

2005/2006 Public Health WORKS Speaker Series
April 18, 2006

Vaccine Safety Pre and Post Licensing

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

Public Health WORKS!!!

Vaccination - an outstanding Public Health achievement

<u>Disease</u>	<u>Pre-vaccine</u>	<u>1999</u>	<u>% change</u>
Diphtheria	9,000	1	-100
Measles	300,000	29	- 99.99
Mumps	52,000	90	- 99.79
Pertussis	25,000	6,096	- 69.92
Polio	20,000	0	-100
Rubella	69,000	24	- 99.9
CRS	2,000	1	- 99.95
Tetanus (deaths)	40-50	0	-100
Invasive Hib	2,000	30	- 97.5
TOTAL	477,050	6,271	- 98.7%

Flu shot not necessary and not most effective

INSIGHT
 SATURDAY, MARCH 4, 2000 THE EXPOSITOR PAGE A10
Taking a shot at vaccination

Dear Editor,

Are you too going to panic and jump on the "there's a flu out-break get a vaccination" bandwagon?

The latter two ingredients are toxic heavy metals that have been linked to an increase in Alzheimer's disease (and they're injecting this in to the elderly!).

More parents refusing vaccinations

HALIFAX (CP) — Public health officials are worried about a growing trend: parents who refuse to get their children vaccinated.

The refusal, based on what officials say are myths about the dangers of vaccines, is putting children at risk of brain damage and complications associated with diseases whooping cough, measles, and hepatitis disease experts say.

"Many parents have a poor unders

Mandatory immunization wrong

Your Opinion

SIR: With immunization in the news again recently, I would like to add my feelings on this very controversial subject.

I think it is wrong for any institution and especially the government, our government, to even consider passing legislation requiring control? Is this why the risks are kept hidden? We are encouraged to eat right, to get enough calcium, vitamins and minerals and to do everything we can to be healthy.

Well, watching what goes into our bodies is obviously very important. Do you really think it is

In Patter Sound saying effecti za." I s breaks vaccin by the ings nursin

Vaccination lecture sparks community debate

Continued from PAGE A10

Some parents will simply take their doctor's advice and have their children immunized.

Others will want to know what the risks of vaccination are and still others will want even more detailed information.

The information so they can make an informed choice," Barker said. "Without the information there isn't an informed choice."

And, he added, whatever the choice, he and other medical professionals should and will respect it.

He acknowledged that the booklet Your Child's Best Shot does address questions concerning the risks associated with vaccinations.

But the publication of the book was sponsored by pharmaceutical companies which, for him, renders it suspect at best. Moreover, the information concerning the risks is limit

Doctors, government won't tell the truth about vaccination

I wasn't surprised to read the conservative tone in your Insight feature on the vaccination controversy and the accompanying editor (Immunization: the best information - March 4).

After all your paper is owned by that famous "progressive" thinker Conrad Black s

ord, Brant County h a provincial ap- biodati accountable ome into a commu- ts, leave and never equences of her ac- eals with a variety

People have a choice

Dr. Stephen Barker believes all people should have as much detailed information as they can possibly get to make an informed decision about vaccination.

READERS' OPINIONS

Informed parents deciding against inoculations

The story, *More parents choose not to vaccinate: study* (SP Dec. 4), indicated concern about the chapter of Vaccination Risk Awareness Network, a national organization. Our mandate is to inform the public. Cure Autism Now Foundation says "approximately one-half of the hundreds of parents who call our office each month report that

.....such negative attitudes toward vaccines and immunization. Why?

Why Has Vaccine Safety and Even Necessity Become a Topic for Debate?

Disease	Pre-vaccine	1999	% change
Diphtheria	9,000	1	-100
Measles	300,000	29	- 99.99
Mumps	52,000	90	- 99.79
Pertussis	25,000	6,096	- 69.92
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Tetanus (deaths)	40-50	0	-100
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TOTAL	477,050	6,271	- 98.7%

AEFI	0	4000	+ 100%
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*Immunization Bottom Line: Public Health vs **Public** Focus*

Vaccine Safety

- ☞ A challenge that will never go away
- ☞ Continued success of immunization programs requires a comprehensive, effective and efficient vaccine safety system
- ☞ Healthcare provider and public education essential components
- ☞ Stakeholders must be convinced of the merit of adverse event reporting

Objectives

By the end of this session participants will be able to:

- ↓ Describe what is and isn't known about a vaccine's safety profile when it is first marketed
- ↓ Illustrate the flow and related activities associated with a report of an adverse event following immunization from the local to an international level and all points in between
- ↓ Summarize the type and quality of evidence available to inform vaccine safety
- ↓ Summarize the current status of key vaccine safety issues

OBJECTIVE 1

What is and isn't known about a vaccine's safety profile when it is first marketed?

Terms Used to Indicate Adverse Event Frequency

Related adjective	Detectable Range
Very common	$>1/10$
common	$> 1/100$ and $<1/10$
uncommon	$> 1/1000$ and $< 1/100$
Rare	$>1/10,000$ and $< 1/1,000$
Very rare	$<1/10,000$

Clinical Phases of Vaccine Evaluation

What is learned about safety?

Phase	Study subjects	Key Study Objectives
I	10-<100	<ul style="list-style-type: none"> ◆ Immunogenicity ◆ Local/systemic reactions
II	50-500	<ul style="list-style-type: none"> ◆ Optimal dose/schedule in target population(s) ◆ Ongoing safety assessment
III	300-30,000	<ul style="list-style-type: none"> ◆ Immunogenicity/Efficacy in target population(s) ◆ Ongoing safety assessment
Regulatory approval for vaccine marketing		
IV	Varies by objective (100s to 1000s)	<ul style="list-style-type: none"> ◆ Immunogenicity/efficacy in unstudied populations ◆ Possible vaccine-vaccine interactions ◆ Expanded safety assessment
Post-market Surv.	General population	<ul style="list-style-type: none"> ◆ “Real world” effectiveness ◆ Rare or unexpected adverse events (“signals”)

Clinical Phases of Vaccine Evaluation

What is learned about safety?

