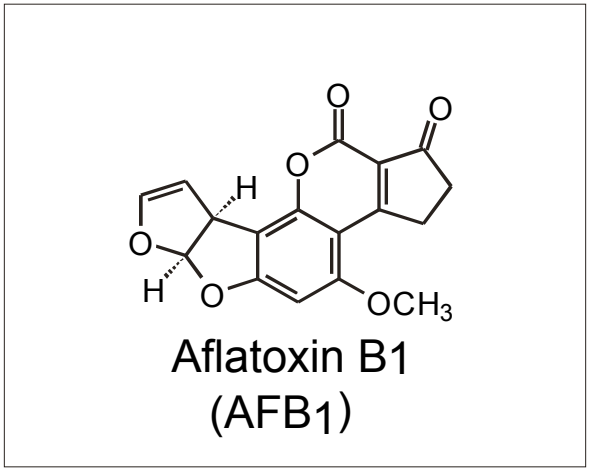
Prevalence of aflatoxin in mothers and young children in Nepal and Bangladesh: Implications for Assessment and Public Health



Aflatoxin B1
(AFB_1)

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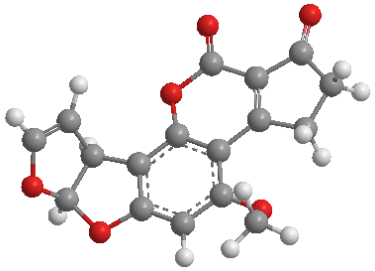
Johns Hopkins School of Medicine

Supported by the Bill and Melinda Gates Foundation (GH 614, GCE 1046227 and GCE 1046227) and NIH P01 ES 006052



Aflatoxin factoids

- **Discovered in UK ~1960 in moldy, toxic animal feed**
- **Frequent contaminant of improperly stored food crops**
  - Produced by *Aspergillus flavus* (***A.flav****us* toxin = "***Afla***toxin")
  - Spores are globally distributed in soil
  - Mold grows on food crops after harvest, before drying

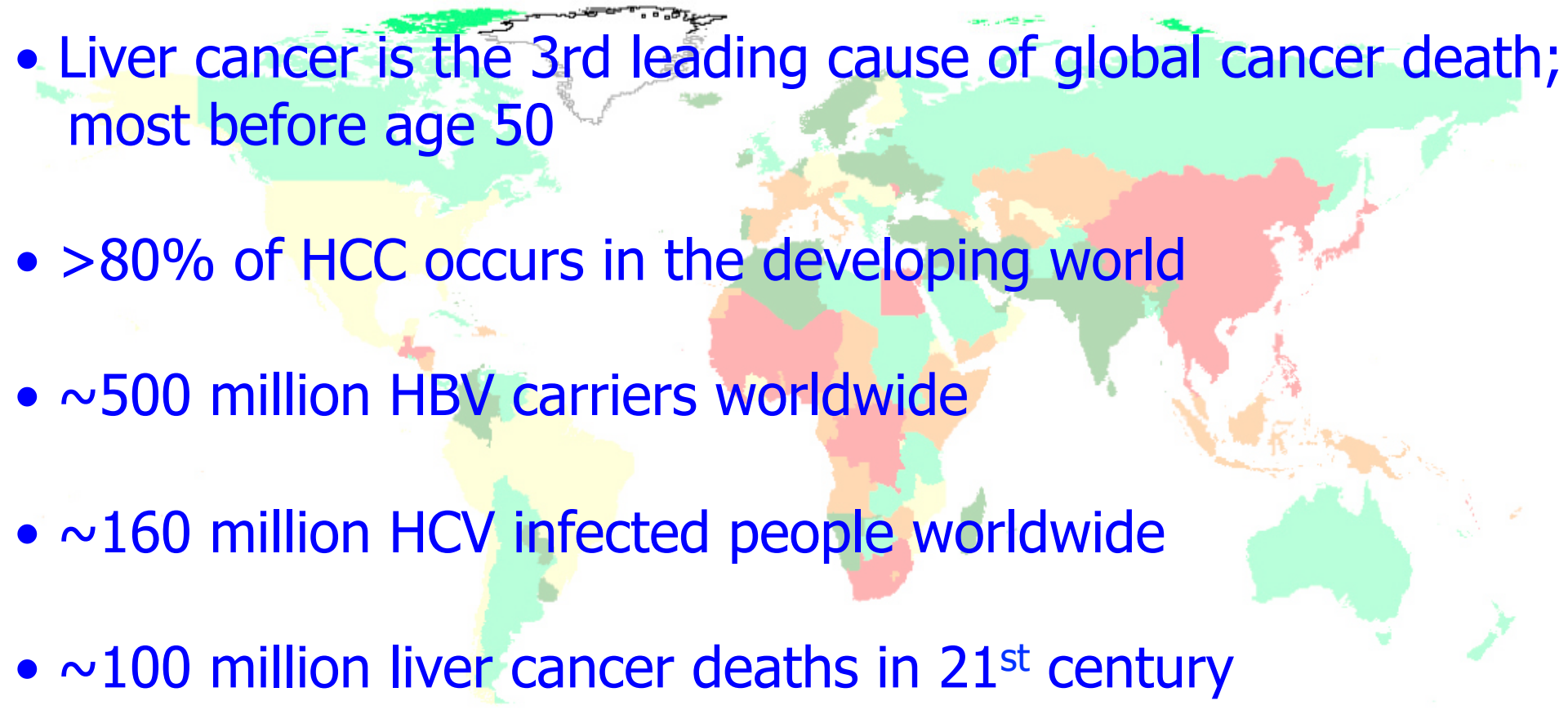
- **Some relevant properties**
  - Highly fluorescent, heat stable
  - Lethal to animals at high levels ("Turkey X disease")
  - Carcinogenic to liver of animals when fed at non-toxic levels
  - Immunotoxic to animals and humans

Aflatoxins in Human Food

Corn
Wheat
Rice
Peanuts
Soybeans

Oats
Sorghum
Millet
Cottonseed
Copra

Liver Cancer Mortality



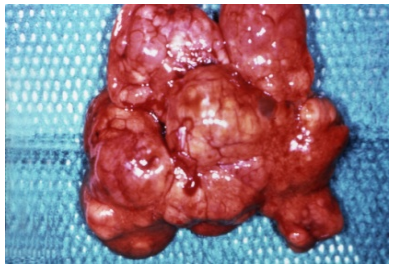
- Liver cancer is the 3rd leading cause of global cancer death; most before age 50
- >80% of HCC occurs in the developing world
- ~500 million HBV carriers worldwide
- ~160 million HCV infected people worldwide
- ~100 million liver cancer deaths in 21st century
- etiology of 90-95% of liver cancer now known

695,000 deaths in 2008 (WHO)

[Baltimore 2008 population 636,919]

GLOBOCAN 2008 (IARC) - 3.6.2010

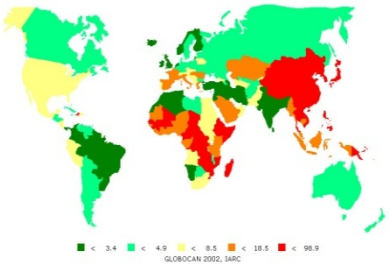
50th Anniversary of Aflatoxin Discovery



1961
AFB1 Causes Liver Cancer in Rats

1968
AFB1 Levels in Diet Linked to Liver Cancer

1969
FDA Sets Action Levels for Aflatoxin

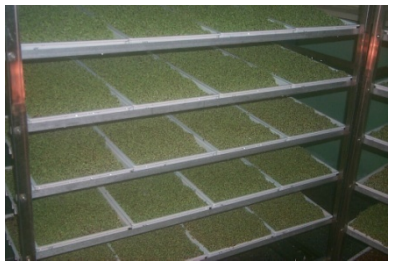


1977
DNA Adduct Identified

1984
Monoclonal Antibodies and IAC

1991
Aflatoxin/HBV Synergy in Liver Cancer Etiology

1993
IARC Classifies Aflatoxins as Group1 Carcinogens

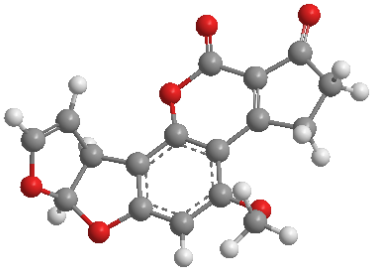


1995 → 2013
Oltipraz/NovaSil/CHL/ Broccoli Sprouts Clinical Trials

ca 1960
Aflatoxin Named

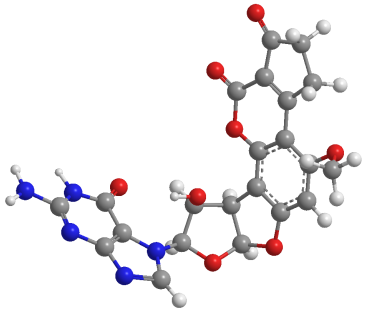
1963
Structures Elucidated

1967 →
Toxicology and Metabolism



1972
First IARC Evaluation

1981
DNA Adduct in Urine



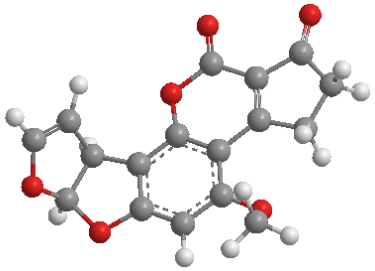
1987
Albumin Adduct Identified

1988-92
Food Intake/ Biomarkers China & Africa

1991
p53 mutations at Codon 249 in Liver Cancer

2001→ 2013
p53 and HBV Mutations in Plasma

Aflatoxin B_1



Hepatocellular Carcinoma

Sampling and testing:

Is 20 ppb an appropriate regulation for aflatoxin contamination?

