Learning objectives

1. Describe adverse events following immunization (AEFIs) reported in Ontario following administration of vaccines in 2014

2. Demonstrate the value of AEFI surveillance with respect to monitoring vaccine safety and building confidence in immunization programs in Ontario
Why is vaccine safety important?

• Public confidence in vaccine safety is critical to immunization program success

• Higher standard of safety is expected of vaccines
  • Administered to large numbers of healthy people, including infants and children
  • Low risk tolerance

• Vaccine are universally recommended, subject to “mandatory choice”

• Increased attention on safety with decreasing disease risk
Vaccine safety in Canada

- Recognized as one of the best vaccine safety systems in the world
- Highly regulated and inspected process
- More stringent than for other drugs
- Safety monitored continuously throughout product lifecycle
- Success depends on communication and coordination across multiple stakeholders
Public health surveillance of vaccine safety

• Cornerstone of post-marketing surveillance of vaccines and publicly-funded immunization programs

• Collaborative system led by Public Health Agency of Canada (PHAC), all 13 P/T public health authorities participate

• Passive (enhanced) reporting of individual case reports (AEFIs)
  ▪ Identifies rare events not detected during clinical trials
  ▪ Generates safety signals that warrant further investigation
  ▪ Informs regulatory actions, public health decision making and communication

• Other post-marketing surveillance activities support ongoing monitoring of safety (e.g., IMPACT)
Adverse event following immunization (AEFI)

An AEFI is any untoward medical occurrence that follows immunization and does not necessarily have a causal relationship with the vaccine.

The adverse event may be any unfavourable or unintended sign, laboratory finding, symptom, or disease.

- AEFIs can be caused by the vaccine or may occur by chance
- Includes both expected (i.e. listed in the product monograph) and unexpected events
- An AEFI is not the same as side effects which are by definition linked to a vaccine by scientific studies

Surveillance of AEFIs in Ontario

**Public health aim:** Early detection and appropriate and timely response to AEFI, to lessen any impact on the health of individuals and immunization programs

- AEFIs are identified and reported by either health care providers, vaccine recipients or their caregivers
  - Health care provider reporting is mandated by provincial public health legislation (*Health Protection and Promotion Act*), all other reporting is voluntary

- Public health units play a central role
  - Receive, assess and investigate AEFI reports
  - Document reports in iPHIS for provincial surveillance
  - Provide information, support and advice to vaccine recipients and health care providers in their community

- Public Health Ontario (PHO) conducts provincial AEFI surveillance and participates in the national AEFI surveillance system
 Annual Report on Vaccine Safety in Ontario, 2014

Objective: To summarize AEFIs reported in Ontario following vaccines administered in 2014

• Reporting trends assessed by comparing with 2010 to 2013 data

• Public health unit (PHU) dissemination (Nov.12), public release (Nov.23)

• “Vaccine in Focus” is influenza vaccine; to be released separately
METHODS

• All reports of AEFIs with a vaccine administration date between January 1 and December 31, 2014 extracted from iPHIS on May 1, 2015

• Reports from 2010-2013 extracted for analysis of temporal trends

• Active immunizing agents only; publicly funded and non-publicly funded vaccines

• Descriptive analysis limited to AEFIs classified as “confirmed” in iPHIS

• Reporting rates calculated based on population estimates/projections for overall rates and doses distributed for vaccine-specific rates

• Serious AEFI defined using WHO/PHAC definition
Notes on interpretation

• AEFI reported in iPHIS are *temporally* associated and are not necessarily causally linked to vaccine

• Assessment is based upon iPHIS data only and not chart review

• Reporting rates are presented for comparison to other AEFI surveillance systems and monitoring reporting trends over time; should not be interpreted as incidence rates

• Trends in reported AEFI are influenced by changes to the publicly funded program
RESULTS – 2014 summary
AEFIs reported in Ontario following vaccines administered in 2014

- 645 AEFIs reported
- 568 (88.1%) of reports had a case classification of “confirmed”, 77 (11.9%) did not meet definition
- Population-based reporting rate of 4.2 per 100 000 population
- 8.4 million doses of publicly funded vaccine distributed
AEFI reports by age and sex