☞ Prior to marketing approval

- ↓ Common (>1%) and uncommon (0.1-1%) adverse reactions in the primary target population
 - Local injection site reactogenicity
 - Systemic reactions - fever, headache, rash
- ↓ May know attributable risk if appropriately controlled studies done

☞ Postmarketing Data required for everything else!

- ↓ Common / uncommon reactions in non-primary target populations
- ↓ Rare events
- ↓ Long term safety issues

OBJECTIVE 2

Illustrate the flow and related activities associated with a report of an adverse event following immunization from the local to an international level and all points in between



National Adverse Event Following Immunization Report Form

Available

Web (www.phac-aspc.gc.ca/im/aefi-form_e.html)

Local public health units

Compendium of Pharmaceuticals and Specialties(CPS)

Current VAAE form

lists several selected AEs deemed to be of interest to Public Health ("Vac-ART")

"ART" = Adverse Reaction Terminology

written text used to code additional AE information using "WHO-ART"

Health Canada / Santé Canada
REPORT OF A VACCINE-ASSOCIATED ADVERSE EVENT
 Protected when completed

in confidence to: Division of Immunization
 L.C.D.C., Tunney's Pasture 0603E1
 Ottawa, Ontario, K1A 0L2
 (613) 957-1340 1-800-363-6456 FAX (613) 998-6431

IDENTIFICATION		PROVINCE/TERRITORY		DATE OF BIRTH	YEAR	MONTH	DAY	SEX	DATE OF VACCINE ADMINISTRATION	YEAR	MONTH	DAY
PATIENT IDENTIFIER								<input type="checkbox"/> Male <input type="checkbox"/> Female				

VACCINES						
VACCINE(S) GIVEN	NUMBER IN SERIES	SITE	ROUTE	DOSAGE	MANUFACTURER	LOT NUMBER

ADVERSE EVENT(S) *Events marked with an asterisk (*) must be disclosed by a physician. Report only events which cannot be attributed to co-existing conditions. Additional information for all events should be provided under SUPPLEMENTARY INFORMATION on reverse side. Record interval between vaccine administration and onset of each event in minutes, hours or days.*

LOCAL REACTION AT INJECTION SITE <input type="checkbox"/> INFECTED ABSCESS (tick one or both of the options below) (i) positive gram stain or culture <input type="checkbox"/> (ii) existence of purulent discharge with inflammatory signs <input type="checkbox"/> <input type="checkbox"/> STERILE ABSCESS/ABSCESSE No evidence of acute microbiological infection <input type="checkbox"/> SEVERE PAIN AND/OR SEVERE SWELLING (tick one or both of the options below) (i) lasting 4 days or more <input type="checkbox"/> (ii) extending past needle (parities) <input type="checkbox"/> <input type="checkbox"/> SCREAMING EPISODE/PERSISTENT CRYING Inconsole for 3 hours or more. OR quality of cry definitely abnormal for child and not previously heard by parents <input type="checkbox"/> FEVER Highest recorded temperature (Report only 38.0°C (102.2°F) or above) Temperature: _____ °C (or _____ °F) Site: rectal <input type="checkbox"/> oral <input type="checkbox"/> axilla <input type="checkbox"/> skin <input type="checkbox"/> tympanic <input type="checkbox"/> Temperature believed to be high but not recorded <input type="checkbox"/> Should be supported by the presence of other systemic symptoms <input type="checkbox"/> ADENOPATHY (tick one or both of the options below) (i) enlarged lymph node(s) <input type="checkbox"/> (ii) drainage of lymph node(s) <input type="checkbox"/> Site(s): _____ <input type="checkbox"/> PAROTITIS Swelling with pain and/or tenderness of parotid gland(s) <input type="checkbox"/> ANAPHYLAXIS OR SEVERE SHOCK Explosive, occurring within minutes after immunization, and evolving rapidly towards cardiovascular collapse AND requiring resuscitative therapy <input type="checkbox"/> OTHER ALLERGIC REACTIONS (tick one or more of the options below) (i) wheezing or shortness of breath due to bronchospasm <input type="checkbox"/> (ii) swelling of mouth or throat <input type="checkbox"/> (iii) skin manifestations (e.g. hives, eczema, pruritus) <input type="checkbox"/> (iv) facial or generalized edema <input type="checkbox"/> <input type="checkbox"/> RASHES (other than hives) Lasting 4 days or more AND/OR requiring hospitalization Generalized <input type="checkbox"/> Localized (indicate site) <input type="checkbox"/> Specify characteristics of rash: _____ <input type="checkbox"/> ARTHRALGIA/ARTHRITIS Joint pain/inflammation lasting at least 24 hours If condition is an acute exacerbation of a pre-existing diagnosis, give details under Supplementary Information	<input type="checkbox"/> SEVERE VOMITING AND/OR DIARRHEA Must be severe enough to interfere with daily routine <input type="checkbox"/> HYPOTONIC-HYPORESPONSIVE EPISODE (in children < 2 yrs. only) Characterized by all 3 categories of: (i) generalized decreases/loss of muscle tone; AND (ii) pallor or cyanosis; AND (iii) decreased level of awareness or loss of consciousness Should not be mistaken for fainting, a post-convulsion state, or anaphylaxis <input type="checkbox"/> CONVULSION/SEIZURE Febrile <input type="checkbox"/> Afebrile <input type="checkbox"/> Past history of: A) Febrile seizures Yes <input type="checkbox"/> No <input type="checkbox"/> B) Afebrile seizures Yes <input type="checkbox"/> No <input type="checkbox"/> Onset timing: seizures occurring within 30 minutes of immunization, and seizures occurring as part of encephalopathy or meningitis/encephalitis <input type="checkbox"/> ENCEPHALOPATHY Acute onset of major neurological illness characterized by any two or more of: (i) seizures; (ii) distinct change in level of consciousness or mental status (behavior and/or personality) lasting 24 hours or more; (iii) focal neurological signs which persist for more than 24 hours <input type="checkbox"/> MEINGITIS AND/OR ENCEPHALITIS Abnormal CSF findings AND an acute onset of: (i) fever with neck stiffness or positive meningeal signs; OR (ii) signs and symptoms of encephalopathy (see ENCEPHALOPATHY above) Results of CSF examination should be provided under Supplementary Information <input type="checkbox"/> ANAESTHESIA/PARAESTHESIA Lasting over 24 hours Generalized <input type="checkbox"/> Localized (indicate site) _____ <input type="checkbox"/> GUILLAIN-BARRÉ SYNDROME Progressive symmetric weakness of more than one limb (typically symmetric) with hypo-reflexia/areflexia <input type="checkbox"/> PARALYSIS (Do not code if Guillain Barre Syndrome is coded) Limb paralysis <input type="checkbox"/> Facial or cranial paralysis <input type="checkbox"/> Describe: _____ <input type="checkbox"/> THROMBOCYTOPENIA Give lab results under Supplementary Information <input type="checkbox"/> OTHER SEVERE OR UNUSUAL EVENTS Include any adverse event believed to be related to immunization, that does not fit any of the categories listed above and for which no other cause is clearly established Report events of clinical interest which require medical attention, and particularly events that are (i) fatal; (ii) life-threatening; (iii) require hospitalization; or (iv) result in residual disability DESCRIPTION: _____
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REPORTER'S NAME	TELEPHONE NUMBER	ADDRESS (Institution/No., Street, etc.)
PROFESSIONAL STATUS: MD <input type="checkbox"/> RN <input type="checkbox"/> OTHER <input type="checkbox"/>		
SIGNATURE	DATE Year Month Day	City Province Postal Code

