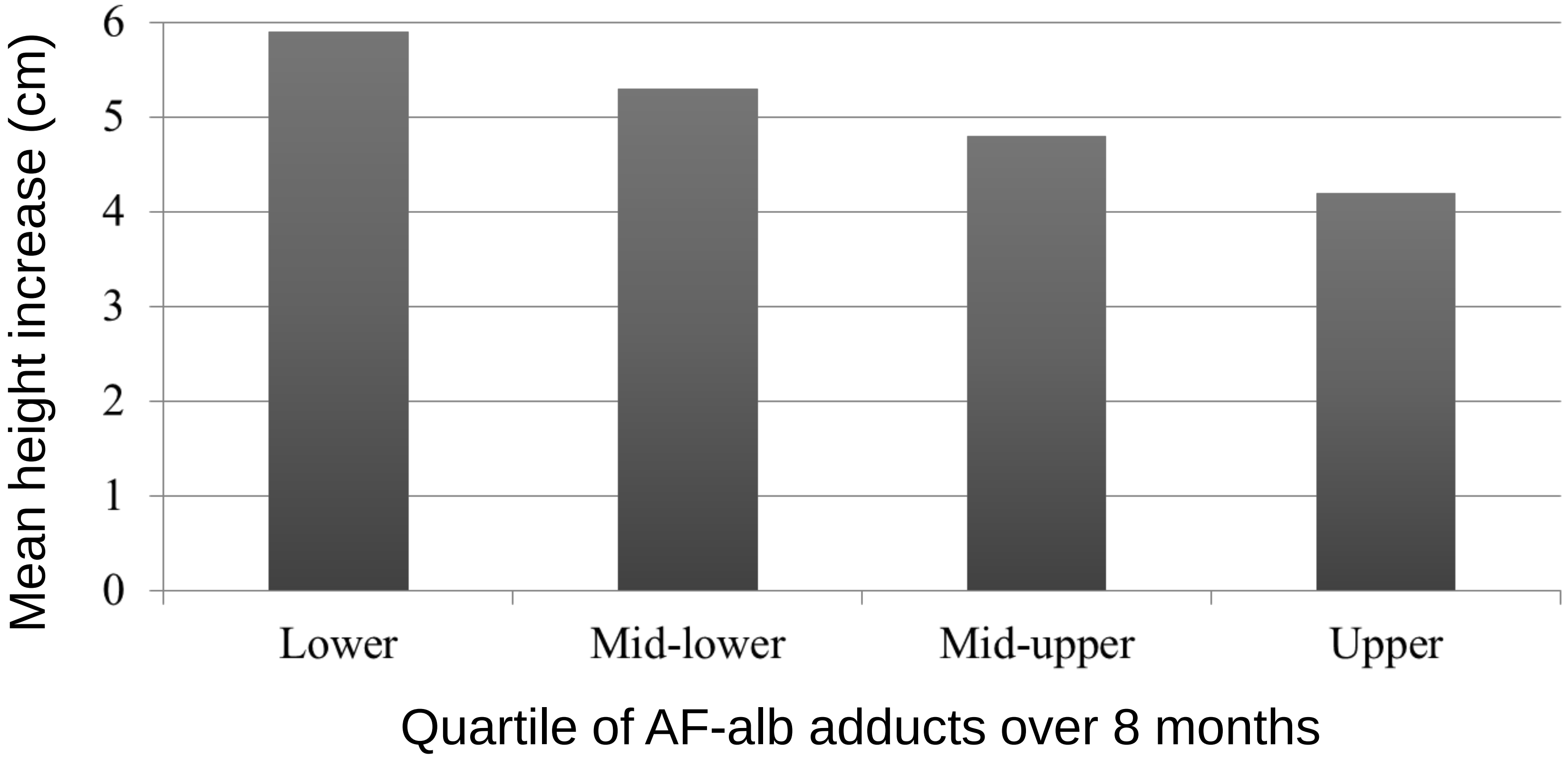
Fig. 1. Growth performance of Gambian infants expressed as percentage of expected weight-for-age according to National Center for Health Statistics (Hamill *et al.* 1979) standards.

