ADVERSE EVENTS FOLLOWING IMMUNIZATION: REPORTING STANDARDIZATION, AUTOMATIC CASE CLASSIFICATION AND SIGNAL DETECTION
Partnership with PCIRN

- PCIRN: PHAC/CHIR Influenza Research Network
- Canadian national network of key influenza vaccine researchers.
- Develops and tests methodologies/methods related to the evaluation of pandemic influenza vaccines as they pertain to safety, immunogenicity and effectiveness, and program implementation and evaluation.
- [http://www.pcirn.ca/](http://www.pcirn.ca/)
Problem statement

- Current adverse events following immunization (AEFIs) reporting systems use different standards (if any) to encode reports.
- Within the Canadian research network I collaborate with, there is no standard terminology used when recording adverse events.
- During aggregation at the federal level, clinical notes recording signs and symptoms, are often not even saved.
- The resultant lack of consistency limits the ability to query and assess potential safety issues.
Goal and significance of my work

- **Goal:** Improve safety signal detection in vaccine AEFI reports
  - **Step 1:** Augment existing standards with logically formalized elements
  - **Step 2:** Perform automatic case classification
  - **Step 3:** Test classification utility to detect safety signals

- **Significance:** Increase the timeliness and cost effectiveness of reliable adverse event signal detection
What is an AEFI?

An adverse event following immunization (AEFI) is an undesirable, unfavorable and unintended medical occurrence presenting in a predetermined time frame following administration of a vaccine.

Adapted from ICH Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
What’s interesting about vaccine surveillance

- Vaccine administration differs from many other therapies in that it is preventive rather than curative.
- Randomized clinical trials are necessarily limited in size and duration, and are underpowered given the broad deployment of vaccines.
- Follow-up studies of the vaccinated population are necessary to assess safety and risk factors.
- Reports come from a wide variety of health care providers, and must be aggregated and normalized.
- Based on these analyses, health authorities will decide whether to withdraw or limit use of a vaccine (e.g., based on such an analysis, a decision was taken to not administer Fluvax to children under 2).
Surveillance of adverse events needs reform

- Reports of adverse events need to be better controlled
  - Terms used to report signs, symptoms, and diagnoses should be defined by clinical guidelines with clear definitions, so even if there are different sources for guidelines they can be clearly understood
  - MedDRA terms and filled text fields are not sufficiently unambiguous or well documented
- Reports need to be encoded in a way that enables automated confirmation of diagnoses
  - Current confirmation by medical specialists is time consuming and error-prone
The Brighton collaboration provides case definitions and guidelines to standardize reporting

- 300 participants from patient care, public health, scientific, pharmaceutical, regulatory and professional organizations


- Good applicability, sensitivity, and specificity


- Performs well against other standards


- Adopted by Public Health Agency of Canada

Benefits of working with Brighton

- They have developed a first software tool, however it is proprietary and uses hard-coded rules that can not easily be modified.
- They work with an extensive network of collaborators, share a vision of how computation can help in this area, and can push adoption.
- They want to develop a new tool that can be applied to classifying a number of large European datasets, and support my research toward accomplishing that effort.
Strategy for encoding adverse event reports

- Model the domain using an ontology encoded using OWL 2
  - OWL reasoning is a solid basis for classification
  - A variety of high quality open source tools available

- Open Biological and Biomedical Ontology Foundry helps with quality, interoperability and avoiding redundant work
  - Define each term textually
  - Reuse ontologies in the suite
  - Define each term logically, by relating it to other entities

Work in progress: [http://purl.obolibrary.org/obo/aero.owl](http://purl.obolibrary.org/obo/aero.owl)
Using MedDRA annotated AE data

- Acquire, from collaborators, existing data that uses MedDRA

- Translate, as best possible, MedDRA annotations to Brighton symptoms
  - Import selected MedDRA terms into OWL, following general strategy of Minimal Information to Reference an External Ontology Terms (Courtot, et al. 2011)
  - Standardized MedDRA Queries provide useful documentation on how to interpret MedDRA
  - OWL used to define Brighton symptoms in terms of MedDRA terms (this will be only approximate)
Using MedDRA annotated AE data

- Use OWL to define Brighton criteria in terms of Brighton symptoms
- Represent adverse event instances as bags of MedDRA terms
- Classify event instances using OWL definitions of Brighton criteria
- Apply existing statistical methods to data retrieved in terms of these automatically classified events
Automatic case classification

Convulsion, Cyanosis, Death, Mydriasis, Pallor, Pulmonary oedema, Pupil fixed, Unresponsive to stimuli, Urinary incontinence

Brighton seizure level 3 = \text{hasPart} \\
\text{brighton:General motor manifestation AND} \\
\text{hasPart} \text{brighton:Loss of consciousness}

MedDRA annotations

\text{brighton:Loss of consciousness} = \text{meddra:Unresponsive to stimuli}

\text{brighton:General motor manifestation} = \text{meddra:Convulsion}

AERO mapping

AERO diagnoses
Current status

- A model of the Adverse Event Reporting Ontology (AERO) has been built
- A Brighton working group has been established to guide our work
- Encoding of Brighton case definitions is in progress
- US Vaccine Adverse Event Reporting System (VAERS) data is freely available and has been acquired
- Agreement in place to receive Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) data
Project extensions under consideration

- Compare results with different statistical methods
  - For example, using arbitrary set of terms vs. Brighton ones
- Replace current ABC tool backend
- Use text-mining to process textual part of AEFIs reports
  - Could increase accuracy of automatic case classification
  - Very preliminary work:
    - Shah group in Stanford works on text-mining of drug related adverse events and is interested in using AERO
- Use text-mining directly on Electronic Health Record data
  - Apply pipeline on data captured in hospital setting without the need for distinct reporting
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ICBO Workshop
Methods for adverse events representation

Graz, Austria. July 22nd 2012. Co-located with ICBO and FOIS.
Check our webpage http://purl.org/icbofois2012/adverse_events/, contact us at info.aeicbo2012@gmail.com or via our G+ page gplus.to/aeicbo2012
Sources

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