HC/SC 4229 (03-96) - 1

Canadian Adverse Event Following Immunization Surveillance System "CAEFISS"



PASSIVE SYSTEM

Parent/Client/Patient

ACTIVE SYSTEM

IMPACT

Vaccine Providers
Healthcare Providers

Vaccine Manufacturers

P/T Health
Local/Central

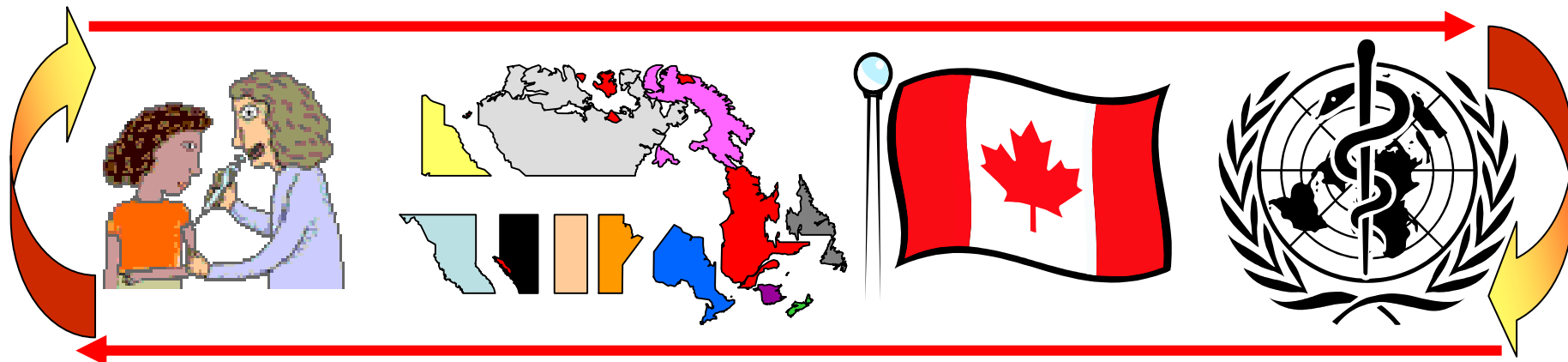
Travel Clinics

PHAC - IRID
Vaccine Safety Unit

WHO Drug Monitoring Program



Adverse Event Report Flow and Activities



Vaccine /Healthcare Provider	Local Health Units and Central P/T Health	Public Health Agency of Canada	World Health Drug Monitoring Program
Inform and Counsel re risks/benefits	Case management regarding AE / AE clusters	National CAEFI database	Global AE database
Recognize and report AEs	Follow-up	Signal Detection	Signal Detection
Manage individual AEs	Public Health Action	Causality Assessment	Expert Advisory Group

Vaccine Safety: Roles and Responsibilities

Parent/Client /Patient	<ul style="list-style-type: none"> ☞ Informed decision making ☞ Reporting adverse events
Healthcare provider	<ul style="list-style-type: none"> ☞ Facilitate informed decision making ☞ Recognize, manage and report adverse events
P/T Health (local/central)	<ul style="list-style-type: none"> ☞ Recognize, manage and report adverse events ☞ Case management and follow-up / Public health action re immunization issues
PHAC	<ul style="list-style-type: none"> ☞ Maintain national AEFI database ☞ National Signal Detection ☞ Causality assessment / Public health action
IMPACT	<ul style="list-style-type: none"> ☞ Case finding and Reporting
WHO	<ul style="list-style-type: none"> ☞ Global Signal detection ☞ Expert advice
Manufacturer	<ul style="list-style-type: none"> ☞ Best practices to produce safe products ☞ Periodic Safety Update Reports
Regulator	<ul style="list-style-type: none"> ☞ Ensure safety of marketed products pre and post licensure