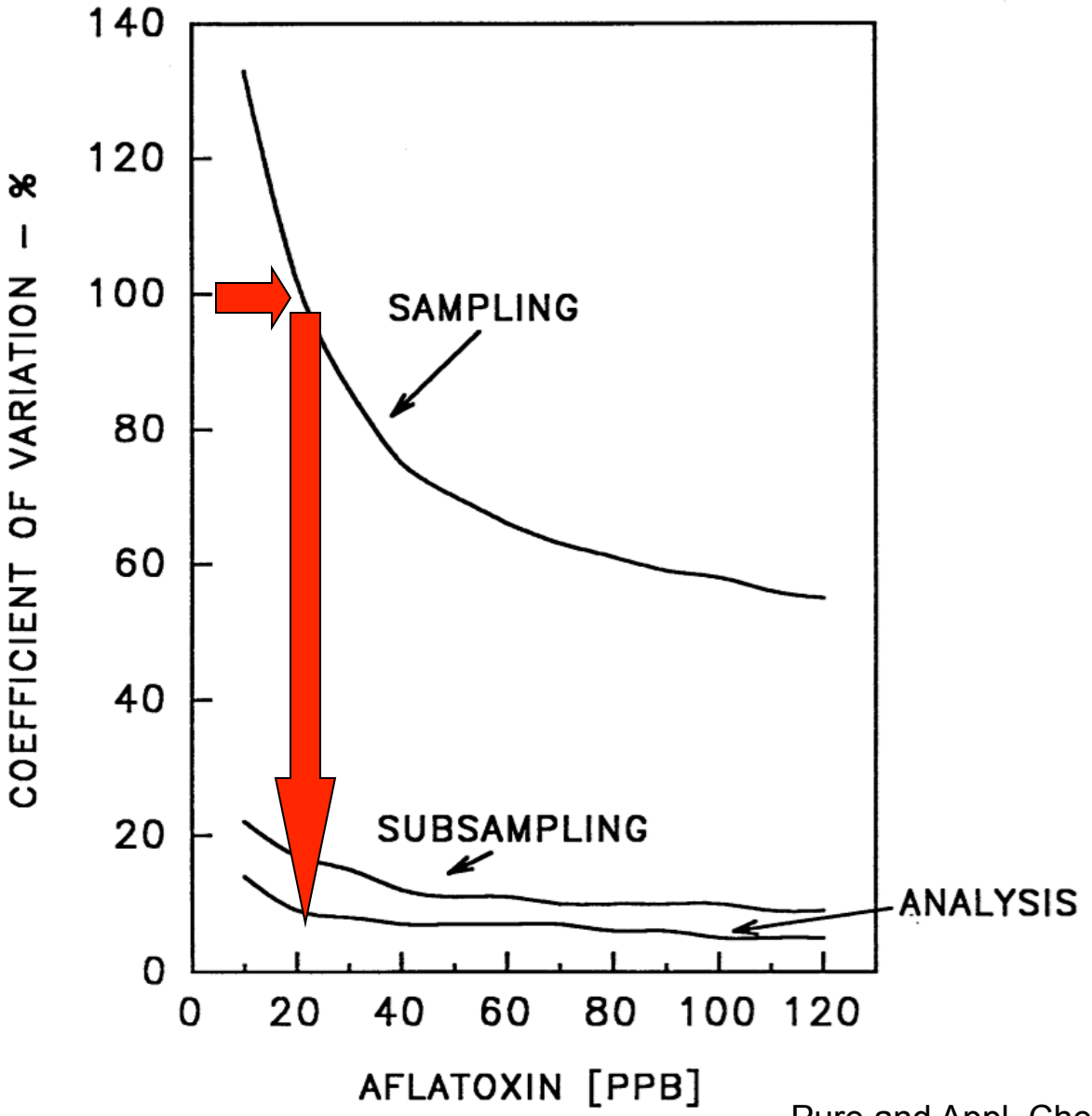
Coefficient of Variation In Analysis of Aflatoxin In a Heterogeneous Lot

