Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Not a shot in the dark: Restoring confidence in vaccine safety

PHO Rounds
October 9, 2012

Shelley Deeks, Medical Director
Tara Harris, Nurse Consultant
Immunization and Vaccine Preventable Diseases

Ontario
Agency for Health Protection and Promotion
Agence de protection et de promotion de la santé

Learning objectives

- Describe the scientific framework used to detect and investigate adverse events following immunization.
- Identify and describe the different AEFI surveillance systems in Ontario and Canada.
- Identify and describe how a background incident of an event of interest could be perceived as an AEFI.
- Describe the strengths and challenges of the current system of AEFI surveillance in Ontario and opportunities for system improvement.

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Social context

- Well organised consumer groups
- Popularity of alternative health care
- Increased competition in media
- Rapid communication technologies

The importance of vaccine safety

- Decrease in disease risks and increased attention on vaccine risks
- Vaccination universally recommended and subject to "mandatory choice"
- Public confidence in vaccine safety is critical and key to success of programs
  - Higher standard of safety is expected of vaccines
  - Lower risk tolerance = need to search for rare reactions
  - Vaccinees generally healthy (vs. ill for drugs)

Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Keeping public and providers well informed may help avoid misconceptions

- May be supported by:
  - Understanding that rate of adverse vaccine reactions is considerably lower than the rate of complications resulting from the disease
  - Being aware of benefits and risks of vaccines

The Provider's Role

- Immunization providers can help to ensure the safety and efficacy of vaccines through proper:
  - vaccine benefit and risk communication
  - management of vaccine side effects
  - reporting of suspected side effects to public health

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Adverse effects of measles and measles vaccine

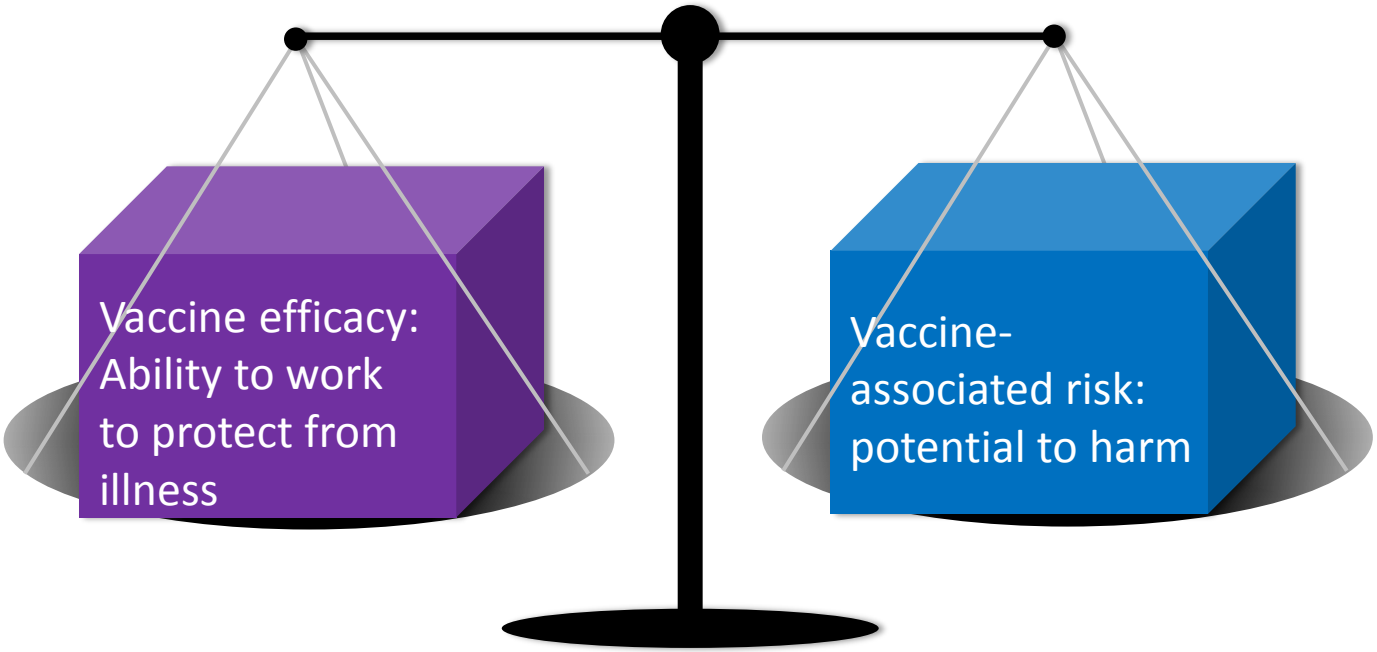
Measles

- hospital admission -1 in 100
- meningitis / encephalitis - 1 in 5,000
- death - 1 in 5,000
- SSPE - 1 in 8,000

