FROM FARM TO FORK TO PHYSICIAN
Assessing the Long-term Sequelae of Foodborne Illness

September 22, 2011
Barbara Kowalcyk
OBJECTIVES

• Understand the role of long-term sequelae of foodborne disease in developing burden of disease estimates and evidence-based medical guidelines for long-term patient management.

• State the current state of knowledge regarding the long-term health outcomes associated with foodborne disease.

• Explain CFI’s efforts to examine the feasibility of systematically studying the long-term health outcomes associated with foodborne disease.
I collected my figures with a purpose in mind, with the idea that they could be used to argue for change. Of what use are statistics if we do not know what to make of them? What we wanted at the time was not so much an accumulation of facts, as to teach the men who are to govern the country the use of statistical facts.

- Florence Nightingale

UNDERSTANDING THE BURDEN

- Foundation for evidence-based medicine and evidence-informed policy making
- Metrics: morbidity, mortality, severity, duration, disability, quality of life (DALY, QALY, etc)
- Two types of burden: population v. individual
- Estimates inform economic assessments and priority setting
48 million Americans are sickened, 128,000 are hospitalized and 3,000 die each year from food-borne illnesses.


<table>
<thead>
<tr>
<th>Pathogen</th>
<th>QALY Loss</th>
<th>Cost</th>
<th>Illnesses</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Salmonella</td>
<td>16,782</td>
<td>3,309</td>
<td>1,027,561</td>
<td>378</td>
</tr>
<tr>
<td>2 Toxoplasma gondii</td>
<td>10,964</td>
<td>2,973</td>
<td>86,686</td>
<td>327</td>
</tr>
<tr>
<td>3 Campylobacter</td>
<td>13,256</td>
<td>1,747</td>
<td>845,024</td>
<td>76</td>
</tr>
<tr>
<td>4 Listeria monocytogenes</td>
<td>9,651</td>
<td>2,655</td>
<td>1,591</td>
<td>255</td>
</tr>
<tr>
<td>5 Norovirus</td>
<td>5,023</td>
<td>2,002</td>
<td>5,461,731</td>
<td>149</td>
</tr>
<tr>
<td>6 E. coli O157:H7</td>
<td>1,565</td>
<td>272</td>
<td>63,153</td>
<td>20</td>
</tr>
<tr>
<td>7 Clostridium perfringens</td>
<td>875</td>
<td>309</td>
<td>965,958</td>
<td>26</td>
</tr>
<tr>
<td>8 Yersinia enterocolitica</td>
<td>1,415</td>
<td>252</td>
<td>97,656</td>
<td>29</td>
</tr>
<tr>
<td>9 Vibrio vulnificus</td>
<td>557</td>
<td>291</td>
<td>96</td>
<td>36</td>
</tr>
<tr>
<td>10 Shigella</td>
<td>1,415</td>
<td>121</td>
<td>131,254</td>
<td>10</td>
</tr>
</tbody>
</table>

Source: Batz M, Hoffman S, Morris JG. *Ranking the risks: The 10 Pathogen-Food Combinations with the greatest burden on public health.* 2011
TIP OF THE ICEBERG
DATA NEEDED TO ESTIMATE BURDEN

- Quantify acute and long-term outcomes
- Types of outcomes
- Probability of outcomes
- Severity and duration of outcomes
- Develop disease outcome trees by pathogen

Source: Raybourne et al. 2000
LONG-TERM BURDEN

- Many suspect that long-term burden may outweigh acute burden.
- Outcomes vary by pathogen and individual health status.
- An estimated 2% to 3% of foodborne illness cases develop secondary long-term health outcomes.
# Long-Term Health Outcomes

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Sequelea</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Campylobacter</em></td>
<td>GBS, ReA, carditis, cholecystitis, endocarditis, meningitis, pancreatitis, septicemia</td>
</tr>
<tr>
<td><em>E. coli</em> O157:H7</td>
<td>HUS, neurological problems, diabetes, gallstones, hypertension, irritable bowel syndrome, intestinal strictures, pneumonia</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Meningitis, neurological dysfunction, sepsis</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>ReA, aoritis, cholecystitis, colitis, endocarditis, epididymo-orchitis, meningitis, ostemyelitis, pancreatitis, septicemia, splenic abscess</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Mental retardation, visual impairment, central nervous system disease, encephalitis, pancarditis, polymyositis, retinochoroiditis,</td>
</tr>
</tbody>
</table>

LONG-TERM HEALTH OUTCOMES

- Convened group of medical experts to explore 5 pathogen-consequence pairs.
  - Campylobacter
  - Salmonella
  - STEC
  - Listeria monocytogenes
  - Toxoplasma gondii
Approximately 1 out of every 1,000 illnesses will result in Guillain-Barre Syndrome (GBS).

GBS: an autoimmune reaction
- GBS causes acquired paralysis & hospitalization
- Permanent disability varies with age
- 100 GBS patients die each year

*Campylobacter* is the most common trigger
- 40% of 5,500 GBS cases in U.S. each year
Children have highest incidence of STEC infection and at greatest risk for developing HUS.