IRID's Vaccine Safety Unit Current Activities / Priorities

- ➡ **National AEFI data management**
- ➡ **Active Surveillance Initiatives**
 - ↓ IMPACT
- ➡ **Causality Assessment**
- ➡ **Feedback / Communication / Education**
- ➡ **Facilitate F/P/T Vaccine Safety Network**
 - ↓ Including efforts to harmonize AEFI definitions / reporting
 - ↓ Pandemic preparedness / postmarketing surveillance of pandemic vaccine
- ➡ **Support Expert Working / Task Groups**
- ➡ **Collaboration / Support for International Endeavours**
- ➡ **AEFI Risk Management**

IMPACT: Description

- ➡ 12 Canadian tertiary care pediatric centres
- ➡ All provinces represented, some indirectly
- ➡ Each centre has a Nurse monitor
 - ↓ Supervised by Pediatric Infectious Disease investigator
- ➡ Active surveillance for selected targets
- ➡ 75,000 admissions annually (90% Cdn total)

IMPACT: Targets

Post-Immunization Adverse Events

- ☞ **Neurological**
 - ↓ seizures
 - ↓ encephalitis/encephalopathy, including SSPE
 - ↓ acute flaccid paralysis
 - ↓ aseptic meningitis
- ☞ **Hypotonic-hyporesponsive episodes (HHE)**
- ☞ **Other**
 - ↓ anaphylaxis
 - ↓ severe local
 - ↓ thrombocytopenia,
 - ↓ arthritis

ACCA: Advisory Committee on Causality Assessment

- ☞ **Committee of experts**
 - ↓ Includes clinical medicine and public health / epidemiology
 - ↓ CDC, FDA, VICP, ACIP
- ☞ **Serious cases reviewed**
 - ↓ Automatic database extracts
 - ↓ Less than 5% of database
- ☞ **Outcomes**
 - ↓ Only 25% of serious cases are likely causally related to vaccination
 - ↓ 1/3 are deemed unrelated
 - ↓ Data for proper assessments are lacking in 1/4

Causality Assessment Form

Identification: _____		Vaccine(s): _____	
1. Primary reason for reporting: _____			Code: [] [] []
1.1 Agreement with report:			
Agree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>
	Error of coding?	Yes <input type="checkbox"/> No <input type="checkbox"/>
		Is the event severe?	Yes <input type="checkbox"/> No <input type="checkbox"/>
		Insufficient data	<input type="checkbox"/>
	To be reviewed again?	Yes <input type="checkbox"/> No <input type="checkbox"/>
2. These questions are related to the primary reason for reporting only:			
2.1 Frequency of occurrence of the adverse event	NPR <input type="checkbox"/>	Rare <input type="checkbox"/>	Intermediate <input type="checkbox"/> Common <input type="checkbox"/>
2.2 Similar events known to occur with other disease		Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.3 Event is known to be related to this vaccine		Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.4 Event is explainable by the biological properties of the vaccine		Yes <input type="checkbox"/>	No <input type="checkbox"/> Unknown <input type="checkbox"/>
2.5 Vaccine-event interval compatible with the event	n/a <input type="checkbox"/>	Typical <input type="checkbox"/>	Compatible <input type="checkbox"/> Incompatible <input type="checkbox"/>
2.6 The patient had similar symptoms in the past	n/a <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/> Unknown <input type="checkbox"/>
2.7 Concomitant or preceding drug therapy		Yes <input type="checkbox"/>	No <input type="checkbox"/> Unknown <input type="checkbox"/>
2.8 Concomitant or preceding condition	Rel. <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/> Unknown <input type="checkbox"/>
2.9 Other contributing factors		Yes <input type="checkbox"/>	No <input type="checkbox"/> Unknown <input type="checkbox"/>
Rel*: assessment of causality to be done in context of <u>relevant</u> condition. NPR: not previously reported			
3. Conclusion with regard to the primary reason for reporting:			
3.1 The association is:		3.2 Possible new entity []	
[] 1 Very likely - certain	[] 4 Unlikely		
[] 2 Probable	[] 5 Unrelated		
[] 3 Possible	[] 6 Unclassifiable:	3.3 insufficient data []	
3.4 The case would benefit from a second review:		Yes <input type="checkbox"/> No <input type="checkbox"/>	
4. Comments: _____			
5. Recommendations: _____			
6. Useful for Education: Yes <input type="checkbox"/> No <input type="checkbox"/>		7. Useful for Publication: Yes <input type="checkbox"/> No <input type="checkbox"/>	

Vaccine Safety Unit, IRID, PHAC

Feedback, Communication, Education

- ☞ **National immunization reports**
 - ↓ Hiatus of reporting since 1998!
 - ↓ 2004 report nearing completion
 - ↓ Plans for annual updates
- ☞ **Electronic transfer of data back to P/Ts**
- ☞ **Enhancements to Safety portion of PHAC website**
 - ↓ Web-access to CAEFISS data
 - ↓ Web-based periodic AEFI summaries by vaccine
- ☞ **New chapter in CIG focused on Vaccine Safety**
- ☞ **Key publications in peer-reviewed journals / CCCR**
- ☞ **Synergy with other NIS initiatives**
 - ↓ Registries: Vaccine Information Database System (VIDS)
 - ↓ Professional / Public Education



Vaccine Safety Unit, IRID, PHAC Facilitate F/P/T Vaccine Safety Network

- ☞ **Consultative Meetings with all P/T Jurisdictions**
 - ↓ Jan 05 - ON
 - ↓ Mar 05 - SK, MB, AB, BC, NT, YU
 - ↓ Feb 06 - QC
 - ↓ Mar 06 - NB, NS, PEI, NL
 - ↓ Apr 06 - NU
- ☞ **Consultative meetings with vaccine manufacturers**
 - ↓ Capture distribution by lot number to P/T jurisdictions
- ☞ **Adverse Event Reporting Standards Task Group**
 - ↓ F/P/T reps working by teleconference/e-mail to update the AEFI report form and key case definitions
- ☞ **Promote/identify expert consultants network for AEFI investigation and management - future priority**