500 gram sub-sample for analysis

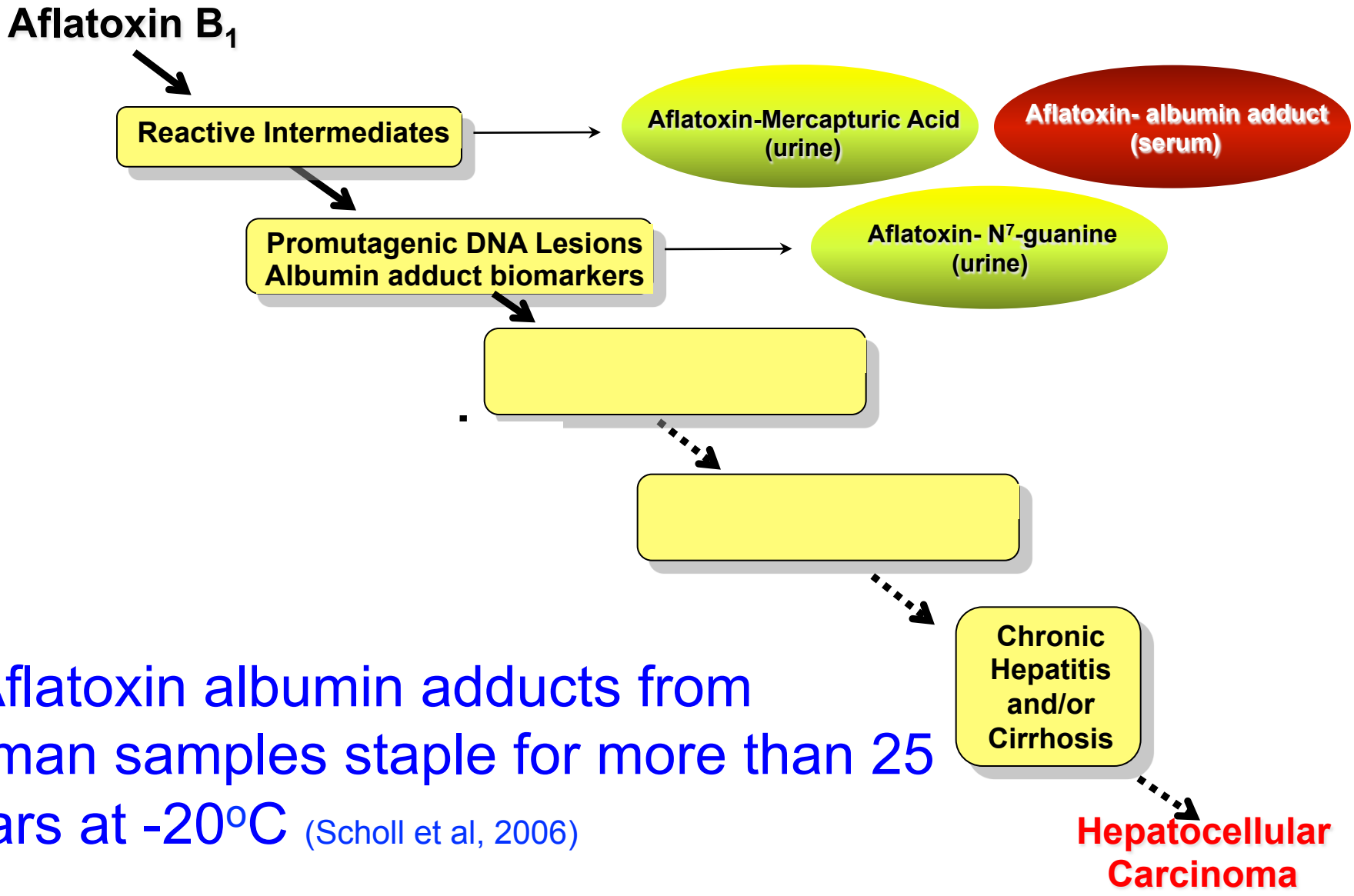
INDIVIDUAL PEANUTS WERE MEASURED

Campbell et al. Pure and Appl. Chem. 58:305-314, 1986

Coefficient of Variation In Analysis of Aflatoxin In a Heterogeneous Lot

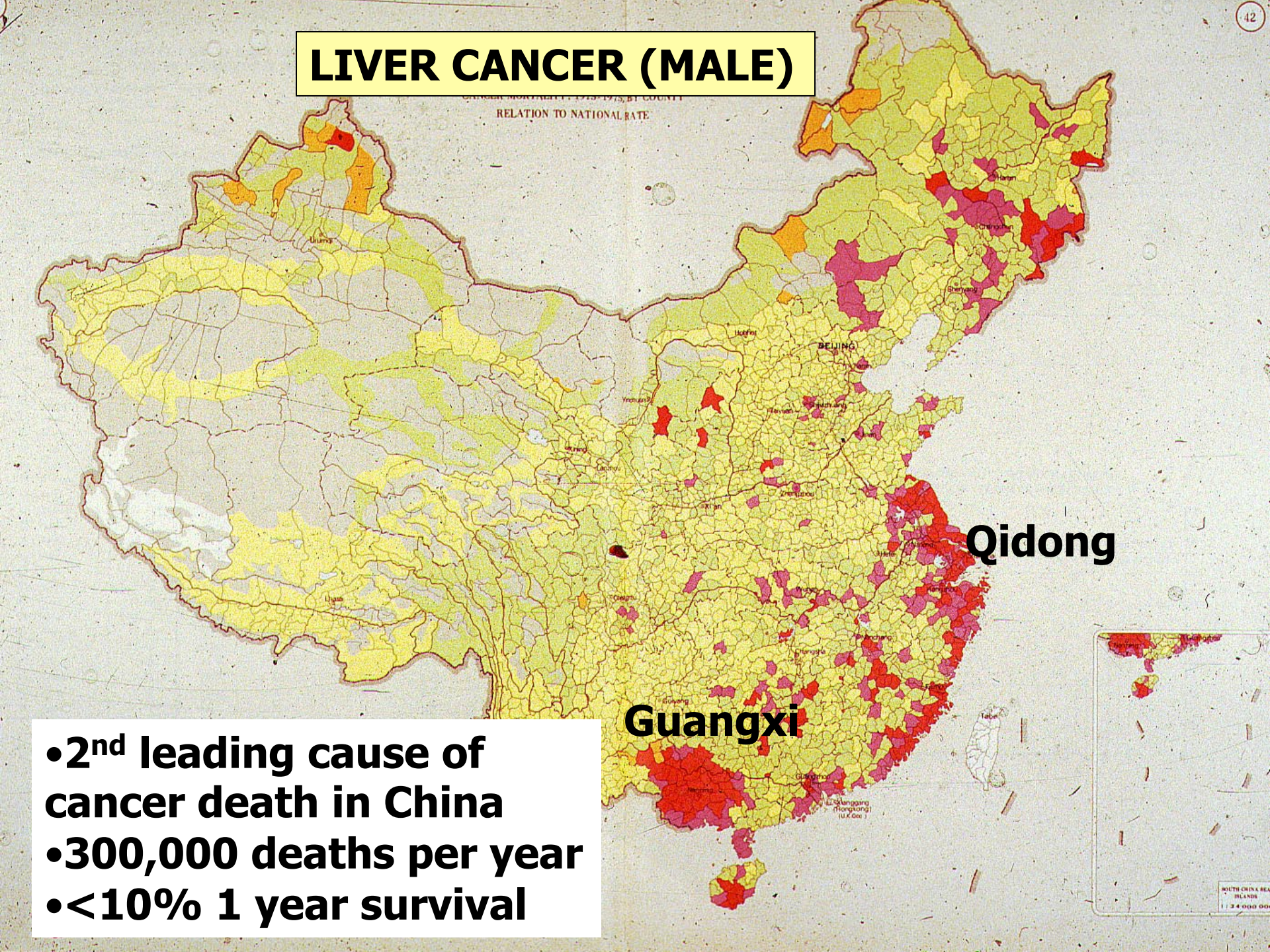


Pure and Appl. Chem. 58:305-314, 1986



**Aflatoxin albumin adducts from human samples staple for more than 25 years at -20°C (Scholl et al, 2006)

LIVER CANCER (MALE)



- 2nd leading cause of cancer death in China
- 300,000 deaths per year
- <10% 1 year survival

Cohort Study of Liver Cancer in P.R.C.: Viral-Chemical Interactions

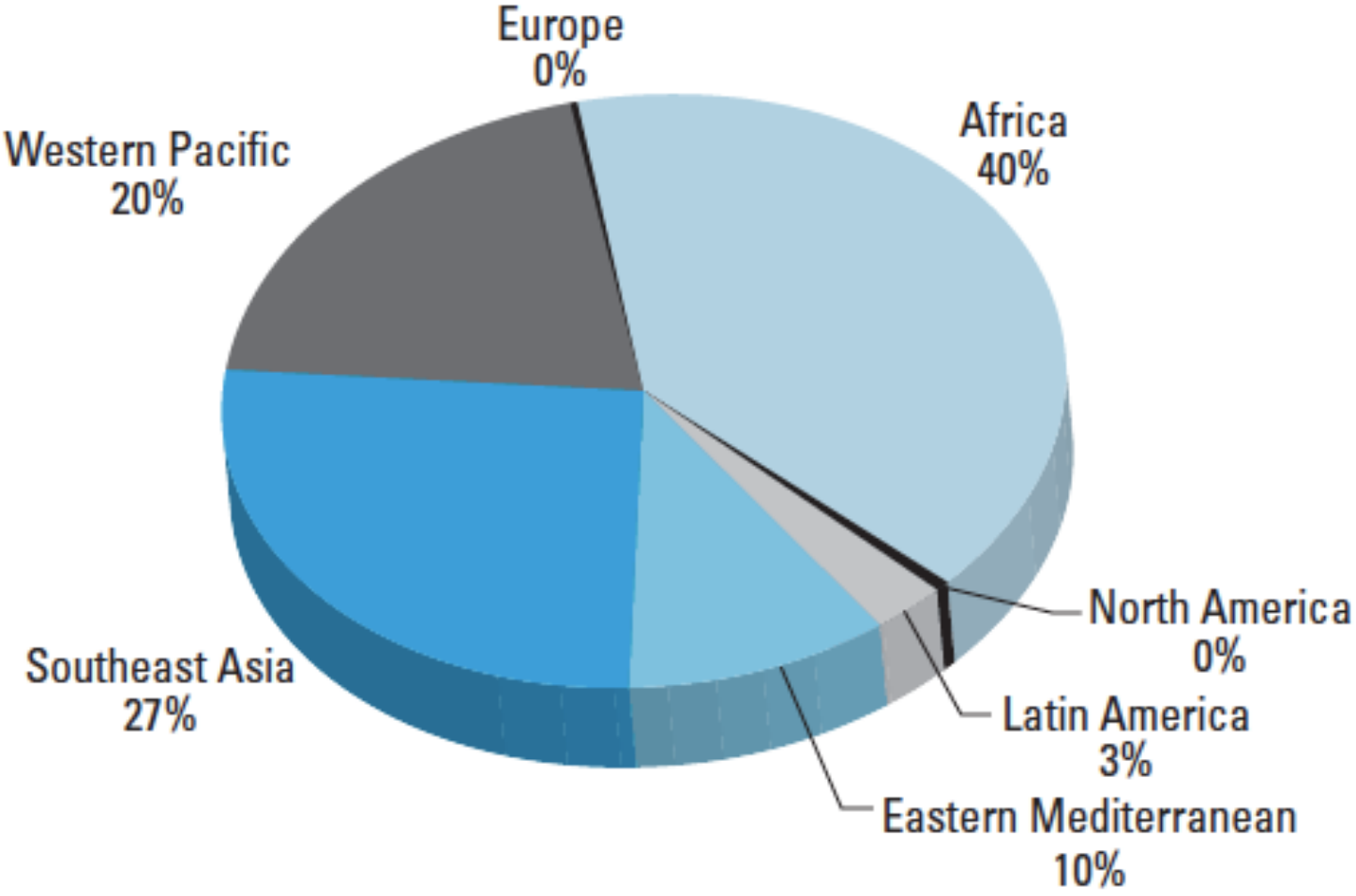
- 18,244 urine and blood samples collected from healthy men age 45-65
- 50 liver cancer cases and 247 controls
- Urinary aflatoxin biomarkers measured in blinded samples
- HBV status determined for each subject

Lancet 339: 943-946, 1992
and *C.E.B.P. 3: 3-11, 1994*

BIOMARKERS: HBsAg AND URINARY AFLATOXINS	RELATIVE RISK FOR LIVER CANCER
NO BIOMARKERS DETECTED	**1.0**
HBV (YES) AFLATOXIN (NO)	**7.3**
HBV (NO) AFLATOXIN (YES)	**3.4**
HBV (YES) AFLATOXIN (YES)	**60.0**

Distribution of the Almost 155,000 cases of HCC Attributed to Aflatoxin-Only Exposure Each Year

13 DALYs per case → **328,000-2,000,000 DALYs/yr**



Environ Health Perspect 118:818–824 (2010)

Human Aflatoxicosis

Africa

802129 (547147) 3-93

FIGURE 1. Districts affected by aflatoxicosis outbreak — Eastern and Central Provinces, Kenya, January–July 2004

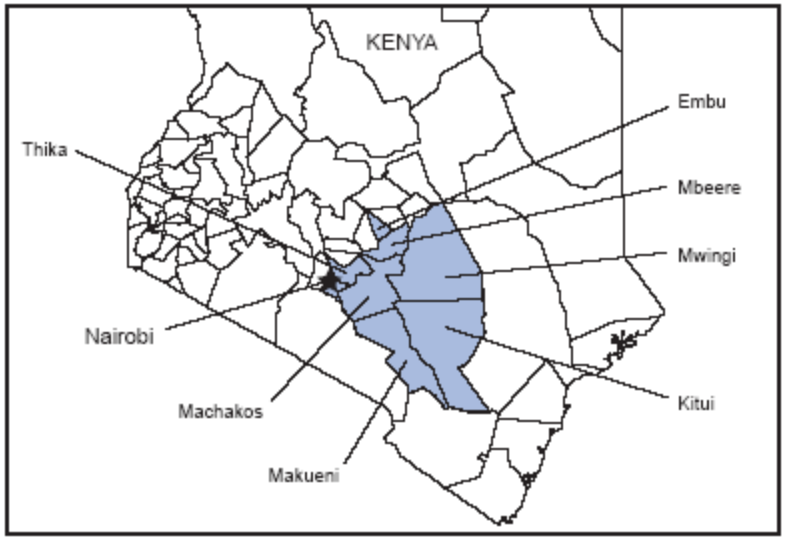


FIGURE 2. Number of aflatoxicosis cases, by date of reporting — Eastern and Central Provinces, Kenya, January–July 2004

