Western Canadian Immunization Forum 2011 - Vancouver
'Immunizations for the Modern Family'

New Developments in Vaccine Safety Monitoring

Canada and the World

Dr. Barbara Law
Chief Vaccine Safety
Public Health Agency of Canada

New Developments in Vaccine Safety Monitoring

Canada and the World

Pharmacovigilance: *The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems (WHO 2002)*

- pharmakon (Greek): 'drug'
- vigilare (Latin): 'to be awake'……'to keep watch'

Key subtext: "Think globally, act locally"

New Developments in Vaccine Pharmacovigilance

Global Perspectives, Canadian Scene

- Global vaccine pharmacovigilance
  - Origins
  - Key players
  - Best practices
- Canadian vaccine pharmacovigilance
  - Origins
  - Key players
  - Current system
  - New Developments

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Origins

Thalidomide Disaster

- marketed 1957-1961
- used to treat morning sickness during pregnancy
- caused congenital malformations

- 1963 - WHO call to global action regarding adverse event monitoring

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

- World Health Organization (WHO)
- Uppsala Monitoring Centre (UMC)
- Council for International Organizations of Medical Sciences (CIOMS)
- Brighton Collaboration

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

- Article 2 of WHO constitution -mandate from member states:

> "to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products"

- Assessment of National Regulatory Systems for Vaccines
- Global Drug Monitoring Programme
- Global Advisory Committee on Vaccine Safety (GACVS)
- Vaccine Safety Net - guide to good web-based info
- Training programs for Low/Middle income countries

WHO Quality Indicators for National Regulatory Authorities (NRAs)

- Developed in 2004 by the WHO
- Primary purpose: provide assessment tools for National Regulatory Authorities able to 'pre-qualify' vaccines for UNICEF programs
  - Eg: Arepanrix + seasonal flu made in GSK Laval plant
  - Canada was assessed in January 2007

- Six spheres of regulatory function assessed
  1. Marketing authorization and licensing activities
  2. Post-marketing activities including surveillance of AEFI
  3. NRA Lot release
  4. Laboratory access
  5. Regulatory inspections
  6. Regulatory oversight of clinical trial

WHO Quality Indicators for Post-marketing activities including AEFI surveillance

1. Institutional regulations and guidelines for post-marketing surveillance including monitoring and management of AEFI
2. *Quality Management System for post-marketing activities*
3. Roles and responsibilities of the key players (NRA, Central Laboratory, surveillance staff, immunization staff)
4. Human resource management (including training)
5. Routine and functional system for regular review of safety and efficacy of the vaccine product for regulatory action including a process to review and share relevant data between key players and taking appropriate action
6. Capacity to detect and investigate significant vaccine safety issues
7. Regulatory outcome regarding vaccine performance
8. System for providing feedback on AEFI from the national to all levels

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

Programme of International Drug Monitoring

- Initiated in 1968 with 10 countries, including Canada, agreeing to pool national adverse event reports to enable rapid detection of safety issues
- Steady growth with 106 countries by July, 2011
- 1978 Uppsala Monitoring Centre (UMC) in Sweden took on coordination of programme for WHO

the UPPSALA MONITORING CENTRE

- Collects, assesses, communicates information from member countries about benefits, harm, effectiveness and risk of drugs
- Collaborates with member countries on pharmacovigilance practice
- Global Adverse event reports collated in Vigibase (~4 million)
  - Ongoing signal detection plus efforts to improve processes
- http://www.who-umc.org/

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

- Global Advisory Committee on Vaccine Safety (GACVS) - 1999
  - *Objective: to respond promptly, efficiently and with scientific rigour to vaccine safety issues of potential global importance*
  - *Annual June & December meetings; publish conclusions*
  - http://www.who.int/vaccine_safety/en/
- Vaccine Safety Net
- Vaccine Safety Training Programs

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

CIOMS (1949; WHO+UNESCO http://www.cioms.ch/)
Council for International Organizations of Medical Sciences

- International, non-government, non-profit organization
- >60 member organizations: biomedical disciplines, national academies of sciences, medical research councils
- Aim to facilitate and promote international activities in biomedical sciences; collaborate with UN (especially WHO, UNESCO)
- Several key long-term programmes
  - Bioethics
  - Health Policy, Ethics and Human Values
  - Drug Development and Use

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

CIOMS

Programs on Drug Development and Use

- Safety requirements for the use of drugs
- Assessment and monitoring of adverse drug reactions and pharmacogenetics

Time-limited Working Groups formed to report on specific topics; members with relevant expertise chosen from

- Pharmaceutical industy – scientists/pharmacovigilance expertise
- Regulatory Agencies
- Governmental institutions
- Academia (industrialised / developing countries / international organizations)

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

CIOMS -WHO WG on Vaccine Pharmacovigilance

- Develop general definitions strictly focused on vaccine pharmacovigilance
- Contribute to development, review, evaluation, approval and dissemination of Brighton Collaboration AEFI definitions
- Collaborate with other CIOMS working groups especially: SMQs, and Signal Detection

Report due for publication in 2012……

CIOMS -WHO WG on Vaccine Pharmacovigilance

Unique aspects of vaccines relative to other drugs

- Complex biologic products
- Often target high % population (eg birth cohorts)
- Benefits of immunization not immediately visible
- Optimal schedule protects before age of greatest risk but….targeted ages may coincide with emergence of underlying disease (eg neurodevelopmental disorders)
- Subpopulations may be more susceptible to AEFIs
- Causality assessment complicated by inability to readily 'dechallenge' and reluctance to 'rechallenge'
- Health professionals who recognize and report AEFI often not the same as those who gave the vaccine

-WHO WG on Vaccine Pharmacovigilance Adverse Events Following Immunization

General definition: Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The AE may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease

Cause-specific definitions

1. **Vaccine product-related reaction:** An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product
2. **Vaccine quality defect-related reaction:** An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
3. **Immunization error-related reaction:** An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable
4. **Immunization anxiety-related reaction:** An AEFI arising from anxiety about the immunization.
5. **Coincidental event:** An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

-WHO WG on Vaccine Pharmacovigilance Adverse Events Following Immunization

General definition: Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The AE may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease

Cause-specific definitions

1. Vaccine product-related reaction
2. Vaccine quality defect-related reaction
3. Immunization error-related reaction
4. Immunization anxiety-related reaction
5. Coincidental event

Application of AEFI definitions depends on the context:

- Spontaneous reporting
- Clinical case assessment and management
- Cluster investigation
- Causality assessment
- Vaccine safety communication and education

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Key Players

Initiated in 2000

- International voluntary non-profit collaboration (Funding from US CDC, WHO, research grant)
- Global collaboration + scientific methods to achieve best-evidence-based standardization of public health tools to support vaccine safety research+surveillance
- Activities, resources, tools
  - Safety data collection standards
  - AEFI case definitions and tool for diagnostic leveling
  - Collaborative studies
  - Linking databases
  - Building capacity
  - Communicating findings

Brighton collaboration

Published Case Definitions

- Abscess at the vaccination site
- Cellulitis at the vaccination site
- Anaphylaxis
- Encephalitis, Myelitis, Acute Disseminated Encephalomyelitis
- Guillain Barre Syndrome and Fisher Syndrome
- Aseptic meningitis
- Seizure
- Hypotonic Hyporesponsive Episode
- Persistent crying
- Intussusception
- Rash
- Thrombocytopenia
- Local Reaction
- Induration
- Swelling
- Nodule
- Fever
- Fatigue
- Diarrhoea
- Vaccinia (smallpox vaccine) specific adverse events
  - Robust take
  - Eczema vaccinatum
  - Generalized vaccinia
  - Inadvertent inoculation
  - Progressive vaccinia
- Unexplained sudden infant death

New Developments in Vaccine Safety Monitoring

Global Pharmacovigilance: Best Practices

- Clinical case management and research
- Population-based surveillance and research
  - Signal detection
  - Hypothesis testing
  - Background incidence in populations
- Causality assessment paradigm for "Did it?"
- Stakeholder communication
- Capacity building

