



# **THE TRUTH ABOUT VACCINE SAFETY IN CANADA**

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# THE IMMUNIZATION PREMISE

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- Administer a safe substitute to elicit protection against a pathogen, before children encounter it and suffer illness
- Immunization must be substantially less risky than the target infection to be acceptable
- Special burden of preventive interventions, as they are offered to healthy individuals



# VACCINE SAFETY

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“Safe substitution” is the core value of immunization, outweighing effectiveness, cost, convenience etc.

Public expectations of vaccine safety rise as the disease target disappears from view



# DIMENSIONS OF VACCINE SAFETY

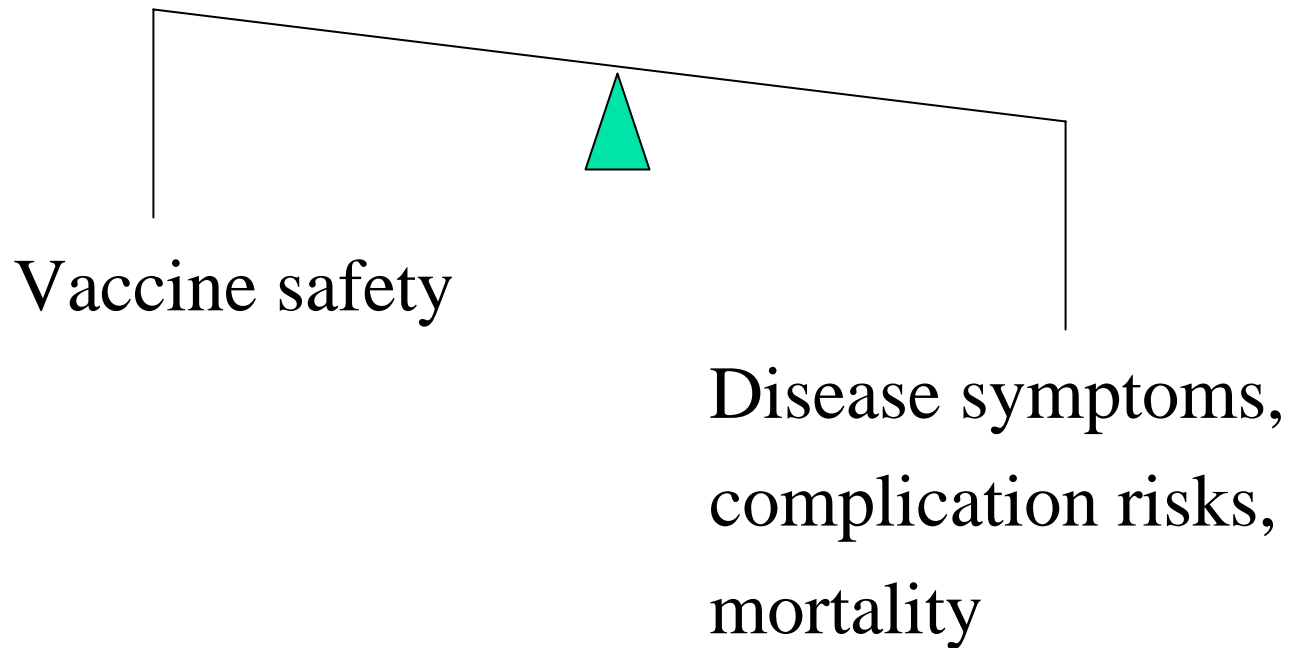
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- Product – purity, consistency, stability
- Injection site effects – pain, inflammation
- Systemic adverse effects – fever, rash etc
- Uncommon severe adverse effects
- Co-incidental but unrelated adverse events



# SUBSTITUTION PREMISE

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# MEASLES VS MEASLES VACCINE

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100% — Fever — 10%

100% — Rash — 5%

3% — Pneumonia — 0%

1:2,000 - Thrombocytopenia - 1:30,000

1:1,000 - Encephalitis - 1 per million



## SUBSTITUTION PREMISE

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- Clearest with familiar childhood infections of recognized severity (actual or potential)
- Less obvious to consumers when target is unfamiliar or non-serious or remote