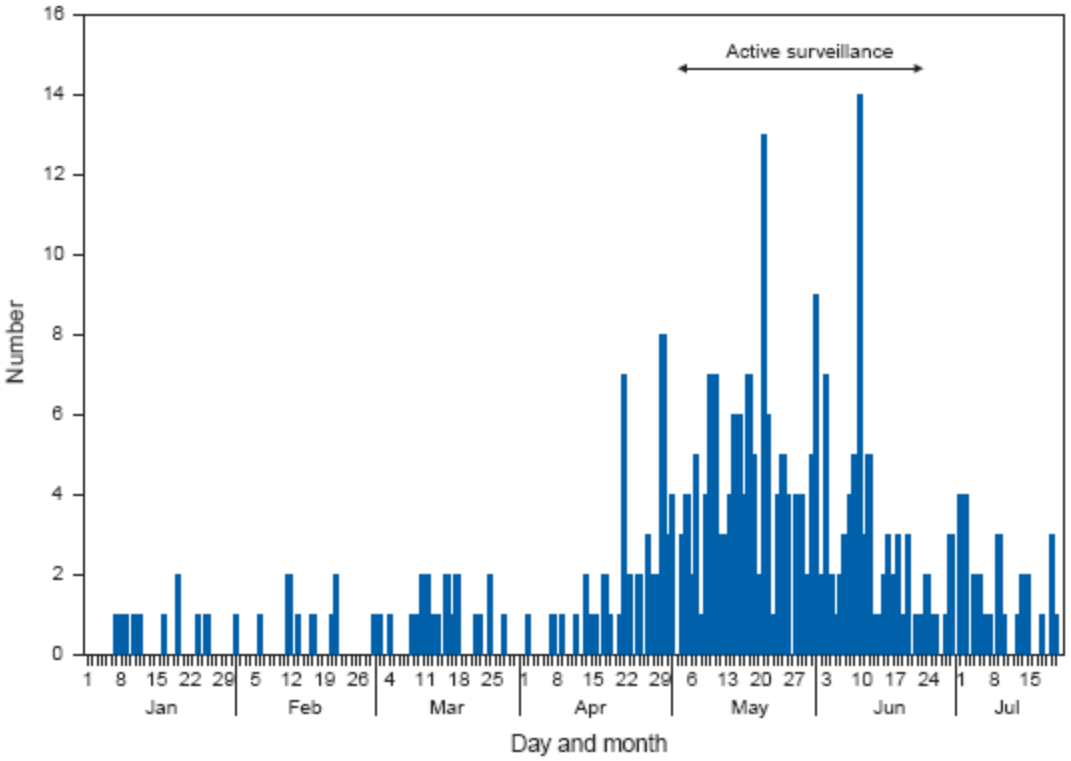


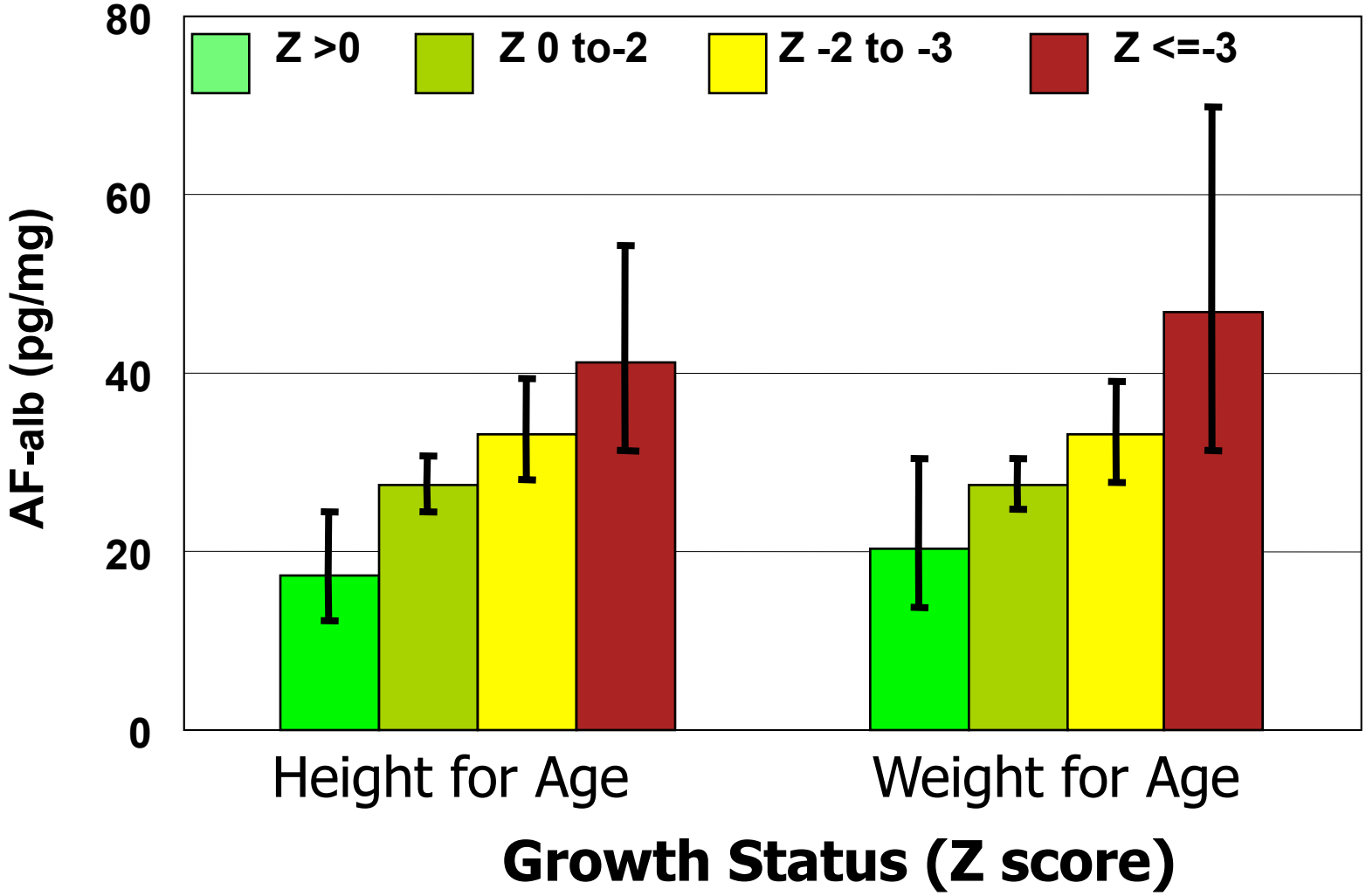
FIGURE 3. A posho (maize flour) mill — Makueni district, Eastern Province, Kenya, 2004

