Vaccine Safety: Current Issues and Misunderstandings

Neal Halsey M.D.

Johns Hopkins University

Institute for Vaccine Safety

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Neal Halsey: Disclosures

- Safety monitoring boards
  - Merck(Gardasil males), Takeda(Norovirus)
- Advisory board: Valneva:
  - Experimental Lyme disease vaccine
- Scientific advisory board for development of a live pertussis vaccine
  - ILiAD Biotechnologies

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Bad Science in Case Reports
Autism after MMR

www.autismpedia.org

EARLY REPORT

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to lymphoid ulceration. Histology showed patchy chronic inflammation in 11 children and reactive lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (one). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls, low haemoglobin in four children, and raised IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously healthy children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351**: 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield MRCS, A Anthony MB, J Linnell PHD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson MRCP, J A Walker-Smith FRCP), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and vomiting and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms, were investigated. All children were admitted to the ward for a week, accompanied by their parents.

Clinical investigations

A history, including details of immunisations and exposure to infectious disease, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with ICD-10 criteria.[7] Developmental history included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum, ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[8] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomysial antibodies and boys were screened for fragile-X if this had not been done

RETRACTED

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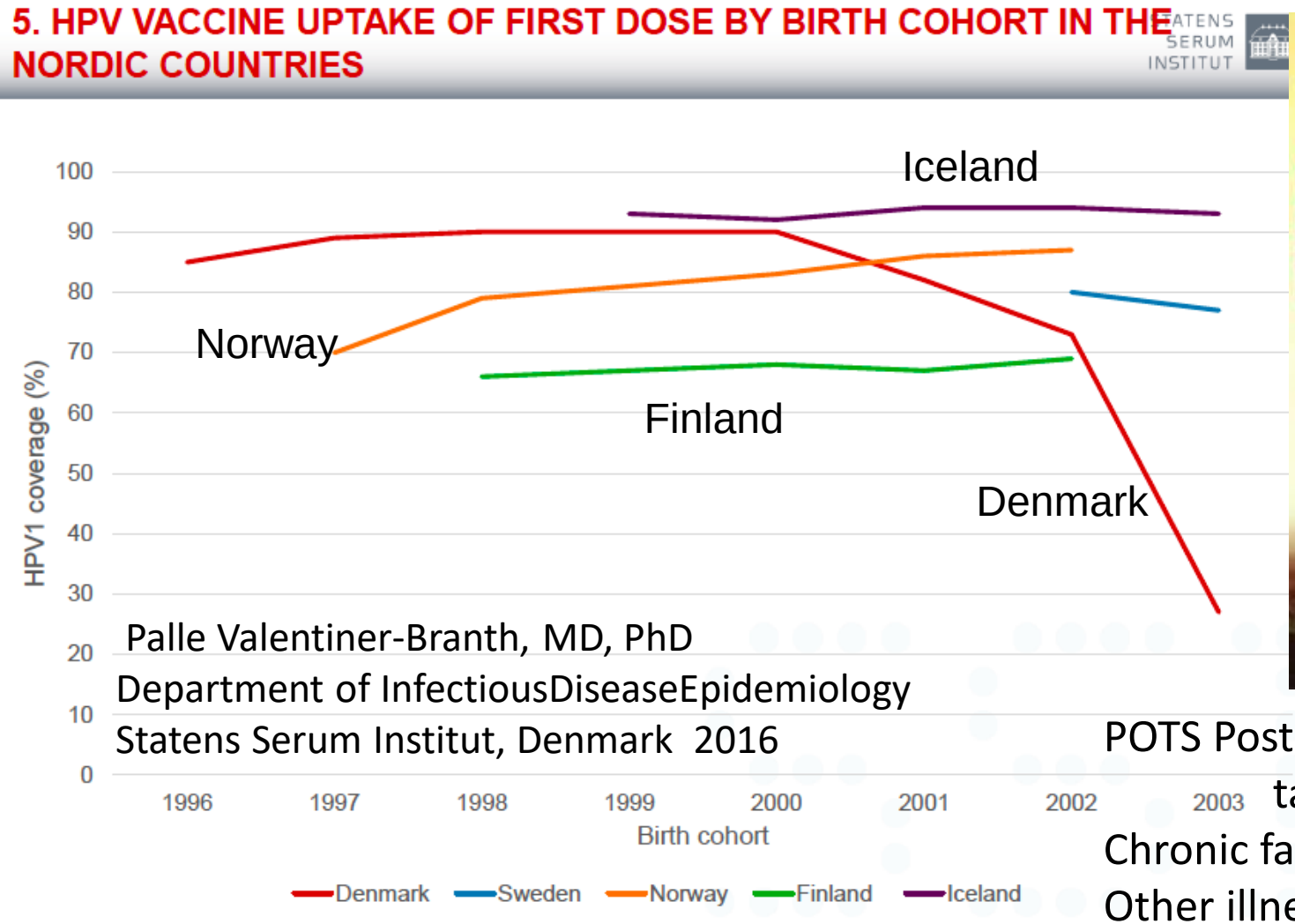
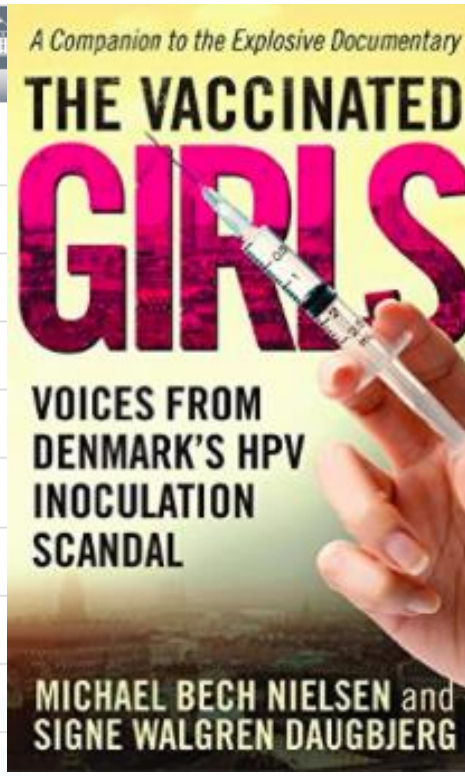
Decrease in HPV Acceptance in Denmark Following Promotion o Rumors by Journalists