Measles vaccine

- allergic response - 1 in 100,000
- meningitis / encephalitis - 1 in 1,000,000
- deaths - 0
- SSPE - not linked

Balancing efficacy and safety of a vaccine



Public Health Ontario | Santé publique Ontario
PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

Global Advisory Committee on Vaccine Safety (GACVS), rotavirus vaccine assessment, Dec 2011

- Both rotavirus vaccines have good safety profile however may be associated with an increased (up to 6-fold) intussusception risk after 1st dose in some populations*
- Risk substantially lower than associated with RotaShield®
- Benefits of rotavirus vaccination for all infants, without age restriction, greatly exceeds risks particularly in developing countries with moderate and high mortality from rotavirus
- Continued surveillance for intussusception encouraged

*http://www.who.int/wer/2012/wer8706.pdf

Is there a perfect vaccine?

Vaccines should cause no adverse reactions and completely prevent the infection that they target

Current technology does not allow for such perfection.

Key is to minimize adverse events and ensure safe use of vaccines

AEFI surveillance monitors adverse events and follows up on severe events that may result from the vaccine.

Monitoring vaccine safety: Pre-licensure

- Clinical trials
- Vaccines are tested in thousands of persons before being licensed
- Common reactions are identified pre-licensure

Monitoring vaccine safety: Post licensure

- Identify rare reactions not detected during pre-licensure studies;
- Monitor increases in known reactions
- Identify risk factors or pre-existing conditions that may promote reactions
- Identify whether there are particular vaccine lots with unusually high rates or certain types of events
- Identify signals of possible adverse reactions that may warrant further study or affect current immunization recommendations

Post-licensure Vaccine Safety Activities

- Phase IV Trials
  - about 10,000 participants
  - better but still limited
- Large-Linked Databases
- Passive surveillance
- Active surveillance
- Observational Studies

An example: Post-marketing safety surveillance: intussusception

- Surveillance has been conflicting regarding association between rotavirus vaccination and intussusception
- Mexico/Australia: risk of intussusception within one week of first dose about 4–6 times higher than in later periods after vaccination *
- USA: recent study demonstrated no increase intussusception risk observed after 786,725 doses*
- Any risk, where found, substantially lower than found with Rotashield

*Patel et al. NEJM, 2011; 364(24). Buttery et al, Vaccine 2011;29(16) , Shui et al. JAMA. Feb 8 2012

Types of vaccine safety issues

- Not all safety issues are related to the vaccine per se
- Vaccine administration errors
  - Storage and handling
  - Administration
  - Documentation
- Adverse events following immunization (AEFI)
  - Temporal associations
  - Causal associations

Types of Administrations Errors

- Wrong vaccine or diluent
- Wrong dosage
- Expired vaccine
- Incorrect route/site/needle size

