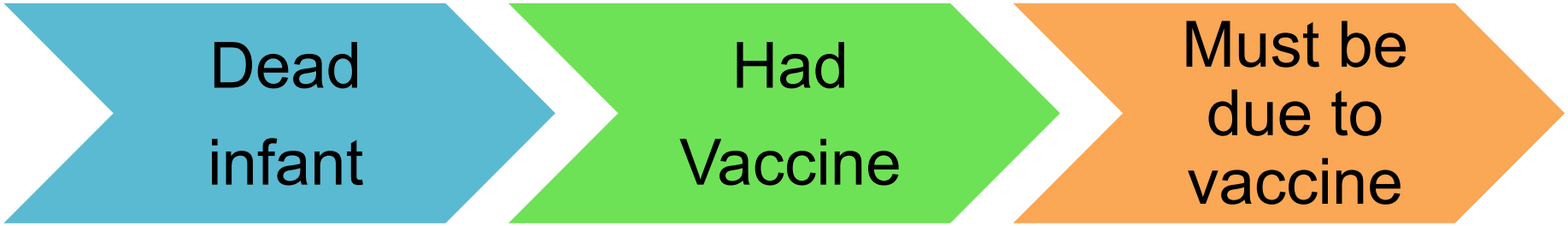
AEFI Causality Assessment

Approach to causality assessment in deaths following immunization

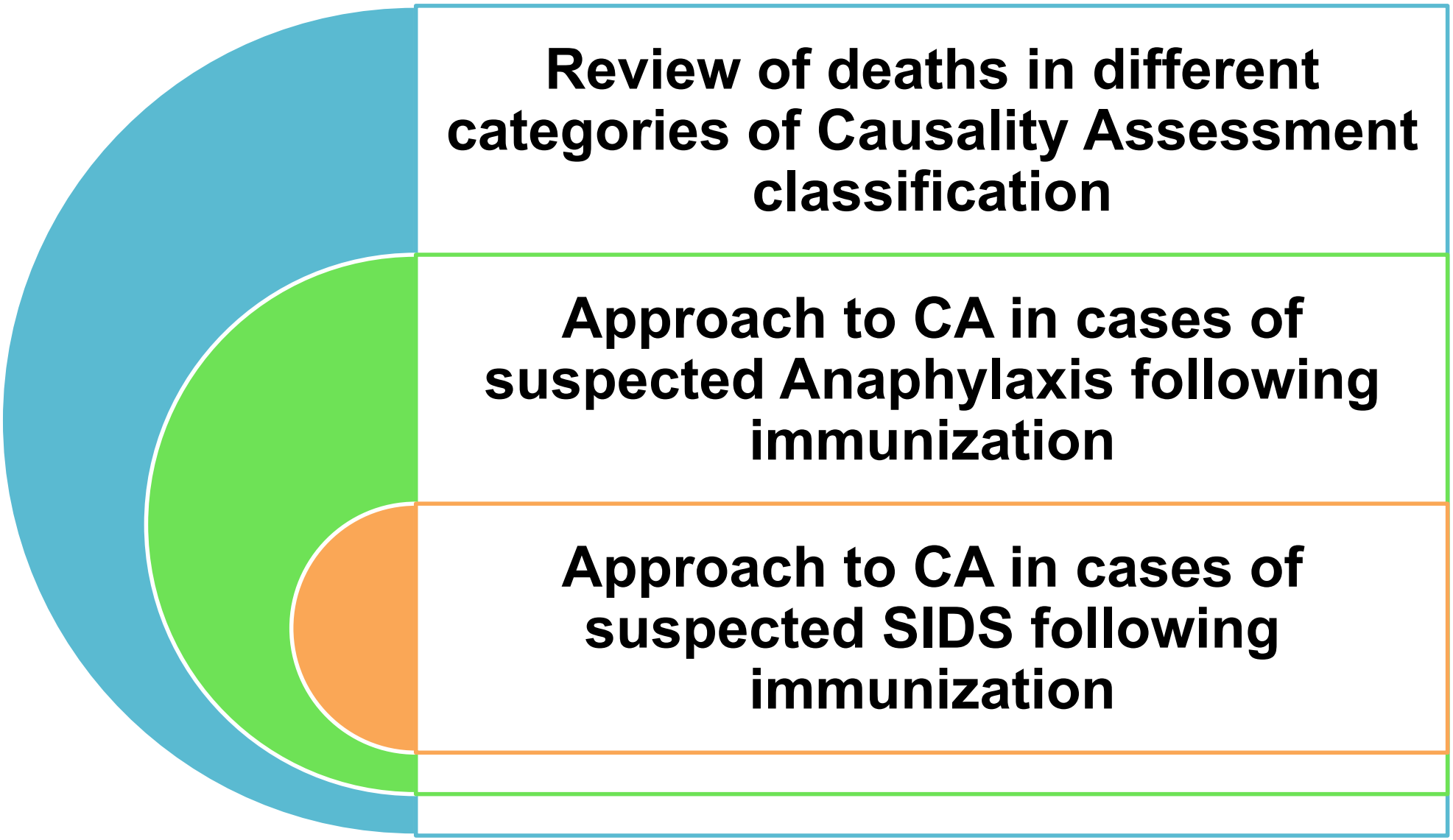
Training workshop on AEFI and Causality Assessment

Common Error

Preconceived diagnosis drives case data collection and causality assessment



Objectives


Review of deaths in different categories of Causality Assessment classification
Approach to CA in cases of suspected Anaphylaxis following immunization
Approach to CA in cases of suspected SIDS following immunization

Heuristics & Risk Assessment

Coincidence Dragon

Kirsty B, grade 5, Emma Doubs Integrated Arts and Technology School, Funkstown, MD. www.wcboe.k12.md.us/