Photo/CDC

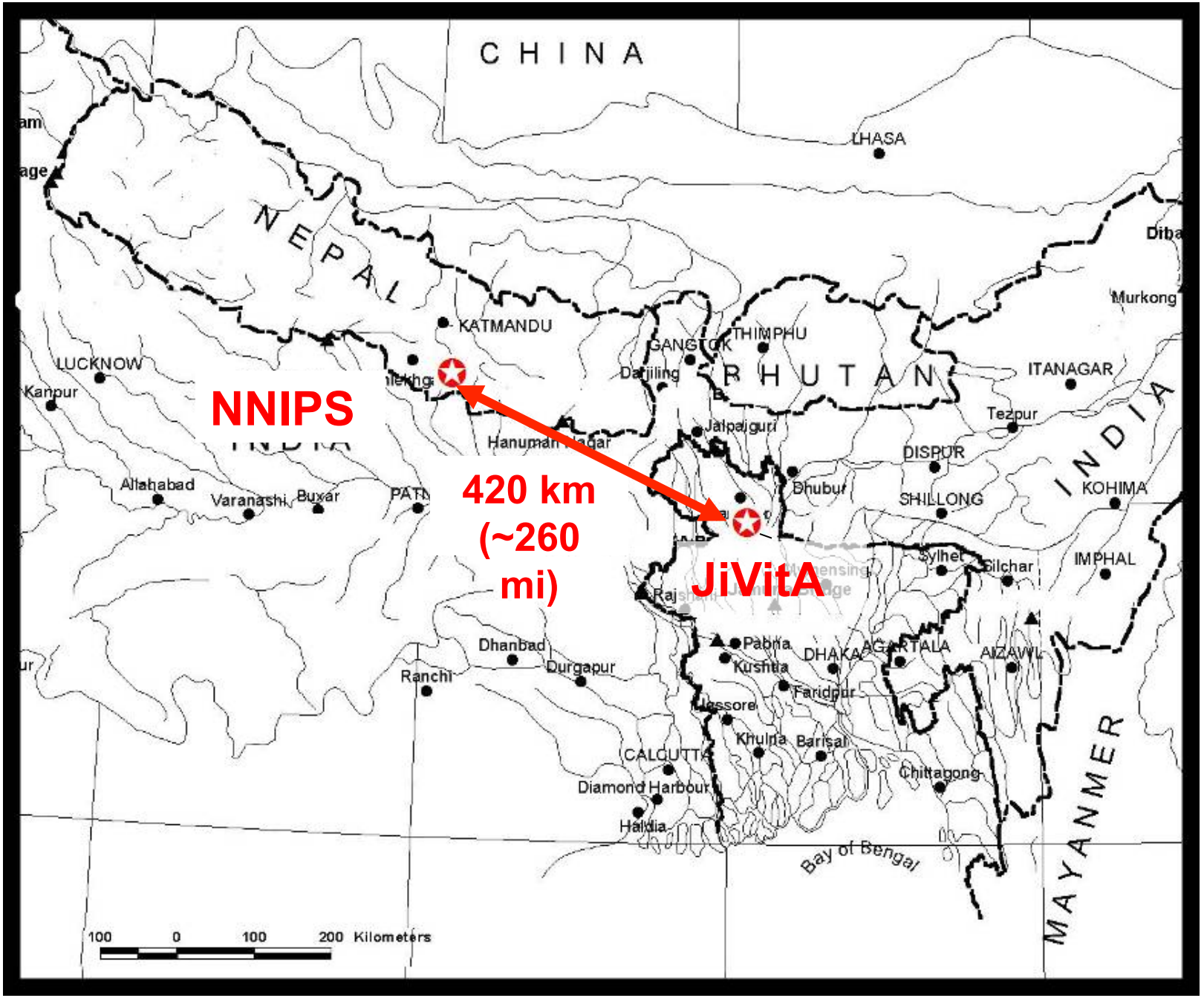
MMRW, 9/3/2004

Aflatoxin and Child Health

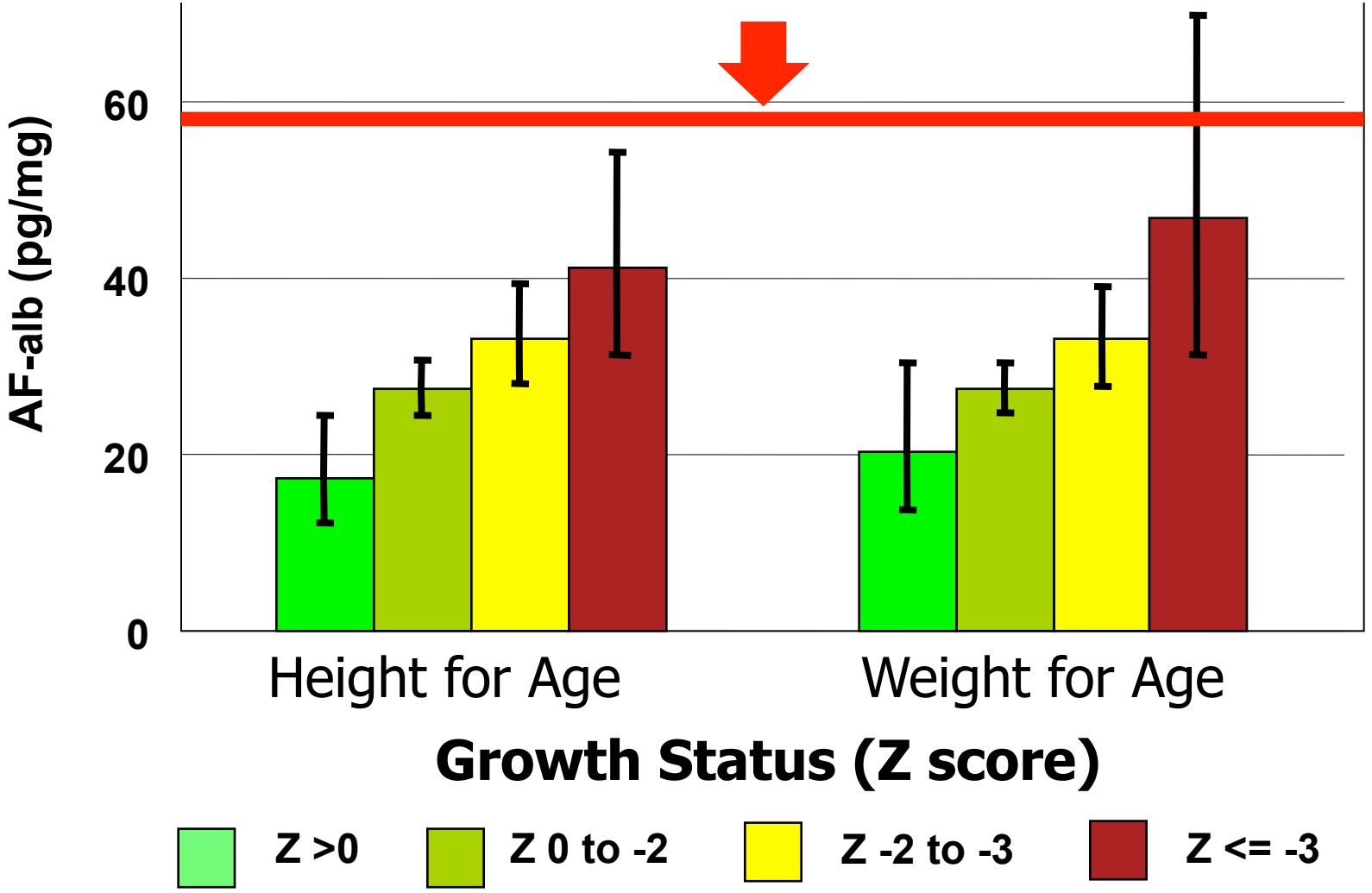
Exposure to Aflatoxin Associated with Reduced Growth in West African Children



BMJ. (2002) 325:20-1

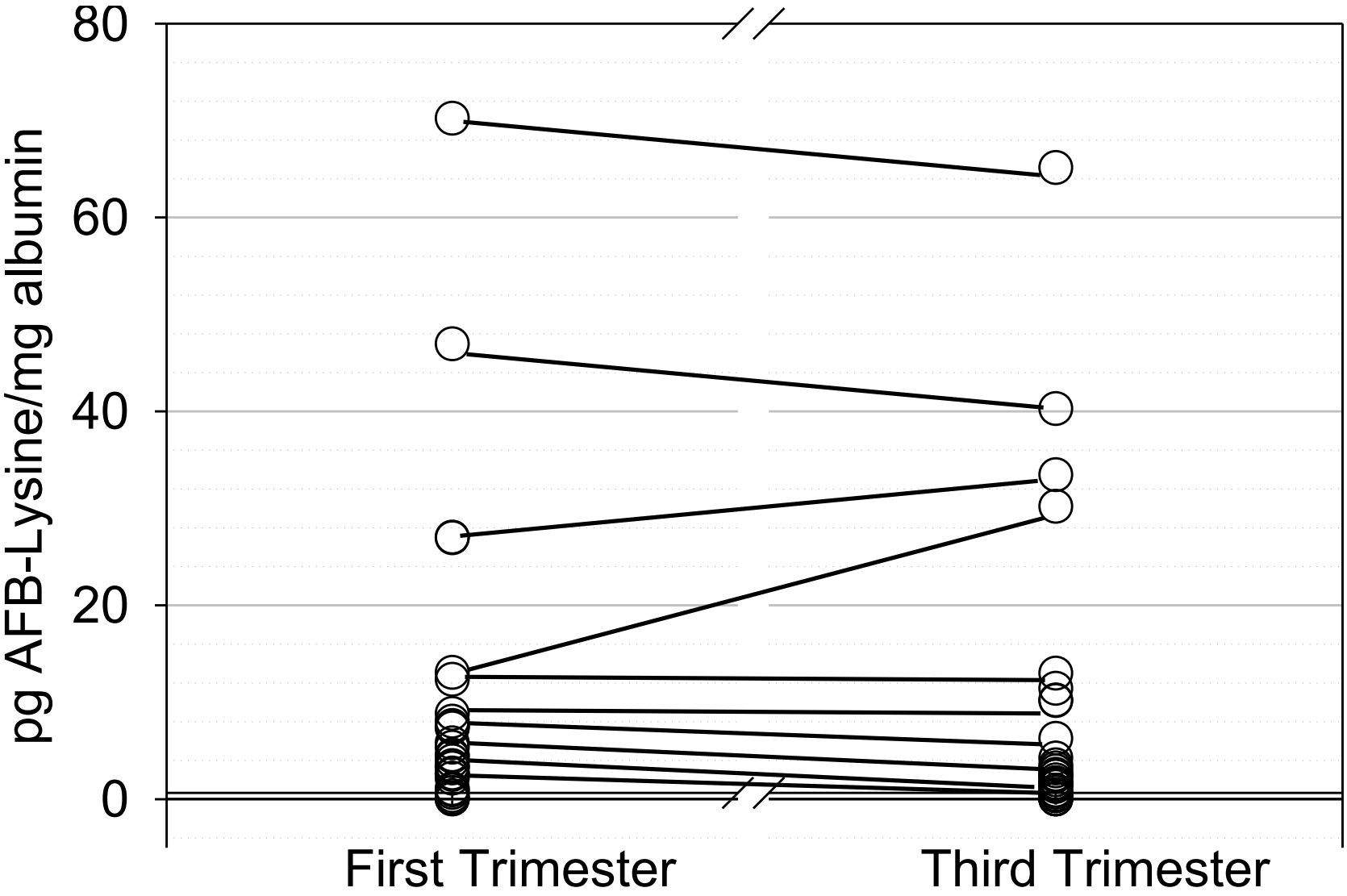

CHINA
LHASA
NEPAL
KATMANDU
THIMPHU
GANGTOK
Darjiling
BHUTAN
ITANAGAR
Murkong
LUCKNOW
Kanpur
NNIPS
Tezpur
Jalpaiguri
Hanuman Nagar
DISPUR
Dhubri
SHILLONG
KOHIMA
INDIA
Allahabad
Varanashi
Buxar
PATN
420 km
(~260
mi)
JiVitA
Sylhet
Silchar
IMPHAL
Dhanbad
Durgapur
Ranchi
Pabna
DHAKA
AGARTALA
AIZAWL
Kushtia
Faridpur
Jessore
Khulna
Barisal
CALCUTTA
Chittagong
Diamond Harbour
Haldia
Bay of Bengal
MAYANMER
100 0 100 200 Kilometers