Proc Nutrition Soc 2000 59:149

Aflatoxins and child growth

- Six studies were considered to be of high quality, with well-defined sample sizes, exposure or dose assessments, outcome measures, and appropriate multivariate analyses

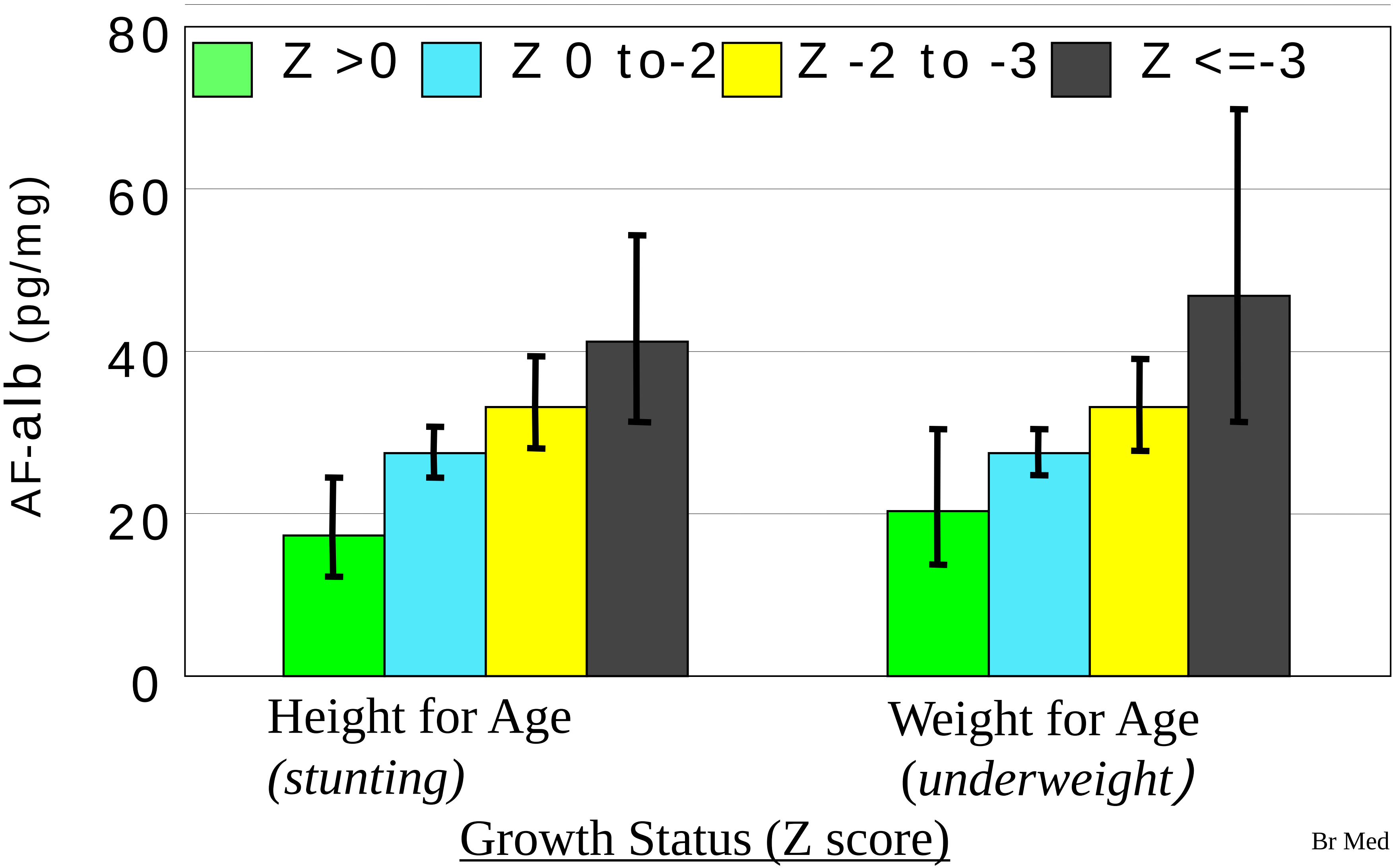
Longitudinal study of aflatoxin exposure and child growth in Benin



200 children, aged 16-37 months followed over 8 months
Adjusted for age, height, weaning status, mothers SES and village