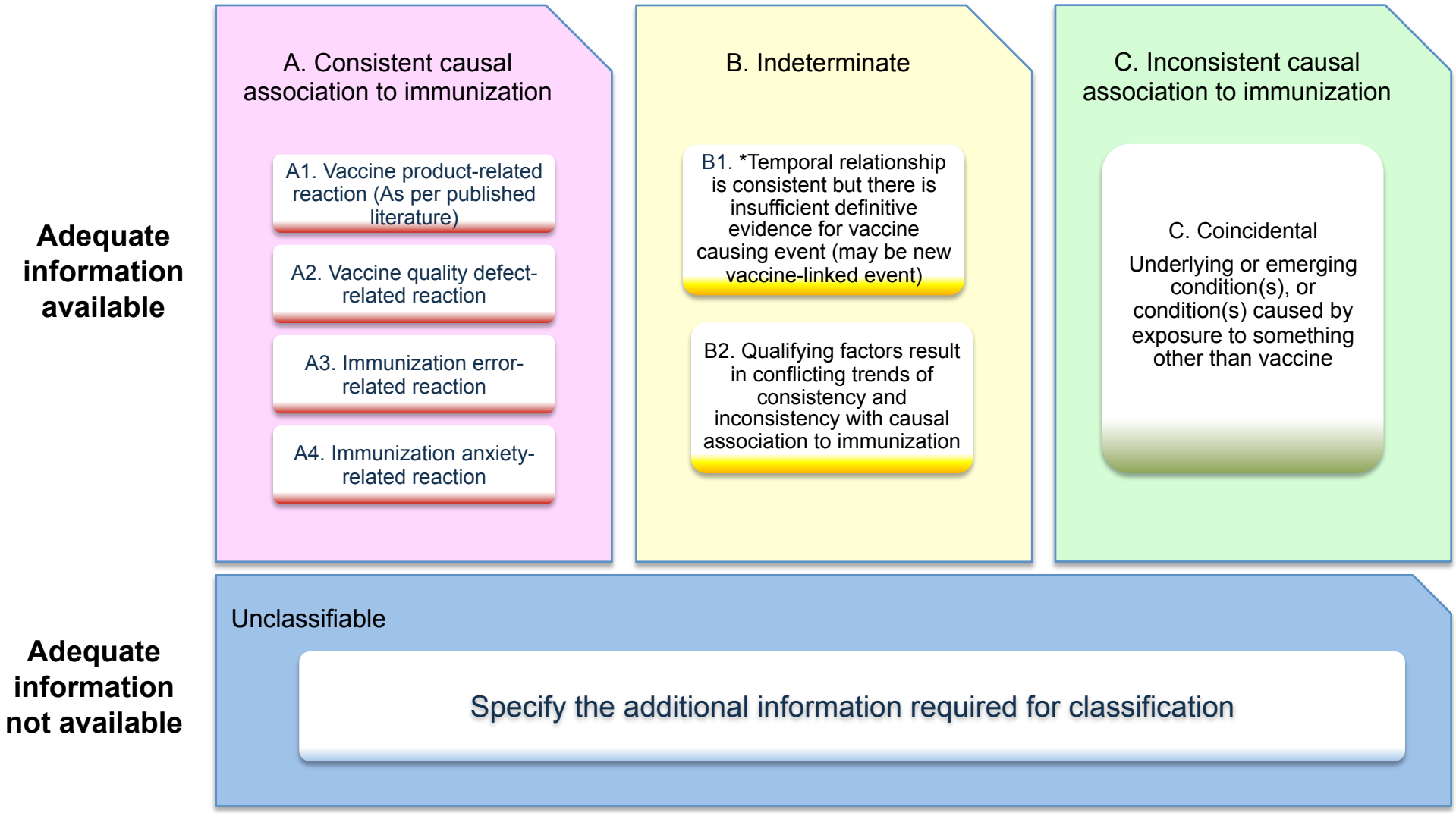
After this, therefore because of this

- HBV vaccine: Multiple Sclerosis
  - Alberto Ascherio et al N Engl J Med 2001; 344:327-332 February 1, 2001
- MMR vaccine: Autism
- Lack of association between measles virus vaccine and autism with enteropathy: a case-control study.
  - Hornig et al Plos One 2008 Sep 4;3(9):e3140
  - Deer B. BMJ. 2011 Jan – 3 articles .
    http://www.ncbi.nlm.nih.gov/pubmed/18769550

DTwP: Encephalopathy

Dravet syndrome: a genetic epileptic disorder. Akiyama et al . Acta Med Okayama. 2012; 66(5):369-76.. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. McIntosh et al. Lancet Neurology 2010; 9: 592-598)
http://www.lib.okayama-u.ac.jp/www/acta/pdf/66_5_369.pdf

AEFI Classification

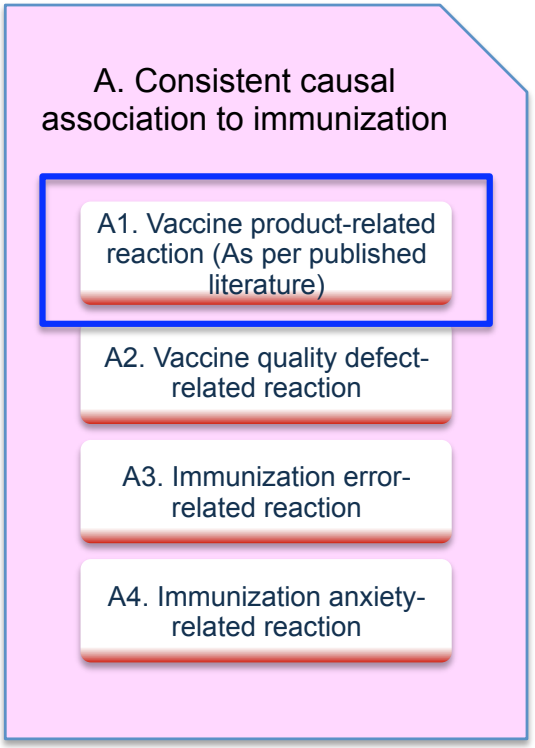


*B1 : Potential signal and maybe considered for investigation

Consistent causal association to immunization

Vaccine product-related reaction (published literature)

- **Anaphylaxis**
  - Any vaccine
  - Immunisers should recognize and treat anaphylaxis
  - Immunisation programmes must be able to identify and determine causal relationship of the event to immunisation



- **Viscerotrophic disease**
  - Yellow fever vaccine and rare instances of deaths in women 19 - 34 years, elderly and thymectomised

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1995783/
http://dx.doi.org/10.3201/eid1710.101789

Vaccine anaphylaxis

- Death due to vaccine anaphylaxis is very very rare
- But not uncommon for an unexpected and serious event (including death) to be diagnosed incorrectly as anaphylaxis.
- This often has significant implications;
  - Individual
  - Public Health Programme

Ukraine halts deadly vaccination

Published: 19 May, 2008, 13:33

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The Ukrainian Ministry of Health has cal
President of Ukraine, Viktor Yushchenk
comes after more than

Last week Ukraine was shaken by the n
in a hospital in the city of Kramatorsk in
(Tresivac ZA 26-X). Later, dozens more
Kramatorsk alone. Similar situations we

By Friday night a total of 87 people had
splitting headache, high temperature an

Medical officials urged journalists not to
Indian enterprise Serum Institute of Indi

Hepatitis B vaccine kills three newborn babies with anaphylactic shock

On July 20th, 2013, three families lost their newborns after their infants received their routine hepatitis B vaccines in Vietnam. Soon after the tragic incident, the Vietnamese Health Department discontinued the use of hepatitis B vaccines for newborns in order to protect other babies.

The primary investigation has shown anaphylactic shock as the main cause of death. However, after this tragedy, the chairman of the vaccine program asked parents to "keep calm" and continue to vaccinate their children. The families of the deceased babies were paid $377 each and the mothers were offered free health care at the hospital where their babies received deadly vaccination.

Is it necessary for newborns to receive hepatitis B?

Hepatitis B is a virus that affects the liver and it's transmitted through direct contact with infected blood or body fluid. If you are a parent, you probably haven't seen or heard any children who have contracted hepatitis B. The reason is that, hepatitis B is a grown-up disease and it's pointless to vaccinate newborns with this vaccine.