- Age range 2 months to 96 years of age; median 14.3 years
- Highest age-specific reporting rates in <1, 1-3 year olds
- Majority of reports (68.8%) female

Counts and reporting rates of AEFI reports in Ontario by age group and sex, 2014
AEFI reports by vaccine

- Vaccine-specific reporting rates range from 1.0 to 24.1 per 100,000 doses distributed.
- Highest reporting rates were for Men-C-ACWY and HPV4 (24.1 and 20.0 per 100,000 doses distributed, respectively).
- Lowest rates were for MMRV and Td (1.0 and 1.9 per 100,000 doses distributed, respectively).
- Influenza vaccine AEFI reporting rate among the lowest (3.3 per 100,000 doses distributed).
Number and reporting rate of AEFIs in Ontario, by vaccine, 2014

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Number of AEFI reports by vaccine</th>
<th>Number of serious reports</th>
<th>Doses distributed</th>
<th>Vaccine-specific reporting rate</th>
<th>2013 vaccine-specific reporting rate</th>
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<tbody>
<tr>
<td><strong>Infant and childhood vaccines</strong></td>
<td></td>
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<tr>
<td>DTaP-IPV-Hib</td>
<td>53</td>
<td>5</td>
<td>564,520</td>
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<td>Pneu-C-13</td>
<td>54</td>
<td>9</td>
<td>432,470</td>
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<tr>
<td>Rot-1</td>
<td>21</td>
<td>4</td>
<td>259,680</td>
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<tr>
<td>Men-C-C</td>
<td>26</td>
<td>6</td>
<td>160,485</td>
<td>16.2</td>
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<td>MMR</td>
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<td>Var</td>
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<td>MMRV</td>
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<td>-</td>
<td>-</td>
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<td>Men-C-ACWY</td>
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<td>1</td>
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<td>35.2</td>
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<td>HB</td>
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<td>1</td>
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<td>16.0</td>
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<td>HPV4</td>
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<td>160,052</td>
<td>20.0</td>
<td>26.4</td>
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<tr>
<td>Tdap</td>
<td>76</td>
<td>2</td>
<td>631,905</td>
<td>12.0</td>
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<td><strong>Routine adult vaccines</strong></td>
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<td>Pneu-P-23</td>
<td>33</td>
<td>3</td>
<td>241,318</td>
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<tr>
<td>Td</td>
<td>5</td>
<td>0</td>
<td>267,105</td>
<td>1.9</td>
<td>4.7</td>
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<tr>
<td><strong>Universal Influenza Immunization Program (UIIP)</strong></td>
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<tr>
<td>Inf</td>
<td>147</td>
<td>3</td>
<td>4,436,080</td>
<td>3.3</td>
<td>4.4</td>
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</table>
Number of serious and non-serious AEFI reports by adverse event and category, 2014

Notes:
1. Non-serious AEFIs within each event category. All serious AEFIs within each event are shaded purple.
2. Pain, redness or swelling at the injection site includes: pain, redness or swelling at the injection site lasting 4-10 days, 10 days and/or pain, redness or swelling at the injection site (of any duration) extending beyond the nearest joint.
Rash

- 89 reports of rash, 43% (n=54) associated with live virus vaccines (MMR, varicella and zoster)
- Over half of MMR (53%) and varicella (56%) rashes were within the expected timeframe for vaccine-associated rash (5 to 42 days), 20% for zoster vaccines
- 7 MMR rashes with measles vaccine-strain virus confirmed by genotyping, 1 report of vaccine strain zoster infection following varicella vaccine

Anaphylaxis

- 11 “events managed as anaphylaxis”; reporting rate of 1.3 per million doses distributed
- Six (55%) met Brighton case definition (four level II and two level III for diagnostic certainty)
- Increased proportion met Brighton definition compared to previous years
Serious AEFIs

