The Global Burden of Foodborne Disease:
Update on the Work of the WHO’s Foodborne Disease Burden Epidemiology Reference Group

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Charge to FERG (2006)
1. Conduct epidemiologic reviews to support estimates of the global burden of foodborne diseases according to age, sex, and region for a defined list of causative agents of microbial, parasitic, and chemical origin
2. Develop causal attribution models to estimate the sources (vectors, pathways) of foodborne diseases
3. Increase awareness and commitment among Member States for the implementation of food safety policy and standards
4. Develop user-friendly tools for burden of foodborne disease studies at country level to strengthen country capacity to conduct burden of foodborne disease assessments
5. Encourage countries to use burden of foodborne disease estimates in cost-effectiveness analyses of prevention, intervention and control measures

WHO Burden of Disease Portfolio

<table>
<thead>
<tr>
<th>Name</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Health Epidemiology Reference Group (CHERG)</td>
<td>Estimate cause-specific morbidity and mortality in children &lt;5 years</td>
</tr>
<tr>
<td>Monitoring and Evaluation Reference Group (MERG)</td>
<td>Develop monitoring and evaluation mechanisms for the Roll Back Malaria Partnership</td>
</tr>
<tr>
<td>Burden of Disease from Environmental Risks</td>
<td>Provide morbidity, mortality, and DALY estimates for selected diseases associated with environmental risks</td>
</tr>
<tr>
<td>WHO Steering and Technical Advisory Group on Neglected Tropical Diseases</td>
<td>Prevent and control NTDs and assess socio-economic impact</td>
</tr>
<tr>
<td>Leptospirosis Burden Epidemiological Reference Group (LERG)</td>
<td>Develop global estimates on Leptospirosis</td>
</tr>
<tr>
<td>Foodborne Disease Burden Epidemiology Reference Group (FERG)</td>
<td>Provide burden of disease estimates to enable policymakers and other stakeholders to set appropriate priorities on area of food safety</td>
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</tbody>
</table>

Primary BoD Metric: Disability-Adjusted Life Year (DALY)

- extends concept of potential years of life lost (YLL) due to premature death to include equivalent years of “healthy” life lost (YLD) due to being in states of poor health or disability
  - YLL + YLD
- YLL: number of deaths at each age multiplied by global standard life expectancy for each age
- YLD: number of incident cases in period X average duration of disease X disability weight
  - disability weight, 0 (perfect health) to 1 (death)
- 3% discounting and non-uniform age weights that give less weight to years lived at young and older ages
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- disability weight, 0 (perfect health) to 1 (death)
- 3% discounting and non-uniform age weights that give less weight to years lived at young and older ages
- burden of disease is the gap between current health status and ideal health. Where everyone lives into old age free of disease and disability

Disability Classes for BoD Analysis

<table>
<thead>
<tr>
<th>Class</th>
<th>Severity Weight</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.00-0.02</td>
<td>Stunting due to malnutrition, schistosomiasis infection</td>
</tr>
<tr>
<td>II</td>
<td>0.02-0.12</td>
<td>Amputated finger, asthma, oedema, mastectomy, severe anemia, stress incontinence</td>
</tr>
<tr>
<td>III</td>
<td>0.12-0.24</td>
<td>Angina, HIV (not AIDS), infertility, alcohol dependence, low vision, rheumatoid arthritis</td>
</tr>
<tr>
<td>IV</td>
<td>0.24-0.36</td>
<td>Amputated arm, congestive heart failure, deafness, Parkinson’s disease, tuberculosis</td>
</tr>
<tr>
<td>V</td>
<td>0.36-0.50</td>
<td>Bipolar affective disorder, mild mental retardation, neurological sequelae of malaria</td>
</tr>
<tr>
<td>VI</td>
<td>0.50-0.70</td>
<td>AIDS (not on ART), Alzheimer’s and other dementias, blindness, Down Syndrome</td>
</tr>
<tr>
<td>VII</td>
<td>0.70-1.00</td>
<td>Active psychosis, severe depression, severe migraine, quadriplegia, terminal stage cancer</td>
</tr>
</tbody>
</table>