## STARTING WITH THE BEST

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- MEASLES, MUMPS, RUBELLA – fine tuning of attenuation of live virus vaccines maximized safety and effectiveness
  - RA27/3 Rubella vaccine
  - Jeryl Lynn Mumps strain
  - Edmonston further attenuated Measles

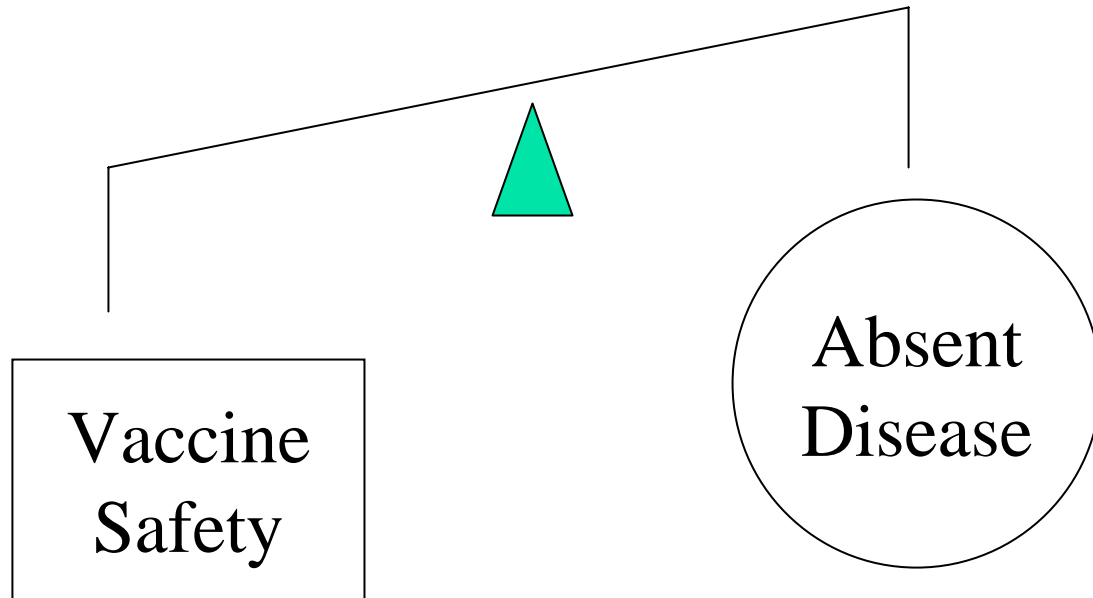


# WHAT ABOUT DISAPPEARING RISKS?

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- Effective immunization programs reduce or eliminate cases so target becomes unfamiliar
- Control requires maintenance of high immunization rates
- Vaccine safety compared to negligible risk of disease exposure – acceptable?

# VACCINE RISKS WITH DISEASE CONTROL





# REMEDIES FOR CHANGING SAFETY MARGIN

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## SMALLPOX

With verified global eradication (1977), routine vaccination could be stopped. Best solution to changing safety margin, rarely possible.



# REMEDIES TO CHANGING SAFETY MARGIN (2)

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## POLIOMYELITIS

Elimination of disease transmission in Americas prompted switch to IPV (1992), avoiding rare cases of OPV-associated paralysis.



# REMEDIES TO CHANGING SAFETY MARGIN (3)

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## PERTUSSIS

Public intolerance of whole cell vaccine risks (real and alleged) prompted development and substitution of acellular pertussis vaccines.



