Risk Factors for a Bleeding Illness during a Reported Outbreak: Western Uganda, Sep – Oct 2015

Steven Ndugwa Kabwama, BSc FST, MSc PH Fellow, Cohort 2015
Mysterious fatal disease alert

- **17 Sept 2015**: Buliisa and Hoima District Health Offices reported unexplained illness
- **Symptoms**
  - Vomiting blood (hematemesis)
  - Bloody diarrhea
  - Fever
- **By 24 Sept**: 4 deaths reported in Butiaba Sub-county
- **VHF suspected**
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda
Objectives

- Establish diagnosis
- Verify existence of outbreak
- Identify risk factors for bleeding illness
- Inform control measures
Onset of bloody diarrhea or bloody vomiting in a resident of Hoima or Buliisa Districts between 1 Aug and October 2015
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda

Case finding

- Review of medical records
- Discussion with doctors
- Community case finding assisted by Village Health Team members (VHT)
Investigations to establish cause of bleeding

- PCR for VHF
- Stool culture
- Ultrasound imaging
- Liver function tests
Ultrasonographic findings non-specific

- Advanced micro-nodular liver cirrhosis, splenomegaly
- Indication of gastric wall inflammation
Liver function tests suggested liver disease

- Patient X: (H) AST/GOT, (H) ALP, (L) CHOL, (L) PROT
- Patient Y: (H) BIL, (H) AST, (H) ALT
- Patient Z: (H) ALP, (L) CHOL, (L) UREA
Stool analysis

- Microscopy
  - Schistosoma ova (1/3)

- Culture
  - No significant bacterial growth (0/2)
VHF ruled out

- Ebola, Marburg, Crimean-Congo, Rift Valley Fever all ruled out by molecular testing
Most patients had vomiting and abdominal pain

- Vomiting
- Abdominal pain
- Diarrhea
- Fever
- Bloody vomiting
- Bloody diarrhea

Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda
### Attack rate 3 times higher in Buliisa District

<table>
<thead>
<tr>
<th>District</th>
<th>n</th>
<th>Population</th>
<th>AR/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoima</td>
<td>30</td>
<td>573903</td>
<td>5.2</td>
</tr>
<tr>
<td>Buliisa</td>
<td>16</td>
<td>104934</td>
<td>15</td>
</tr>
</tbody>
</table>
### Attack rate by sub-county

<table>
<thead>
<tr>
<th>District</th>
<th>Sub-county</th>
<th>n</th>
<th>Population</th>
<th>AR/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buliisa</td>
<td>Buliisa Town</td>
<td>3</td>
<td>3768</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Council</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butiaba</td>
<td></td>
<td>7</td>
<td>29181</td>
<td>24</td>
</tr>
<tr>
<td>Hoima</td>
<td>Buhimba</td>
<td>2</td>
<td>39039</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Hoima Municipality</td>
<td>4</td>
<td>100625</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Buhaguzi</td>
<td>2</td>
<td>264163</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda
Epidemic curve of 56 cases over 4 months

Active case finding and community mobilization

Date of Onset/ Admission

Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda
# of cases recorded at Hoima Regional Referral Hospital by months, 2014-2015
No persons <15 years were affected

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>Population</th>
<th>AR/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>0</td>
<td>109741</td>
<td>0</td>
</tr>
<tr>
<td>15-24</td>
<td>7</td>
<td>97046</td>
<td>7.2</td>
</tr>
<tr>
<td>18-30</td>
<td>12</td>
<td>113144</td>
<td>11</td>
</tr>
<tr>
<td>&gt;60</td>
<td>2</td>
<td>24604</td>
<td>8.1</td>
</tr>
</tbody>
</table>
Males in Buliisa District had highest attack rate

<table>
<thead>
<tr>
<th>District</th>
<th>Gender</th>
<th>n</th>
<th>Population</th>
<th>AR/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoima</td>
<td>Female</td>
<td>19</td>
<td>287198</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>11</td>
<td>286705</td>
<td>3.8</td>
</tr>
<tr>
<td>Buliisa</td>
<td>Female</td>
<td>4</td>
<td>53361</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>12</td>
<td>51573</td>
<td>23</td>
</tr>
</tbody>
</table>
Those who had/did not have bloody diarrhea were different diseases

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Vomited blood &amp; had bloody diarrhoea n (%)</th>
<th>Vomited blood only n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (self-reported)</td>
<td>23 (82)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>11 (33)</td>
<td>12 (67)</td>
</tr>
</tbody>
</table>
Potential associations with illness

- Schistosomiasis
- Liver diseases
- Alcohol use
- Use of NSAIDs
- Ulcer diseases
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda

Case-control study

- **Cases**: Persons who had vomited blood (whether or not they had bloody diarrhea)
- **Controls**: Neighborhood controls, no history of hematemesis matched by sex and age (±10)
- **Case/Control ratio**: 1:4
### Pre-existing conditions associated with illness

<table>
<thead>
<tr>
<th>Pre-existing conditions</th>
<th>Number</th>
<th>% exposed</th>
<th>OR_{M-H} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Liver disease</td>
<td>5/12</td>
<td>0/77</td>
<td>42</td>
</tr>
<tr>
<td>Ulcers</td>
<td>10/14</td>
<td>28/81</td>
<td>71</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>7/12</td>
<td>25/79</td>
<td>58</td>
</tr>
</tbody>
</table>
### Substance use prior to onset associated with illness

<table>
<thead>
<tr>
<th>Substance/drug use before onset</th>
<th>Number</th>
<th>% exposed</th>
<th>OR_{M-H} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases: Controls</td>
<td>Cases: Controls</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3/11: 11/81</td>
<td>27: 14</td>
<td><strong>6.0 (1.0-36)</strong></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2/11: 7/81</td>
<td>18: 8.6</td>
<td><strong>2.3 (0.35-16)</strong></td>
</tr>
<tr>
<td>Alcohol</td>
<td>2/3: 20/37</td>
<td>67: 55</td>
<td><strong>1.8 (0.15-22)</strong></td>
</tr>
</tbody>
</table>
Limitations of investigation

- Self assessment of pre-existing conditions
- Recall bias
Conclusions

- Risk factors for bleeding
  - Liver disease (probably) due to alcohol use
  - Ulcer
  - Use of NSAIDs
- Viral Hemorrhagic Fevers ruled out
- Increase in cases likely due to increased awareness and reporting
Recommendations

- Control of alcohol use
- Warning on NSAID use in persons pre-disposing conditions (e.g. liver disease, schistosomiasis, ulcer)
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda

Acknowledgements

- US CDC
- MakSPH
- Ministry of Health
- PHFP
- Hoima Health Center Staff
- WHO
- UVRI
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda
Establishing diagnosis of disease

- Case definition – bloody diarrhea and hematemesis
- Case finding
  - Health Centers
- Lab investigation
Hypothesis generation

- Descriptive analysis of data
- Discussions with doctors
- Discussions with Village Health Team members (VHTs)
- Interviews of case-patients or (if case-persons deceased) family members/friends
### LFTs for patients X and Z

#### Patient X

<table>
<thead>
<tr>
<th>Test</th>
<th>Result (Ratio)</th>
<th>Unit</th>
<th>Expected Value</th>
<th>Alarm</th>
</tr>
</thead>
<tbody>
<tr>
<td>UREA</td>
<td>4.9</td>
<td>mmol/L</td>
<td>(2.7–6.4)</td>
<td></td>
</tr>
<tr>
<td>CREATININE</td>
<td>87</td>
<td>umol/L</td>
<td>(44–106)</td>
<td></td>
</tr>
<tr>
<td>ALT/GPT</td>
<td>21.7</td>
<td>U/L</td>
<td>(0–40)</td>
<td></td>
</tr>
<tr>
<td>AST/GOT</td>
<td>48.3 H</td>
<td>U/L</td>
<td>(0–40)</td>
<td></td>
</tr>
<tr>
<td>ALKALINE PHO</td>
<td>184 H</td>
<td>U/L</td>
<td>(40–129)</td>
<td></td>
</tr>
<tr>
<td>BILIRUBIN DI</td>
<td>1.4</td>
<td>umol/L</td>
<td>(0.0–3.4)</td>
<td></td>
</tr>
<tr>
<td>CHOLESTEROL</td>
<td>3.08 L</td>
<td>mmol/L</td>
<td>(3.7–5.7)</td>
<td></td>
</tr>
<tr>
<td>TOTAL PROTEIN</td>
<td>60.6 L</td>
<td>g/L</td>
<td>(63–83)</td>
<td></td>
</tr>
<tr>
<td>BILIRUBIN TO</td>
<td>6.5</td>
<td>umol/L</td>
<td>(0.0–17.0)</td>
<td></td>
</tr>
</tbody>
</table>

