Adverse Events Following Immunisation

Castlebar, Nov. 8, 2013

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Outline of presentation

Definitions

Safety assessment

Timing of reactions

Causality-real and coincidence

Errors

Occasional diversions

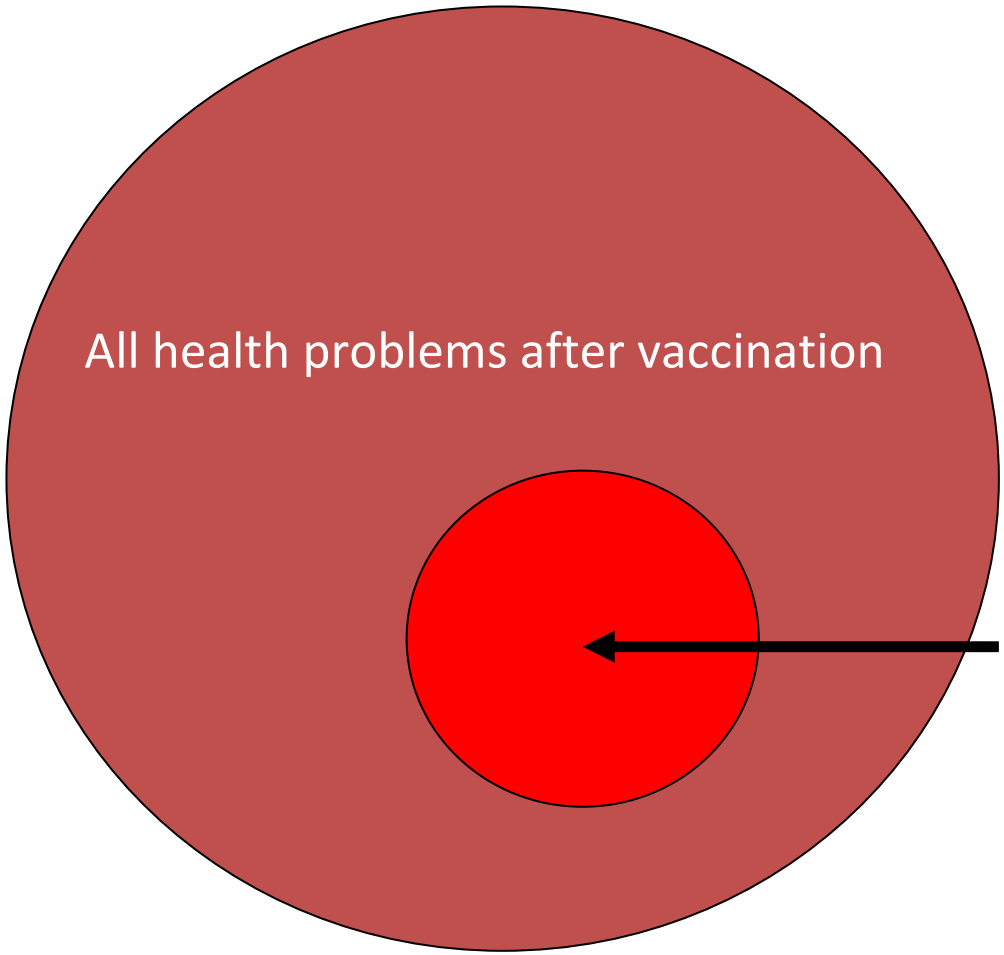
Abbreviations

- **ADR**-adverse drug reaction
- **AE-** adverse event
- **AEFI**-adverse event following immunisation
- **AESI**-adverse event of special interest
- **SAE-** serious adverse event
- **SUSAR**-suspected unexpected serious adverse reaction

Adverse Event Following Immunization (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 unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

AEFI-coincidence or Vaccine Injury?



Health problems caused by the vaccine

Bradford-Hill criteria for causation (does A cause B?)

- **Strength of association.** How large is the effect?
- **Consistency of association.** Has the same association been observed by others, in different populations, using a different method?
- **Specificity.** Does altering only the cause alter the effect?
- **Temporal relationship.** Does cause precede effect?