# WHOLE CELL VERSUS ACELLULAR PERTUSSIS VACCINES

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50%

Fever

15%

+++

Irritability,  
crying

+

1:2000

Febrile seizure

< 1:10,000

1:2000

HHE

< 1:10,000

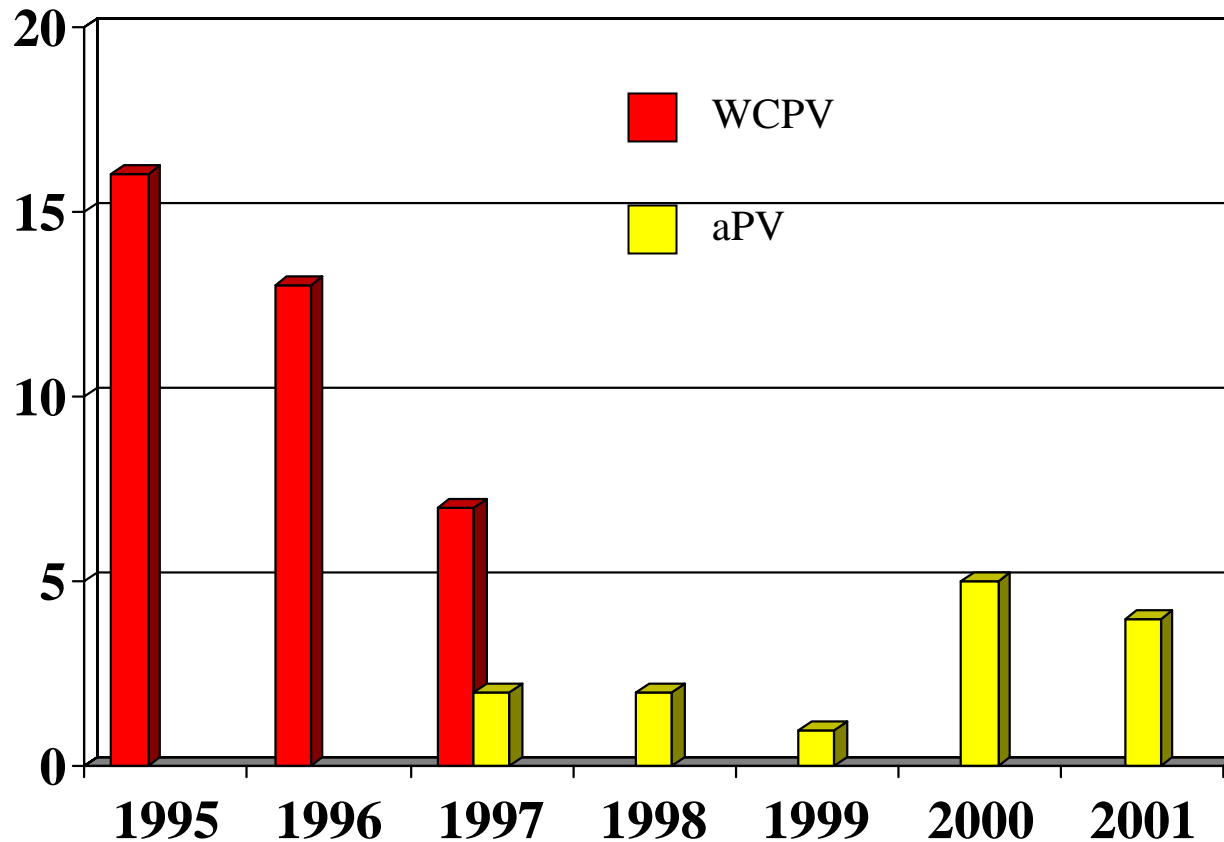


# CPS/HEALTH CANADA “IMPACT” SURVEILLANCE

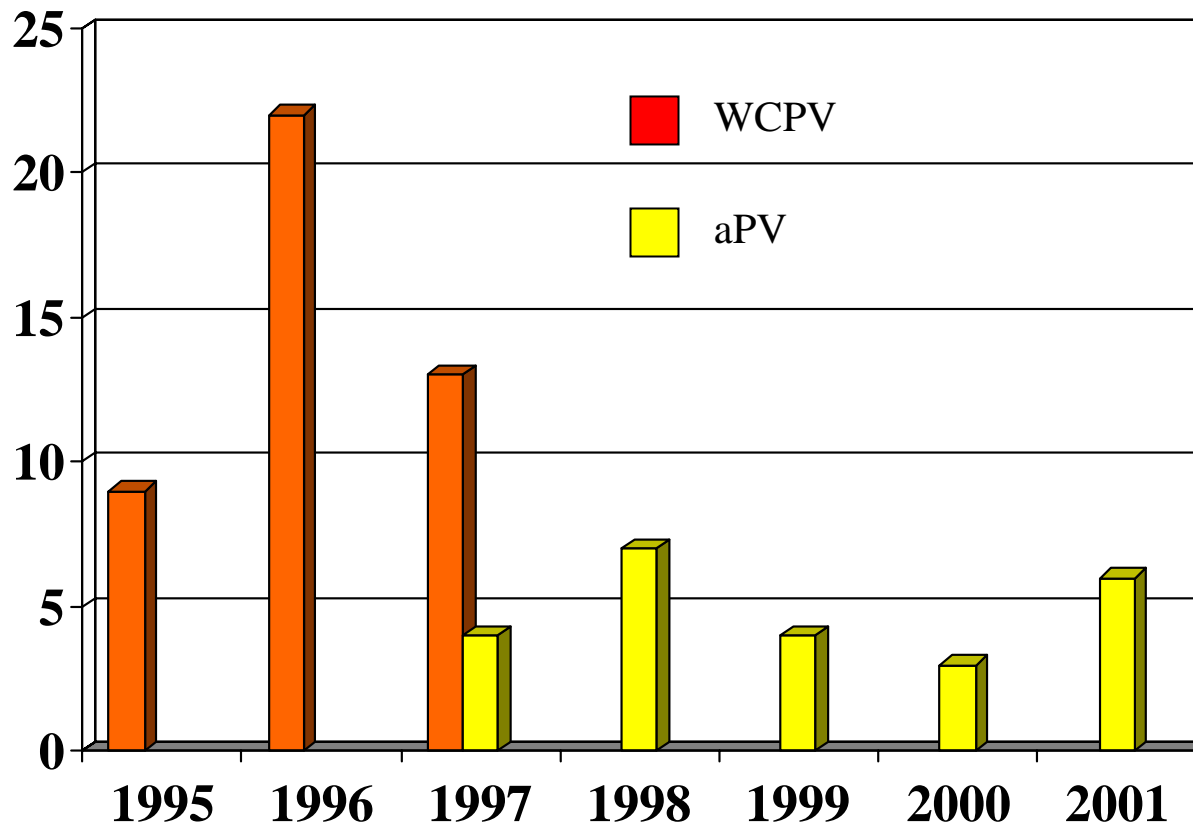
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- Active surveillance by nurse monitors at 12 pediatric centers
- Review each neurologic admission for recent immunization
- Ongoing since 1992
- Able to observe effect of switch to aP in 1997

# FEBRILE SEIZURES AFTER PERTUSSIS-BASED VACCINES



# HYPOTONIC-HYPORESPONSIVE EPISODES AFTER PERTUSSIS VACCINATION





# SUMMARY OF IMPACT NETWORK OBSERVATIONS

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- Switch to aP-based vaccines associated with:
  - 80% decrease in febrile seizures
  - 60-67% decrease in HHE

Both risks estimated at  $< 1$  per 10,000 doses

Follow-up studies show no neurologic impact



# ENCEPHALOPATHY AFTER PERTUSSIS VACCINATION

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- Fear of possibility caused loss of public confidence in UK, low immunization rates led to large epidemic in 1980's
- Large National Childhood Encephalopathy Study in UK showed little or no risk associated with wP vaccine
- IMPACT study since 1992 detected no instance of encephalopathy likely due to wP or aP vaccine



# IMPACT CASES OF ENCEPHALOPATHY AFTER PERTUSSIS VACCINES

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<u>Year</u>	<u>Age</u>	<u>Onset/vaccine</u>	<u>Neurologic diagnosis</u>
1993	4 yr	d6 (WCPV)	Herpes simplex encephalitis
1993	2 mo	d4 (WCPV)	Influenza A encephalopathy
1997	2 mo	d3 (WCPV)	Parainfluenza 2 encephalopathy
1998	18 mo	d1 (aP)	Influenza A encephalopathy
1998	2 mo	d7 (aP)	Influenza A encephalopathy
1998	4 mo	d5 (aP)	Gastroenteritis, hemorrhagic
2002	4 yr	d2 (aP)	Metabolic encephalopathy