• 23 serious AEFIs (4.0% of reports); reporting rate of 2.6 per million doses distributed
• All but one report was hospitalized for a mean length of stay of 3.9 days; 8 documented as reported by IMPACT
• Majority under 18 years (82.6%); 21.7% under 1 year
• Most (69.6%) were completely recovered at the time of reporting
Serious AEFIs

- 7 fever/rash illness
  - 3 Kawasaki disease and one lab-confirmed vaccine-strain measles infection

- 5 cellulitis

- 4 seizures
  - Two diagnosed seizure disorders, one diagnosed as infantile spasms, one febrile seizure

- One possible vaccine-associated encephalitis following yellow fever vaccine

- One report of death in an infant 4 days after receipt of routine vaccines
  - Coroner’s investigation was completed which found the cause of death to be unascertained, with unsafe sleep environment as a contributing factor (No link with vaccine was reported)
AEFI reports by health care utilization and outcome

Out-patient medical consultation  72.4%
ER visit  20.5%
Hospitalization  3.9%

• Most individuals (74.6%) were recovered at the time of reporting, 22.8% not yet recovered, 2.4% with residual effects

• Reports with residual effects reviewed, none met the definition (persistent/significant disability or incapacity)
RESULTS - Reporting trends
Number of “confirmed” AEFI reports and reporting rate by year, 2010-14
Number of AEFI reports and publicly funded vaccine distribution in Ontario, by month, 2012-14)

Notes:
1. Includes net vaccine distribution from Ontario Government Pharmacy & Medical Supply Service (OGPMSS) (i.e., publicly funded vaccine doses) only. Counts include all confirmed AEFIs reported 2012-2014.
Reporting trends by age

AEFI reporting rate per 100,000 population in Ontario, by age group, 2012-14

Graph showing the reporting trends by age group from 2012 to 2014.
Trends by reporting source

Percent distribution of AEFIs by reporting source, 2012-14

- Physician
- Other health care professional
- Family member
- Self (client)
- Other

Reports by year:
- 2012
- 2013
- 2014
### Counts and reporting rates of AEFIs for school-administered and primary care-administered agents, 2012-14

<table>
<thead>
<tr>
<th>Reporting source</th>
<th>2014</th>
<th>2013</th>
<th>2012</th>
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</thead>
<tbody>
<tr>
<td>School-administered vaccines(^1)</td>
<td>89</td>
<td>115</td>
<td>103</td>
</tr>
<tr>
<td>Reporting rate (per 100,000 doses(^3) distributed)</td>
<td>15.1</td>
<td>20.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Primary care-administered vaccines(^2)</td>
<td>110</td>
<td>122</td>
<td>101</td>
</tr>
<tr>
<td>Reporting rate (per 100,000 doses(^3) distributed)</td>
<td>5.6</td>
<td>6.0</td>
<td>4.9</td>
</tr>
</tbody>
</table>

**Notes:**

1. Includes AEFI reports occurring after the administration of Men-C-ACWY, HB, or HPV4 vaccines, in adolescents between 11 and 17 years of age, inclusive.
2. Includes AEFI reports occurring after the administration of DTaP-IPV-Hib, Pneu-C-13, Rot-1, Men-C-C, MMR, or Var vaccines, in children less than 4 years of age.
3. Doses distributed are obtained from Ontario Government Pharmacy and Medical Supply Service (OGPMSS) and are calculated for school- and physician-administered agents.
DISCUSSION
Overall provincial AEFI reporting rate

• Increasing trend 2010-2014; reason for decrease in 2014 unknown; not limited to one vaccine or type of event
• Provincial AEFI reporting rate continues to be substantially lower than the national reporting rate
  • 4.2 vs. 10.1 per 100,000 population, respectively
• Higher overall reporting rate is an indicator of a robust passive vaccine safety surveillance system
• Reassuring the public health delivered programs have higher reporting rate
Under-reporting

- Inherent limitation of all passive AEFI surveillance systems although more pronounced in Ontario
- One of the lowest reporting rates is for the largest program (UIIP); although consistent with other jurisdictions
- Lower reporting for primary care-delivered programs compared with public health-delivered programs
- Potential barriers include: time constraints, uncertainty about how to report, what to report, who is responsible for reporting
Female predominance in AEFI reports