There were only 3,374 cases of hepatitis B reported in US in 2010. However, according to the National Vaccine Information Center's (NVIC) website, since March 2012, there have been about 1500 hepatitis B vaccine-related deaths. Besides the deaths report, there has been a total 66,654 complaints of brain damage and inflammation, convulsions, lupus, multiple sclerosis, headaches, lupus, rheumatoid arthritis, and Guiilain-Barre Syndrome reported to federal Vaccine Adverse Events Reporting System (VAERS).

So why babies are getting vaccinated with Hepatitis B vaccine?

So far, in 2013, nine children in the US have died after receiving hepatitis B vaccines. Although, hepatitis B is a rare childhood disease, infants and newborns are vaccinated against this disease on a regular basis.

Some medical professionals believe that hepatitis B vaccine is necessary for babies when their mothers are already infected with hepatitis B at the time of birth. However, one would wonder why mother cannot simply get screening test in advance to determine whether or not they have hepatitis B. So, instead of a simple screen test, the newborns are put at high risk by being vaccinated.

"With hepatitis B vaccine, the case for mandatory immunization with few exemptions is far less persuasive than with smallpox or polio vaccines, which protected against highly lethal or disabling, relatively common, and easily transmissible diseases. For most children, the risk of a serious vaccine reaction may be 100 times greater than the risk of hepatitis B" says Dr. Jane Orient, the member of the Association of American Physicians and Surgeons (AAPS).

Also, according to a study (based on 6 years of data obtained from National Health Interview Survey (NHIS) 1997–2002 datasets), giving hepatitis B vaccines to newborn baby boys triples the risk of the babies developing autism spectrum disorder. Find more about Government cover-up and the truth

Epidemiology

- Rate per million vaccines
  - Stated in public health information as 1-2 cases
  - However, range is 0.65-120 cases

    http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1995783/
- Variation in rate accounted for by;
  - Case ascertainment
    - Passive or active surveillance
  - Case definition
    - Variable
  - Denominator
    - Population, vaccine distributed, administered

Journal of CLINICAL PATHOLOGY
Current TOC | Instructions for authors

J Clin Pathol. Jul 2007; 60(7): 737–739.
Published online May 4, 2007. doi: 10.1136/jcp.2006.037457
PMCID: PMC1995783

Anaphylaxis as an adverse event following immunisati

Michel Erlewyn-Lajeunesse, Jan Bonhoeffer, Jens U Ruggeberg, and Paul T Heat

Author information ► Article notes ► Copyright and License information ►

In case there is no internet… here is the article…

Incidence

Go to:

Anaphylaxis following immunisation is a rare event. Even the largest pre-licensure vaccine trials are unlikely to detect a single case, let alone provide an estimate of incidence. The onus for detection of anaphylaxis falls to national post-marketing surveillance systems. The "yellow card" reporting system of the Medicines and Healthcare products Regulatory Agency in the UK (www.mhra.gov.uk) received 130 reports of anaphylaxis associated with immunisation in the six years from 1997 to 2003, suggesting a rate of 1 per million doses.[5] Likewise, the US Vaccine Adverse Event Reporting System (http://vaers.hhs.gov) recorded 452 reports of "anaphylactoid reactions" in over 1.9 billion doses of vaccine administered countrywide over a 10-year period.[6] This yields an estimated incidence of 0.2 cases per million doses. All post-marketing surveillance systems rely on passive reporting of cases and are prone to under-reporting. Also these incidences are of overall rates of reaction and do not reflect incidences following individual vaccines.

There are a limited number of studies specifically addressing the incidence of anaphylaxis as an AEFI. Patja *et al* describe 30 cases of anaphylaxis occurring after MMR vaccination over a 14-year period, deriving an incidence estimate of 1 per 100 000.[7] In a retrospective analysis of hospital discharge records, Bohlke *et al* identified five cases of anaphylaxis in 7.5 million doses of vaccine, giving an incidence rate of 0.65 cases per million doses.[8] Yet in two of these five "cases", uncertainties remained about the true nature of these events. The retrospective design of this study made it impossible to clarify these further. As with most advanced immunisation programmes, children received combination vaccines with multiple immunisations at a single clinic visit, making it impossible to attribute risk to a single vaccine or component. These studies exemplify the difficulty of describing anaphylaxis as an AEFI in any detail using retrospective analyses.

Clinical symptoms

Go to:

Anaphylaxis is a clinical syndrome characterised by its sudden onset, rapid progression and the involvement of multiple organ systems. At its most severe, the cardiovascular and respiratory system are involved with shock, bronchoconstriction and laryngeal oedema.[4,9] Erythema, itching and urticaria are

Table 2: Summary of rates of anaphylaxis following immunization

Surveillance type, program	Period	Vaccine	Anaphylaxis rate, per 100 000	95% Poisson confidence interval
School-based program				
New South Wales	Apr–Dec 2007	Quadrivalent HPV	2.60	1.04–5.35
D Souza et al.[5]	Aug–Nov 1998	Measles–mumps–rubella	0.41	0.17–0.85
New South Wales Department of Health	2003	Conjugated meningococcal C	0.12	0.003–0.68
Dobson et al.[6]	1992	Hepatitis B	0.78	0.02–4.36
UK Department of Health[7]	1994	Measles–rubella	1.00	0.79–1.24
Enhanced surveillance				
Sakaguchi et al.[8]	Apr 1994–Mar 1997	Measles	1.68	1.28–2.17
		Mumps	1.96	0.90–3.72
		Rubella	1.60	1.02–2.37
		Varicella	2.35	1.35–3.82
		Varicella 1996 (peak rate)	4.52	2.33–7.89
Patja et al.[9,10]	1982–1996	Measles–mumps–rubella	0.05	0.02–0.08
Bohlke et al.[11]	1991–1997	All vaccines, all study sites	0.07	0.02–0.15
		All vaccines, enhanced site	0.15	0.004–0.85
Passive national surveillance				
Nakayama and Onoda[12]	1994–2004	Japanese encephalitis	0.06	0.02–0.14
		Diphtheria–tetanus–pertussis (acellular)	0.09	0.05–0.17
		Influenza	0.07	0.04–0.10
Pool et al.[13]	1991–1997	Measles–mumps–rubella	0.18	0.15–0.21
UK Department of Health[14]	1997–2003	All vaccines	0.11	0.09–0.13
Zhou et al.[15]	1991-2001	All vaccines	0.02	0.022–0.026
Kelso et al.[16]	1990–1997	Yellow fever	0.76	0.55-1.04

Case example

10 am: 6 ½ month old baby received routine DPT + OPV at a clinic session

1:30 pm: baby brought to University Medical Centre with respiratory distress (fast breathing) and mottling

- **Diagnosed as anaphylactic shock**
- **Fluids, oxygen, antihistamine, steroids**
- **Admitted**

Examination

General	No rash or swelling
ENT	No pharyngeal swelling
Resp	Wheeze and no stridor
CVS	Well perfused, BP Normal