- **Biological gradient.** Is there a dose response?
- **Biological plausibility.** Does it make sense?
- **Coherence.** Does the evidence fit with what is known regarding the natural history and biology of the outcome?
- **Experimental evidence.** Are there any clinical studies supporting the association?
- **Reasoning by analogy.** Is the observed association supported by similar associations?

What is a serious AE?

- Fatal
- Life-threatening
- Permanently/significantly disabling
- Requires hospitalisation
- Causes Congenital abnormality
- Requires intervention to prevent permanent impairment or damage

Pre- and Post-marketing Testing

- Preclinical - assure no major side effects
- Clinical trials
- After approval (MA), samples of each lot of vaccine tested for safety, potency, and purity.

Clinical Trials

Pre-license	Phase 1	Safety, in healthy adult volunteers (10-20)
	Phase 2	Safety and immunogenicity in target population (100-200)
	Phase 3	Protective efficacy in target population (large)
Post-license	Phase 4	Pharmacovigilance to detect (rare) AEs

Timing of Vaccine Reactions

- **Inactivated vaccines**: generally within 48hrs

- **Live vaccines**: according to time for virus to replicate

  e.g. MMR:

  -measles (fever, rash) in 6-11 days

  -rubella (stiffness or arthritis) in 2nd week

  -mumps (parotid swelling) in 3rd week
  (may occur up to 6 weeks)

AEFIs: potential sources

- Manufacturing potency issues
  - over-attenuation of live vaccines
  - instability over time
  - reconstitution, mixing interferences
- Storage issues (cold chain)
- Administration issues
  - technique
  - concommitant administrations
- Patient profile
  - age, weight, immune deficiency
- Environmental
  - epidemiology: strain variation

Errors in manufacture

- Use of wrong diluent
- Transmission of pathogens
- Incomplete inactivation of virus or bacterium (vaccine is virulent)

Role of Administrator in vaccine safety

- Storage and Handling
- Timing and Spacing
- Administration Issues
  - Equipment
  - Injection site recommendations
  - Identify contraindications
- Education
- Report and treat AEFIs

Needle Size

Orange	**25 gauge**	**16 mm**
Blue	**23 gauge**	**25 mm**
Green	**21 gauge**	**40 mm**

- **25mm** needle is preferable and suitable for most
- **16mm** only recommended for <2.5-3kgs, sc, id
- **40mm** may be needed in heavier adults

Frequency of reactions

- Very common >10%
- Common 1-10%
- Uncommon 1/100-1/1,000
- Rare 1/1,000-1/10,000
- Very rare <1/10,000

Known Vaccine AEs

More Common (More than 1 in 100)	Less Common
• Redness • Swelling, nodule • Pain • Fever, irritability, loss of appetite, nausea, D+V.	• Encephalitis • Paralysis • Arthritis • Allergic reaction • Coagulopathies • Febrile seizure • Fainting • Narcolepsy • Death

Anaphylaxis: Treatment in the Community

Anaphylaxis is likely if a patient who, within minutes of exposure to a trigger (allergen), develops a sudden illness with rapidly progressing skin changes and life-threatening airway and/or breathing and/or circulation problems.

Get help
Call ambulance[1]

↓

Assess airway, breathing, and circulation

↓

Stridor, wheeze, respiratory distress or clinical signs of shock[2]

↓

For hypotension, lie patient flat with legs raised (unless respiratory distress increased)[3]

↓

Epinephrine 1:1000 *(1mg/ml) IM*[4]

0 -5 years	*0.15ml (150micrograms)*
6-12 years	*0.3ml (300micrograms)*
> 12 years	*0.5ml (500micrograms)*
Adult	*0.5ml (500micrograms)*

Those ≥ 100 kgs can be given 1mg IM (use 21G, 37mm needle)

↓

Repeat every 5-10 mins, up to 3 doses
Remember urgency of hospital transfer

1. Ambulance will be equipped with oxygen, Salbutamol and fluids.
2. If profound shock judged **immediately** life threatening, give CPR/BLS if necessary.
3. If respiratory distress present, elevate head.
4. Epinephrine maximum effect 10 minutes after IM injection.

