Global Collaborative Network for Vaccine Safety Studies

Potential......Significance!

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Public Health Agency of Canada
Define potential
Meeting objectives
Vaccine safety history 101
- Disasters breed legacies
- Signals bring changes
- Perfect Storms happen........repeatedly
- Complacency is not an option
7 Habits of Highly Effective ‘Networks’
Potential defined
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

Define Potential

- currently unfulfilled capacity to improve, develop, and achieve impressive feats
  
  en.wicktionary.org/wiki/

- inherent capacity for coming into being
  
  wordnetweb.princeton.edu/perl/webwn

- having potential as a particular thing or for a particular purpose
  
  encarta.msn.com

Purpose: an anticipated outcome that is intended or that guides your planned actions
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

Meeting Objectives

- bring together investigators who have or want vaccine safety evaluation infrastructure
- share information, practical lessons and experiences, what works, what doesn’t
- create links to facilitate rapid communication and future collaboration on emerging vaccine safety concerns
- delineate levels of evidence for vaccine safety from signal detection to refutation/confirmation
- link attainable levels of evidence to infrastructure for a given adverse event
- explore regulatory implications of making improvements beyond the current infrastructure
- discover & describe synergies of a global network
- identify next steps
Impact of vaccine safety concerns

- Real and perceived
- Plausible and implausible
- Proven and theoretical
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

Historically reactive > proactive

Safety disasters...............Changes made

1. 1900s Tetanus contamination of smallpox vaccines
2. 1920s Septic deaths due to contamination of multi-dose vials
3. 1954 Cutter incident—Incomplete inactivation of vaccine polio virus
4. 1950s/60s Thalidomide disaster
5. 1970s/80s Pertussis encephalopathy issue + lawsuits
6. 1990s to present Allegations of autism link to MMR, thimerosal

1. State regulations that each vial must be inspected
2. Preservatives in multi-dose vials (thimerosal)
3. Vaccine regulation plus US IES proving ground
4. Mandatory / voluntary reporting systems
5. National Childhood Vaccine Injury Act (US), IOM panel
6. Linked administrative data studies, new methodologies to assess vaccine causation
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

Historically reactive > proactive

Problems identified............Action taken

1. Aseptic meningitis following MMR vaccine containing Urabe mumps
2. Highly reactogenic whole cell pertussis vaccine
3. Vaccine associated paralytic polio due to vaccine > wt polio in NA
4. Intussusception following first reassortant rotavirus vaccine

1. Vaccine taken off market
2. Replaced by less reactogenic acellular pertussis vaccine
3. Oral polio replaced by inactivated polio vaccines
4. Vaccine taken off market
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

Historically reactive > proactive

Problems identified ............... Action taken but remained vulnerable to the...
Vaccine Safety 'Perfect Storms'
Whole cell pertussis vaccine and brain damage

- 1933 Danish case report death post-pertussis vaccine
- 1946-1960 case reports+series seizure, brain damage
- 1973-John Wilson reported 50 brain-damaged children post DPT to Royal Society of Medicine
- UK “This Week” TV show interviewed Wilson + caption 'every year about 100 children are brain damaged'
- Media firestorm erupted
  - Association of Parents of Vaccine Damaged Children
  - Other MDs joined in (notably Gordon Stewart - epidemiologist)
- Jul76-Jun79: UK Childhood Encephalopathy Study
  - Statistically significant association with DPT - about 1/100,000
- 1985 First of several UK court cases
Vaccine Safety ‘Perfect Storms’
Whole cell pertussis
vaccine and brain damage

- 1988 ‘Loveday’ lead case in class action lawsuit (>200)
- Judge Murray Stuart-Smith conducted trial in 2 parts:
  - Could vaccine cause permanent damage?
  - Who qualified for compensation?
  - Trial lasted 4 months, with 19 expert witnesses + cost > $1 million
- Judgment read over 2 days (>1 million words, 14 chapters) Citing Samuel Johnson (“it is incident I am afraid, in physicians above all men, to mistake subsequences for consequences.”) he noted:
  - only possible to assess pertussis vaccine as a risk factor for brain damage if background incidence considered
  - Miller study: effort to appease vaccine damage lobby introduced unfair bias vs vaccine; bowing to political pressure, published prematurely
- Concluded pertussis vaccine didn’t cause permanent brain damage
- 1956-2001: multiple studies in different countries; definite risk of febrile seizure post DTP but no association with brain damage
### Europe - United Kingdom
- 73: Wilson discusses case series report on ‘This week’
- Media barrage ensues
- Assoc. of Parents of Vaccine Damaged Children formed
- 76-79: nat'l encephalopathy study (1/100000 damaged)
- GPs: reduced immunizations
- Major pertussis epidemics
  - >100000 infections, >1000 hospitalizations, >100 deaths
- 88: Loveday class action lawsuit
  - actually a trial of encephalopathy study