Vaccine Safety Unit, IRID, PHAC
Support Expert Working / Task Groups

- ☞ **Vaccine Safety Expert Working Group (VSEWG)**
 - ↓ Terms of Reference under development
 - ↓ Membership to be completed by end of March/06
 - ↓ Annual meetings, and ad hoc as needed

- ☞ **Advisory Committee on Causality Assessment (ACCA)**

Vaccine Safety Unit, IRID, PHAC

Collaboration/Support for International Endeavours

- ☞ **WHO - Global Advisory Committee on Vaccine Safety**
- ☞ **Uppsala Drug Monitoring Program**
- ☞ **Brighton Collaboration**
- ☞ **Council for International Organizations of Medical Sciences / WHO Working Group on Vaccines**
- ☞ **U.S. initiatives in vaccine safety**
 - ↓ U.S. Vaccine Safety Data Link
 - ↓ Centers for Immunization Safety Assessment (CISA)

OBJECTIVE 3

Summarize the type and quality of evidence available to inform vaccine safety

Evidence on Vaccine Safety

👉 Empirical

- ↓ Case reports/series that allege but don't prove an association
- ↓ Personal testimonials

👉 Surveillance data

- ↓ Passive systems
- ↓ Active systems

👉 Scientific data

- ↓ Placebo-controlled randomized trials
- ↓ Population-based epidemiologic studies
- ↓ Ecologic studies
- ↓ Rigorous Case reports that provide definitive proof

👉 Expert / Systematic Reviews

Empirical Evidence

☞ Oxford English Dictionary

↓ Noun: A member of the sect among ancient physicians called *Empirici* (), who (in opposition to the *Dogmatici* and *Methodici*) drew their rules of practice entirely from experience, to the exclusion of philosophical theory.

↓ Adjective: guided by mere experience, without scientific knowledge

Adverse Event Following Immunization

"AEFI"s = Temporal Associations

"post hoc ergo propter hoc"

⇒ Occurring afterward therefore occurring because..

- ☞ Major problem for vaccines, especially child vaccines
- ☞ Neurologic and other problems due to
 - genetic influences
 - intrauterine damage - toxins, infections, maternal illness
 - birth injury
 - bacterial or viral infections
 - post-natal toxins / injuries
- ☞ Onset during the time when many vaccines are given

Evidence on Vaccine Safety Surveillance Data

- ☞ **VAERS - Vaccine Associated Adverse Event Reporting System**
 - ↓ U.S.A.
 - ↓ Commonly cited to support empirical observations
 - ↓ Misused and poorly understood
- ☞ **CAEFI data will soon be on the web**
- ☞ **Main purpose is for signal detection**
 - ↓ Rotavirus vaccine and intussusception
 - ↓ Influenza vaccine and oculorespiratory syndrome
 - ↓ Urabe mumps vaccine and parotitis
- ☞ **Many limitations which must be appreciated in order to educate the public**

Evidence on Vaccine Safety Surveillance Data: Limitations

- ☞ Lack of an appropriate control group
- ☞ Reporting bias may give false appearance of increased frequency of an event when in fact it is only the rate of reporting that has increased possibly due to
 - ↓ major media focus on allegations such (eg autism and MMR vaccine)
 - ↓ markedly increased frequency of immunization (eg mass campaigns)
 - ↓ enhanced awareness following recognition of clusters of specific adverse events (eg ORS)
- ☞ Lack of use and/or adherence to standard case definitions
- ☞ Incomplete detail to support a given diagnosis and/or consider other possible causes (eg intercurrent infection /concomitant drugs)
- ☞ Underreporting
- ☞ Lack of appropriate denominators