Definition of an AEFI*

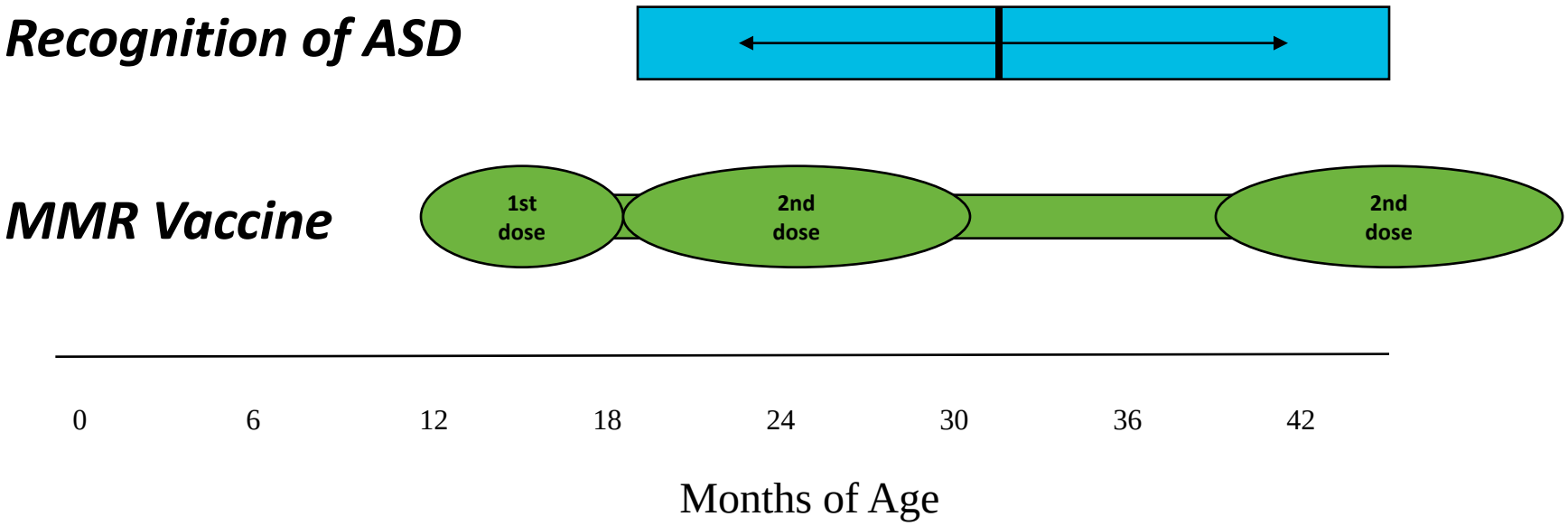
- Any untoward medical occurrence which **follows** immunization and which does **not necessarily have a causal** relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

*http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Coincidence versus Causality



Considerations for causal association

- Event occurs during a plausible time period following vaccination
- Event corresponds to ones previously associated with a particular vaccine
- Event conforms to a specific clinical syndrome whose association with vaccination has strong biologic plausibility (e.g., anaphylaxis) or occurs following the natural disease
- A laboratory result confirms the association (e.g., isolation of vaccine strain varicella virus from skin lesions of a patient with rash)
- Event recurs on re-administration of the vaccine ("positive rechallenge")
- A clinical trial or epidemiologic study shows greater risk of specific adverse event among vaccinated versus unvaccinated groups

Each vaccine component can potentially lead to adverse reaction

ANTIGENS
(processed through attenuation, inactivation, recombination DNA technology.)

Components and processes **ENHANCING IMMUNE RESPONSE,** e.g.

- Adjuvants
- Protein conjugation.

Components **REDUCING CONTAMINATION** during the manufacturing process, transport and storage:

- Antibiotics
- Stabilizers
- Preservatives.

Public Health Ontario | Santé publique Ontario

PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

Frequency of vaccine reactions

Frequency	Occurrence among persons vaccinated in percent	Severity of reactions
Very common	≥ 10%	**Common and usually minor reactions:** 1. Part of the immune response to vaccine, 2. Reactions resolve on own, 3. Examples include: – Fever – Malaise
Common (frequent)	≥ 1% and < 10%	
Uncommon (infrequent)	≥ 0.1% and < 1%	**Rare, usually more severe reactions:** 1. Usually require clinical management, 2. Examples: • Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component, • Vaccine specific reactions, such as vaccine-associated measles
Rare	≥ 0.01% and < 0.1%	
Very rare	< 0.01%	

Types of adverse events

- Local Reactions
  - More common with non-live vaccines containing adjuvants
  - Pain, redness, swelling at injection site
- Systemic Reactions
  - Generally more common following live vaccine, but less severe with subsequent doses
  - Fever, headache, loss of appetite
- Allergic Reaction
  - Anaphylaxis/Severe systemic allergic reaction

What is anaphylaxis?