#### Patient Z

<table>
<thead>
<tr>
<th>Test</th>
<th>Result (Ratio)</th>
<th>Unit</th>
<th>Expected Value</th>
<th>Alarm</th>
</tr>
</thead>
<tbody>
<tr>
<td>UREA</td>
<td>1.9 L</td>
<td>mmol/L</td>
<td>(2.7–6.4)</td>
<td></td>
</tr>
<tr>
<td>CREATININE</td>
<td>70</td>
<td>umol/L</td>
<td>(44–106)</td>
<td></td>
</tr>
<tr>
<td>ALT/GPT</td>
<td>14.0</td>
<td>U/L</td>
<td>(0–40)</td>
<td></td>
</tr>
<tr>
<td>AST/GOT</td>
<td>20.6</td>
<td>U/L</td>
<td>(0–40)</td>
<td></td>
</tr>
<tr>
<td>ALKALINE PHO</td>
<td>165 H</td>
<td>U/L</td>
<td>(40–129)</td>
<td></td>
</tr>
<tr>
<td>BILIRUBIN DI</td>
<td>0.8</td>
<td>umol/L</td>
<td>(0.0–3.4)</td>
<td></td>
</tr>
<tr>
<td>CHOLESTEROL</td>
<td>1.68 L</td>
<td>mmol/L</td>
<td>(3.7–5.7)</td>
<td></td>
</tr>
<tr>
<td>TOTAL PROTEIN</td>
<td>77.9</td>
<td>g/L</td>
<td>(63–83)</td>
<td></td>
</tr>
<tr>
<td>BILIRUBIN TO</td>
<td>3.0</td>
<td>umol/L</td>
<td>(0.0–17.0)</td>
<td></td>
</tr>
</tbody>
</table>
Legislation on dispensing drugs in UG

- The National Drug Policy and Authority Act;
- Class B or controlled drugs
- “The following drugs may be supplied by retail only on the prescription of a duly qualified medical practitioner, dentist or veterinary surgeon, but only for medical, dental or animal treatment respectively”
- Indomethacin, its salts
- Wide gap between policy & implementation
Association between ulcers and hematemesis

- In reviewing detailed clinical information of 31 patients with a post-mortem diagnosis of peptic ulcers, Felix and Stahlgren found that hematemesis was the initial symptom for 35% (11/31) of the patients; autopsy showed that 58% (18/31) of the patients had an ulcer located in the duodenum and 12 patients had an ulcer in the stomach and 10 of those patients had a bleeding ulcer.
Association between NSAID use and GIT bleeding

- Block synthesis of prostaglandins (promote production of mucus)
- A case-control study conducted in the UK of 1457 cases of upper gastro-intestinal bleeding and 10000 control subjects, the RR associated with NSAIDs use was 4.7 (95% CI: 3.8-5.7)
Association between Schisto and hematemesis

- Region has highest prevalence of symptomatic and asymptomatic *S. Mansoni* in UG
- Enlarged abdomen = hepatosplenic morbidity
- Hematemesis frequently occurs in patients with schistosomal splenomegaly
Alcohol use, NSAID use and hematemesis

- Alcohol use = liver morbidity – portal hypertension and varices
- Among persons who use NSAIDS, risk of acute upper GIT bleeding increases with the level of alcohol consumed
Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda

Liver disease → Hematemesis

Alcohol use

\[ \text{OR}_{\text{M-H}} (95\% \text{ CI}) \approx (3.7-\infty) \]

\[ \text{OR}_{\text{M-H}} (95\% \text{ CI}) \approx 0.86 (0.29-2.5) \]
The doctor may ask questions such as

- Has this ever happened before?
- When did you first begin vomiting blood?
- How much blood did you vomit?
- Was the color bright red, or darker?
- What medical conditions do you have?
- What medicines do you take?
- Do you drink alcohol or smoke?
IDENTIFYING POTENTIAL CAUSES OF ILLNESS
Identify the probable presence of bleeding

- Hematemesis
- Melena
- Hematochezia
- Hypovolemia (syncope, faintness)
Estimate the amount and rapidity of bleeding

- Frequency and volume of stools or emesis
- Symptoms of hypovolemia
- Hematemesis
Ask about site and potential causes

- **Upper gastrointestinal**
  - Melena and/or hematemesis
  - Symptoms of peptic ulcer, varices, gastritis, esophagitis, Mallory-Weiss tears, and malignancy

- **Lower intestinal**
  - Hematochezia
  - Symptoms of arteriovenous malformations, diverticulosis, cancer, hemorrhoids, inflammatory bowel disease, ischemic colitis
Determine the presence of diseases or situations having poorer prognosis

- Congestive heart failure or prior myocardial infarction
- Chronic obstructive lung disease
- Cirrhosis
- Renal failure
- Advanced malignancy
- Age over 60 years
- Clotting disorder
Possibilities of missclassification

Have you been diagnosed with an illness of the liver?

Risk Factors for a Bleeding Illness during a Reported Outbreak, Western Uganda
Jaundice (yellow eyes) found in 3 case patients