	AEFI	No AEFI
Vaccine	a	b
No vaccine	c	d

Evidence on Vaccine Safety

Scientific Data

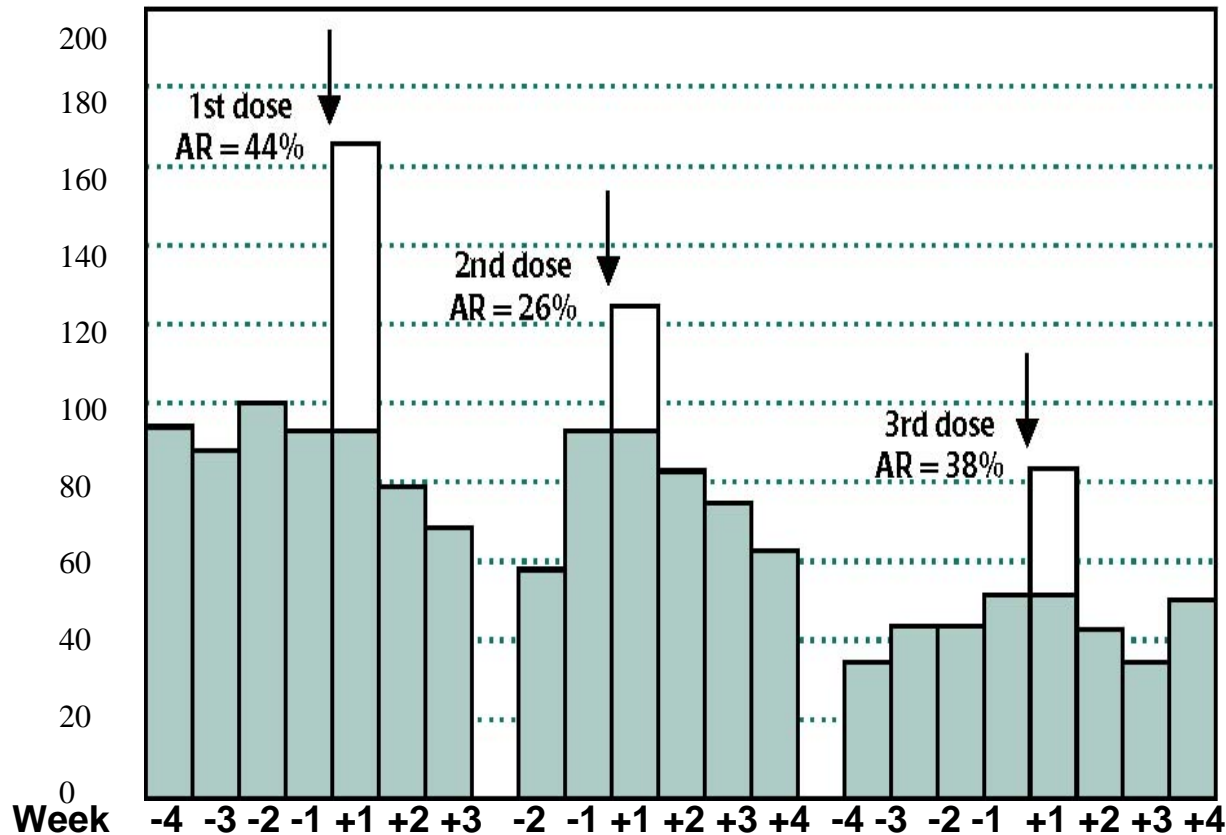
Randomized controlled trials

↓ May be very helpful for risk communication

↓ May allow determination of attributable risk

8 week period of Observation post:	VZV vaccine (n=491)	Placebo (n=465)
Irritability	24%	20%
Tiredness	20%	22%
Headache	15%	16%
Cough	45%	48%
Common cold	63%	65%
Poor sleep	12%	13%
Loss of appetite	11%	13%

Total adverse events before and after each of the 3 Doses of Hepatitis B Vaccine



The white bars indicate attributable risk due to Hepatitis B vaccine

De Serres G. et al, 2001; Am J Public Health 91(2):313-15.

Evidence on Vaccine Safety

Scientific Data

☞ Population-based epidemiologic studies

- ↓ Cohort studies: compare AE rate in immunized versus non-immunized populations
- ↓ Case-Control studies: compare immunization rate for cases with AE to controls without AE
- ↓ Validity, generalizability and utility of data highly dependent on study design

☞ Ecologic studies

- ↓ utilize "natural experiments" involving historical or geographic variation in vaccine use to compare incidence of adverse events
- ↓ may be confounded by differences in diagnostic criteria, healthcare standards, health seeking behavior to name a few

☞ Rigorous Case Studies

- ↓ May be able to prove a causal association between vaccine and AE
 - Measles vaccine encephalitis
 - Disseminated BCG

Evidence on Vaccine Safety Expert / Systematic Reviews

- ☞ **Institute of Medicine (www.iom.edu)**
 - ↓ Formed in 1970 by US National Academy of Sciences
 - ↓ Two independent, expert review panels considered issues related to vaccine safety (1977-1994; 2001-2005)
 - ↓ Review all pertinent written evidence and hear oral presentations
 - ↓ Neutral starting point and judge whether the evidence is sufficient or insufficient to either accept or reject a causal association
 - ↓ Anonymous external panel with immunization expertise reviews and make suggestions, but final report represents IOM consensus only.
- ☞ **WHO Global Advisory Committee on Vaccine Safety (www.who.int/immunization_safety)**
 - ↓ Established in 1999 to provide prompt, scientific evidence-based responses to safety issues of global concern
 - ↓ Meets twice annually (Dec, Jun) and publishes reports in Weekly Epidemiological Record (www.who.int/wer/en)
- ☞ **Cochrane Collaboration (www.cochrane.org)**
 - ↓ Limited to randomised controlled trials, so little information on vaccine safety, especially uncommon or rare events

OBJECTIVE 4

**Summarize the current status
of key vaccine safety issues**

Key Vaccine Safety Issues: Current Status

Exposure	Not causally associated with:	Year Reviewed / National Academies Press Site Address for Specific Citation
Multiple immunizations	Increased susceptibility to infection Type 1 diabetes mellitus Sudden infant death syndrome	2002 http://fermat.nap.edu/catalog/10306.html 2003 http://fermat.nap.edu/catalog/10649.html
MMR vaccine Thimerosal containing vaccines	Autism	2004 http://fermat.nap.edu/catalog/10997.html
H. influenzae b conjugate vaccines	<i>H. influenzae</i> infection shortly after immunization	1994 http://fermat.nap.edu/catalog/2138.html
Hepatitis B vaccine	Incident cases / Relapses of multiple sclerosis in adults	2002 http://fermat.nap.edu/catalog/10393.html
Influenza vaccine	Relapses of multiple sclerosis	2004 http://fermat.nap.edu/catalog/10822.html
Diphtheria and/or tetanus toxoid containing vaccines	Acute / chronic encephalopathy Sudden infant death syndrome Infantile spasms (hypsarrythmia)	2003 http://fermat.nap.edu/catalog/10649.html 1994 http://fermat.nap.edu/catalog/2138.html
Whole cell pertussis vaccines	Sudden infant death syndrome	2003 http://fermat.nap.edu/catalog/10649.html