4 pm: cyanosis, worsening respiratory distress, change in state, cool skin with mottling, prolonged capillary refill time, cardio-respiratory arrest and death

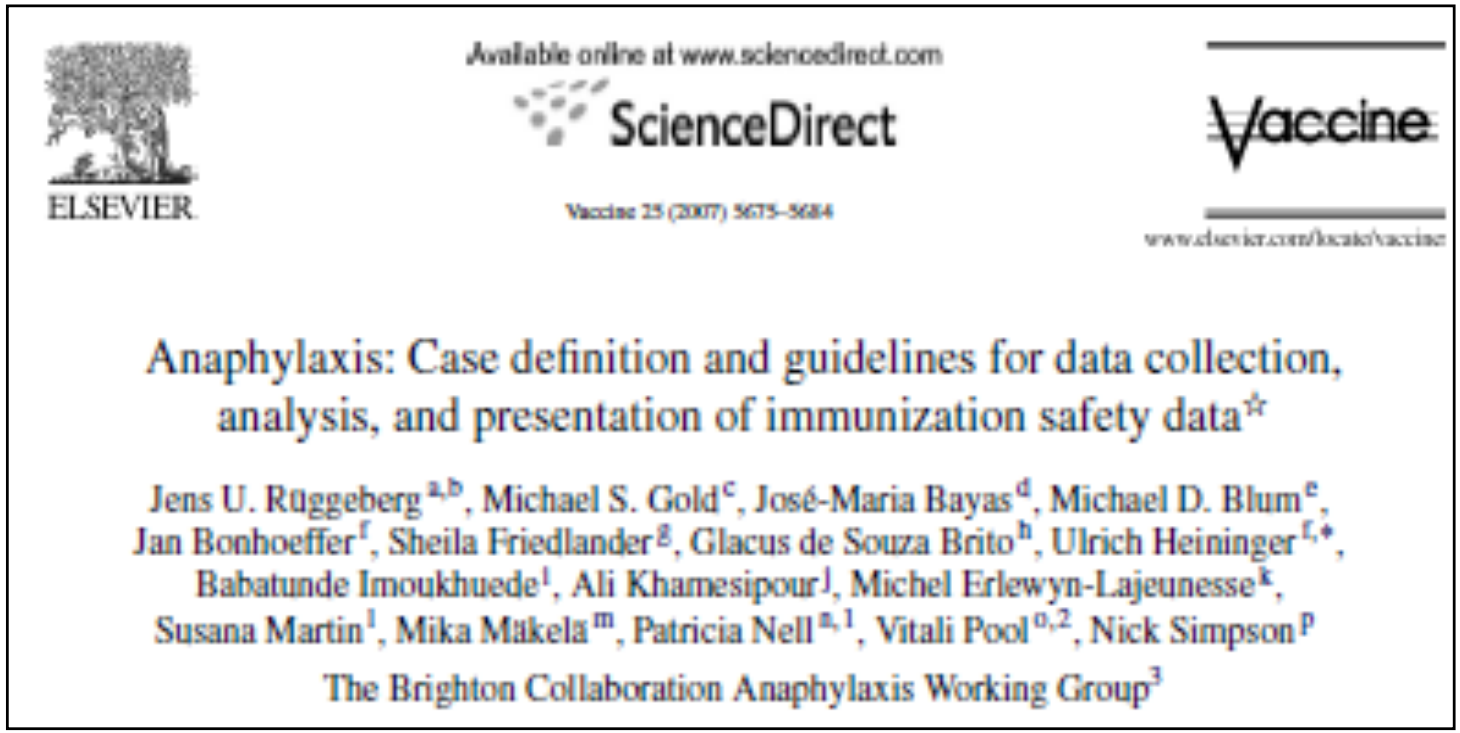
Diagnosis at death

Anaphylaxis

Is the case definition for anaphylaxis met ?

Brighton collaboration

https://brightoncollaboration.org/public.html



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Vaccine 25 (2007) 5675–5684

Vaccine

www.elsevier.com/locate/vaccine

Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data☆

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The Brighton Collaboration Anaphylaxis Working Group[3]

Case definition

Case Definition of Anaphylaxis - For All Levels of Diagnostic Certainty:

Anaphylaxis is a clinical syndrome characterized by
- sudden onset AND
- rapid progression of signs and symptoms AND
- involving multiple (≥2) organ systems, as follows:

Level 1 of diagnostic certainty
- ≥1 major dermatological AND
- ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion

Level 2 of diagnostic certainty
- ≥1 major cardiovascular AND ≥1 major respiratory criterion

OR
- ≥1 major cardiovascular OR respiratory criterion AND
- ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems)

OR
- ≥1 major dermatologic AND
- ≥1 minor cardiovascular AND/OR minor respiratory criterion

Level 3 of diagnostic certainty
- ≥1 minor cardiovascular OR respiratory criterion AND
- ≥1 minor criterion from each of ≥2 different systems/categories

Brighton: Anaphylaxis diagnostic criteria

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life -threatening reaction.

Major criteria

Dermatologic or mucosal	• generalized urticaria (hives) or generalized erythema • angioedema*, localized or generaliz • generalized pruritus with skin rash
Cardiovascular	• measured hypotension • clinical diagnosis of uncompensated shock, indicated by the combination at least 3 of the following: • tachycardia • capillary refill time >3 s • reduced central pulse volume • decreased level of consciousness loss of consciousness
Respiratory	• bilateral wheeze (bronchospasm) • stridor • upper airway swelling (lip, tongue, throat, uvula, or larynx) • respiratory distress—2 or more of th following: • tachypnoea • increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, e • recession • cyanosis • grunting

Minor criteria

dermatologic or mucosal	• generalized pruritus without skin rash • generalized prickle sensation • localized injection site urticaria • red and itchy eyes
Cardiovascular	• reduced peripheral circulation as indicated by the combination of at least 2 of • tachycardia and • a capillary refill time of >3 s without hypotension • a decreased level of consciousness
Respiratory	• persistent dry cough • hoarse voice • difficulty breathing without wheeze or stridor • sensation of throat closure • sneezing, rhinorrhea
Gastrointestinal	• diarrhoea • abdominal pain • nausea • vomiting
Laboratory	• Mast cell tryptase elevation > upper normal limit

Differential diagnosis of acute “collapse”

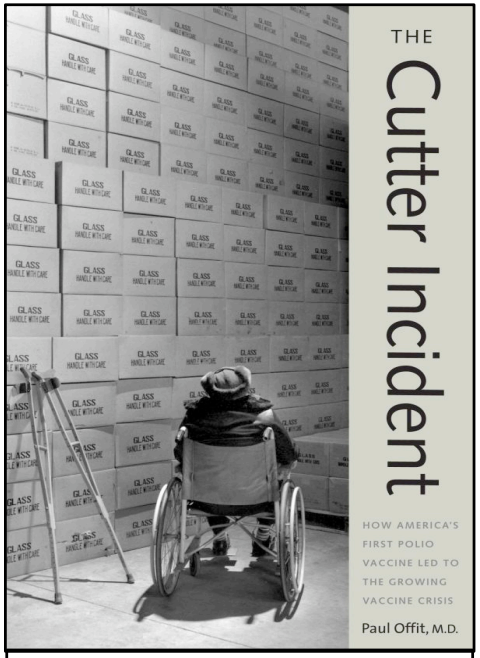
- **Vaccine related;**
  - Vaso-vagal event
  - Hyporesponsive-Hypotonic Episode (HHE)
  - Apnea of prematurity
  - Toxic shock (Vaccine contamination)
  - Aspiration and bronchospasm – oral vaccines
- **Co-Incidental**
  - Congenital heart disease
  - Shock – Septic, Hypovolaemic
  - Acute Asthma
  - Aspiration and bronchospasm – GOR
  - Seizures

Was anaphylaxis triggered by the vaccine (s) ?