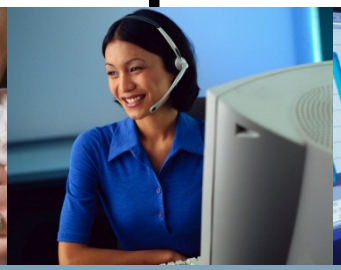
- Essentially an inappropriate immune response
- Occurs as a result of exposure to an allergen to which a person has been sensitised and previously made specific immunoglobulin E (IgE)
- Anaphylaxis can occur on re-exposure to the antigen when explosive amounts of histamine and other chemical mediators are released following the binding of the antigen to IgE coated mast cells.

Potential triggers for anaphylaxis

- Various common food and non food triggers
  - Nuts, shellfish, dairy products, wasp or bee stings, latex, antibiotics, anti-inflammatories)
- Vaccine specific
  - Thiomersal
  - Antibiotics (Neomycin streptomycin and polymixin B)
  - Toxoid (DTaP, Td)
  - Stabilisers and other vaccine components (Yeast, gelatin)

Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Roles and responsibilities in AEFI surveillance


Immunization provider	Public health units	Public Health Ontario	Public Health Agency of Canada	WHO/ Uppsala Monitoring Centre
Inform and counsel re: risks/benefits	Case assessment & management	Provincial surveillance	National AEFI database	Global AEFI database
Recognize and report AEFIs	Reporting of AEFIs (iPHIS)	Case / cluster management advice	Signal detection	Signal detection
Manage AEFIs	Advice re: future immunization	Public health action	Causality assessment	Expert advisory Group

Global Advisory Committee on Vaccine Safety

GACVS is key mechanism to provide prompt and efficient response to concerns about vaccine-related adverse events.

GACVS's committee (14 members) provides:

- **Independent and unbiased** recommendations regarding all aspects of vaccine safety.
- **Broad expertise**, including familiarity with drug regulatory process and special needs of low-income countries.
- **Analysis undertaken with Scientific rigor** based on best available fact, scientific evidence, and process.

Public Health Ontario
PARTNERS FOR HEALTH

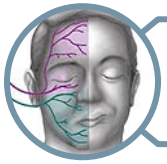
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Examples of Concerns GACVS has addressed

RV vaccine and intussusception

Hepatitis B vaccine
and multiple sclerosis

MMR vaccine and autism



Intranasal influenza vaccination
and the risk of Bell's Palsy

The safety of pneumococcal conjugate
and HPV vaccines

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Acknowledgements

- Patrick Zuber, WHO
- Natasha Crowcroft, PHO
- Barbara Law, PHAC
- Sarah Wilson, PHO

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

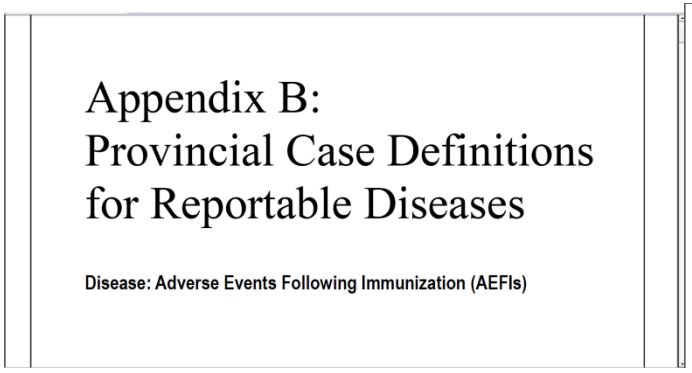
AEFI REPORTING IN ONTARIO

Public Health Ontario | Santé publique Ontario

PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

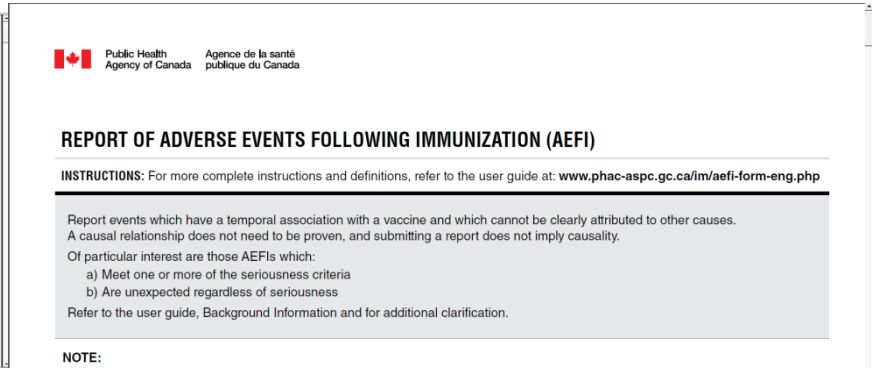
AEFI reporting in Ontario: Guiding documents