Global Best Practices - Vaccine Safety Monitoring

Clinical Case Management and Research

- Italy - Veneto Green Channel (1992)
- Australia - Immunisation Adverse Events Clinic (1996)
- US - Clinical Immunisation Safety Assessment Network (2001)

Global Best Practices - Vaccine Safety Monitoring

Clinical Case Management and Research

Italy - Veneto Green Channel (1992)

- Created by local Public Health authority
- Immunology Unit at the University of Verona
- Consultant service to PHUs, physicians to evaluate:
  - individuals with previous AEFI
  - suspected contraindications
- Manage regional AEFI surveillance system
- Surveillance of specific AEFIs
- Help detect and manage signals
- Assist in training of immunization staff
- Publish annual reports

16 years, from 1992-2008

- Evaluated 1280 cases, 76% <14 yrs
- Of 724 immunized after the evaluation, 7.6% had mild, short-lived AEFI

Global Best Practices - Vaccine Safety Monitoring

Clinical Case Management and Research

Australian Immunisation AE Clinics 1994

- Hospital-based consultant services in several cities (Sydney, Canberra, Melbourne, Adelaide, Perth)
  - Selected AEFI cases (eg anaphylaxis, HHE, seizure)
  - Children with possible contraindications due to pre-existing medical conditions
- Referrals from health professionals and public health
- Cross clinic collaboration via teleconferences
- Research to address specific management issues
  - Revaccination of children with prior HHE (Paediatr Child Health 1999; 35:549-52)
- Working to develop:
  - Common data collection elements
  - Standard AEFI management protocols
  - Clinical trials to address specific issues (eg HHE, large local reactions)

Global Best Practices - Vaccine Safety Monitoring

Clinical Case Management and Research

CISA Clinical Immunization Safety Assessment Network

- **2001 collaborative project**
  - 6 medical research centers with immunization safety expertise,
  - Immunization Safety Office
  - America's Health Insurance Plans
- **Goals**
  1. Study pathophysiologic basis of AEFI
  2. Study individual risk factors associated with developing an AEFI
  3. Provide consultation on complex clinical vaccine safety issues
  4. Assist policy makers in developing strategies to assess individuals who may be at increased risk for AEFI
- **2010 - Expert Peer Review of CISA network for CDC**
  - Modify activities to be more consistent with CDC's public health mission
  - basic science research goals (1,2) outside the mandate
  - Goals 3 and 4 should be the primary focus

Global Best Practices - Vaccine Safety Monitoring

Population-based Surveillance and Research

- Background rates for Adverse Events of Special Interest (AESI)
- New Epidemiologic Study Methodology
- Vaccine Safety Data Links (VSDLs)
  - Single country
  - Multiple networked countries

Global Best Practices - Vaccine Safety Monitoring

Population-based Surveillance and Research

Population-based background rates for AESI

Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines

Steven Black, Juhani Eskola, Claire-Anne Siegrist, Neal Halsey, Noni MacDonald, Barbara Law, Elizabeth Miller, Nick Andrews, Julia Stowe, Daniel Salmon, Kirsten Vannice, Hector S Izurieta, Aysha Akhtar, Mike Gold, Gabriel Oselka, Patrick Zuber, Dina Pfeifer, Claudia Vellozzi

www.thelancet.com Published online October 31, 2009

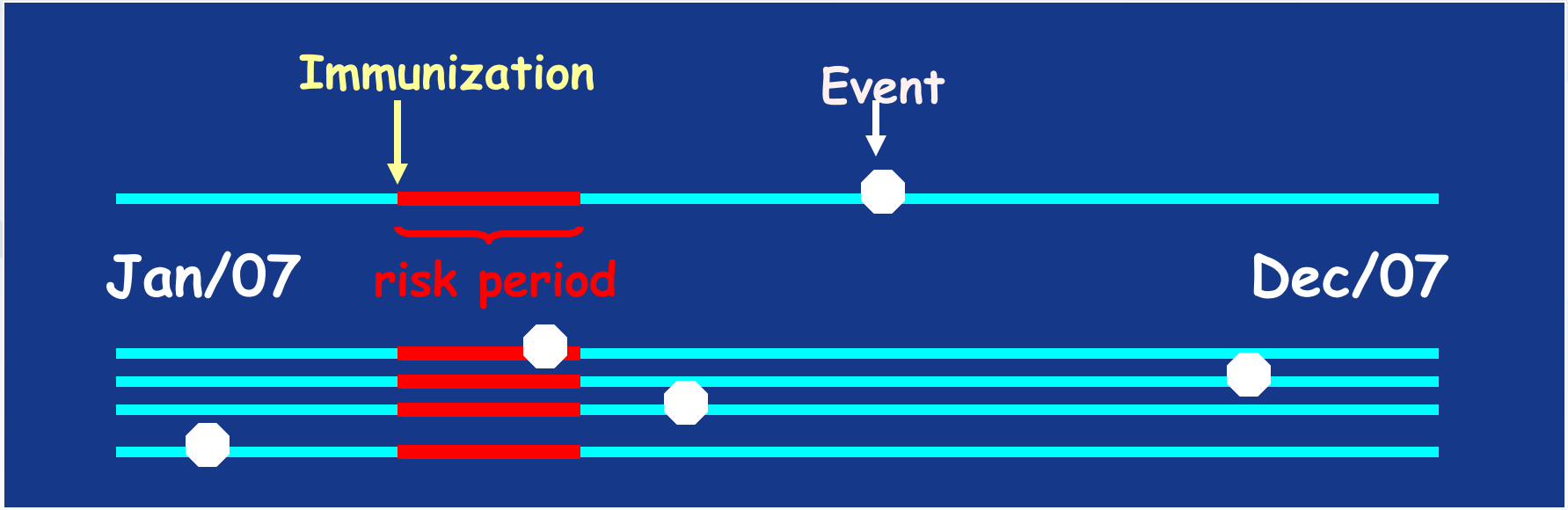
Adverse Event	Vaccine 'Placebo' Recipients	Coincident events since a vaccine dose		
		≤ 1 d	≤ 1 wk	≤ 6 wk
Spontaneous abortion	1 million pregnant	397	2780	16684

Global Best Practices - Vaccine Safety Monitoring

Population-based Surveillance and Research

Self-Controlled Case Series Methodology

- Define total study period and risk period following immunization
- Identify cases in given age group during study period
- Test hypothesis that events caused by vaccine more likely to occur in the risk period than outside of it
- Each case serves as own control. Highly effective way to study vaccine-adverse event association in highly immunized populations



Paddy Farrington, http://statistics.open.ac.uk/sccs/

Global Best Practices - Vaccine Safety Monitoring

Population-based Surveillance and Research

Vaccine Safety Data Links (VSDLs)

- administrative health databases contain demographic data, vaccination data, healthcare utilization, outcome data, laboratory diagnostics, prescriptions etc
- Possible to link the databases using a common identifier without compromising confidentiality
- Combined with innovative analytic methodology provide powerful tools to study vaccine safety
  - U.S. Vaccine Safety Datalink (1990) (http://www.cdc.gov/od/science/iso/vsd/)
  - UK General Practitioners Research Database
  - Denmark: entire population (1968)
  - Capability in some developing countries (Vietnam)

Global Best Practices - Vaccine Safety Monitoring

Population-based Surveillance and Research

Vaccine Safety Data Links (VSDLs)

Hypothesis testing

- Prove vaccine-AEFI association:
  - MMR and thrombocytopenia
  - MMR and febrile seizures
- Reject hypothesis that there is an association
  - MMR and autism
  - Thimerosal and neurodevelopmental disorders