Environ Health Persp 112:1334

Exposure to Aflatoxin is Associated with Reduced Growth in West African Children

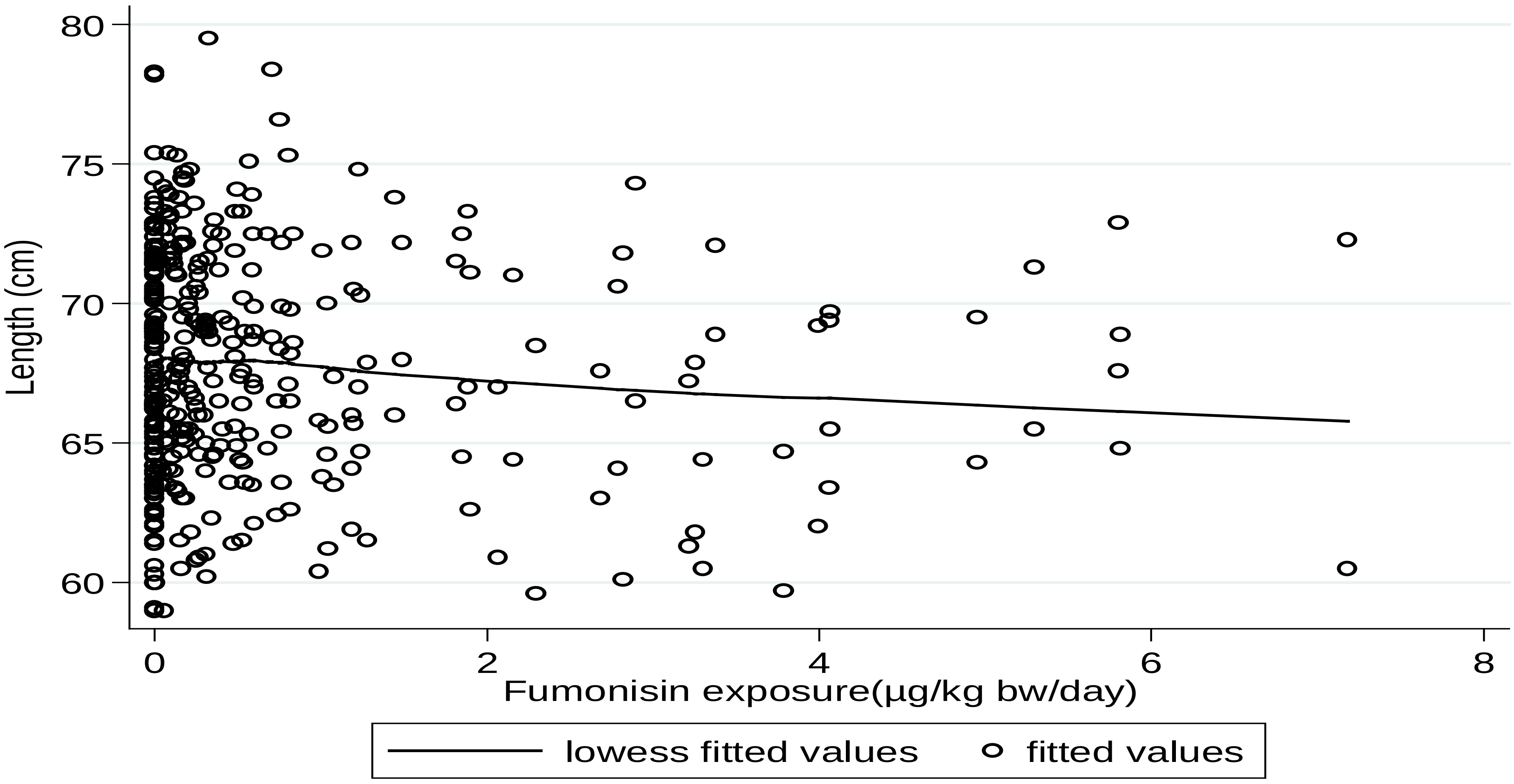


Br Med J 325:20

Fumonisins and child growth

- Two recent studies from Tanzania suggest that fumonisin exposure may also be associated with stunting in children

Fumonisins exposure is inversely associated with linear child growth in Tanzania (Kimanya *et al.* (2010), Mol. Nutr. & Food Rs.)