**Conclusion:** pertussis vaccine didn’t cause permanent brain damage

### North America - United States
- Apr 82: Vaccine roulette airs
- Media barrage ensues
- Dissatisfied Parents Together created (becomes NVIC)
- May 82: Senate hearings
- 82-86: DTP lawsuits - 17 to 255/yr
- 82-85: DTP price - 12cents to $4.29/dose
- 82-85: 2 of 3 Mfrs quit (7 in 1960)
- Apr 86: Last mfr gives notice of plan to quit
- Oct 86: Childhood Vaccine Injury Act passed
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Vaccine Safety

“Perfect Storm” Pattern

- ‘popularized’ alert to potential harm
- media outcry in support of victims
- advocacy groups formed seeking compensation
- ‘experts’ aligned on both sides
- lawyers and judges get involved
- Some manufacturers get out of the market
- seemingly never ending suspicion that vaccines do more harm than good
- time, effort, resources to study ‘safety’ issue
- doubt remains - can’t prove absence of association
- Helps if cause(s) of event in question understood
33 fatal outcomes referred to vaccine court examined by pediatric neuropathologist - none could be blamed on vaccine
- malformations, degenerative diseases, vascular disorders, infectious diseases, accidental smotherings, child abuse

Samuel Berkovic (Melbourne) 14 children with severe epilepsy/developmental delay onset ≤ 48 hrs post DPT (Lancet Neurology 2006;5:488)
- 11 had specific defect in SCN1A gene - regulates Na+ transport in brain cells; (Dravet syndrome)
- Parents lacked mutations; so had to occur de novo after conception
- 100% of children with mutation affected regardless of vaccine

follow up to original study (McIntosh et al, Lancet Neurology 9:592–8)
- Divided children with Dravet syndrome and confirmed SCN1A mutation into two groups: ‘vaccination-proximate’ (disease onset ≤ within 2 day post-immunization) & ‘vaccination-distant’ (disease onset 3–98 days after immunization)
- No group differences in intellectual outcome, subsequent seizure type or mutation type
Paul Offit (Deadly Choices): “After Berkovic’s paper, it was clear that

- all the time spent by parents to get health officials to admit that pertussis vaccine had permanently harmed children,
- all the money spent by pharmaceutical companies to compensate alleged victims,
- all the work of lawmakers to create a system to deflect lawsuits away from these companies, and
- all the ink devoted by the media to support these children and their parents

had been an enormous diversion from the real cause of the problem.

But when Samuel Berkovic finally found the answer to the question of what had actually caused the problem, no one noticed. Not a single newspaper, magazine, radio or television program carried the story.”
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Consequences of Reactivity

- Complacency breeds mistrust and contempt
  - complications from whole cell pertussis vaccine “reaction on the part of the scientific community was a collective shrug.”
  - Thimerosal - ‘somewhat blasé attitude to potential risks’
- “playing catch-up leaves openings for reporters like Lea Thompson, self-styled renegades like Andrew Wakefield + impassioned activists like the mercury Moms to raise... troubling questions”
- Without satisfactory answers “impossible to stop the spread of... most outlandish strains of vaccine skepticism from ... fringes to ... Mainstream”
- In highly pitched environment efforts “to bring clarity to the debate inevitably ended up fueling the controversy”
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

7 Habits of Highly Effective 'Networks'

- Be proactive
- Begin with the end in mind
- First things first
- Think win-win
- Seek first to understand, then to be understood
- Synergize
- Sharpen the saw
Seven Habits of Highly Effective 'Networks'