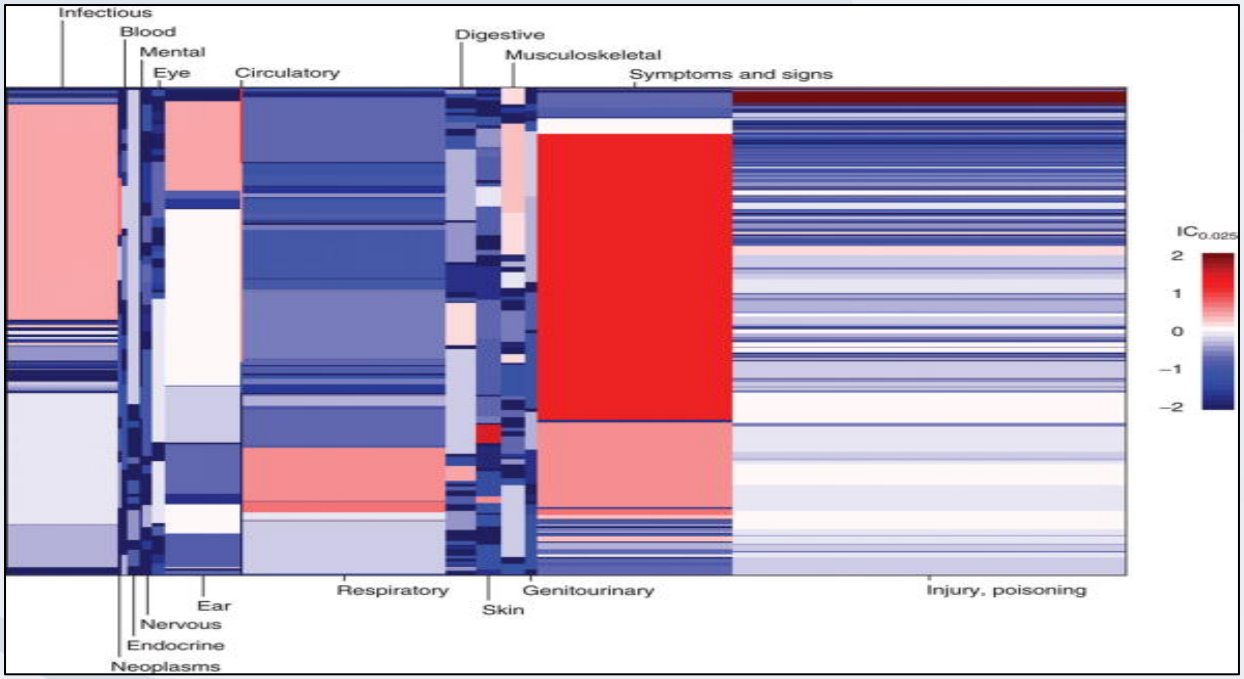
Signal detection

- Rapid cycle analysis - US VSDL
  - Influenza vaccine and selected neurologic or allergic events,
  - whole cell / acellular pertussis and fever, seizures
  - rotavirus vaccine and intussusception;
  - meningococcal conjugate vaccine and GBS;
- Cohort-based disproportionality Hviid group, Denmark
  - 'heat-seeking' methodology

Global Best Practices - Vaccine Safety Monitoring

Population-based Surveillance and Research

Vaccine Safety Data Links (VSDLs)



Svanstrom H, Callreus T, Hviid A. Temporal Data Mining for Adverse Events Following Immunization in Nationwide Danish Healthcare Databases. Drug Safety 2010; 33:1015-25

- cohort-based disproportionality analysis
- significant risk windows post MMR (evaluated: 0-13, 14-27, 28-41, 42-55, 56-69 days)
  - Febrile seizure: 0-13 days (1.31; 1.23, 1.28); 28-41 days (0.13; 0.01, 0.25)
  - Rash: 0-13 days (0.87; 0.27-1,36)
  - Idiopathic Thrombocytopenic Purpura: 14-27 days (1.40; 0.67, 1.98)
  - Lymphadenopathy: 14-27 days (1.88; 0.57, 2.78)

Global Best Practices - Vaccine Safety Monitoring

Distributed Data Networks

US CDC Vaccine Safety Data Link

- Early example of distributed data model

VAESCO

- Vaccine Adverse Event Surveillance and COmmunication Consortium
- Funded by European CDC
- Distributed data model applied to multiple countries
  - Background rates
  - Test for Vaccine - AE association

GLOBAL VSDL (WHO-FDA proof of concept)

- Test for possible association: H1N1 vaccines & GBS

Global Best Practices - Vaccine Safety Monitoring

Capacity Building - WHO & Partners

PROBLEM

- limited vaccine pharmacovigilance capacity in low/middle-income countries
- More vaccines available for use, some specifically tailored to developing country needs (meningococcus A)

GLOBAL VACCINE SAFETY BLUEPRINT PROJECT

- Strengthen national vaccine pharmacovigilance capacities
- Engage broad groups of vaccine safety stakeholders
- Share methodologies for AEFI investigation.
- Facilitate global information exchange system.
- Provide decentralized support structure for crisis management.
- Ensure strong communication component .

New Developments in Vaccine Safety Monitoring

WHO Global Vaccine Safety Blueprint Project

Global capacity building and harmonized tools

- WHO and partners
- Brighton Collaboration
- CIOMS-WHO working group

Global analysis and response

- Global Advisory Committee on Vaccine Safety (GACVS)
- Other global or regional advisory bodies

National AEFI surveillance, investigation and response

- Immunization programme
- Regulatory authority
- AEFI review committee
- Other support groups

Global signal detection and evaluation

- Uppsala Monitoring Centre
- Global vaccine safety data link
- Other partners

Product monitoring

- Vaccine manufacturers
- Licensing authorities in countries of manufacture
- Procurement agencies

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Safety 'Blueprint'

Global capacity building and harmonized tools

National Capacity building

Global analysis and response

National Analysis and Response

National AEFI Activities

F/P/T Immunization Program AEFI Activities

Global signal detection and evaluation

National Signal Detection and Evaluation

Global Product monitoring

National Product Monitoring

New Developments in Vaccine Safety Monitoring

Canadian Pharmacovigilance: Origins

- 1965 Vaccine + Drug Adverse Reports Sent to Laboratory Centre for Disease Control (LCDC)
- 1987 Vaccine + Drug Systems Separated
- Strong F/P/T Epi Network one reason vaccine safety monitoring remained at LCDC

Ed Napke's 'pigeon-hole' system for AR reports
Blue/Red: serious
Green: unexpected

New Developments in Vaccine Safety Monitoring

Canadian Pharmacovigilance: Origins

- **1989-96** Federal funding and F/P/T collaboration to develop vaccine postmarket surveillance in Canada:
  - Defined broad scope of postmarket surveillance
  - National AEFI report form (1990)
  - Case definitions for AEFI of public health importance
  - Immunization Monitoring Program – Active (1991)
  - Advisory Committee on Causality Assessment (1994)
- **2000-2008** National Immunisation Strategy (NIS) Development and Roll Out
  - Vaccine Safety one of five key themes
  - 37 surveillance/public health action priorities identified, with most considered 'must do'
  - Vaccine Vigilance Working Group (VVWG) initiated
- **2009 Pandemic:** having operationalized key NIS priorities facilitated preparations and response

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Key Players

- Market Authorization Holders
- **Health Canada**
- **Public Health Agency of Canada**
- **F/P/T Immunization Programs / Agencies**
- **Vaccine Research / Surveillance Networks**
- Healthcare Providers
- Public
- Research funding agencies / NGOs

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Key Players

Health Canada Regulators
Health Products & Food Branch - HPFB)

- **Biologics and Genetic Therapies Directorate (BGTD)**
  - Approval of vaccines for marketing
  - Lot-release program
  - Review/approval of any product changes that could impact quality, safety, efficacy or effectiveness
- **Inspectorate**
  - Licences Manufacturing Facilities
  - Ensures compliance with Good Manufacturing Practices
  - Audits compliance with Food and Drug Act Regulatory reporting
- **Marketed Health Products Directorate (MHPD)**
  - Health portfolio lead on consistent approach to post-approval safety surveillance for all marketed health products
  - Conduct risk / benefit assessments of marketed health products
  - Manage Canada Vigilance monitoring program
  - Overview regulatory activities re product advertising

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Key Players

PHAC - Infectious Disease Prevention and Control Branch

Centre for Immunization and Respiratory Infectious Disease (CIRID)
Surveillance and Outbreak Response Division (SORD)
Vaccine Safety Section