Leading Causes of Burden of Disease (DALYs), all ages, 2004

<table>
<thead>
<tr>
<th>Disease or Injury</th>
<th>DALYs (millions)</th>
<th>Percent of total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lower respiratory infections</td>
<td>94.5</td>
<td>6.2</td>
</tr>
<tr>
<td>2. Diarrhoeal diseases</td>
<td>73.9</td>
<td>4.8</td>
</tr>
<tr>
<td>3. Unipolar depressive disorders</td>
<td>65.5</td>
<td>4.3</td>
</tr>
<tr>
<td>4. Ischemic heart disease</td>
<td>62.6</td>
<td>4.1</td>
</tr>
<tr>
<td>5. HIV/AIDS</td>
<td>50.5</td>
<td>3.2</td>
</tr>
<tr>
<td>6. Cerebrovascular disease</td>
<td>48.8</td>
<td>3.1</td>
</tr>
<tr>
<td>7. Prematurity and low-birth weight</td>
<td>48.3</td>
<td>2.9</td>
</tr>
<tr>
<td>8. Birth asphyxia and birth trauma</td>
<td>41.7</td>
<td>2.7</td>
</tr>
<tr>
<td>9. Road traffic accidents</td>
<td>41.2</td>
<td>2.7</td>
</tr>
<tr>
<td>10. Neuronal infections</td>
<td>40.4</td>
<td>2.7</td>
</tr>
<tr>
<td>11. Tuberculosis</td>
<td>34.2</td>
<td>2.2</td>
</tr>
<tr>
<td>12. Malaria</td>
<td>24.9</td>
<td>1.5</td>
</tr>
<tr>
<td>13. COPD</td>
<td>30.2</td>
<td>2.0</td>
</tr>
<tr>
<td>14. Reiter’s arthritis</td>
<td>21.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>


Enteric Task Force
- Bacterial toxins (Bacillus cereus, C. perfringens, S. aureus)
- Brucella sp.
- Campylobacter sp.
- Clostridium botulinum
- Hepatitis A
- E Coli.
  - Enterotoxigenic
  - Enteropathogenic
  - Enterotoxigenic
  - Shiga-toxin producing
- Listeria monocytogenes
- Mycobacterium bovis
- Non cholera vibrio parahemolyticus
- Non cholera vibrio vulnificus
- Vibrio cholera 01/0139
- Norovirus
- Shigella sp.
- Yersinia sp.
- Salmonella sp.
  - Non-typhoidal
  - typhoidal

GBoD 2004 Update: Other Findings
- Years of Life Lost (YLL) 7 times higher in Africa than in high-income countries
- South-East Asia and Africa account for 54% of total BoD, due predominantly to communicable diseases and maternal, perinatal, and nutritional conditions
- Almost 50% of disease burden in low- and middle-income countries now from non-communicable diseases (ischemic HD, stroke)
- Disease burden in children falls almost entirely in low- and middle-income countries (36% of total burden in world)

Early Results: Child Mortality (<5) Due to Diarrheal Diseases in Developing Countries

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Average of diarrhoea-proportional mortality (by alphabetical stratum)</th>
<th>Estimated diarrhoea deaths (thousands)</th>
<th>Uncertainty (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (AFR)</td>
<td>MS D 17.8</td>
<td>402</td>
<td>346-455</td>
</tr>
<tr>
<td></td>
<td>MS E 17.5</td>
<td>385</td>
<td>315-413</td>
</tr>
<tr>
<td>America (AMR)</td>
<td>MS B 13.3</td>
<td>35</td>
<td>30-40</td>
</tr>
<tr>
<td></td>
<td>MS D 14.9</td>
<td>14</td>
<td>12-16</td>
</tr>
<tr>
<td>Eastern Mediterranean (EMR)</td>
<td>MS B 13.4</td>
<td>12</td>
<td>10-14</td>
</tr>
<tr>
<td></td>
<td>MS D 16.9</td>
<td>221</td>
<td>190-250</td>
</tr>
<tr>
<td>South-East Asia (SEAR)</td>
<td>MS B 22.3</td>
<td>44</td>
<td>34-53</td>
</tr>
<tr>
<td></td>
<td>MS D 24.5</td>
<td>651</td>
<td>500-793</td>
</tr>
<tr>
<td>Western Pacific (WPR)</td>
<td>MS B 13.8</td>
<td>105</td>
<td>90-118</td>
</tr>
<tr>
<td>World</td>
<td>18.7 1870</td>
<td>1558-2193</td>
<td></td>
</tr>
</tbody>
</table>