Moore et al PIDJ 2004



## CONCLUSION OF IMPACT STUDY

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No evidence for attributable brain injury with over 3 million doses of aP vaccine given to children living near IMPACT centers and over 12,000 neurologic admissions screened

(Source Moore D et al PIDJ 2004;23:568-71)



# LOOKING AHEAD TO NEXT SUBSTITUTIONS

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## MEASLES

- Live attenuated vaccine occasionally causes high fever, febrile seizures, thrombocytopenia, encephalitis
- Whereas, wild virus circulation has ceased and is nearing elimination in Americas
- Inactivated nasal spray vaccines in development



# THROMBOCYTOPENIA AFTER MMR VACCINE

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- Rate estimated at 1:29,000 first doses
- IMPACT case series of over 70 children shows generally good outcome with IVIG Rx
  - complications rare
  - most resolve within 30 days
  - Most have an alternate cause

(Source Jadavji T et al PIDJ 2003)



# TECHNICAL ADVANCES IN VACCINE SAFETY

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- Elimination of thimerosal preservative from all infant and childhood vaccines
- Search continues for less reactogenic adjuvant than aluminum salts
- Optimization of immunization schedule to minimize adverse events



# LOCAL INFLAMMATION WITH “BABY SHOTS”

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- Progressive increase in rate and size of local reactions through the recommended DTaP series
- Dose 1-3.....3-5% >10 mm
- Dose 4 ( 18 mo)... 20% >35mm, 3% >50mm
- Dose 5 ( 4-6 yrs)....33-50% >50mm

Similar pattern was seen with DwPT vaccines



## BOOSTER DOSE TRIAL , DOSE 5

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- Healthy 4-6 year old children, 4 previous doses of Pentacel
- Randomly assigned to receive DTaP.IPV or Tdap in observer blinded fashion
- Examined by research nurse 2 days later, at reaction peak
- Primary outcome was rate of redness, swelling >50mm



## TRIAL RESULTS, DAY 2

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	DTaP ( 145)	Tdap (143)	p value
<b>Redness</b>			
>25mm	26.2%	9.8%	0.0003
>50mm	17.2%	6.3%	0.004
<b>Swelling</b>			
>25mm	35.9%	23.1%	0.017
>50mm	13.8%	7.7%	0.09
>100mm	3.4%	3.5%	



# BOOSTER STUDY CONCLUSIONS

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- Rate of large reactions after DTaP.IPV was lower than in previous studies of same design
- Reaction rates similar to a study in BC by Skowronski et al ( R 24%, Sw 16% > 46mm)
- Tdap reduced but did not eliminate large reactions
- Reactors more often had elevated levels of antibody to D, P toxin, pertactin
- Reactors more often had elevated CMI to PT
- Delaying this dose might also reduce reactions



# ADVANCES IN VACCINE SAFETY SURVEILLANCE (1)

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- Major step forward is analysis of large, linked databases
  - permits recognition of unanticipated risks, rare associations
  - methodology developed by US HMO's
  - soon possible for provinces to do likewise
  - registries will aid IMPACT surveillance
- Offers powerful means to discount untrue allegations



# ADVANCES IN VACCINE SAFETY SURVEILLANCE (2)

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- Interesting advance is new CDC-sponsored network of centers to investigate sufferers of VAAE's
  - using standard protocols, new technology
  - could reveal mechanisms, predispositions, strategies for avoidance
- Parents appreciate attention to concerns, less likely to join “disaffected lobby” on internet etc



## VACCINE SAFETY ADVANCES (3)

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- New products are being evaluated in larger numbers of subjects than ever before, both before and after initial licensure
- Can expect licensure delays in secondary markets while safety studies are extended
- Result will be increased product costs



# CONCLUSIONS

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- 1. Canadian children are presently offered the safest vaccines ever available, although none is perfectly safe.**



## CONCLUSIONS

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2. **Vaccine safety is being evaluated more closely now than ever before,** although more likely needs to be done to reassure a skeptical populace.



## CONCLUSIONS

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3. Proactive approach to replacing reactogenic vaccines with safer alternatives is necessary when diseases are well controlled, but runs contrary to economics.