Liver cancer prevention: HBV vaccination and aflatoxin control

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Global Burden of Cancer (2012)

Mortality: 8.2 million deaths worldwide (both sexes)
(2.9 in more developed regions, 5.3 in less developed regions)

Source: GLOBOCAN 2012
http://globocan.iarc.fr
Incidence of HCC worldwide
Prevalence of HBV infection worldwide

Cancers attributable to infections (2008)

570,000 liver cancer cases linked to HBV and HCV

De Martel et al., Lancet Oncol., 2012
**Decreased incidence of HCC following HBV vaccination**

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Person-yrs</th>
<th>No. HCC</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-vaccinated</td>
<td>78 496 404</td>
<td>444</td>
<td>1.00</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>37 709 340</td>
<td>64</td>
<td>0.31 (0.24 – 0.41)</td>
</tr>
</tbody>
</table>

* Age and sex-adjusted relative risk

- Universal HBV vaccination introduced in Taiwan in 1984
- Vaccine coverage rate >90%
- Identified children aged 6-19 years diagnosed with HCC
- Compared HCC in vaccinated versus unvaccinated birth cohorts

* World Health Organization
Gambia Hepatitis Intervention Study – randomized trial of HBV vaccine

• Evaluation of the HBV vaccine to prevent liver disease and liver cancer
• Begun in mid-1980s including ~120,000 children – expected results in next 5-10 years
• Identification of cases through the Gambian National Cancer Registry

• Collaboration between IARC, MRC UK and The Gambian Government
Stepped wedge design for introducing HBV vaccine in the EPI

Vaccination team No

Start of HB Vaccination program

Time (years) Since start of program

Countrywide coverage

Usual EPI vaccines

Usual EPI Vaccines + HB vaccine
# Impact of routine EPI on chronic HBV infection in The Gambia

<table>
<thead>
<tr>
<th>Age</th>
<th>HBsAg-</th>
<th>HBsAg+</th>
<th>Percentage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-4.9</td>
<td>1,918</td>
<td>3</td>
<td>0.2</td>
<td>1,921</td>
</tr>
<tr>
<td>5.0-9.9</td>
<td>1,585</td>
<td>6</td>
<td>0.4</td>
<td>1,591</td>
</tr>
<tr>
<td>10.0-14.9</td>
<td>815</td>
<td>10</td>
<td>1.2</td>
<td>825</td>
</tr>
<tr>
<td>15.0-18.5</td>
<td>271</td>
<td>5</td>
<td>1.8</td>
<td>276</td>
</tr>
<tr>
<td>Total</td>
<td>4,589</td>
<td>24</td>
<td>0.5</td>
<td>4,613</td>
</tr>
</tbody>
</table>

Aflatoxins and human health

Widespread exposure through contamination of staple foods (cereals and nuts):
• Aflatoxicosis
• Liver cancer
• Growth impairment
• Immune modulation?

See Wild and Gong, Carcinogenesis 31, 71-82, 2010
Interaction between HBV infection and aflatoxins in HCC

Relative Risk of hepatocellular carcinoma

- HBV (HBsAg): 7.3
- Aflatoxins (urinary biomarkers): 3.4
- HBV and Aflatoxins: 59.4
- none: 1

adapted from Qian et al, CEBP 1994, following Ross et al., Lancet 1992
Reduced aflatoxin exposure and falling liver cancer rates in China
IARC – scientific evidence review for aflatoxin control

• Summary of evidence:
  • occurrence,
  • adverse effects and
  • available interventions
Optimum strategies for aflatoxin control and reducing liver cancer incidence

**Aflatoxin Intervention**

**Individual Level**
- Dietary Change
- Chemoprevention (e.g. modified metabolism, absorptive clays)

**Commnunity Level**
- Pre-harvest
  - Genetic resistance in crops - natural/GM
  - Biocontrol e.g. atoxigenic strains
  - Agricultural practices (reduce crop stress - irrigation, insecticides, fungicides)
- Post-harvest
  - improved drying, sorting and storage
Biomarkers and intervention studies – aflatoxin in subsistence farms in Guinea

20 Villages (10 intervention, 10 control), 30 subjects per village

- Survey 1: Sept/Oct
- Intermediate Survey 1
- Survey 2: Dec/Jan
- Intermediate Survey 2
- Survey 3: Feb/Mar

Blood sample collection
Groundnut sample collection
Mean blood levels of aflatoxin are reduced in individuals following intervention

IARC Working Group: evaluation of interventions against aflatoxins (June 2014)

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

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<table>
<thead>
<tr>
<th>Approach</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage, sorting and agronomic techniques</td>
<td>1</td>
<td>Ready to implement; requires use of package of measures developed with end-users</td>
</tr>
<tr>
<td>Sorting</td>
<td>1</td>
<td>Acceptable but requires formal training; concern over rejected food use</td>
</tr>
<tr>
<td>Nixtamalization</td>
<td>1</td>
<td>Requires water for washing; not adapted from Latin America to Africa or Asia</td>
</tr>
<tr>
<td>Biocontrol (non-aflatoxigenic strains)</td>
<td>2</td>
<td>Requires evidence of consistency of effect across geography and users; concern over genetic recombination</td>
</tr>
<tr>
<td>Chemoprevention (broccoli, dithiolethiones, green tea)</td>
<td>2</td>
<td>Locally acceptable products needed; possible use in toxic outbreaks</td>
</tr>
<tr>
<td>Adsorbents (clays, chlorophyll)</td>
<td>2</td>
<td>Delivery strategies; possible use in toxic outbreaks; effects on infants, children, pregnant women?</td>
</tr>
<tr>
<td>Genetic resistance</td>
<td>3/4</td>
<td>Large environmental effects on phenotype; resistance is polygenic</td>
</tr>
</tbody>
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