Health Jurisdiction Immunization Programmes

Provinces, Territories, FNIHB,
DND, Corrections Canada, RCMP

Vaccine Vigilance Working Group

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Key Players

Vaccine Vigilance Working Group

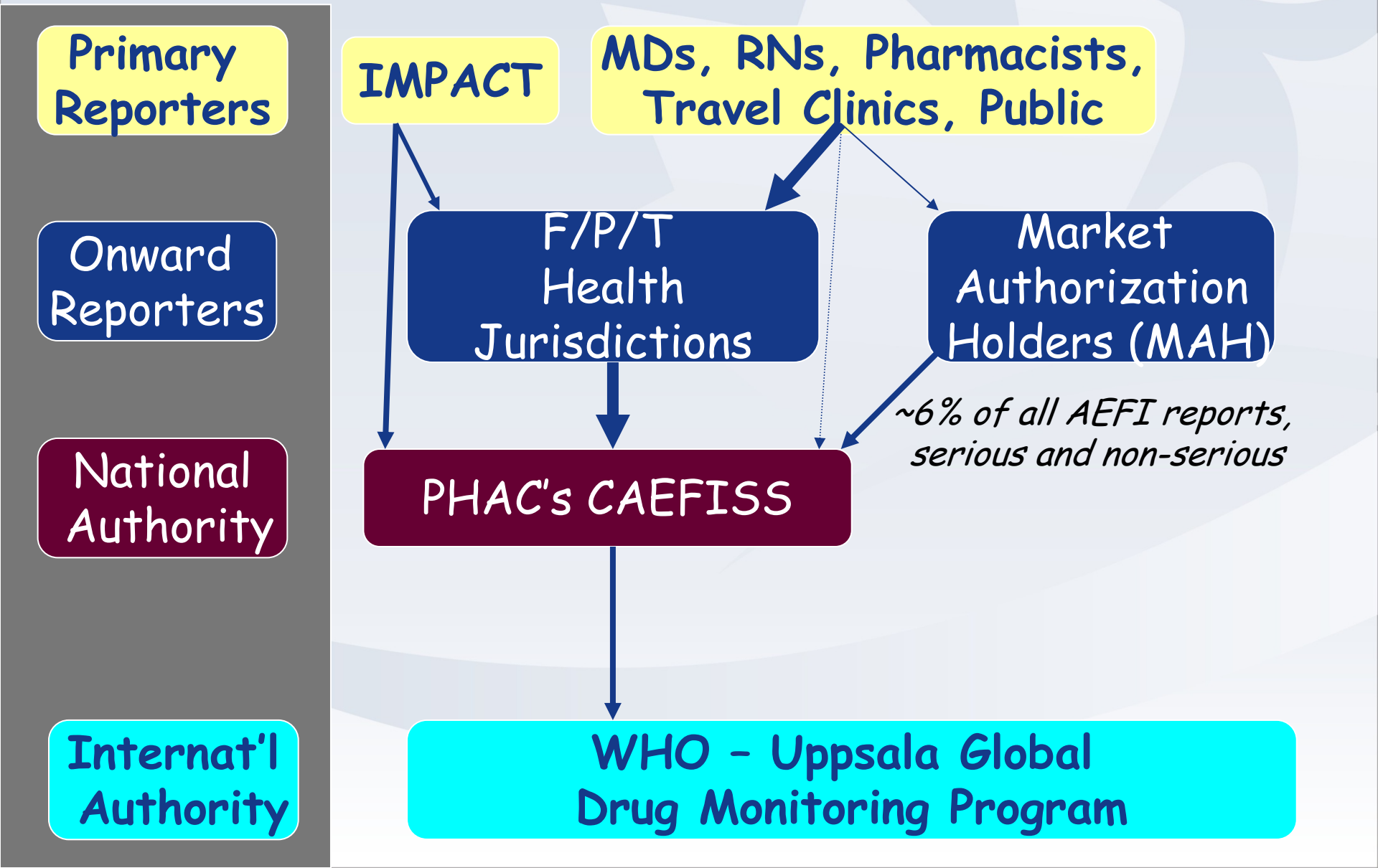
- **Mandate:** to assist Canadian Immunization Committee in realizing improvements in vaccine safety as recommended in final NIS report
- **F&P/T co-chairs; P/T, DND, RCMP, CC, FNIHB, HC, IMPACT represented**
- **National guidelines/procedures for AEFI monitoring & management**
  - AEFI report form and user manual
  - National AEFI case definitions
  - Expedited reporting of 'serious' AEFI
  - AEFI signal 'outbreak response protocol'
  - Standard analysis templates for reporting on vaccine safety monitoring to stakeholders
- **National network of safety sentinels that can rapidly share and disseminate information to appropriate stakeholders regarding emerging vaccine safety issues or signals**
  - CIOSC module (CNPHI)
  - Weekly / bi-weekly F/P/T health jurisdiction teleconferences during annual flu campaign
- **Health jurisdiction forum to identify, share and promote best vaccine safety practices including training in AEFI reporting and management**

New Developments in Vaccine Safety Monitoring

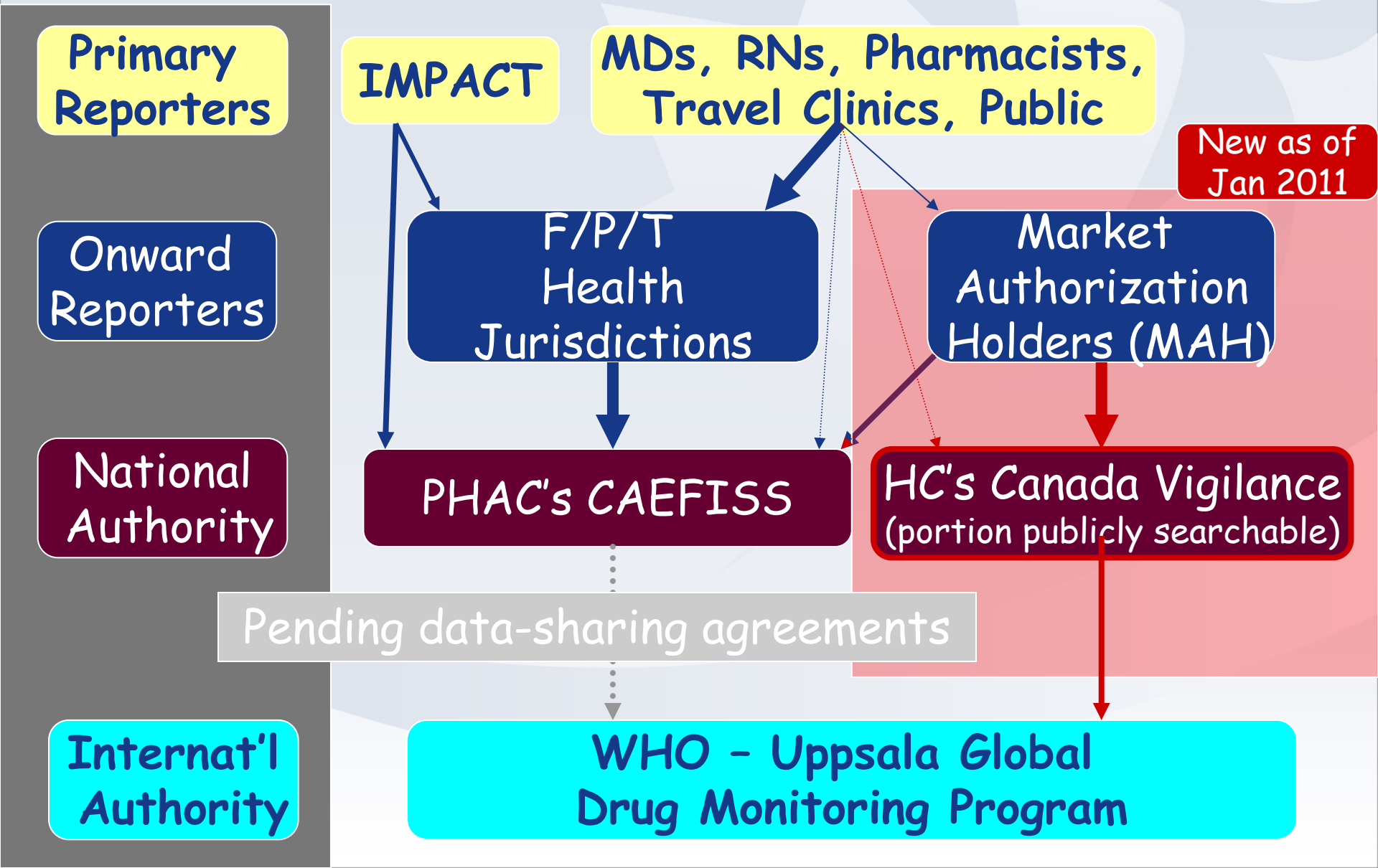
Canadian Vaccine Pharmacovigilance: Current System

