ADVERSE EVENTS FOLLOWING IMMUNIZATION: REPORTING STANDARDIZATION, AUTOMATIC CASE CLASSIFICATION AND SIGNAL DETECTION
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 AEFIs 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
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
  
Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation

Jan Bonhoeffer\textsuperscript{a,*}, John Menkes\textsuperscript{b}, Michael S. Gold\textsuperscript{c}, Glacu\textsuperscript{d} de Souza-Brito, Margaret C. Fisher\textsuperscript{e}, Neal Halsey\textsuperscript{f}, Patricia Vermeir\textsuperscript{g}, The Brighton Collaboration Seizure Working Group\textsuperscript{h,i,1}

\textsuperscript{a} University Children’s Hospital, PO Box, 4005 Basle, Switzerland
\textsuperscript{b} Cedars Sinai Medical Center, Los Angeles, CA, USA
\textsuperscript{c} University Department of Paediatrics, Adelaide, Australia
\textsuperscript{d} University Medical School, Sao Paulo, Brazil
\textsuperscript{e} Monmouth Medical Center, Long Branch, NJ, USA
\textsuperscript{f} The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
\textsuperscript{g} National Institute of Public Health and Environment, Bilthoven, The Netherlands
\textsuperscript{h} Centers for Disease Control and Prevention, Atlanta, GA, USA
\textsuperscript{i} University Children’s Hospital, Basle, Switzerland
Brighton case definition – seizure example

It is recognized that the manifestation of some seizure types may be almost identical to those of other seizure types and that an electroencephalogram (EEG) is a useful adjunct for diagnosis and classification. However, EEG was not included as a necessary criterion in the definition. First, EEGs are frequently not readily available. Second, even if EEG is available, its use and interpretation is complex. Third, with an interictal sensitivity of about 40% [2], a normal EEG neither excludes the diagnosis of seizure nor of epilepsy.

As fever is rarely measured prior to the seizures and temperatures measured after the seizure are often altered by antipyretics; febrile seizures are not defined separately. However, the presence of fever in the context of seizures following immunization should be recorded and presented as outlined in the guidelines of this document.

2. Case definition of generalized convulsive seizure as an adverse event following immunization

- Level 1 of diagnostic certainty
  - witnessed sudden loss of consciousness AND
  - generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.
- Level 2 of diagnostic certainty
  - history of unconsciousness AND
  - generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.
- Level 3 of diagnostic certainty
  - history of unconsciousness AND
  - other generalized motor manifestations.
  - biologic characteristics of seizures including patterns identified in previous trials (e.g., early-phase trials).
  - Monitoring of a seizure still present on the last day of follow-up should be extended to recovery or until a final outcome is reached.

(3) For all cases and/or all study participants, as appropriate, the following information should be recorded:
  - Date of birth, sex, and ethnicity.
  - History of premature birth for infants (<37 weeks gestation).
  - Date and time of immunization.
Benefits of working with Brighton

- They have developed a first software tool, however it is proprietary and uses hard-coded rules that cannot 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
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
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
Pipeline

BRIGHTON GUIDELINES

ADVERSE EVENT REPORTING ONTOLOGY (AERO)

AUTOMATIC CASE CLASSIFICATION

SIGNAL DETECTION

Policy makers

INFORMATION RECALL SOPs

GENERAL POPULATION
Related efforts

- **MSrv: the Medical Surveillance Ontology**
  - mid-level resource built under BFO, OGMS, IDO
  - Will encompass common elements between the Ontology of Adverse Events (OAE) and the AERO
  - Will provide basis for extension — e.g. device adverse events

- **OMRE: the Ontology of Medically Relevant Entities**
Acknowledgements

- Oliver He, Yu Lin, Lindsay Cowell, Alan Ruttenberg, Barry Smith, Ryan Brinkman, Peter d’Eustachio, Albert Goldfain
- Robert Pless, Barbara Law, Jan Bonhoeffer, Jean-Paul Collet