Vaccine Safety Surveillance in Canada

Back to the Future

- ☞ What can we learn from “The Great Vaccine Mess”?
- ☞ Pandemic planning

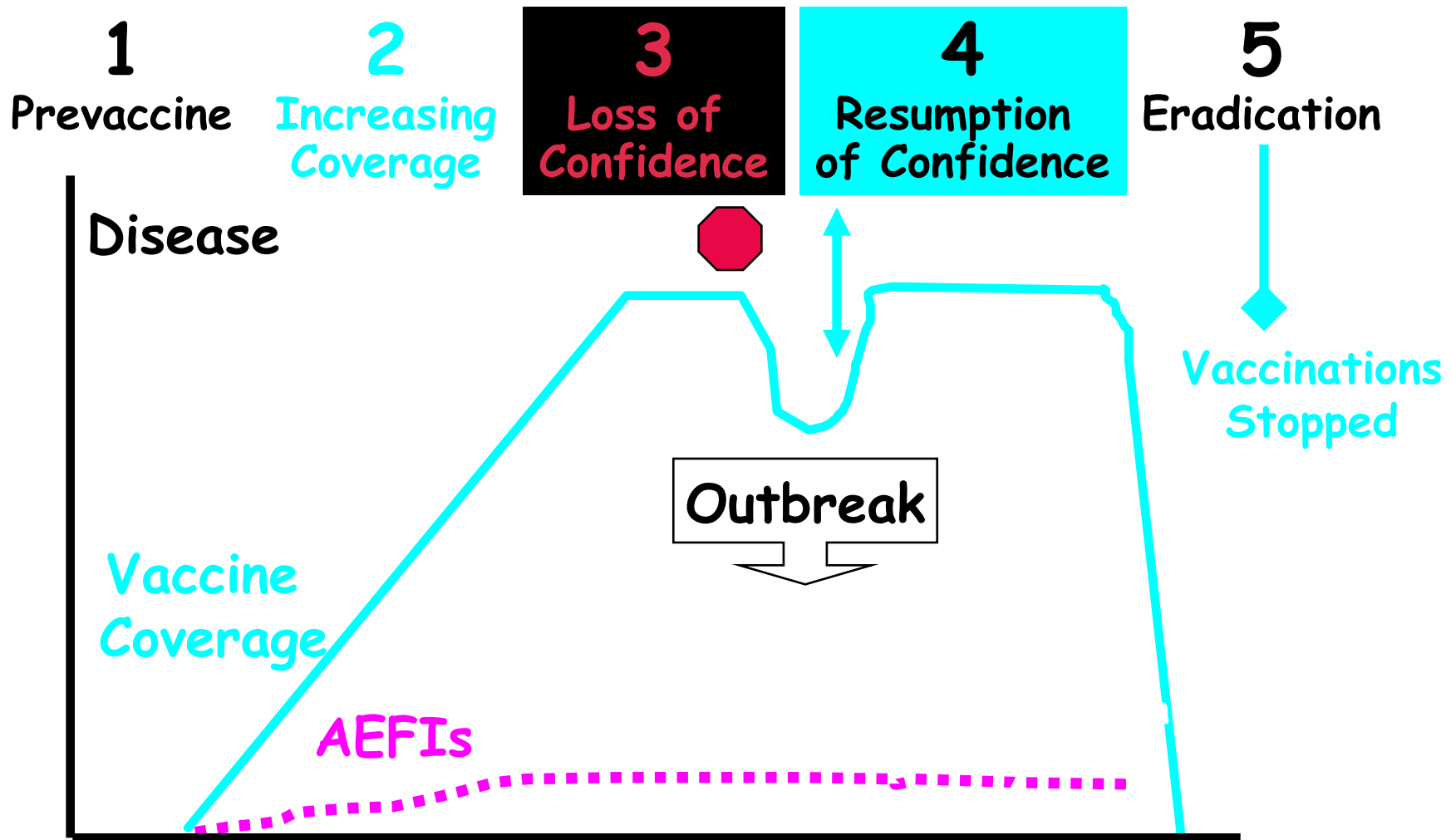
Vaccine Safety Challenges Surveillance + Research

☞ "Minimally the practice of evidence-based public health requires that the right people have the right information at the right time and in the right format (ie "just in time" access to evidence)"

*Evidence-based Decision Making in Canada, Kiefer et al, Cdn J Pub Hlth
May-Jun/05*

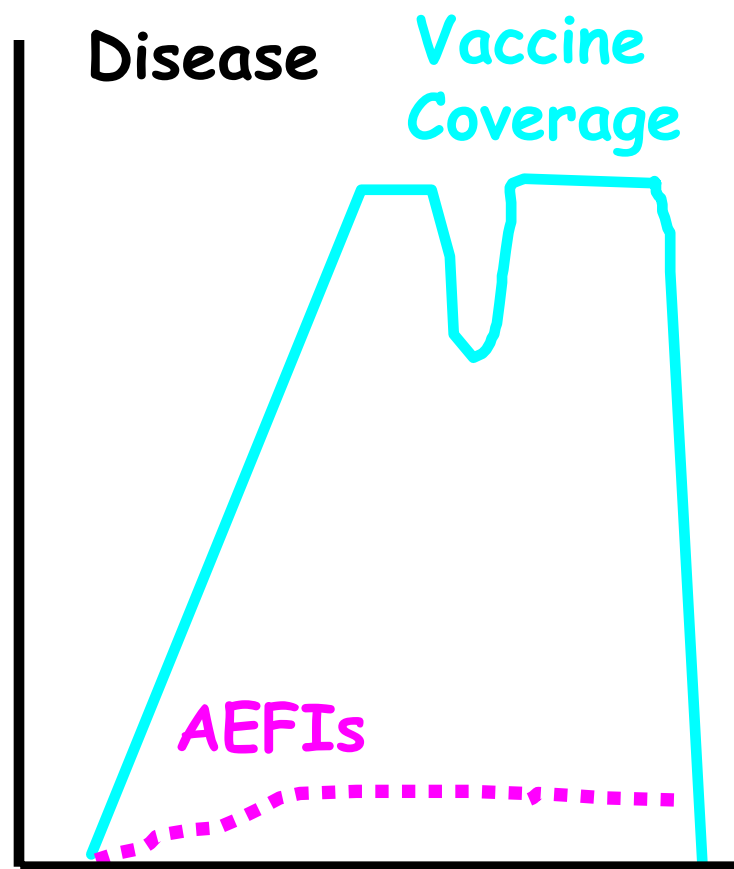
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Natural History of Immunization Programs