- Product Monitoring
- Signal Detection and Evaluation
- Analysis and Response
- Capacity Building

AEFI Report Flow in Canada (pre2011)



AEFI Report Flow in Canada



New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

Product Monitoring: Health Portfolio

Health Canada - PHAC Vaccine Safety Review

- Information sharing on vaccines marketed in Canada as appropriate to mandate
- **BGTD**: clinical trial serious or unexpected AEFIs; new approved products; change in Product monograph; lot release
- **MHPD**: MAH expedited AEFI reporting, routine and ad hoc product safety updates; systematic literature review and assessment; other AEFIs reported to Canada Vigilance; International regulatory updates
- **PHAC**: CAEFISS data summaries; VVWG alerts; International public health safety updates

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

Canadian Adverse Event Following Immunization Surveillance System

CAEFISS

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

CAEFISS Objectives

- monitor vaccine adverse events
- identify any unusually high rates of adverse events
  - By vaccine
  - By vaccine lot
- provide timely information to inform the health care provider – client risk/benefit discussion
- identify problems that require immediate investigation
- identify areas that require further epidemiologic investigation and research

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Most Popular Content

- **It's Time to Immunize**: A web site and guide offering immunization information specifically for parents.
- Vaccine Safety Frequently Asked Questions
- Vaccines and Autism
- Statement on Seasonal Influenza Vaccine for 2011–2012
- **The Automated Identification of Vaccine Products Advisory Task Group (AIVP ATG)**: Canadian Consensus Statement on Proposed Standards for Bar Codes on Vaccine Products

Immunization Competencies for Health Professionals were developed

By Topic
- Immunize Your Child
- 9th Canadian Immunization Conference
- Canadian Immunization Guide, 7th Edition 2006
- Immunization Competencies
- Immunization Registries
- Immunization Schedules
- Influenza
- National Advisory Committee on Immunization (NACI)
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Research & Statistics

Vaccine Safety

News

Canada's new national *Adverse Event Following Immunization (AEFI) Reporting Form* is now available (Updated: 07 October 2010)

A - Z Index of topics

Childhood Immunization

Frequently Asked Questions

Misconceptions about Vaccines and Facts

Montreal study finds no link between autism and vaccines containing thimerosal

Polio Vaccine and SV40

Thimerosal in Vaccines and Autism

Vaccine Safety Surveillance Systems in Canada

Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) (*formerly VAAESS)*

Immunization Monitoring Program ACTive (IMPACT)

Reporting Adverse Events

Adverse Event Following Immunization (AEFI) Report Form

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

REPORT OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

○ Initial report
○ Follow up report *(Unique episode number)*

1a) UNIQUE EPISODE NUMBER:	1b) REGION NUMBER:	2) IMPACT LIN:

3) PATIENT IDENTIFICATION

First name: Last name: Health number:

Address of usual residence:

Province/Territory: Postal code: Phone: ( ) (ext.)

Information Source: First name: Last name: Relation to patient:

Contact info, if different:

4) INFORMATION AT TIME OF IMMUNIZATION AND AEFI ONSET

4a) At time of immunization
Province/Territory of immunization:
Date vaccine administered (Y / M / D): (hr: ○ am / ○ pm)
Date of birth (Y / M / D): Age:
Sex: ○ Male ○ Female ○ Other

4b) Medical history (up to the time of AEFI onset)
(Check all that apply and provide details in section 10)
☐ Concomitant medication(s)
☐ Known medical conditions/allergies
☐ Acute illness/injury

4c) Immunizing agent	Trade name	Manufacturer	Lot number	Dose #	Dosage/unit	Route	Site
					/		
					/		
					/		
					/		
					/		

REPORT OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

UNIQUE EPISODE NUMBER: **REGION NUMBER:** **IMPACT LIN:**

9) AEFI DETAILS: Complete all sections as appropriate; for each, check all signs/symptoms that apply. Item(s) with asterisk (*) should be diagnosed by a physician. If not, provide sufficient information to support the selected item(s). Use **SECTION 10** for additional information including, clinical details and test results.

☐ **9a) Local reaction at or near vaccination site**
Interval: → ____ Min ____ Hrs ____ Days from immunization to onset of 1st symptom or sign
Duration: → ____ Min ____ Hrs ____ Days from onset of 1st symptom/sign to resolution of all symptoms/signs

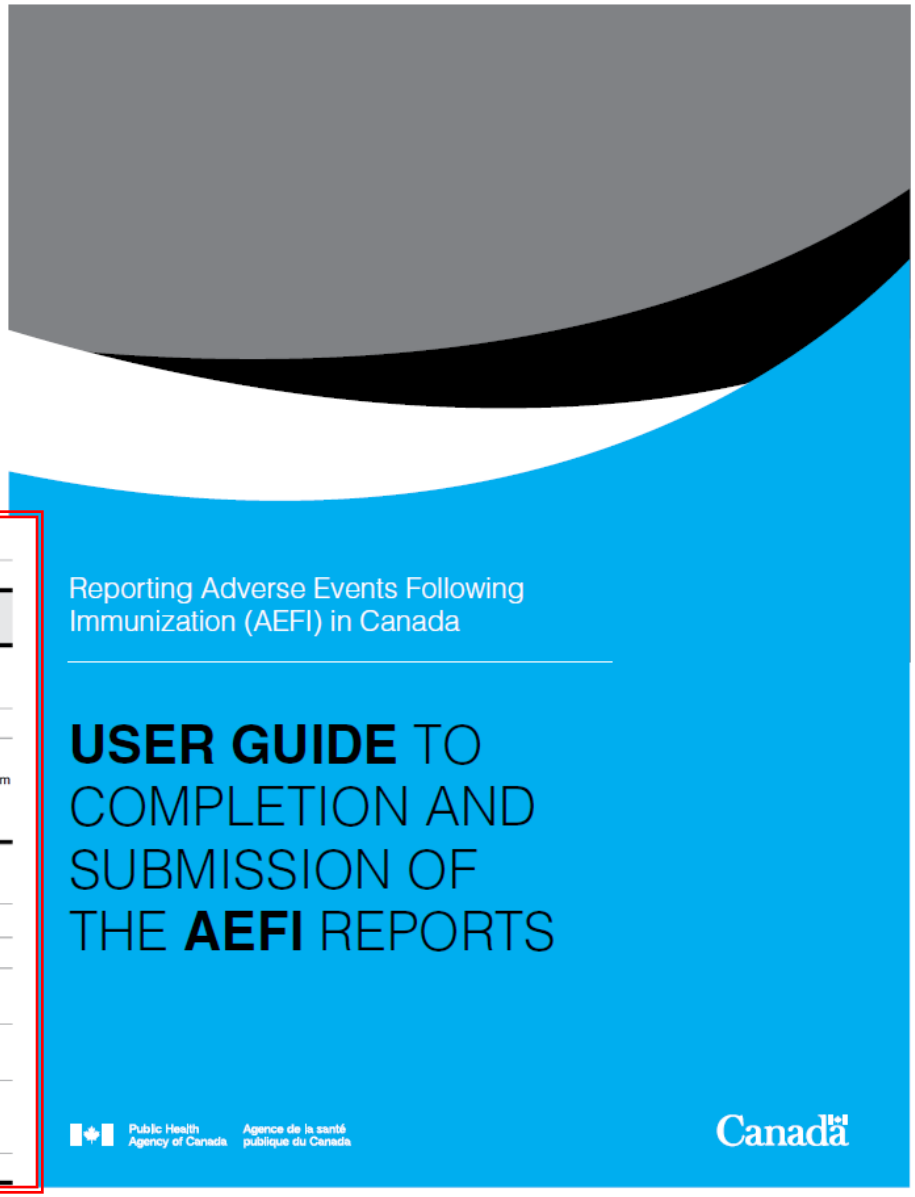
☐ Infected abscess ☐ Sterile abscess ☐ Cellulitis ☐ Nodule ☐ Reaction crosses joint ☐ Lymphadenitis ☐ Other, *specify*:

For any vaccination site reaction indicated above, check all that apply below and provide details in section 10:
☐ Swelling ☐ Pain ☐ Tenderness ☐ Erythema ☐ Warmth ☐ Induration ☐ Rash ☐ Largest diameter of vaccination site reaction: ____ cm
Site(s) of reaction _____ (e.g. LA, RA) ☐ Palpable fluctuance ☐ Fluid collection shown by imaging technique (e.g. MRI, CT, ultrasound)
☐ Spontaneous/surgical drainage ☐ Microbial results ☐ Lymphangitic streaking ☐ Regional lymphadenopathy

☐ **9b) Allergic and Allergic-like events**
Interval: → ____ Min ____ Hrs ____ Days from immunization to onset of 1st symptom or sign
Duration: → ____ Min ____ Hrs ____ Days from onset of 1st symptom/sign to resolution of all symptoms/signs

Chose one of the following: ○ **Anaphylaxis** ○ **Oculo-Respiratory Syndrome (ORS)** ○ **Other allergic events**

Skin/mucosal	☐ Urticaria ☐ Erythema ☐ Pruritus ☐ Prickle sensation ☐ Rash *(For these events, specify site of reaction)*	
	Angioedema: ☐ Tongue ☐ Throat ☐ Uvula ☐ Larynx ☐ Lip ☐ Eyelids ☐ Face ☐ Limbs ☐ Other, *specify*:	**Eye(s):** ☐ Red bilateral ☐ Red unilateral ☐ Itchy
Cardio-vascular	☐ Measured hypotension ☐ ↓ central pulse volume ☐ Capillary refill time >3 sec ☐ Tachycardia ☐ ↓ or loss of consciousness *(Duration):*	
Respiratory	☐ Sneezing ☐ Rhinorrhea ☐ Hoarse voice ☐ Sensation of throat closure ☐ Stridor ☐ Dry cough ☐ Tachypnea ☐ Wheezing ☐ Indrawing/retractions ☐ Grunting ☐ Cyanosis ☐ Sore throat ☐ Difficulty swallowing ☐ Difficulty breathing ☐ Chest tightness	
Gastrointestinal	☐ Diarrhea ☐ Abdominal pain ☐ Nausea ☐ Vomiting	



New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

What to report….

Report events which have a temporal association with a vaccine and which cannot be clearly attributed to other causes. A causal relationship does not need to be proven, and submitting a report does not imply causality.

Of particular interest are those AEFIs which meet one or more of the following criteria:

a) Meet one or more of the seriousness criteria
b) Are unexpected regardless of seriousness

Refer to the user guide, Background Information and for additional clarification.

- Serious AEFI: one that meets ≥ 1 of:
  - Results in hospitalization
  - Results in prolongation of existing hospitalization
  - Results in fatality
  - Results in lasting residual disability
  - Results in congenital abnormality
  - Is life threatening
- Unexpected AEFI: event that is not listed in the product information

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

National AEFI Case Definitions

- **Published 'Brighton Collaboration' case definitions**
  - Local reactions at or near site of vaccination
    - Abscess
    - Cellulitis
  - Anaphylaxis
  - Encephalitis
  - Acute Disseminated Encephalomyelitis
  - Myelitis
  - Guillain Barre Syndrome
  - Aseptic meningitis
  - Generalized convulsion
  - HHE
  - Persistent crying
  - Intussusception
  - Rash
  - Thrombocytopenia

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

AEFI Report Flow at PHAC

Electronic uploads: received q2-4wks;uploaded by IMIT; V number assigned

Hard copy reports: Scanned, V number assigned, data entered

MedDRA coding

- Unique 'V' number
- 2 dedicated staff
- Reports processed according to SOPs
  - <24 hours for SAEs
  - Non-serious flu and new vaccines
  - All other non-serious AEFI
- Some backlog generated by e-loads

Daily Medical Case Review

- Daily review of all cases received at PHAC prior workday
- trained health professional staff
- Assign primary reason for reporting and severity level
- 2nd level review by VSS chief /designate
- Case classification by seriousness and type of AEFI into 6 categories
- Brighton level of diagnostic certainty assessed for some
- Priority assigned for ACCA review

Classification for Daily Medical Case Review

Category	1	2	3	4
Case Severity	Serious	Hsp <24hrs Med supervision Outpt IV abx Prevents daily activities >3days	Sought direct medical care Urgent care limited to imm clinic New drug Prevents daily activities <3d	Doesn't meet any category 1,2 or 3 criterion AND
AEFI type	Anaphylaxis Encephalitis ADEM Myelitis GBS Oth paralysis of >1 day Ataxia Intussuscep. Thrombocyt. Unexpected	Paraesthesia > 1d Arthritis > 1d Bell's Palsy ORS Parotitis Vaccinated limb pain >7 d Haematochezia Orchitis Suppurative lymphadenitis of nodes draining injection site	Allergic-other Arthralgia>1d Rash-generaliz urticaria HHE Persistent cry Rash ≥4 days Vaccination site reaction of >7 days	Primary review assessment: -expected event OR -Case reviewed, no action pending

Category 5: Immunization Error **Category 6:** Not an AEFI

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Current System

Signal Detection and Evaluation

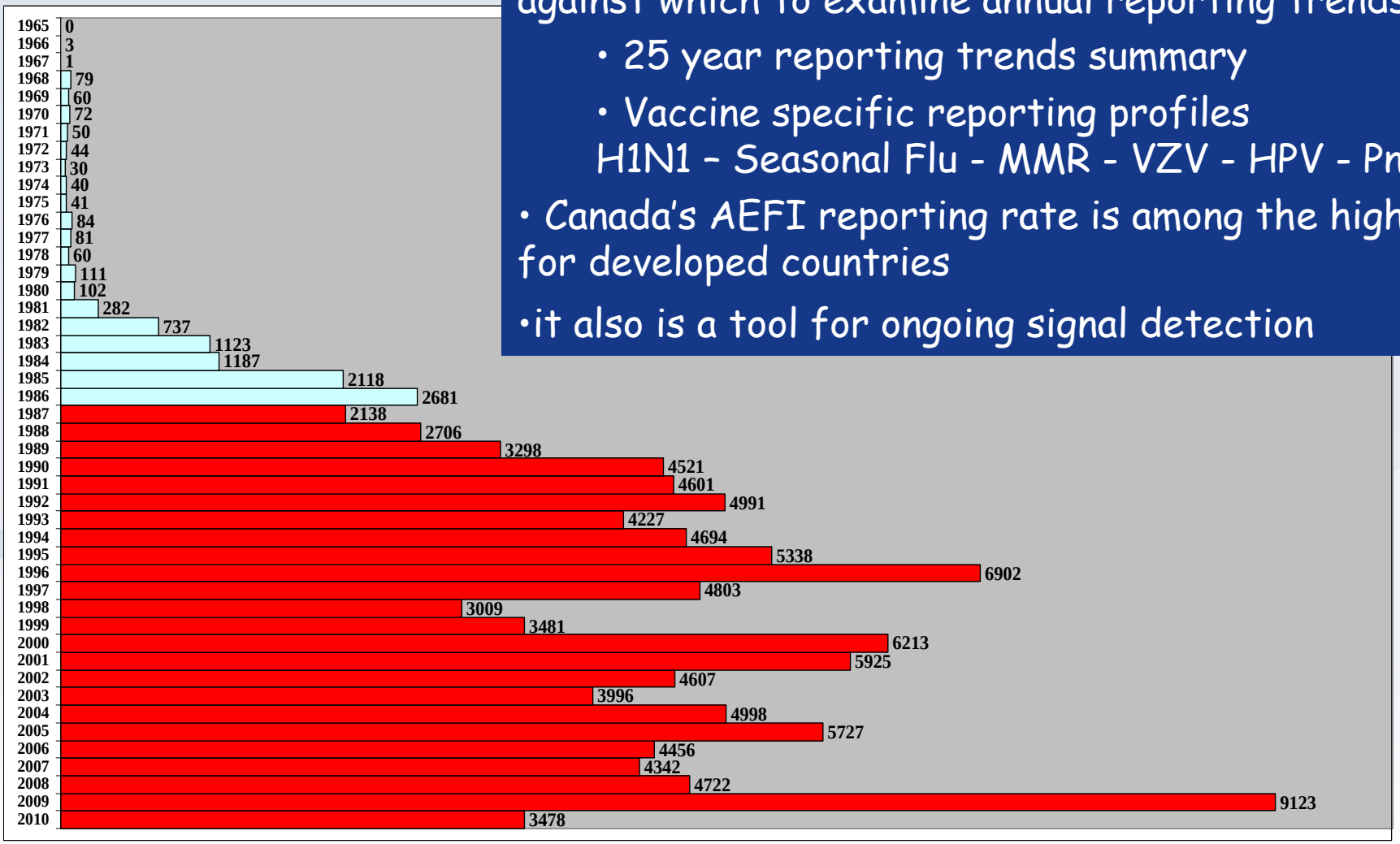
- VVWG alert network
- Testing CAEFISS for disproportionate reporting
- Daily case medical review- for unexpected AEFI
- VVWG signal response protocol under development
- ACCA review process under revision