56.5 pg AFB-lys/mg in 1000 person pool from NNIPS



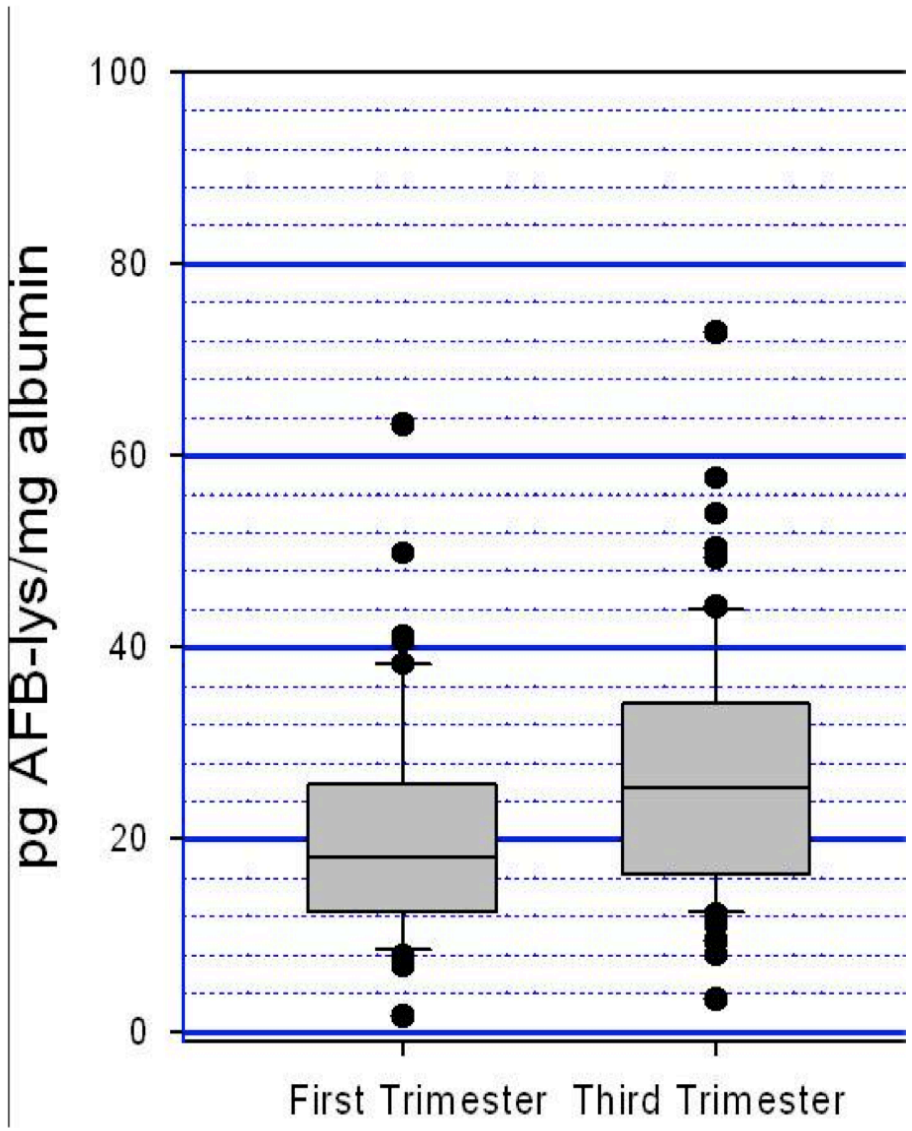
BMJ. (2002) 325:20-1

NNIPS Trial: Tacking of Aflatoxin-lysine Adducts Across First and Third Trimester



Groopman et al, 2013

Bangladesh Studies: First, Third Trimester, Cord Blood and 2 year olds



Groopman et al, 2013

Strategies for Aflatoxin Prevention

PRIMARY

- Reduced aflatoxin consumption:
  - improve food storage
  - biocontrol
  - changes in dietary staples

SECONDARY

- Chemopreventive interventions:
  e.g., oltipraz, broccoli sprouts, chlorophyllin, green tea

Intervention Package in Kindia, Guinea

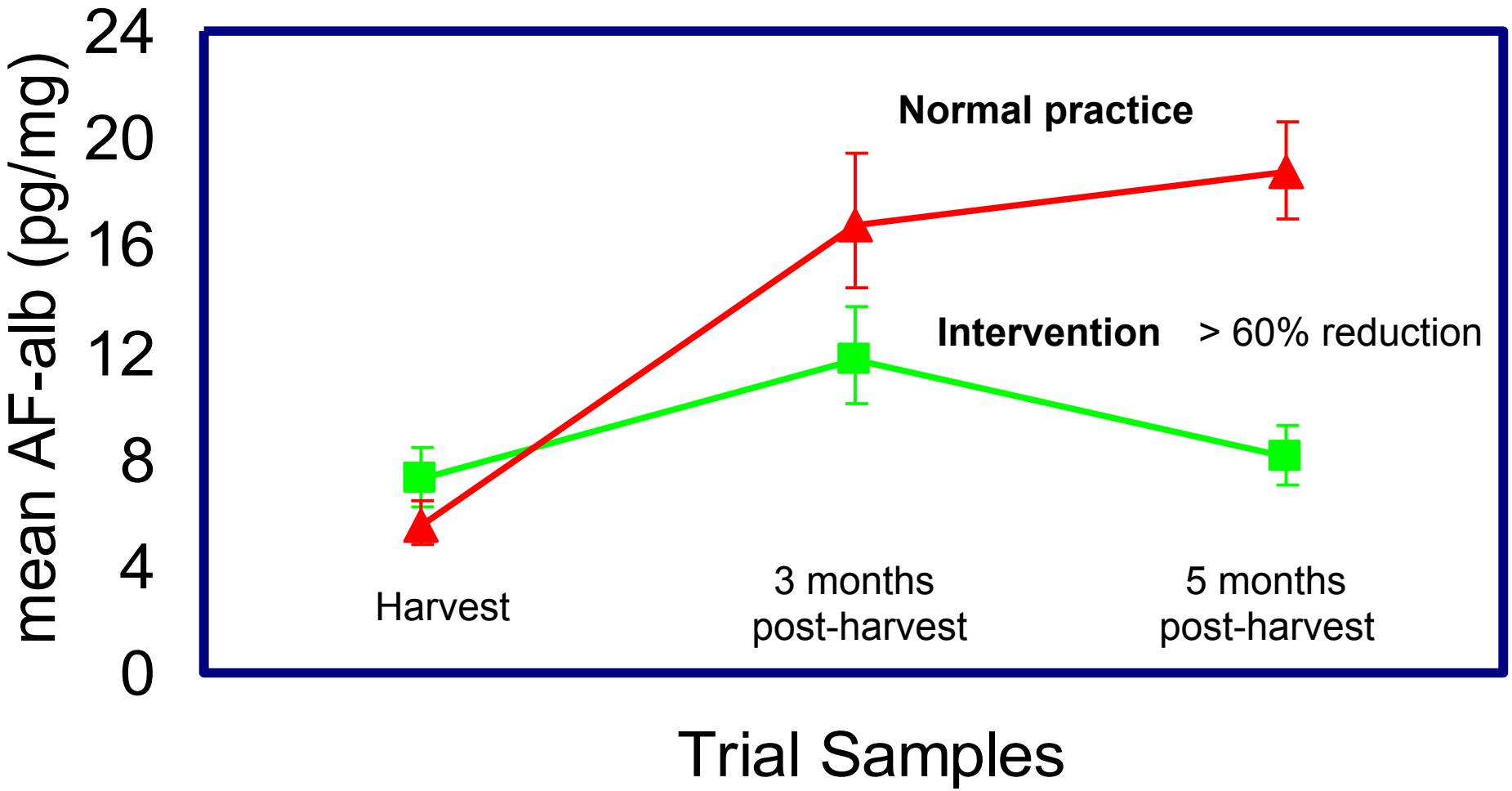
Intervention villages

- **Hand sorting:** *Training in removal of groundnuts that were visibly mouldy or had the shells damaged*
- **Drying on mats:** *Provision of locally produced natural fibre mats for the sun drying process*
- **Sun drying:** *Training in sun drying by shaking the kernels to listen for the free movement of the dried nuts*
- **Storage in natural fibre bags:** *Provision of natural fibre jute bags to replace plastic or other synthetic bags*
- **Wooden pallets:** *Provision of locally made wooden pallets on which to store the bags*
- **Insecticide:** *Provision of locally available insecticide (acetilite) to sprinkle on the floor of the storage facility*

