TIME MODELING OF VACCINE ADVERSE EVENTS IN VAERS FOR TEMPORAL ANALYSIS

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BACKGROUND

- Effective analyses of time trends for post-vaccine adverse events (AEs) can help:
  - Safety analyses
  - Causality assessments
  - retrospective studies

- The CDC/FDA Vaccine Adverse Event Reporting System (VAERS) provides data, but a lot of time-related information is embedded in text.
**BACKGROUND - VAERS INTRODUCTION**

<table>
<thead>
<tr>
<th>Event Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAERS ID:</strong> 25319</td>
</tr>
<tr>
<td><strong>Age:</strong> 28.0</td>
</tr>
<tr>
<td><strong>Gender:</strong> Female</td>
</tr>
<tr>
<td><strong>Location:</strong> Kentucky</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Manufacturer</th>
<th>Lot</th>
<th>Dose</th>
<th>Route</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEP</td>
<td>SMITHKLINE BEECHAM</td>
<td>591A4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Administered by:** Unknown  **Purchased by:** Unknown

**Symptoms:** *Arthralgia, Influenza, Injection site reaction, Malaise, Myalgia, Nausea, Pruritus, Rash*

**SMQs:** Rhabdomyolysis/myopathy (broad), Anaphylactic reaction (broad), Acute pancreatitis (broad), Gastrointestinal nonspecific symptoms and therapeutic procedures (narrow), Eosinophilic pneumonia (broad)

**Write-up:** PT RECVD 1ST ENGERIX-B DOSE (DELT) 3-29-90 AM. SAME DAY EXPER RED AREA AT SOI, NAUSEA. FOLLOWING DAY ACHES SUBSIDING 4-1-90; NAUSEA CONTINUED. 3-31-90 FLU-LIKE SYMPTOMS. 4-4-90 RASH AT LF AXILLARY AREA NOT AT SOI. TREATMENT TYLENOL BENADRYL

**Life Threatening Illness?** No  **Died?** No
**Disability?** No  **Recovered?** No
**ER or Doctor Visit?** No  **Hospitalized?** No
**Previous Vaccinations:**
**Other Medications:** NONE  **Current Illness:** NONE
**Preexisting Conditions:** NONE  **Diagnostic Lab Data:** N/A
**CDC 'Split Type':** EEU900122
BACKGROUND - CHALLENGES

- Most studies that leveraged the VAERS data only focused on structured data.
- The unstructured nature of the write-ups in the reports make them difficult for further analyses.
- They usually provide more information:
  - Age of the patients
  - Timestamps for a series of events post vaccination
THE TIMER SYSTEM
TIME INFORMATION MODELING, EXTRACTION, AND REASONING

TEO: Time Event Ontology
OAE: Ontology of Adverse Events
VO: Vaccine Ontology
The TIMER System
Time Information Modeling, Extraction, and Reasoning

- Ontology representation of the post-vaccine adverse events: Semantic (normalized) representation of
  - Vaccine names
  - Adverse events
  - Time and temporal relations
- Semi-automatic extraction of important events and their temporal relationships
- Automatic temporal-relation reasoning for adverse events
TIME EVENT ONTOLOGY (TEO)
Ontology of Adverse Events (OAE)

- Adverse Event: a *pathological bodily process* that occurs after a medical intervention and is likely induced by the medical intervention
- Aligned with BFO and RO
- Coverage: > 1000 terms
VACCINE ONTOLOGY (VO)

- A community-based biomedical ontology in the area of vaccine and vaccination
- Aligned with BFO and RO
- Representing over 2000 vaccines, including all licensed human and animal vaccines in the USA.
- With hierarchical and semantic definitions

Note: The HEP vaccine is the one used in the previous VAERS example.

INFORMATION EXTRACTION & SEMANTIC ANNOTATION
INFORMATION EXTRACTION & SEMANTIC ANNOTATION

Semantator:
- A GUI for users to browse, query, & edit annotated results in the original context
- Protégé plug-in
- Manual annotation
- Semi-automatic annotation
- Reasoning: consistency checking
- Inter-annotator agreements

http://informatics.mayo.edu/CNTRO/index.php/Semantator
Temporal Relation Reasoning

“18month-old vaccinated w/MMR on July 6th. Eighteen days after vaccination she developed a fever of 104 and macular rash of the face, torso & legs. Dx: vasculitis 2 wks later. Patient hospitalized 08-08”

- 07/06, vaccination
- 07/24, fever, rash
- 08/08, dx: vasculitis
- 08/08, hospitalized
TEMPORAL RELATION REASONING

- Temporal Representation Normalization
- OWL DL Reasoning
- SWRL (Semantic Web Rule Language)-based Reasoning
Visualization
INTERPRETATION

- Many symptoms are shared but may occur at different time points
- Frequency of a symptom may be different
- Sequence of the adverse events may be different
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CONCLUDING REMARKS AND FUTURE WORK

- An ontology-based approach for temporal information representation of VAERS data
- TIMER system for temporal information modeling, extraction, and reasoning
- Future work:
  - Automatic extraction
  - Statistical analysis