- ~15% develop Hemolytic Uremic Syndrome (HUS)
- Leading cause of acute kidney failure in children under age 5 in U.S.
- Most recover but consequences can be very serious:
  - Renal sequelae
  - Hypertension
  - Diabetes
  - Cardiovascular disease
- 3% - 5% of die.
LISTERIA HEALTH OUTCOMES

- Infants with acute listeriosis
  - 80% recover
  - 20% have long-term health outcomes
    - 20% mild disability & often need education assistance
    - 60% moderate to severe disability
    - 20% total impairment with life-long residential care

- Adult cases in Netherlands study
  - Acute illness seizures, cardio-respiratory failure
  - 60% recover, 40% die or seriously disabled
SALMONELLA & REACTIVE ARTHRITIS

- Leading predictor for reactive arthritis (ReA).
- ReA causes painful and swollen joints and can greatly affect quality of life.
- Rates vary from 2.3% to 15%.
- Raybourne et al.
  - 40% recover
  - 60% develop progressive or recurrent arthritis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percent with Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>15</td>
</tr>
<tr>
<td>Yersinia</td>
<td>14.3</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>12.7</td>
</tr>
<tr>
<td>Shigella</td>
<td>9.7</td>
</tr>
<tr>
<td>E. Coli O157:H7</td>
<td>8.9</td>
</tr>
</tbody>
</table>

TOXOPLASMA GONDII

- Acute toxoplasmosis, 50% foodborne
  - 112,500 illnesses, 2,500 hospitalizations, 375 deaths
- Newborn health impairments by age
  - 45% impaired in 1st year
  - 64% impaired by 2nd year
  - 80% impaired by 17th year
    - 33% have severe mental retardation
    - 17% moderate mental retardation
    - 8% blind in both eyes
    - 53% moderate visual impairment
CONCLUSIONS

- Most foodborne pathogens have both acute illness outcomes & long-term outcomes.
- Few guidelines for medical care of long-term outcomes.
- Need follow-up studies to assess the connections between acute foodborne illness & long-term outcomes.
- Population-based studies, improved public health surveillance, and increased data sharing to improve knowledge.
- Long-term health outcome studies will help prioritize foodborne pathogen control goals.
FILLING IN THE GAPS

- Goal is to examine the feasibility (and benefit) of systematically studying the long-term health effects of foodborne illness.
- Received $200,000 in FY2010 through Rep. Rosa DeLauro (D-CT).
- Administered by FDA and overseen by external Steering Committee.
- Outcome is scientific white paper and peer-reviewed publications.
HOW TO IMPROVE OUR KNOWLEDGE?

1. Focused research studies
   - Better for addressing specific questions

2. Registries
   - Better for identifying /detecting problems
   - Very expensive!

3. Pre-existing databases
   - Inexpensive but may not be fit for purpose
IRRITABLE BOWEL SYNDROME

- Chronic gastrointestinal disorder with no structural cause
- Characterized by episodic abdominal pain and altered bowel habits
- Affects ~ 12% of global population; 10% to 20% of Western populations
- Causes significant morbidity, places substantial burden on healthcare systems, greatly affects quality of life
  - Accounts for 2.4 to 3.5 million physician visits in U.S.
- Etiology, pathogenesis, prognosis not well understood
- Acute gastroenteritis (GE) can increase risk of IBS.
STUDY DESIGN

• Prospective cohort study in Dutch population

• Primary Care Network Utrecht (PCNU)
  – Routine primary care data on cohort of patients
  – 38 general practitioners in 6 primary care centers
  – Approximately 60,000 patients consult annually
  – ICPC coded diagnosis, ATC coded prescriptions/referrals entered into centralized database
Hypothesis

IBS is frequent long-term sequelae of GE in Netherlands.

Aim 1: Determine annual incidence of GE consultations in PCNU by age and sex.

Aim 2: Estimate relative risk of IBS one year post-GE in patients compared to unexposed individuals.

Aim 3: Identify risk factors associated with IBS in patients with history of GE.
## Exposures

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE Confirmed</td>
<td>Gastrointestinal infection (D70)</td>
</tr>
<tr>
<td>GE Presumed</td>
<td>Gastrointestinal infection (D70), Gastroenteritis presumed infection (D73), Diarrhea (D11)</td>
</tr>
<tr>
<td>GE Symptomatic</td>
<td>Gastrointestinal infection (D70), Gastroenteritis presumed infection (D73), Diarrhea (D11), Nausea (D09), Vomiting (D10)</td>
</tr>
<tr>
<td>GE Broad</td>
<td>Gastrointestinal infection (D70), Gastroenteritis presumed infection (D73), Diarrhea (D11), Nausea (D09), Vomiting (D10), Abdominal pain (D06), Flatulence/gas/belching (D08)</td>
</tr>
</tbody>
</table>

## Outcomes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome (D93)</td>
</tr>
<tr>
<td>FBD</td>
<td>Irritable bowel syndrome (D93), Diverticular disease (D92), Chronic enterisitis/ulcerative colitis (D94)</td>
</tr>
</tbody>
</table>
# RESULTS - RELATIVE RISK OF IBS AND FBD