Data Analysis and Report Generation

- VVWG annual reporting template (start with 2011)
- 21 year CAEFISS trends paper under development: 1987 to 2010
- Several vaccine specific analylses planned:
  - H1N1, seasonal influenza; MMR; Varicella; HPV; Pneumococcal, meningococcal conjugates

Canadian AEFI Reports 1965-2010

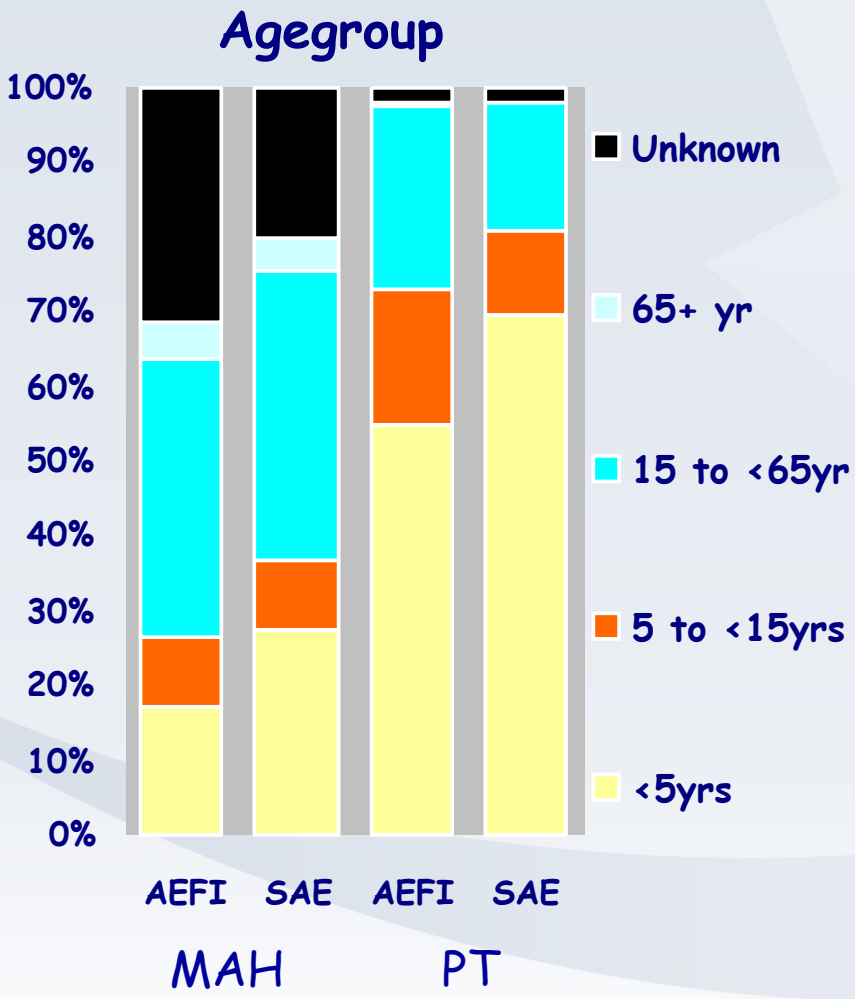
- CAEFI database now has >115,000,000 reports
- the database now represents a valuable resource against which to examine annual reporting trends
  - 25 year reporting trends summary
  - Vaccine specific reporting profiles
    H1N1 – Seasonal Flu - MMR - VZV - HPV - PneuC
- Canada's AEFI reporting rate is among the highest for developed countries
- it also is a tool for ongoing signal detection

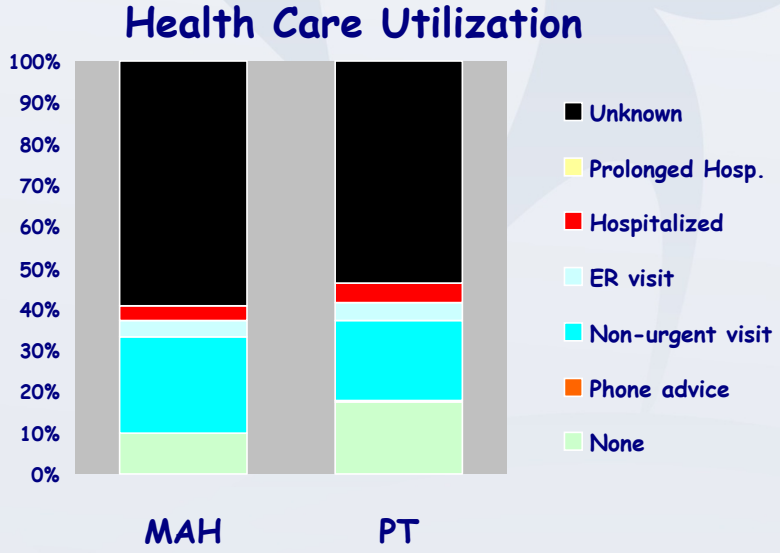


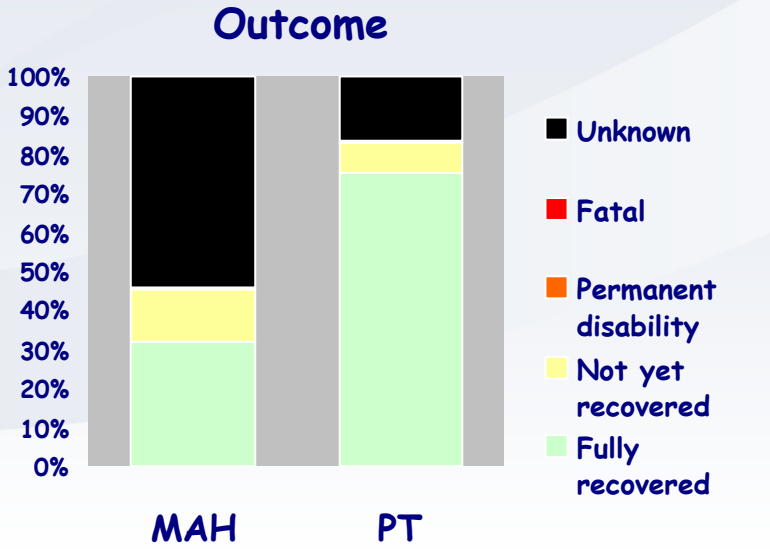
AEFI Report Profile by Onward Reporter: 1987–2011