Suggested Anaphylaxis Kit

The availability of protocols, equipment and drugs necessary for the management of anaphylaxis should be checked before each vaccination session

- Copy of "Anaphylaxis: Treatment in the Community" from Immunisation Guidelines for Ireland
- 3 x 1 ml ampoules of epinephrine (1:1000, 1mg/ml)
- 3 x 1 ml syringes
- Needles 3 x 16mm, 3 x 25mm, 3 x 40mm
- 1 pocket mask
- Sphygmomanometer (optional)
- Stethoscope (optional)
- Pen and paper to record time of administration of epinephrine.

The kits should be kept closed to ensure the **drugs are not exposed to light** and stored at room temperature. The kits require regular verification to replace drugs before their expiry date.

What Do We Mean by “Less Common”?

Frequency of known injury*	What else is this common?
1 in 1,000 to 1 in 100,000 – Fainting or collapse – Seizure from vaccine caused fever – Blood clotting problems	**Having quadruplets**
1 in 100,000 to 1 in a million – Serious allergic reaction – Arthritis	**Getting struck by lightning**
Less than 1 in a million – Encephalitis – Paralysis – Death	**Winning the lottery**

*Injury rates differ for different vaccines; this table shows the highest rate for any childhood vaccine

Pertussis

Pertussis vaccine

Reaction	DTwP	DTaP
• Pain	25	9
• Cry >3 hrs	0.4	0.04
• High fever	0.24	0.04
• Convulsions	0.02 0.007	
• Limpness	0.07	-

Pertussis

Pertussis Complications in Infants

Condition Reported	%
• Hospitalization	~50
• Pneumonia	23
• Convulsions	1.6
• Encephalopathy	0.4
• Death	1.6

Pertussis vaccine

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Why monitor AEFIs?

- No vaccine 100 % safe
  - Safety profile established in prelicensure trials
  - Detectable frequency depends on numbers studied

    (rule of 3)

    Rare events require huge numbers
- Risk / benefit balance changes over time
  - as incidence falls: VAPP, TB
  - as society becomes more critical ...

Reporting AEFIs

- 1-10% are reported
- 90-99% are not reported
- Safety is provisional at time of licencing-
  Rotashield, Vioxx, Pandemrix, etc
- If in doubt, write one out
- Every report is important

The Seven Rights of Immunisation

- Right patient
- Right vaccine, diluent
- Right time (age, interval, expiry)
- Right dose
- Right site
- Right route
- Right documentation

AEFI: "a medical incident ....after an immunisation, causes concern, and believed to be caused by immunisation".

- Does not restrict type of event (other than being a health consequence)
- Does not limit the time after immunisation,
- Does not attempt to determine causality

The belief that immunisation was responsible may be correct, incorrect, or impossible to assess

Safety and Efficacy

Safety: "Relative freedom from harmful effect… when prudently administered, taking into account the character of the product in relation to the condition of the recipient at the time."

Quality: "Relative freedom from extraneous matter in the finished product,…"

Efficacy: "Specific ability of the product … to *effect* a given result."

(N.B. differs from effectiveness).

OPD Fever Visits by 12-23 Month Olds after First Dose
VSD Automated Data 2000-2008

Vaccine	Days	RR	P Value
MMRV (N=83,107)	7-10	6.1	0.0001
MMR + V (N=376,354)	7-10	4.4	0.0001
MMR (N=145,302)	7-10	4.3	0.0001
Varicella (N=107,744)	9-14	1.2	0.06

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Alleged associations

all unproven

Condition	Vaccine	Country
Neurological damage	DPT	Scotland
Chronic fatigue syndrome	Hepatitis B	Canada
SIDS	DPT	France
Multiple Sclerosis	Hepatitis B	France
Autism	MMR	UK
Mental retardation	Thimerosal	USA

What Causes AEFI?

Vaccine – due to vaccine's inherent properties

Programme Error

Injection reaction - anxiety or pain of injection

Unknown - cause cannot be determined