<table>
<thead>
<tr>
<th></th>
<th>FBD Relative Risk (95% CI)</th>
<th>IBS Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE Confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/132 (0%)</td>
<td></td>
<td>0/132 (0%)</td>
</tr>
<tr>
<td>9/137 (6.6%)</td>
<td></td>
<td>6/137 (4.4%)</td>
</tr>
<tr>
<td><strong>18.31 (1.08, 311.5)</strong></td>
<td><strong>12.53 (0.71, 220.23)</strong></td>
<td></td>
</tr>
<tr>
<td>GE Presumed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/2386 (0.5%)</td>
<td></td>
<td>9/2386 (0.4%)</td>
</tr>
<tr>
<td>83/2424 (3.4%)</td>
<td></td>
<td>66/2464 (2.7%)</td>
</tr>
<tr>
<td><strong>6.18 (3.45, 11.06)</strong></td>
<td><strong>7.10 (3.55, 14.22)</strong></td>
<td></td>
</tr>
<tr>
<td>GE Symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/3013 (0.5%)</td>
<td></td>
<td>10/3013 (0.3%)</td>
</tr>
<tr>
<td>102/3128 (3.3%)</td>
<td></td>
<td>83/3128 (2.7%)</td>
</tr>
<tr>
<td><strong>6.55 (3.82, 11.24)</strong></td>
<td><strong>7.99 (4.16, 15.38)</strong></td>
<td></td>
</tr>
<tr>
<td>GE Broad</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/5967 (0/5%)</td>
<td></td>
<td>20/5967 (0.3%)</td>
</tr>
<tr>
<td>252/6173 (4.1%)</td>
<td></td>
<td>201/6173 (3.3%)</td>
</tr>
<tr>
<td><strong>8.40 (5.73, 12.32)</strong></td>
<td><strong>9.71 (6.14, 15.36)</strong></td>
<td></td>
</tr>
</tbody>
</table>
LIMITATIONS

• PCNU patients may not be representative of entire Dutch population.
• Many GE patients do not seek medical care.
• Healthcare seeking behaviors may be related to severity of disease.
• Criteria used to diagnose GE and IBS can greatly impact results.
• Due to lack of stool studies, cannot verify cause of GE.
• Absence of data on pre-morbid bowel habits precludes identifying undiagnosed IBS.
• Limited amount of electronic information
HOW TO IMPROVE OUR KNOWLEDGE?

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FRAMEWORK FOR ASSESSING FEASIBILITY

1. Evaluation of stated purpose
2. Review of function, duration and scope
3. Consideration of existing alternative data sources
4. Assessment of practical feasibility
5. Likelihood of sufficient start-up and long-term funding
6. Evaluation of cost-effectiveness

EVALUATION OF STATED PURPOSE

1. How will the data be used?
2. What actions will be taken based on data?
3. How will it impact public health?
   - Reduce morbidity and/or mortality?
   - Facilitate delivery of health services?
   - Provide contribution to health research?
4. How will data be used to make policy decisions?
5. Would improved data be useful in risk management or for other purposes?
1. How do we prioritize information needs on LTHO?
   - Should all foodborne illnesses be included?
   - What is operational definition for foodborne illness?
   - Which long-term sequela should be included?
     What is operational definition for sequela?

2. How long should patients be followed? How often should they be contacted?

3. How should information be collected?

4. Are there existing systems that could be leveraged?

5. Are there lessons that can be learned from existing models and international data collection?
PRACTICAL FEASIBILITY

1. Case ascertainment – how do we identify people to be registered?

2. Compliance – do health professionals perceive this as important? Will they be responsive?

3. Timeliness – can data be collected and processed quickly enough to be useful?

4. Expense – does the expense make it impractical?

5. Measurement – do we have reliable and valid measures of crucial outcomes?
FUNDING AND COST-EFFECTIVENESS

- Requires long-term commitment
- May take years to realize benefits
- Significant start-up and maintenance costs
- What are the costs? How will it be funded?
- Do the potential benefits outweigh the costs?
- How do we assess the benefits?
DEVELOPMENT CONSIDERATIONS

1. Implementation – identify and resolve problems early!
2. Adequate documentation to ensure quality and efficiency
3. Quality control procedures – ensure completeness, validity, timeliness
4. Case definition/ascertainment procedures – inclusion/exclusion criteria
5. Data elements – what data should be recorded?
6. Data collection/processing procedures
7. Data access policy – who should have access?
8. Dissemination of findings
FUTURE DIRECTIONS

• Systematic literature reviews of long-term sequelae
  – *Campylobacter*
  – *Salmonella*
  – *Listeria monocytogenes*
  – Shiga-toxin producing *E. coli* (STEC)
• Workshop on disease burden and long-term sequelae
• Peer-reviewed publications and scientific white paper
• Targeted pilot project to assess long-term sequelae
ACKNOWLEDGEMENTS

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CFI Team
Tanya Roberts          Evan Henke
Pat Buck              Elizabeth Allen
Jayne Murdock         Rob Herrick
Patti Waller          Elizabeth Kopras

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Richard Siegler       Jim Hadler
Thank You!

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