- Health Protection and Promotion Act (HPPA), Reg. 38
- Ontario Public Health Standards
- Infectious Disease Protocol, Appendix B
- iPHIS AEFI User Guide
- PHAC AEFI Reporting Form and User Guide



Appendix B:
Provincial Case Definitions
for Reportable Diseases

Disease: Adverse Events Following Immunization (AEFIs)



Public Health Agency of Canada | Agence de la santé publique du Canada

REPORT OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

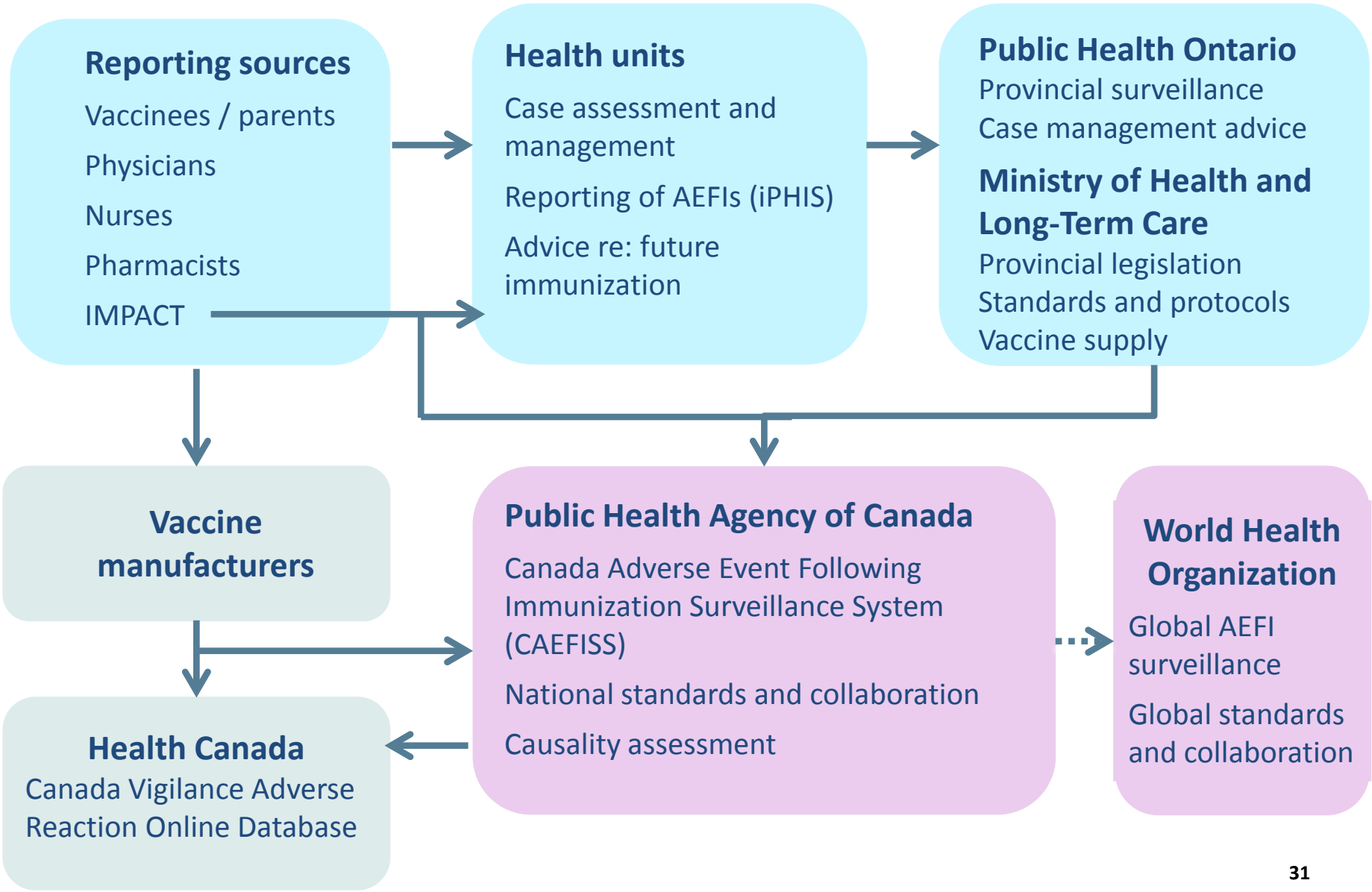
INSTRUCTIONS: For more complete instructions and definitions, refer to the user guide at: **www.phac-aspc.gc.ca/im/aefi-form-eng.php**

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:
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.