Robert Chen, CDC

Natural History of Pertussis Immunization Programs

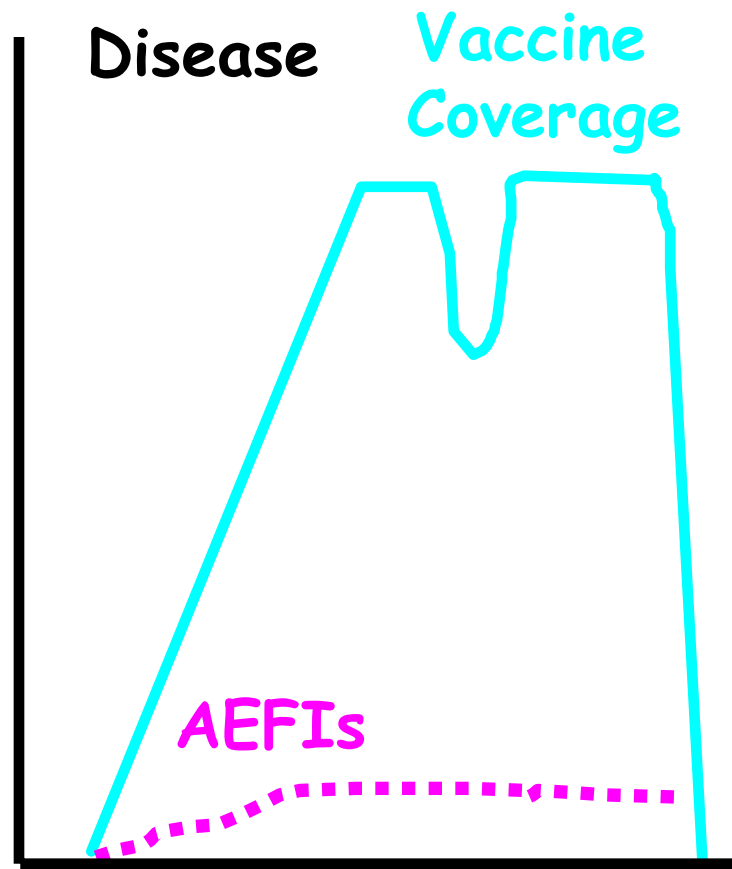


Concept: Bob Chen, CDC

- Pre-vaccine(~1950):
 - >100,000 cases/yr
- 1974: 90% vaccine coverage
 - 200-400cases/yr;
 - 2-3 deaths/yr
- 1975: 2 infants died post DPT
- Vaccine stopped for 2 months
- But loss of public confidence
 - Vaccine coverage fell to <40%
- 1976-79: epidemic of pertussis
 - ✉ >13,000 cases
 - ✉ >100 deaths

Reality: Japan, 1970s

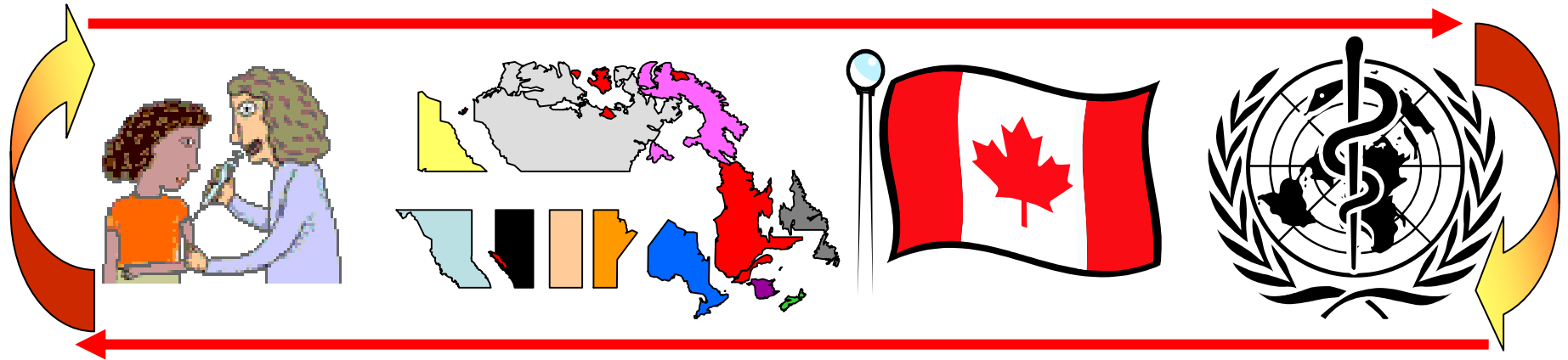
Natural History of Immunization Programs



- Japanese "pertussis experience" repeated in many countries
- UK: Autism scare / drop in MMR coverage / measles outbreaks
- Manitoba: MS allegation / France stops HBV school program / poor compliance with grade 4 school-based HBV program
- Is this cycle inevitable or.....
- Can a comprehensive Vaccine Safety System prevent or limit the impact of perceived and real threats of vaccine-associated damage to health?

Concept: Bob Chen, CDC

Adverse Event Report Flow and Activities



Vaccine /Healthcare Provider	Local Health Units and Central P/T Health	Public Health Agency of Canada	World Health Drug Monitoring Program
Inform and Counsel re risks/benefits	Case management regarding AE / AE clusters	National CAEFI database	Global AE database
Recognize and report AEs	Follow-up	Signal Detection	Signal Detection
Manage individual AEs	Public Health Action	Causality Assessment	Expert Advisory Group