Control villages: *farmers were left to follow their normal post-harvest practices*

Turner et al., (2005) *The Lancet*, **365**, 1950-1956

Levels of Aflatoxin Biomarkers are Reduced in Children in West Africa by Primary Intervention

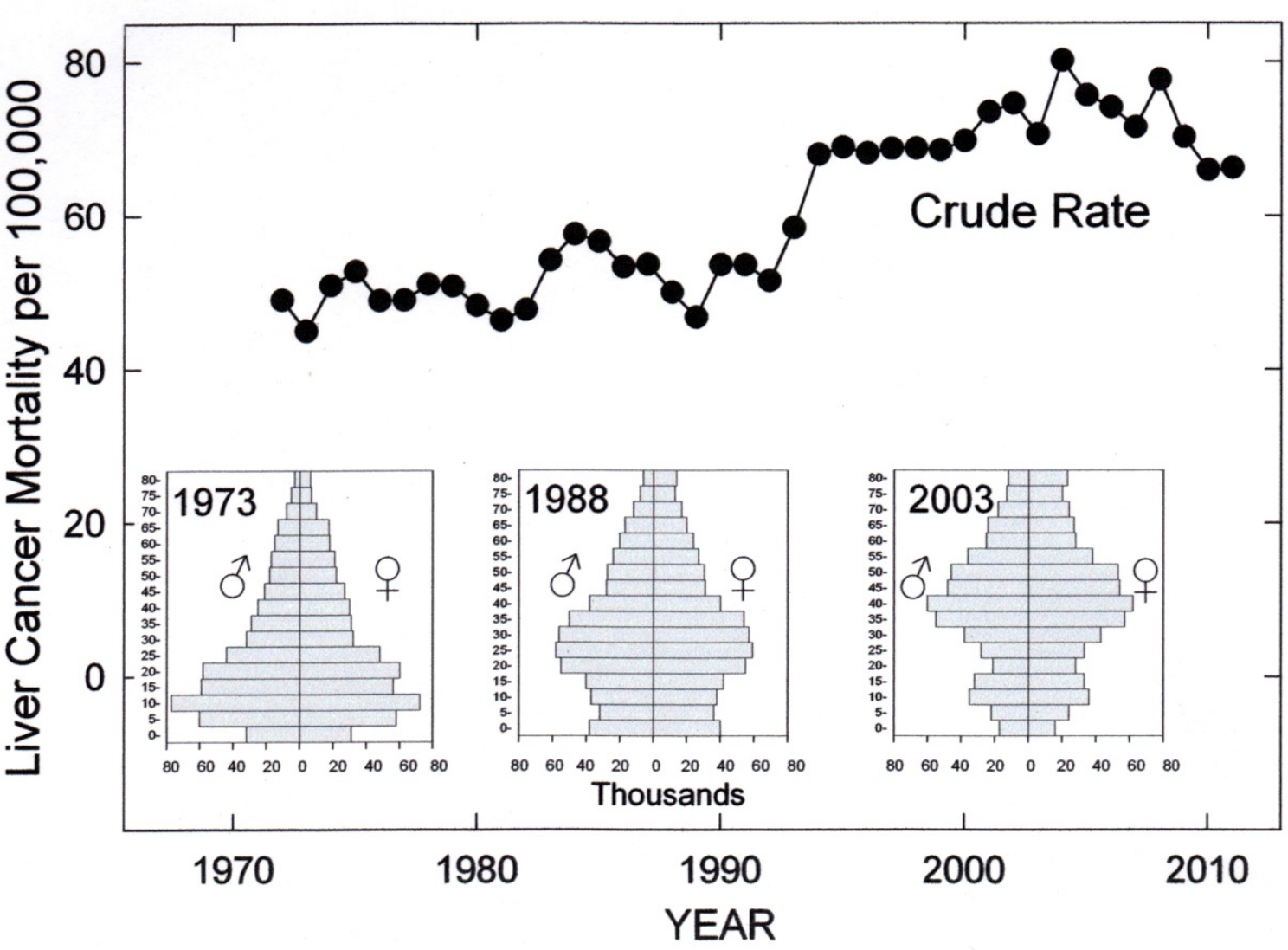


Turner et al., (2005) *The Lancet*, **365**, 1950-1956

Strategies for Aflatoxin Prevention

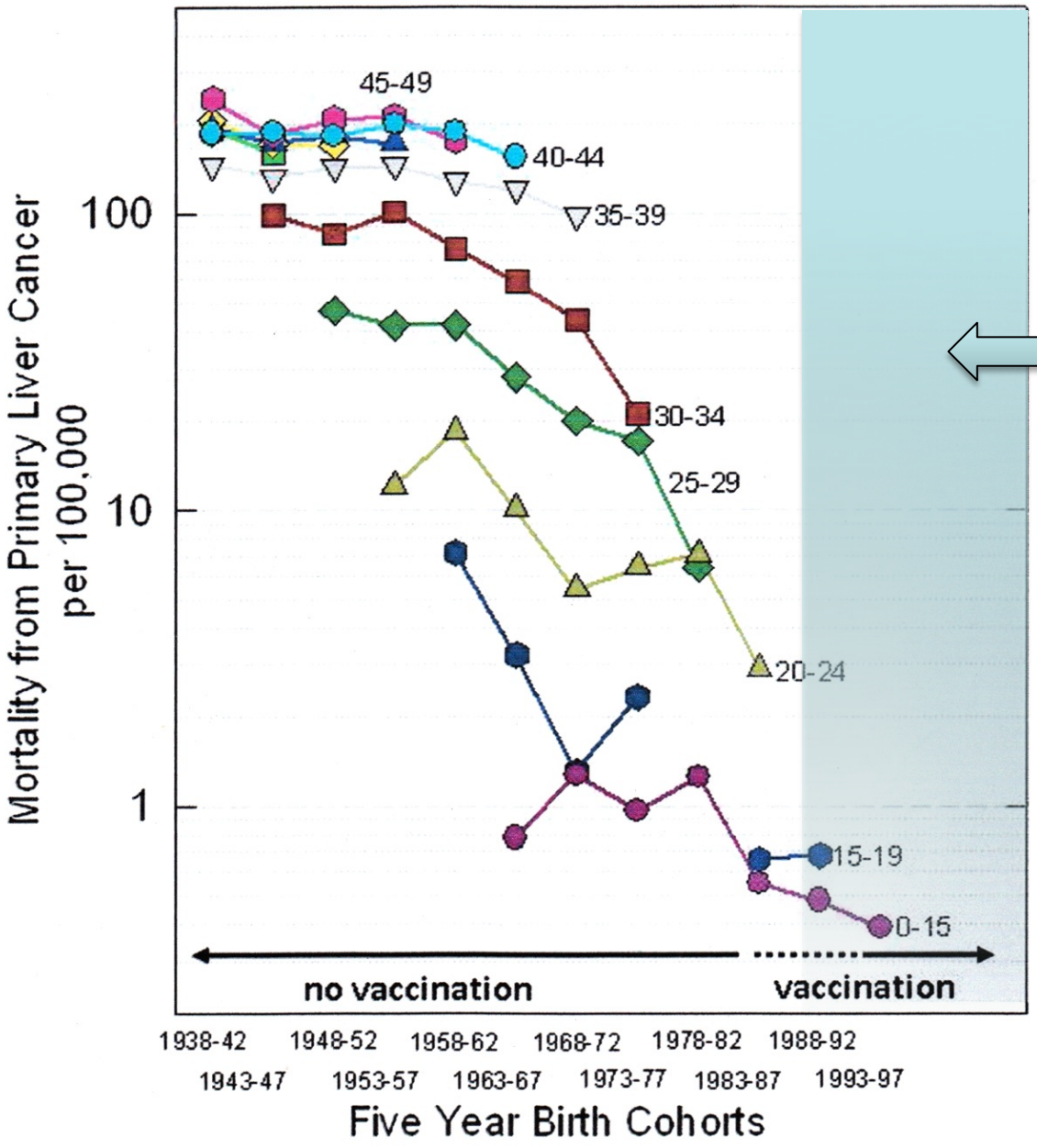
- Does it make a difference in cancer?