115,837 reports in total; 6180 (5.3%) Serious

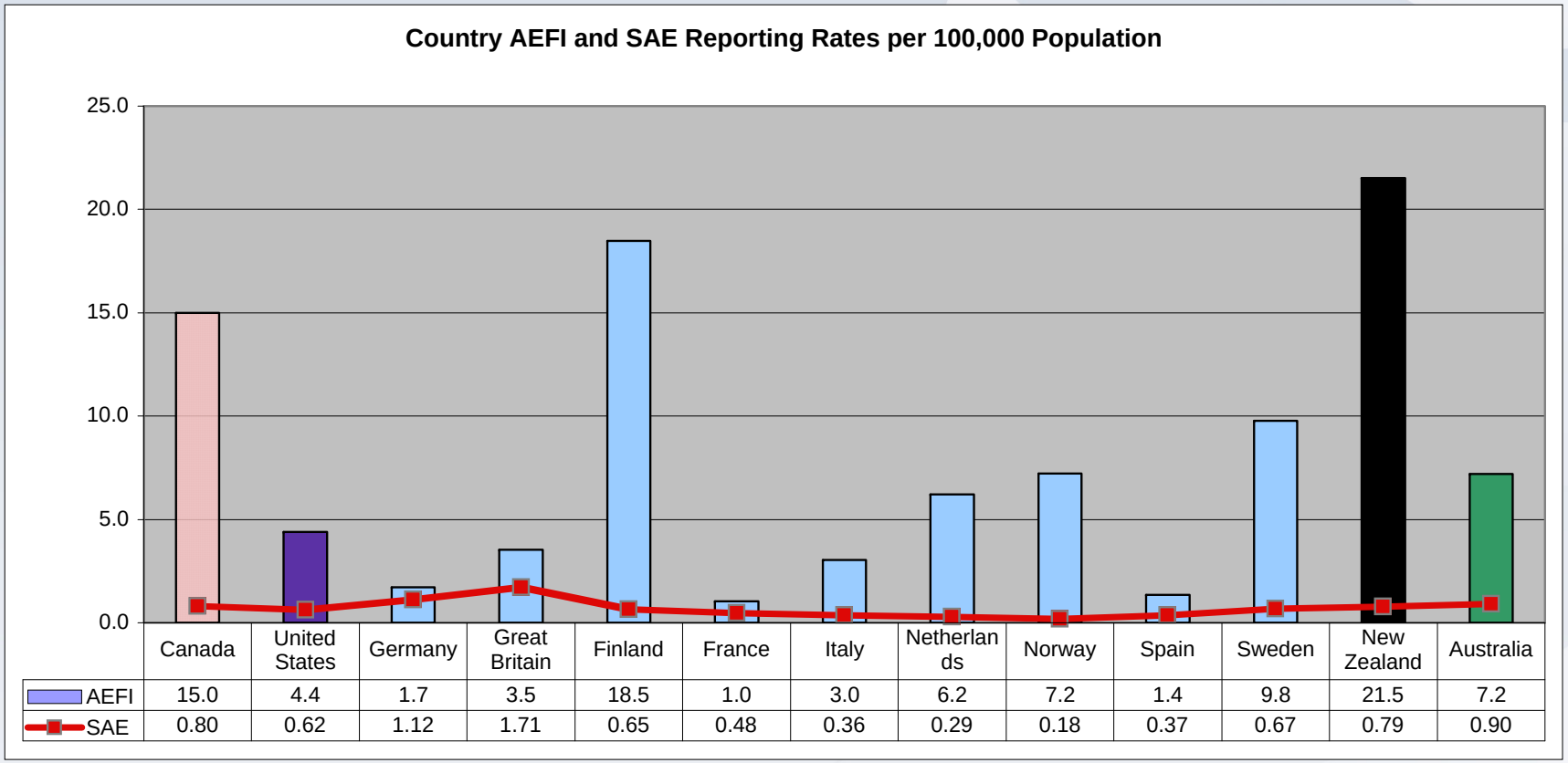
~94% from F/P/T programs; 6% from MAH







CAEFISS: International Comparisons



	Canada	United States	Germany	Great Britain	Finland	France	Italy	Netherlands	Norway	Spain	Sweden	New Zealand	Australia
AEFI	15.0	4.4	1.7	3.5	18.5	1.0	3.0	6.2	7.2	1.4	9.8	21.5	7.2
SAE	0.80	0.62	1.12	1.71	0.65	0.48	0.36	0.29	0.18	0.37	0.67	0.79	0.90

- Canadian data an average of trends from 1997 through 2010 excluding pandemic
- US data from VAERS summary report, 1991-2001
- European data: Zanoni et al 2009 for 05 AEFI/SAEs & published population data
- Australian Data from 2009 annual report
- New Zealand data from summary report, 2005-2009

Causality Assessment: What is it?

Institute of Medicine 1994, re Evidence Bearing on Causality

- Can it? **'Potential causality'**
  - Can the vaccine cause the adverse event, at least in certain people under certain circumstances
- Will it? **'Predictive causality'**
  - How frequently will vaccine recipients experience the adverse event as a result of the vaccine?
- Did it? **' Retrodictive' causality**
  - Given an individual who has received the vaccine and developed the adverse event, was the event caused by the vaccine?

Causality Assessment in Canada Historical Origins

- 1989 - Vaccine injury compensation program under consideration but concern regarding unknowns
  A. How often AEFIs follow immunization
  B. How likely it is that the immunization caused the AEFI
- 1990 - special federal funding for the Vaccine Associated Adverse Events Initiative included
- 1991 – IMPACT pilot project - to answer 'A'
- 1994 - Advisory Committee on Causality Assessment (ACCA) - to answer 'B'
- Purpose:
  - To analyze, classify & interpret selected AEFI
  - To recommend further investigations as needed

Causality Assessment in Canada

- Selection criteria–based on 'seriousness' (Int'l criteria)
  - Fatal outcome
  - Led to hospitalization, or prolonged existing hospitalization
  - Life threatening event
  - Residual damage
  - Selected adverse events of public health importance (eg GBS)
- Modified early on to limit cases admitted to hospital primarily for observation
  - eg febrile seizures only if >3 days in hospital
- Members: volunteers with expertise in clinical medicine, pediatric and adult infectious disease, neurology, allergy/immunology, epidemiology
- Annual 2 day meeting / monthly teleconferences
- Standard consensus process followed for each review

Causality Assessment
Issues with current practice for AEFI

Causality	Vaccine to AE onset interval	Concurrent disease/ drugs/chemicals
Very likely	Plausible	Can't explain AE
Probable	Reasonable	Unlikely to explain
Possible	Reasonable	Plausible cause of AE
Unlikely	Improbable	Plausible cause of AE
Unrelated	Incompatible	Can explain AE
Unclassifiable	Insufficient information to permit assessment and identification of cause	

- For drugs, 'dechallenge' & 'rechallenge' key for 1st two categories;
- Concepts removed in a modification of term definitions for AEFI because rarely applicable, especially dechallenge
- Data often missing for concurrent disease/drugs/chemicals
- Places undo emphasis on temporal association

New Developments in Vaccine Safety Monitoring

Canadian Vaccine Pharmacovigilance: Capacity Building

Immunization Monitoring Program Active

- added capacity since 1991 to detect and assess serious adverse events

PHAC-CIHR Influenza Research Network

- newly added capacity - 2009
- Rapid clinical trial network
- Serious Outcomes Surveillance
- Vaccine safety
  - Specific population cohorts followed for safety
  - National approach to allergic, neurologic AEFIs
  - Training Workshops in special epidemiologic methodology, risk benefit assessments
  - Adaptation of clinical investigation models like CISA to Canada

PHAC-funded Vaccine Safety Pilot Projects