NOTE:

Public Health Ontario | Santé publique Ontario
PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

AEFI Reporting Process Flow in Ontario



Public Health Ontario | Santé publique Ontario

PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

What type of AEFI should be reported?

- AEFIs should be reported when the event
  - Is temporally associated with a vaccine
  - Has no other clear cause at the time of reporting
- A causal relationship between the vaccine and the event is not required to report and reporting does not imply causality
- ID Protocol (Appendix B) contains criteria for specific AEFIs

Pop quiz: To report or not to report?

Scenario #1

- 14 y.o. female experiences urticaria (hives) at the injection site within 10 minutes of receiving dose #1 of HPV vaccine
- Treated with ice at the school clinic, no progression to other signs / symptoms; hives resolved within 1 day

Scenario #2

- 13 y.o. female faints within 5 minutes of receiving dose #1 of HPV vaccine at a school clinic
- Student recovered after 30 minutes; well enough to return to class
- No injuries or any other signs / symptoms were present

Public Health Ontario | Santé publique Ontario

PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

Assessment of AEFI surveillance:
Vaccine Safety Surveillance meeting (March 1, 2012)

- Canadian and international experts invited to explore best practice and models of AEFI surveillance
- To inform an evidence and experience-based approach to the renewal and enhancement of AEFI surveillance in Ontario
- Key themes:
  - Partnerships across jurisdictions
  - Capacity and infrastructure at provincial level
  - Support for local / regional networks
  - Database development
  - Analysis and feedback of data

Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Assessment of AEFI surveillance:
Strengths and challenges

- Review of key guidance documents
- Interviews with key informants
- Weekly review of all reported AEFI cases to assess iPHIS data
- Analysis of HPV AEFI data in iPHIS

Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Challenges

- Inconsistent guidance across key documents on AEFI management and reporting (e.g. Appendix B, iPHIS User Guide)
- Data quality issues; limited configuration possible in iPHIS
- Misalignment with national case definitions
- Limited analysis and reporting of AEFI data

- Multiple, interconnected issues, information systems and documents

Strengths

- Committed network across HUs
- Broad support for system improvements
- Rich data being collected at the HU level
- Collaboration across provinces and territories and with PHAC to align AEFI surveillance definitions and processes
- Timely opportunity to implement change

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Enhancing AEFI surveillance in Ontario

Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Enhancing AEFI surveillance in Ontario

- Increased monitoring of AEFIs
- Enhanced collaboration with stakeholders
  - Ontario Vaccine Safety Surveillance Working Group (VSSWG)
- Increased reporting of AEFI surveillance information

Key system improvements - January 1, 2013

- Revised Appendix B (AEFI Case Definitions)
- Updates to iPHIS application and User Guide
- Ontario AEFI reporting form

"Information is knowledge, knowledge is power, and sharing knowledge is empowerment."[1]

1 Rykin SB, Pridmore P. Partners in Planning: Information, Participation and Empowerment . London: Macmillan Education; 2001.
2 © Microsoft Images. 2012. Reproduced with permission.

Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Acknowledgements

VSSWG Members

- Jill Fediurek, Chair
- Dr. Shelley Deeks
- Dawn Williams
- Marlon Drayton
- Tsui Scott
- Ruth Gratton
- Joanne Orr
- Christina Taylor
- Lois Lacroix
- Katie Souliere
- Joanne Vieira
- Mary Ann Holmes
- Karen Dowsett
- Susan O'Gorman
- Julie Lafleche
- Dr. Vinita Dubey
- Dr. Ian Gemmill

Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Questions about vaccine safety?
Send an email to **ivpd@oahpp.ca**

Questions?