Liver Cancer Mortality in Qidong, PRC



Chen et al, 2013

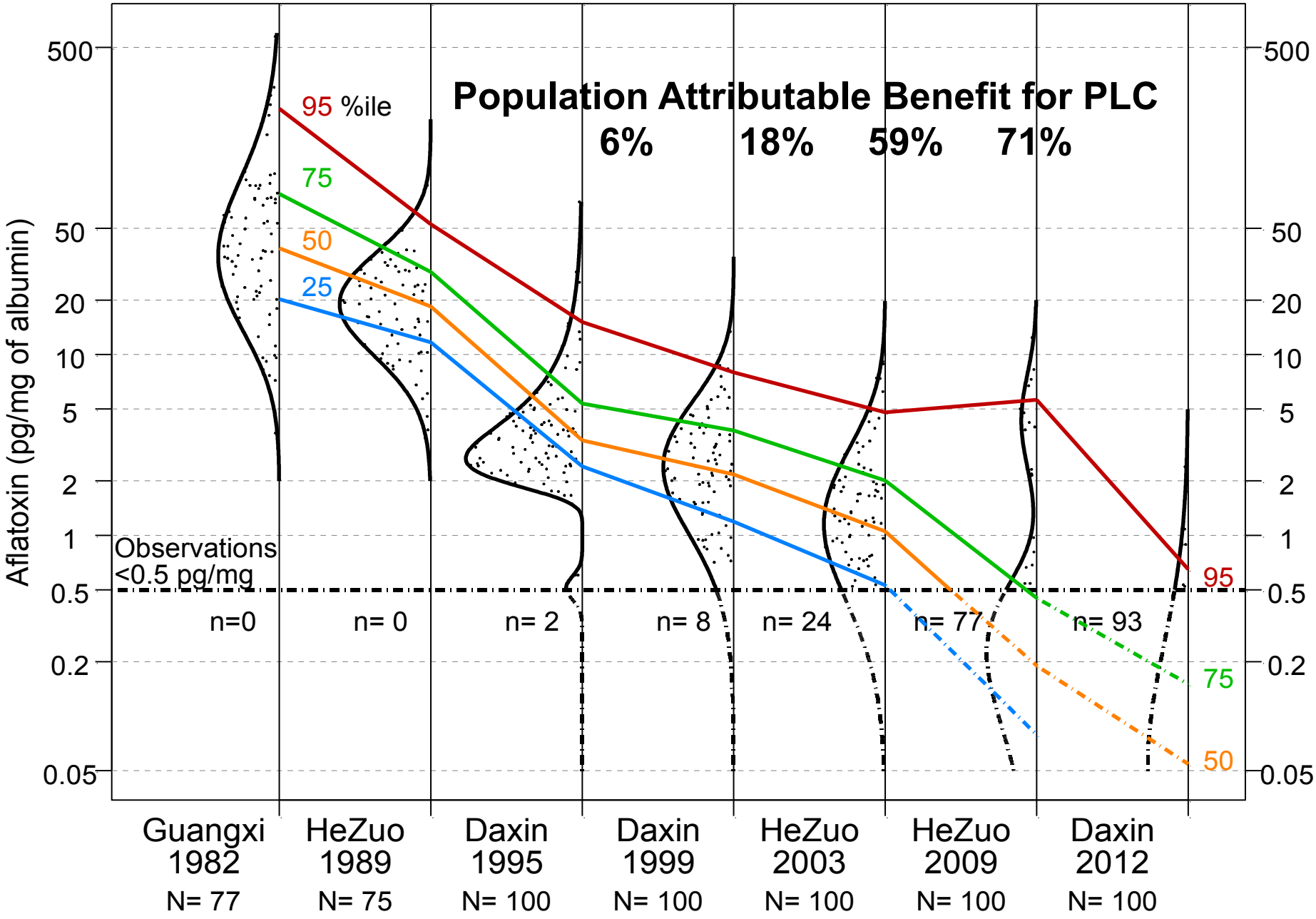
Liver Cancer Mortality in Qidong, PRC By Birth Cohort



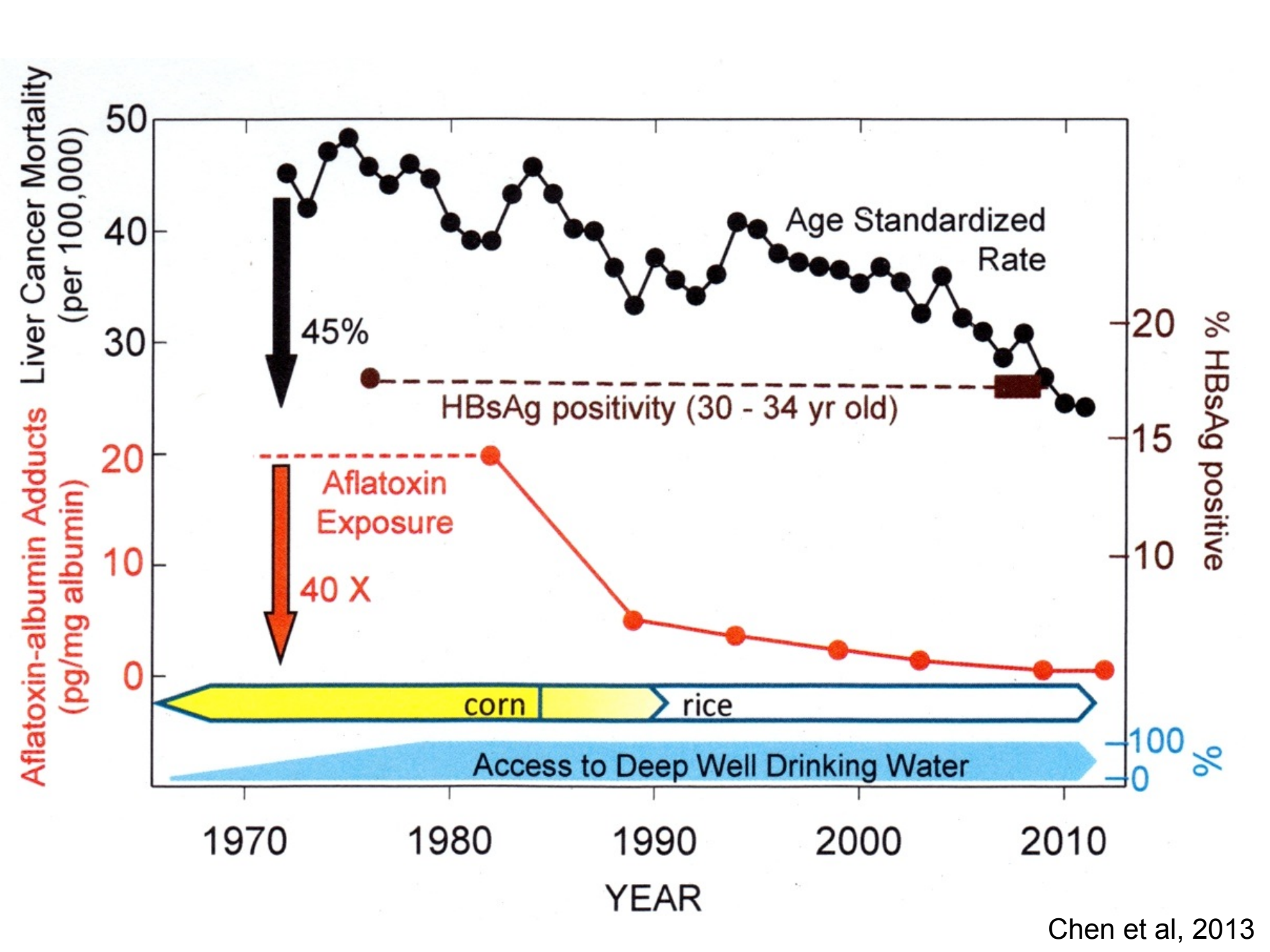
Use of HBV Vaccine

Chen et al, 2013

Aflatoxin-Albumin Adduct Levels

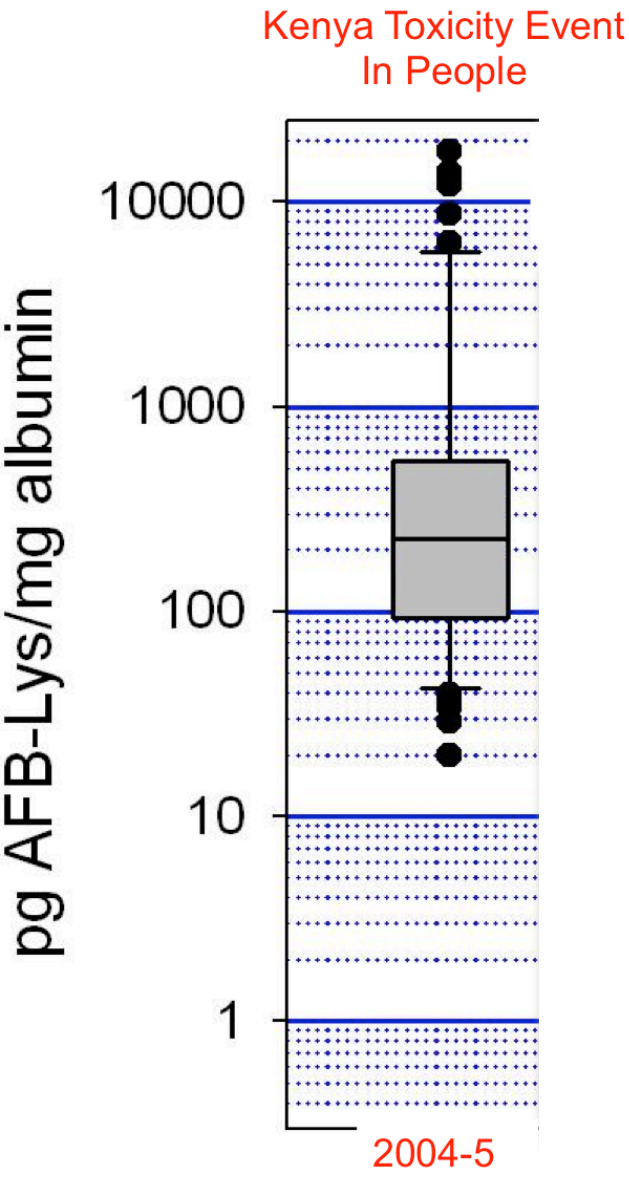


Chen et al, 2013



Chen et al, 2013

Aflatoxin-albumin adduct summary



Groopman et al, 2013