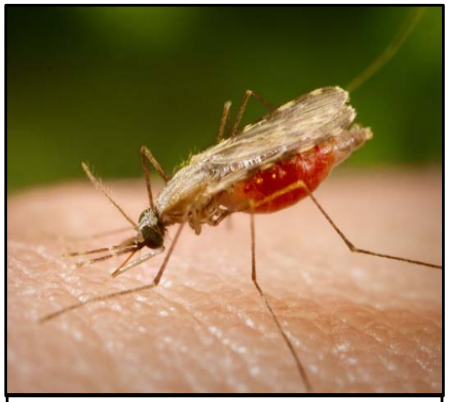
- Temporal relationship
  - 15-120 minutes
  - < 5 minutes, unlikely to vaccine
- Sensitisation to vaccine antigen or exipient
  - Skin testing to the vaccine
- Absence of alternate triggers
  - Note that in high income countries anaphylaxis in infants and children is not uncommon to foods
  - Other triggers include medications, latex and venoms
  - Idiopathic (no cause indentified) anaphylaxis not uncommon in adults

Consistent causal association to immunization

Vaccine quality defect-related reaction

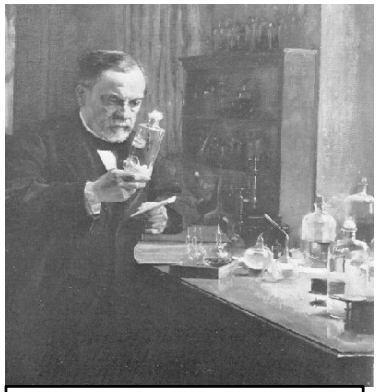


1955- IPV-
120,000 injected
40,000 mild polio
200 paralysed
10 died



1942-YF, HepB,
330,000 infected,
50,000 hepatitis,
62 died

1930 –TB-Lubeck
252 vaccinated
72 died



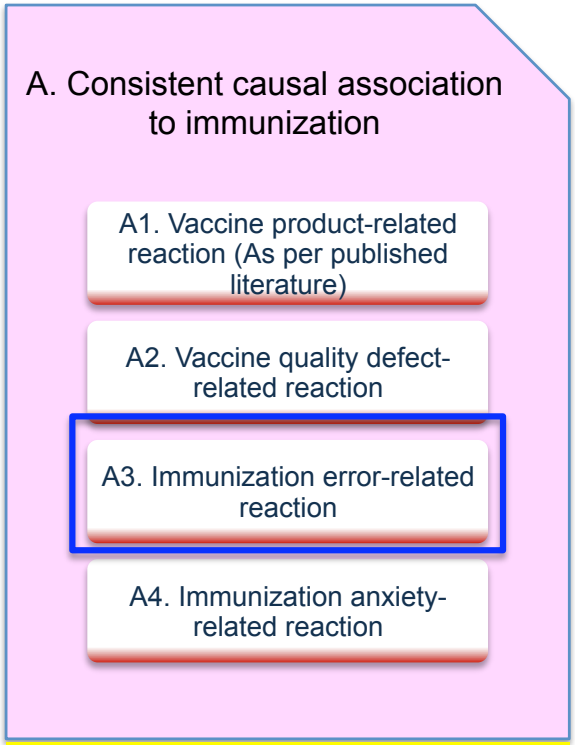
1800-Rabies
1 in 230
seizures,
paralysis
coma

A. Consistent causal association to immunization

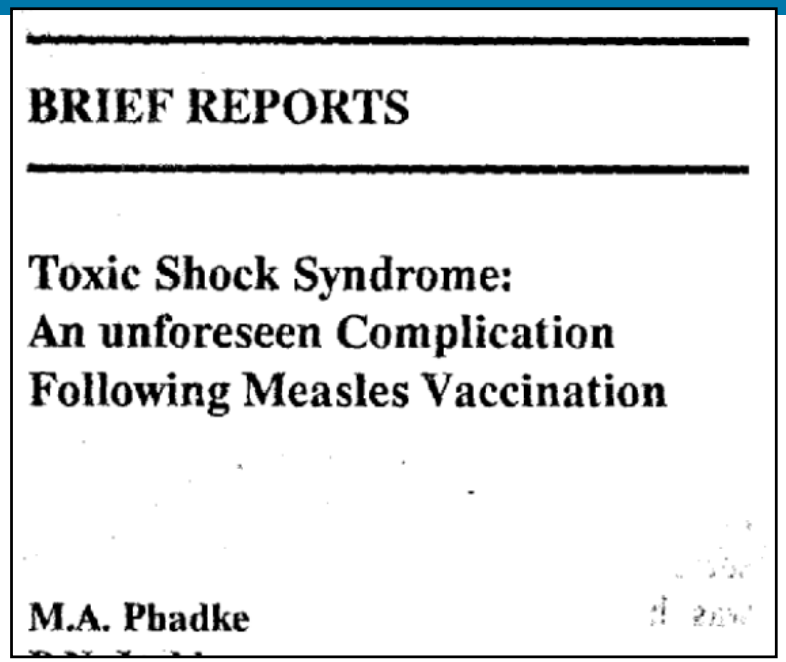
- A1. Vaccine product-related reaction (As per published literature)
- A2. Vaccine quality defect-related reaction
- A3. Immunization error-related reaction
- A4. Immunization anxiety-related reaction

Consistent causal association to immunization

Immunization error Related reaction	
Error in vaccine handling	Systemic or local reactions due to changes in the physical nature of the vaccine such as agglutination of aluminium-based excipients in freeze-sensitive vaccines. Failure to protect as a result of loss of potency or non-viability of an attenuated product.
Error in vaccine prescribing or non-adherence to recommendations for use	Anaphylaxis, Disseminated infection with an attenuated live, VAPP Systemic and/or local reactions, Neurologic, muscular, vascular o bony injury due to incorrect injection site, equipment or technique
Error in administration	Failure to vaccinate due to incorrect diluent , Reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent. Infection at the site of injection/ beyond the site of injection



When immunization errors are suspected, a detailed examination of all operational aspects of the immunization program has to be thoroughly investigated