* 78% of all diarrhoea deaths in developing countries are in AFR and SEAR regions

Parasitic Task Force

- Intestinal protozoa (Giardia, E. histolytica, Cryptosporidium)
- Fasliosis
- Alveolar echinococcosis
- Cystic echinococcosis
- Cysticercosis
- Trichinellosis
- Aniskiasis
- Toxoplasmosis
- Clonorchiasis and Opisthorchiasis
- Ascariasis

Early Results: Alveolar Echinococcosis

- Torgerson et al., PLoS NTD 2010;4(6), e272
  - 18,235 incident cases per year (11,900-28,200), 91% in China
  - Combined age and sex-specific incidence with case fatality rate and disability weight for hepatic carcinoma.
  - Estimated DALYs: 666,434 per year (331,000-1.3 million)

Work Initiated on Chemical Contaminants

- Cassava cyanide
  - Acute poisoning, konzo, tropical ataxic neuropathy
- Aflatoxin
  - Acute aflatoxicosis, hepatocellular carcinoma, stunted growth
- Peanut allergen
  - Anaphylaxis/death; oral allergy syndrome; skin, GI, respiratory symptoms
- Dioxin, dioxin-like PCBs
  - Cancer, neurodevelopmental impairment, reduced sperm count
- Lead
  - Cognitive impairment, cardiovascular morbidity
- Cadmium
  - Renal disease

Other Chemical Contaminants Under Consideration

- Methylmercury
- Arsenic
- Organophosphate pesticides
- Seafood toxins (e.g., ciguatera, scombroid, domoic acid, tetrodotoxin, paralytic shellfish poisoning, neurotoxic shellfish poisoning)
- Phytotoxins (e.g., aristolochic acid)
- Manganese
- PBDEs
- Acrylamide
- Melamine

Early Results: Aflatoxin

- From:
  - Prevalence of chronic HBV infection, by WHO region
  - Cancer potency factors (slope of D-R curve) for HBV+ vs HBV-
  - Estimated aflatoxin exposure based on maize and peanut consumption by WHO region

- Estimated worldwide annual incidence of aflatoxin-induced hepatocellular carcinoma (with/without HBV synergism) to be 25,200-155,000 cases (5-28% of all cases globally)

Aflatoxin-related HCC, by WHO Region

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>HCC cases attributable to aflatoxin, HBsAg-</th>
<th>HCC cases attributable to aflatoxin, HBsAg+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2,150-6,300</td>
<td>9,230-50,600</td>
</tr>
<tr>
<td>North America</td>
<td>9</td>
<td>2-5</td>
</tr>
<tr>
<td>Central/ South America</td>
<td>589-2,980</td>
<td>84-2,060</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>446-3,720</td>
<td>341-13,200</td>
</tr>
<tr>
<td>South East Asia</td>
<td>1,740-17,300</td>
<td>1,460-27,600</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>2,710-6,510</td>
<td>6,310-21,200</td>
</tr>
<tr>
<td>Europe</td>
<td>99-184</td>
<td>62-372</td>
</tr>
</tbody>
</table>

Detailed Example of a BoD Analysis for a Chemical: Lead (Fewtrell et al., 2003)

Country/Region Exposure Data Requirements

- geometric mean blood lead level
- standard deviation
- sample size

- Ideally, exposure data derived from a probability sample that is representative of the entire population
- otherwise extrapolate to population for which disease burden to be calculated (e.g., apply weighting factors)

- Sometimes cohort effect “correction factor” needed
  - e.g., adjust for significant changes in population exposure since blood lead data collected (e.g., removal of lead from gasoline)

Criteria for Selecting Key Disease Outcomes

- strength of evidence supporting causal relationship with lead
- availability of quantitative information on association between blood lead and health effect (i.e., dose-response or exposure-risk relationship)
- Outcome is a well-defined disease (i.e., ICD-10 diagnosis), or can be converted into such

Health Outcomes Selected

- IQ points lost (resulting in mild mental retardation) (children)
- Anemia (children, adults)
- Gastrointestinal symptoms (children)
- Increased blood pressure (adults) (resulting in ischemic heart disease, cerebrovascular disease, hypertensive disease, other cardiac diseases)