Be Proactive

- Anticipate issues before they happen as much as possible
- Define background incidence of potential 'AEFI'
- Identify and seek to understand regional variations in background incidence
  - Narcolepsy
- Applaud and encourage scientists who seek to understand diseases that could be blamed on vaccine
- Maintain rapid response capacity when unforeseen arises

Luck is what happens when preparation meets opportunity
Seneca

The windshield is bigger than the rearview mirror
Tom Daschle
Seven Habits of Highly Effective ‘Networks’

Begin with the end in mind

- Power to assess causality of rare (between 1 in 1000 to 1 in 10,000 doses) and very rare events (<1 in 10,000)
- Power to assess causality of given event in specific subgroups that may be at increased risk
- Shorten timeframe needed to assess key safety signals
- Capacity to compare products – if required
- Expand global capacity to conduct safety studies
  - New infrastructure
  - Expanded infrastructure
- Strengthen postmarket surveillance capacity for vaccines distributed only in low and middle income countries
- Maximize utility of safety data through standardization
Seven Habits of Highly Effective ‘Networks’

First Things First

- Recognize what is important as well as what is urgent
- Much has already been done - potential realized
  - Self-controlled case series methodology applied using large linked administrative databases (notably in Denmark, US, UK)
  - ‘proof of concept’ pilot near completion
  - Availability of standard case definitions and tools to assess diagnostic level of certainty - Brighton Collaboration
  - Ability to assess burden of disease - Kenya
  - Capacity to assess both risk and benefit - Rotavirus vaccine in Mexico and Brazil
- Much remains to be done - no time like the present

“Coming together is a beginning. Keeping together is progress. Working together is success” Henry Ford
Seven Habits of Highly Effective 'Networks'

Think win-win

Should be the essence of a network that could bring

- Benefits for all stakeholders
  - Expanded vaccine safety evidence base
  - Heightened vaccine effectiveness through maintained and/or restored public confidence

- Benefit to vaccine pharmacovigilance as a discipline
  - Increased capacity on a global scale
  - Innovative methodology
  - Harmonized standard tools that are used worldwide

- Benefits to low, middle and high income countries

- Benefits to individual network participants
  - collegiality
  - productivity

The law of Win/Win says, “Let’s not do it your way or my way; let’s do it the best way” Greg Anderson
Seven Habits of Highly Effective 'Networks'

Seek first to understand..

Many barriers to a global network
- Political & jurisdictional
- Privacy legislation, ethics approvals
- Regional variation in capacity
- Regional and professional differences in 'culture'
- Language differences
- Intellectual property issues
- Financial / conflict of interest issues

Anticipate, accommodate, alleviate bumps along the way

“Don't wait until everything is just right. It will never be perfect. There will always be challenges, obstacles and less than perfect conditions. So what. Get started now. With each step you take, you will grow stronger and stronger, more and more skilled, more and more self-confident and more and more successful.” MV Hansen
Seven Habits of Highly Effective ‘Networks’

Synergize..

**Synergy**: teamwork will produce an overall better result than if each person was working toward the same goal individually.

- Increased collegiality through regular communication and working together
- Shared best practices and tools
- Innovation through cross fertilization
- Enhanced capacity to evaluate signals could help to strengthen national surveillance systems

The journey is the reward  
*Chinese proverb*
Seven Habits of Highly Effective ‘Networks’

Sharpen the saw..

- All about ongoing improvement in all relevant areas
  - Original sense: Body, mind, spirit, inter-personal connections
  - Global level: improved preparedness for pandemic like situations, other crises
  - Country level
    - New and/or improved infrastructure
    - Access to new resources, collaborations
  - Individual level
    - Training opportunities
    - Teaching opportunities
    - Collaborations, possible funding, publications
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

Potential Defined

- Harmonized global approach to vaccine pharmacovigilance
- Strengthened global infrastructure to monitor vaccine safety: routine and extraordinary
- Anticipation and measurement of 'what lies ahead'
- Power to assess rare event causality in low, middle and high income countries
- Generation of evidence for vaccine benefit and risk to maximize effectiveness of immunization programmes
- Linked collegial synergistic global community actively engaged and flexibly poised to ramp up and respond when necessary
Potential Significance of a Global Collaborative Network for Vaccine Safety Studies

- Confirm where we are
- Determine where we are going
- Then get moving

Continuous GPS reference stations