BRIEF REPORTS

Toxic Shock Syndrome:
An unforeseen Complication
Following Measles Vaccination

M.A. Phadke

11 children immunised with Measles vaccine

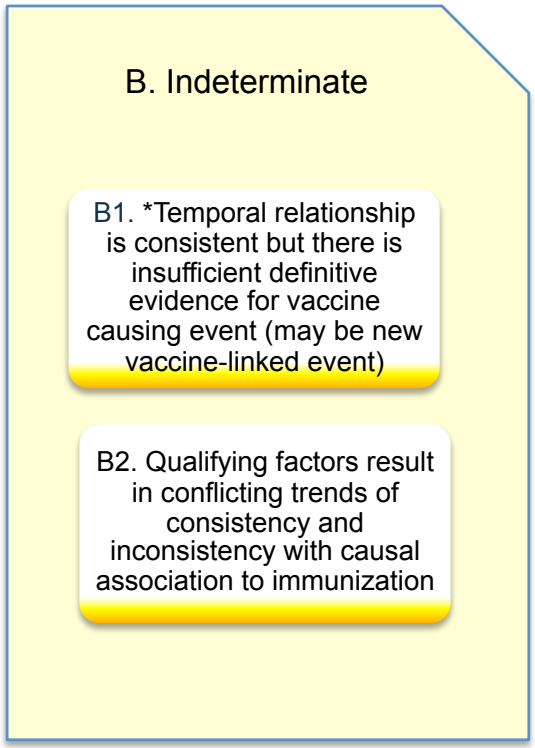
Within 3 hours 4 children had D and V
2/4 died within 24 hours
Remaining two hospitalised

- •High fever “toxic”
- •Shock
- •Conjunctival injection
- •Red palms and soles
- •Mucosal ulceration
- •Necrosis at injection site
- •(*Culture Staph Aureus*)

One used vial probably kept in “earthen pot” for 7 days- used to immunise these 4 children

INDIAN PEDIATRICS VOLUME 28—JUNE 1991

Indeterminate causal association



B1 – Example

SUDS 10 days after MMR vaccine
Autopsy shows some myocarditis
No viral cause identified
SIGNAL

B2 – Example

Death from anaphylaxis
Occurred 45 minutes post vaccination
Child known to be nut allergic
Had nut exposure post vaccination

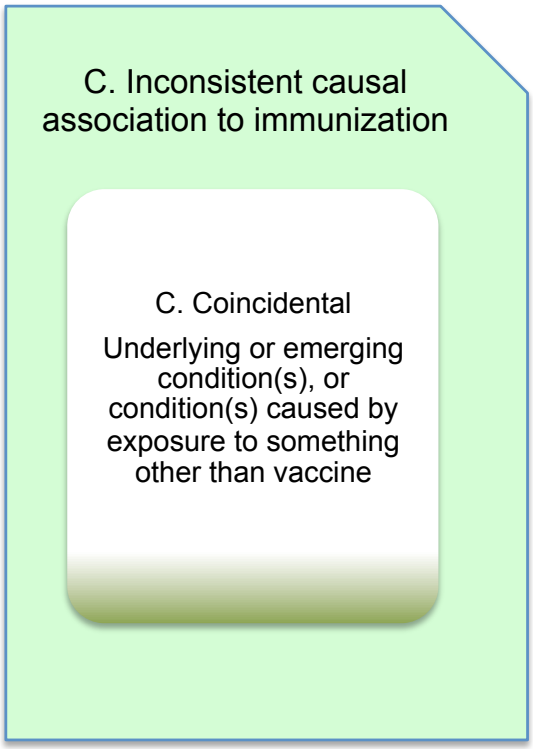
Inconsistent causal association to immunization

Coincidental

Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

The death of a teenage girl in the United Kingdom following vaccination with the human papilloma virus (HPV) vaccine was initially attributed to the vaccine. A post-mortem found it to be due to a malignant mediastinal tumour

:
http://www.nhs.uk/news/2009/09September/Pages/Cervical-cancer-vaccine-QA.aspx



Estimated number of coincidental infant deaths that could be temporally linked to immunization in the month, week and day after immunization (for eg DTP, PVV) in selected countries

Country	Infant Mortality Rate per 1000 live births (IMR)	Number of births per year (N)	Estimated number of infant death in			Estimated number of PVV/ DTP immunizations* in		
			a month	a week	a day	a month	a week	a day
Bhutan	42	15,000	53	12	2	3,233	746	106
Canada	5	388,000	162	37	5	86,864	20,045	2,856
China	13	16,364,000	17,728	4,091	583	3,634,035	838,624	119,475
Indonesia	25	4,331,000	9,023	2,082	297	950,113	219,257	31,237
Iran	21	1,255,000	2,196	507	72	276,445	63,795	9,089
Mexico	13	2,195,000	2,378	549	78	487,455	112,490	16,026
Sudan	57	1,477,000	7,016	1,619	231	313,382	72,319	10,303
United Kingdom	4	761,000	254	59	8	170,540	39,355	5,607

Note: Assumes uniform distribution of deaths and immunization over the time. IMR= Infant mortality rate per 1000 live birth; IMR/1000 Infant mortality and births from 2011 immunization summary, WHO/UNICEF (2013). http://www.unicef.org/videoaudio/PDFs/EN-ImmSumm-2013.pdf (accessed 07 December 2013)

Inconsistent causal association to immunization

Coincidental - Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

Mortality in low and middle income countries

Underlying condition

- Congenital disease, usually unrecognized
  - Congenital Heart Disease#
  - (Primary Immunodeficiency and live vaccines ##)
  - SIDS

Exposure to something other than the vaccine

- Infection +++ Malnutrition
- Non-accidental, Trauma, Poisoning

- Vaccine may act as a trigger for compromise ## Dissemination post vaccination

Sudden Infant Death Syndrome - Epidemiology

SIDS occurs in all countries around the world

Koehler. *The importance of a forensics investigation of sudden infant death syndrome: recommendations for developing, low and middle income countries.* Acta Medica Academica 2010;39:165-174

Rates vary by population/location/ethnic

Hong Kong 0.05/1000; American Indian 6.7/1000

Sharma. Sudden infant death syndrome: a subject of medicolegal research.". The American journal of forensic medicine and pathology 2007; 28: 69–72.

SIDS: Sudden Infant Death Syndrome

Table 1
Definition and classification of sudden infant death syndrome and unclassified sudden infant deaths

General	Sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history
Category IA	Classic features[a] of SIDS present and completely documented
Category IB	Classic features of SIDS present but incompletely documented
Category II	Classic features of SIDS not present
Unclassified sudden infant death	No autopsy or alternative diagnoses of natural or unnatural causes of death are equivocal

Developed by international panel of SIDS experts in 2004 (based on the publication by Krous et al. [12]).