Exposure-Risk Relationships Used to Quantify Disease Burden

IQ Loss and Mild Mental Retardation (MMR)

- IQ loss not a disease per se, so burden is incurred only when IQ loss results in MMR (i.e., IQ<70)
- To attribute a disease burden to loss of IQ points, calculated number of children who are pushed into MMR range as a result of lead exposure

IQ Loss and MMR: Adjustment Ratio

- background risk of MMR differs in developed and developing regions because distributions of other MMR risk factors differ (e.g., meningitis, pertussis, encephalitis, ascariasis, iodine deficiency, etc.)
- Apply region-specific adjustment ratio:
  \[
  AR = \frac{P_{R} - P_{\text{baseline}}}{P_{\text{MR standard}}} \cdot \frac{P_{\text{MR standard}}}{P_{\text{MR standard}}}
  \]

- \(P_{R}\) = region-specific prevalence of MR from known causes
- \(P_{\text{baseline}}\) = prevalence of MMR from known causes in developed countries
- \(P_{\text{MR standard}}\) = prevalence of MMR according to standard distribution of IQ score

Region*: AfrD AmrA AmrB EurA EurB SearB SearD WprA WprB
AR 2.05 1.00 2.71 1.00 1.53 3.25 2.06 1.00 3.03

*classification depending on child and adult mortality
Foundation for Estimating Lead-Associated CVD Morbidity

relative risks for different forms of CVD for defined increases in blood pressure, by age and sex

Blood Pressure (BP) and Cardiovascular Disease

- blood lead level divided into intervals
- estimate BP increase associated with each blood lead interval (sex-specific)
- population distribution of blood lead level is combined with the relative risk for each BP interval to calculate the impact fraction:

\[
\text{IF} = \frac{\sum (P_i \times RR_i) - 1}{\sum P_i \times RR_i}
\]

where:
- \(\text{IF}\) = impact fraction
- \(P_i\) = proportion of population at exposure interval \(i\)
- \(RR_i\) = RR at exposure interval \(i\), compared to reference level

Estimated Blood Lead Levels, by WHO Region

In 2000, <10% of children had BLL >20, but 99% were in developing countries

Estimation of Incidence Rates, by Region, for Mild Mental Retardation and Increased Systolic Blood Pressure Attributable to Lead Exposure

Lead-Associated DALYs, by WHO Region

Bottom line: MMR accounts for 9.8 million DALYs. CVD diseases 3 millions DALYs; together account for almost 7% of global burden of disease
Limitations

• Uncertainties inherent in data available
  – accuracy of blood lead measurements in sample
  – degree to which sample representative of population as a whole

• Uncertainties associated with method used to adjust exposure data (e.g., cohort effects associated with lead reduction measures)
  – distribution of effect modifiers (e.g., genetics, nutritional status, health status) might differ between populations and so affect risk of disease

• Uncertainties in model parameters (e.g., exposure-response relationships derived from literature)

• Likelihood that some disease burden is associated with outcomes for which no ICD-10 diagnosis

Blood Lead Levels and Performance on End-of-Grade Reading Achievement Test, 2000-2004, NC 4th graders (N=8,600)

Blood Level and ADHD (physician-diagnosed, on meds)

Source Attribution is a Major Problem for FERG: How Much Lead-Associated Morbidity is Food-Related?

Approach 1: Generic Estimation of Daily Lead Absorption
Approach 2: Estimated Dietary Lead Intake Based on WHO Regional Diets and Average Residues from U.S. Total Diet Study (JECFA, 2000)

- Assumption: levels of lead in U.S. foods accurately estimate levels elsewhere.

Approach 3: Estimate Dietary Lead Intake Based on Country-Specific Data (diverse methodologies) (JECFA, 2000)

Sources:
- GEMS/Food database
- Market basket surveys
- National nutrition surveys
- Total diet studies

Problem: Data not available for most developing countries

- Whichever approach, use estimated dietary intake to calculate contribution of foodborne lead to blood lead level (empirically, PK model), by age and region, as an estimate of fraction of disease burden attributable to it.

Future of FERG

- FERG originally designed as a 5-year project (2007-2012)
- Will take longer
- Funding a major issue
  - US CDC, European CDC, RIVM (Netherlands), USDA, governments of UK, Japan, Germany, Ireland, Sri Lanka, as well as in-kind contributions (US FDA)