• Females consistently outnumber males in AEFI reports overall and specifically in adult age groups

• Analysis of 2012-13 Ontario data\(^1\) showed
  • Highest reporting rate ratios for specific types of reactions (allergic events, anaesthesia/paraesthesia)
  • Higher female predominance among self-reported AEFIs compared to reports from health care providers
  • No disproportionate reporting for serious AEFIs

• Possible influencing factors include vaccine uptake, health care seeking behaviors and biological differences

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Injection site reactions

- Typically mild, self-limited events which resolve completely; not a contraindication to further doses of vaccine
- Continues to be the most frequently reported type of event in Ontario
- Consistent with the safety profile of most vaccines
- Volume of reports has decreased slightly (~8%) compared to previous years
- Case definition revised in 2013 to reduce reporting burden (exclude reactions lasting less than 4 days)
Rash

- Frequent reporting similar in other passive surveillance, particularly after live virus vaccine

- Estimated to occur in 5-10% and 3-5% for MMR and varicella vaccines\(^1\), respectively; much less common with 2nd dose

- Lab-confirmation of vaccine virus is rare, usually the result of measles investigation

- More likely to be vaccine associated if accompanied by local injection site reaction

- Not a contraindication to further vaccines

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Image source: Centers for Disease Control and Prevention


Serious AEFIs

• Serious events to vaccines are very rare
  • 3 reports for every 1 million doses distributed
  • Reporting rate has been stable over time

• Most frequently reported events among serious AEFIs were febrile/rash illness and cellulitis
  • Both events are known to rarely occur after vaccines, not a contraindication to further doses of vaccine

• Report of sudden infant death subject to coroner’s investigation and Pediatric Deaths Under Five Review Committee; no link to immunization made
  • Temporal association not unexpected given timing of infant vaccines and peak onset of sudden infant death
SIDS and vaccines

- Infant deaths temporally linked to vaccines rare but consistently observed in passive systems
- Background rate of SIDS in Canada is 18.5 per 100,000 live births\(^1\)
- No causal association between vaccines and SIDS has been shown\(^2\); vaccines may actually reduce the risk of SIDS\(^3\)
- The cause of SIDS is unknown but is likely multifactorial including genetic, metabolic, and environmental factors\(^4\)
- Studies have identified important modifiable risk factors including infants sleeping in prone position and maternal smoking during pregnancy\(^4\)

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Limitations

• Data quality and completeness

• Reporting bias
  • Under-reporting (mild or common events), stimulated reporting in response to media coverage/public awareness.

• Lack of a population-based provincial immunization registry to estimate the number of individuals who were immunized or doses administered

• Doses distributed used as proxy denominator for vaccine-specific reporting rates
  • Only in established programs with stable distribution
  • Can result in over/underestimation of reporting rates due to lack of reliable wastage information, data on private purchase
CONCLUSIONS

• Vaccines administered in Ontario in 2014 resulted in a low rate of reported adverse events
• Most reported events were mild and resolved completely
• No unexpected safety issues were identified
• Under-reporting of AEFI continues to be an important limitation of AEFI surveillance in Ontario
• Further research is needed to
  • Assess AEFI reporting awareness and practices among Ontario health professionals
  • Inform strategies to increase AEFI reporting and strengthen provincial vaccine safety surveillance
Next steps

- Release of report and supporting materials on PHO website
- Poster presentation at TOPHC
- Dissemination of “Immunizer Overview” to health care providers
- Evaluation
TOP 5 AEFI REPORTING TIPS

1. Advise patients to contact you if they experience an adverse event after vaccination.
2. Report AEFIs to your local public health unit
3. Use the Ontario AEFI reporting form
4. Report events that are temporally associated with vaccination, which cannot be clearly attributed to other causes
5. If in doubt, report!

www.publichealthontario.ca/vaccinesafety
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Questions

www.publichealthonario.ca/vaccinesafety