[a] Age more than 21 days and less than 9 months of age, normal clinical history, term pregnancy, normal growth and development, no similar deaths among siblings, or close genetic relatives, or other infants in the custody of the same caregiver, no evidence of unexplained trauma, abuse, neglect, or unintentional injury in clinical history, no evidence of substantial thymic stress effect at autopsy, absence of potentially fatal pathologic findings (but minor respiratory inflammatory infiltrates are acceptable).

Brighton CD: Sudden Infant Death Syndrome

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 5707–5716
Vaccine
www.elsevier.com/locate/vaccine

Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: Case definition and guidelines for collection, analysis, and presentation of immunization safety data☆

Gerhard Jorch[a], Terhi Tapiainen[b,c], Jan Bonhoeffer[b,*], Thea K. Fischer[d,1], Ulrich Heininger[b], Bernard Hoet[e], Katrin S. Kohl[d], E.M. Lewis[f], Christiane Meyer[g], Tony Nelson[h], Synne Sandbu[i], Martin Schlaud[g], Ann Schwartz[j], Frederick Varricchio[j,1], Robert P. Wise[j], The Brighton Collaboration Unexplained Sudden Death Working Group[2]

Level 1 of diagnostic certainty
(Unexplained after complete postmortem investigation)

Sudden death of any child under 2 years of age which remains unexplained[a] after *excluding other causes of death*[b] by

1. Review of clinical history[c] AND
2. History of final events[c] AND
3. Review of *complete autopsy* report with a standardized protocol[d] that includes
   - Macroscopic examination AND
   - Microscopic examination AND
   - Microbiologic samples AND
   - Toxicological samples AND
   - Screen for metabolic diseases AND
   - Radiological studies

AND

4. Review of circumstances of death including examination of death scene performed by a suitably qualified person, such as homicide investigator or medical scene investigator or medical examiner[c]

Level 2 of diagnostic certainty
(Unexplained after clinical and final event history and autopsy)

Sudden death of any child under 2 years of age which remains unexplained[a] *after excluding other causes of death at least by*

1. Review of clinical history[c] AND
2. History of final events[c] AND
3. Review of incomplete[e] autopsy result

Level 3 of diagnostic certainty
(Unexplained after clinical and final event history but without autopsy[f])

Sudden death of any child under 2 years of age which remains unexplained[a] *after excluding other causes of death at least by*

1. Review of clinical history AND
2. History of final events

For any level of diagnostic certainty

Children under 2 years of age found unresponsive who are resuscitated and later die are included if they otherwise meet the criteria

[a] All deaths without an explained cause of death are included. Deaths labeled as "unascertained" or "possible" SIDS should be included if they otherwise meet the criteria. All "borderline cases" should be included.
[b] The original or a copy of the full autopsy report should be reviewed for completeness of postmortem investigation for level 1. Equivalent informa-

Sudden Infant Death Syndrome - Pathogenesis

Anatomical evidence

Associated with specific pathological medullary changes

Neuromodulators known to be involved in breathing control

Genetic determinants

Environmental determinants

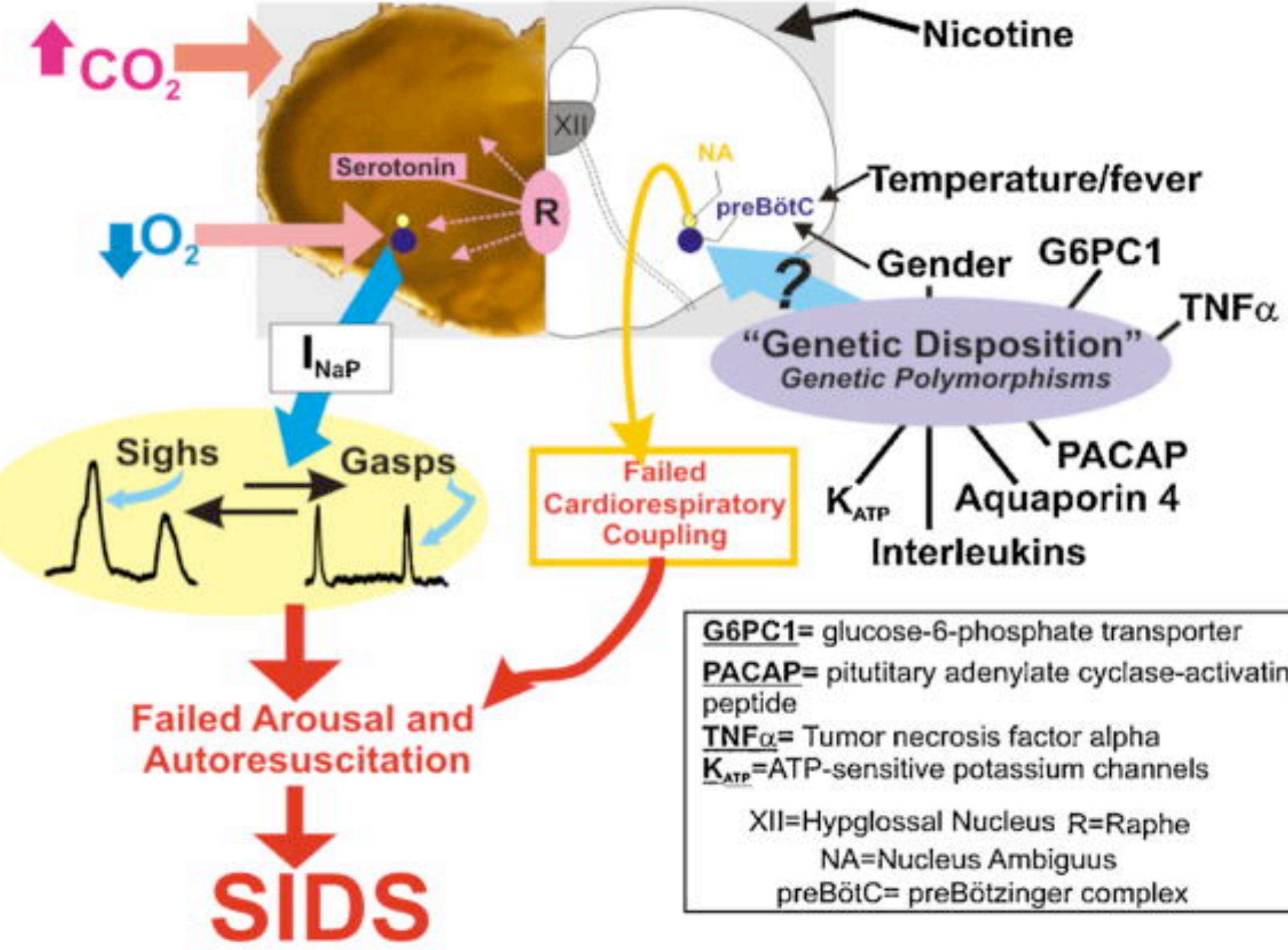
Prematurity, Low birth weight, Young mothers, Sleeping prone – tummy, Cigarette smoke

Not likely to be anaphylaxis to allergen (food/vaccine)

Nishio H[1], Serum tryptase levels in sudden infant death syndrome in forensic autopsy cases. Forensic Sci Int. 2004 Jan 6;139(1):57-60.