Children in the high exposure group were on average 1.3cm shorter and 328 g lighter

Fumonisins exposure is inversely associated with linear child growth in Tanzania (Shirima et al. In press)

Fumonisin exposure biomarker	Outcome	Regression coefficient	p-Value
Exposure levels at recruitment	LAZ at 12 months	-0.20	0.014
Mean exposure levels at recruitment and 6 months after recruitment	LAZ at 12 months	-0.39	0.000
Mean exposure levels from all three sampling times	Length velocity over 12 months	-0.52	0.004

LAZ: Length for age Z-scores

Summary on mycotoxins and child growth

- Taken together, the studies suggest that mycotoxin exposure contributes to child growth impairment
- The weight of evidence linking aflatoxin with growth impairment has increased over the last five decades of research
- If these associations are established, then the global burden of disease associated with mycotoxin exposure may be far greater than that which has previously linked mycotoxins with cancer

Summary on mycotoxins and child growth

- One critical knowledge gap is the mechanism(s) by which mycotoxins may cause child growth impairment
- Possible mechanisms for aflatoxin specifically include:
  - enteropathy may be partly attributable to aflatoxin related toxic damage on the intestine epithelium, resulting in poor uptake of nutrients;
  - aflatoxin associated immune suppression could increase children’s susceptibility to infections such as diarrhea;
  - liver toxicity of aflatoxin may damage the production of insulin like growth factor pathway proteins in the liver and an adverse impact on child growth

Recommendations of interventions according to evidences

1. Sufficient evidence for implementation
2. Needs more field evaluation
3. Needs formative research
4. No evidence/ineffective

Intervention	Evidence	Context	Gap (research/translation)	Combination/ Issues/Comments
Dietary diversity	*	Dose effect reduction of HCC	• Investment in appropriate crops for the target region suitable for both the climate and culturally acceptable.	Difficult in food insecure situations or in food, arable land or water insecure countries
Genetic resistance		Contamination		
Aflatoxin in maize	3		• Movement of resistance in agronomic lines. • Identification of resistance genes.	Combination: Biocontrol; Agronomic and post-harvest practices. Issues: Small research community, large environmental effect on phenotype expression; resistance is polygenic.
Fumonisin in maize	2			Combination: Agronomic and post-harvest practices; Issues: Small research community, large environment effect on phenotype expression; resistance is polygenic.
Aflatoxin in peanuts	4		• Identification of sources of resistance. • Movement into agronomic lines.	Combination: Biocontrol; Agronomic and post-harvest practices Issues: large environmental on phenotype expression limits resistance expression over large areas; small research community; resistance is polygenic; resistance not well described

Intervention	Evidence	Context	Gap (research/translation)	Combination/ Issues/Comments
Biological control		**Contamination**		
Atoxigenic strains	2		• Frequency and outcomes of genetic recombination. • Consistency of efficacy evaluated across geography and users.	Combination: Agronomic and post-harvest practices; Comment: On-going translational research in US and Africa.
Primary prevention		Dose effect		
Dioctahedral smectite clay	2		• Dose and time on efficacy and safety. • Effects on infants, children and pregnant women.	Combination: Clay amended with chlorophyllin and other trapping agents; Issues: Delivery strategies;** Comments: Possible enhanced efficacy during outbreaks; potential to mitigate aflatoxins and fumonisins.
Chlorophyllin	2			

Intervention	Evidence	Context	Gap (research/translation)	Combination/ Issues/Comments
Post-harvest		**Dose effect/ contamination**		
Package of storage, sorting & agronomic techniques	1		• Knowledge Translation (KT) is cultural. • Modules need to be developed in partnership with farmers, area agricultural extension workers, traditional leaders, church groups, health workers and civil society.	Comment: Ready to be implemented; Use in chronic exposure situation as an on-going intervention package; Needs to be applied as a multifactorial intervention package.
Sorting	1		• Done in all cultures for all crops however best practices need to be formally taught a village level.	Comment: Important for complementary food; Issues: Fate of the rejected food.
Nixtamalization	1		• Requires adequate water for washing. • Has not been adapted in Africa or Asia.	
Chemoprevention		Dose effect		
Broccoli sprout extract	2		• To date Phase II clinical trials for efficacy, need for scaling to longer term interventions. • Translation to local, cultural acceptable foods with these enzyme inducers. • Biomarker studies to date, no health endpoint studies as yet.	Comment: Opportunity for use in acute exposure situations; Native plants; Dietary diversification
Dithiolethiones	2			
Green Tea Polyphenols	2			

Important messages

1. Aflatoxins co-occur with fumonisins in staple foods
2. Presently, the association of aflatoxins and fumonisins with stunting is the driving force for interventions
3. Interventions should address both aflatoxins and fumonisins
4. Advocate for a package of Agronomic , Storage and Sorting Practices: Intervention for which there is sufficient evidence for implementation
5. Advocate for bio-controls: Needs more field evaluation