Garcia et al The physiological determinants of Sudden Infant Death Syndrome Respir Physiol Neurobiol 2013 ; 189(2) :10.1016

A Final Common Pathway for SIDS



G6PC1= glucose-6-phosphate transporter

PACAP= pitutitary adenylate cyclase-activating peptide

TNFα= Tumor necrosis factor alpha

K_{ATP}=ATP-sensitive potassium channels

XII=Hypglossal Nucleus R=Raphe
NA=Nucleus Ambiguus
preBötC= preBötzinger complex

Sudden Infant Death Syndrome - Vaccination

Negative studies

Kuhnert R[1], Reanalyses of case-control studies examining the temporal association between sudden infant death syndrome and vaccination. Vaccine. 2012 Mar 16;30(13):2349-56.

Fleming PJ[1] **The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study.** BMJ. 2001 Apr 7;322(7290):822.

Essery SD[1] **The protective effect of immunisation against diphtheria, pertussis and tetanus (DPT) in relation to sudden infant death syndrome.** FEMS Immunol Med Microbiol. 1999 Aug 1;25(1-2):183-92.

Jonville-Bera AP[1], **Sudden infant death syndrome and diphtheria-tetanus-pertussis-poliomyelitis vaccination status.** Fundam Clin Pharmacol. 1995;9(3):263-70.

Byard RW, **No association between DTP vaccination and SIDS.** Med J Aust. 1991 Jul 15;155(2):135-6.

Sudden Infant Death Syndrome - Vaccination

Table 3 Relative risk of SIDS associated with DTPP ± Hib immunization and with other factors.

	Proportion (%) of:		*Multivariate analysis*
	Cases	*Controls*	*Odds ratio (95% CI)*
DTPP ± Hib immunization			
no	100/114 (88)	294/341 (86)	1
yes	14/114 (12)	47/341 (14)	1.08 (0.49, 2.36)
Usual sleeping position			
side or back	64/114 (56)	310/341 (91)	1
prone	50/114 (44)	31/341 (9)	9.8 (5.8, 9.9, 18)
Birth weight			
≥2500 g	98/113 (87)	333/341 (98)	1
<2500 g	15/113 (13)	8/341 (2)	6.53 (2.29, 18.9)
Illness the week before death			
no	69/114 (61)	279/341 (82)	1
yes	45/114 (39)	62/341 (18)	3.44 (1.84, 6.41)
Type of mattress			
firm	64/97 (66)	300/341 (88)	1
not firm	33/97 (34)	41/341 (12)	3.26 (1.69, 6.29)
Maternal tobacco consumption			
no	55/99 (56)	232/340 (68)	1
yes	44/99 (44)	108/340 (32)	1.72 (0.95, 3.11)
Sex			
male	70/114 (61)	210/341 (62)	1
female	44/114 (39)	131/341 (38)	1.16 (0.64–2.11)
Breastfed at birth			
no	74/111 (67)	181/341 (53)	1
yes	37/111 (33)	160/341 (47)	0.55 (0.3–1)

Jonville-Béra AP[1] **Sudden unexpected death in infants under 3 months of age and vaccination status- -a case-control study.** Br J Clin Pharmacol. 2001 Mar;51(3):271-6

Koehler. Acta Medica Academica 2010;39:165-174

Table 1 Standard Protocol for Sudden infant death syndrome Investigation

Standard Protocol for Sudden Infant Death Syndrome Investigation	
Death Scene Investigation	Secure Death Scene Location Separate Infant and Parents Photo-document the Scene and Infant Conduct Witness Interviews (Parents/Care Givers) Re-enactment of the discovery of the infant (use dolls) Collect Atmospheric Air Samples Remove infant and other critical evidence Prepare Death Investigation Reports
Pre-Autopsy Review	Obtain and Review Infant's Past Medical Records Obtain and Review Mother's Past Medical Records Review Death Investigation Case Information Review First Responder Reports Review Police Reports
External Examination	1. Photograph Infant 2. Establish Infant Growth and Development Parameters 3. Document all signs of recent and remote trauma
Internal Examination	Gross Examination of Internal Organs Remove/Weight Internal Organs including the brain Microscopic Examination of Organs Collect Body Fluids: Blood, Bile, Urine, Eye Fluids Conduct Toxicological Analysis Conduct Microbiology/Genetic Screening Save representative samples of tissues
Post Examination Actives	Collection of Epidemiological Data Collection of Anatomical Data Collection of Pathological Data Dissemination of SIDS Information Publication of Case Reports Conduct Retrospective Studies

Autopsy and Verbal Autopsy

Autopsy problems

- Consent – Culture
- Expertise, cost, access to resources

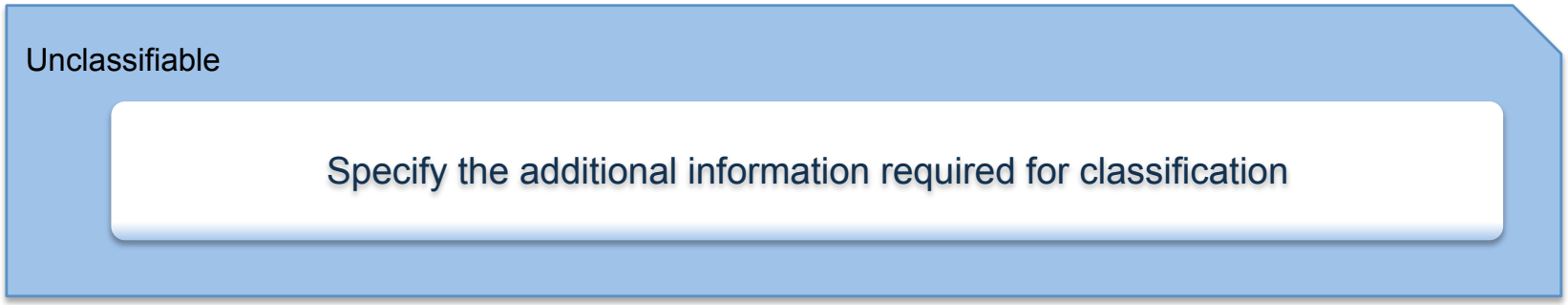
Verbal autopsy

- Questions – what and by whom ?
- Sample collection and investigation
- Expertise
- Cost, access to resources

Need to share experiences and have standard of practice

Unclassifiable - Adequate information not available

- In cases of death, information obtained through verbal autopsy and testing of available ante mortem or postmortem specimens are critical at arriving at conclusion.
- Information from unclassified cases should be kept in a repository for identification of potential signals later



Conclusions

For Infant / Child death post immunization

Apply causality assessment and do not jump to conclusion that it is caused by vaccine

1. **Consistent** causal association with death
   - Anaphylaxis and Viscerotrophic disease
2. **Indeterminate**
   - Possible signal
3. **Inconsistent** association
   - Underlying condition and exposure
4. **Unclassifiable**
   - Importance of Autopsy
   - Possible signal