Palle Valentiner-Branth, MD, PhD
Department of InfectiousDiseaseEpidemiology
Statens Serum Institut, Denmark 2016

POTS Postural orthostatic tachycardia syndrome
Chronic fatigue syndrome
Other illnesses

Japan Stopped HPV School Immunizations 2013

Grade	School Year	
	2012	2013
7th grade (junior high school)	65.4%	3.9%
8th grade (junior high school)	74.8%	66.5%
9th grade (junior high school)	65.3%	75.4%
10th grade (high school)	57.8%	65.0%

Concerns regarding adverse events including complex regional pain syndrome.
No systematic review of adverse events

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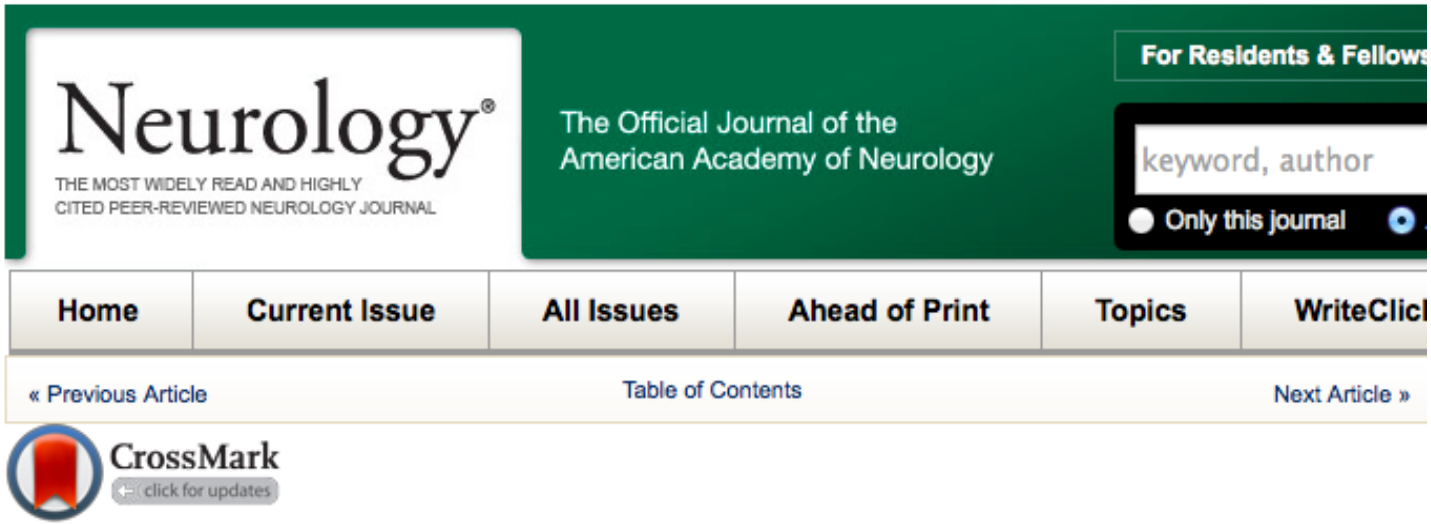
American Journal of Obstetrics & Gynecology 2015 212, 405-406

Bad Science in Case Reports Continues



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CrossMark click for updates

Clinical/Scientific Notes

Neuromyelitis optica following human papillomavirus vaccination

Til Menge, MD, Bruce Cree, MD, PhD, Andreas Saleh, MD, MPH, Tim Waterboer, PhD, Achim Berthele, MD, Sudhakar Reddy Kalluri, MSc, Bernhard Hemmer, MD, Orhan Aktas, MD, Hans-Peter Hartung, MD, Axel Methner, MD and Bernd C. Kieseier, MD

+ SHOW AFFILIATIONS | + SHOW FULL DISCLOSURES
Correspondence & reprint requests to Dr. Menge: menge@uni-duesseldorf.de

Published online before print June 20, 2012, doi: 10.1212/WNL.0b013e31825fdead
Neurology July 17, 2012 vol. 79 no. 3 285-287

4 cases
onset 4, 5, 5
and unknown
months
after vaccine

AJRI American Journal of Reproductive Immunology
Official Journal of the American Society for Reproductive Immunology
Explore this journal >

Original Article

Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants

Serena Colafrancesco, Carlo Perricone, Lucija Tomljenovic, Yehuda Shoenfeld

First published: 31 July 2013 Full publication history

DOI: 10.1111/aji.12151 View/save citation

View issue TOC
Volume 70, Issue 4
October 2013
Pages 309–316

Onset 1, 2, and ? years after HPV
Authors falsely assumed causal

Multiple causes of POI 4% autoimmune

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Review in preparation
Christianson, Halsey and Talaat

Junk Science

25+ Journals of Case Reports

False Assumptions of Causal Associations Based Solely on Temporal Relationships

Addressing Serious Adverse Events(SAEs)

1. Journal editors should institute standard criteria for accepting causality assessments in case reports
2. All countries should have a standing committee to review SAEs
3. Methods for assessing SAEs should be standardized

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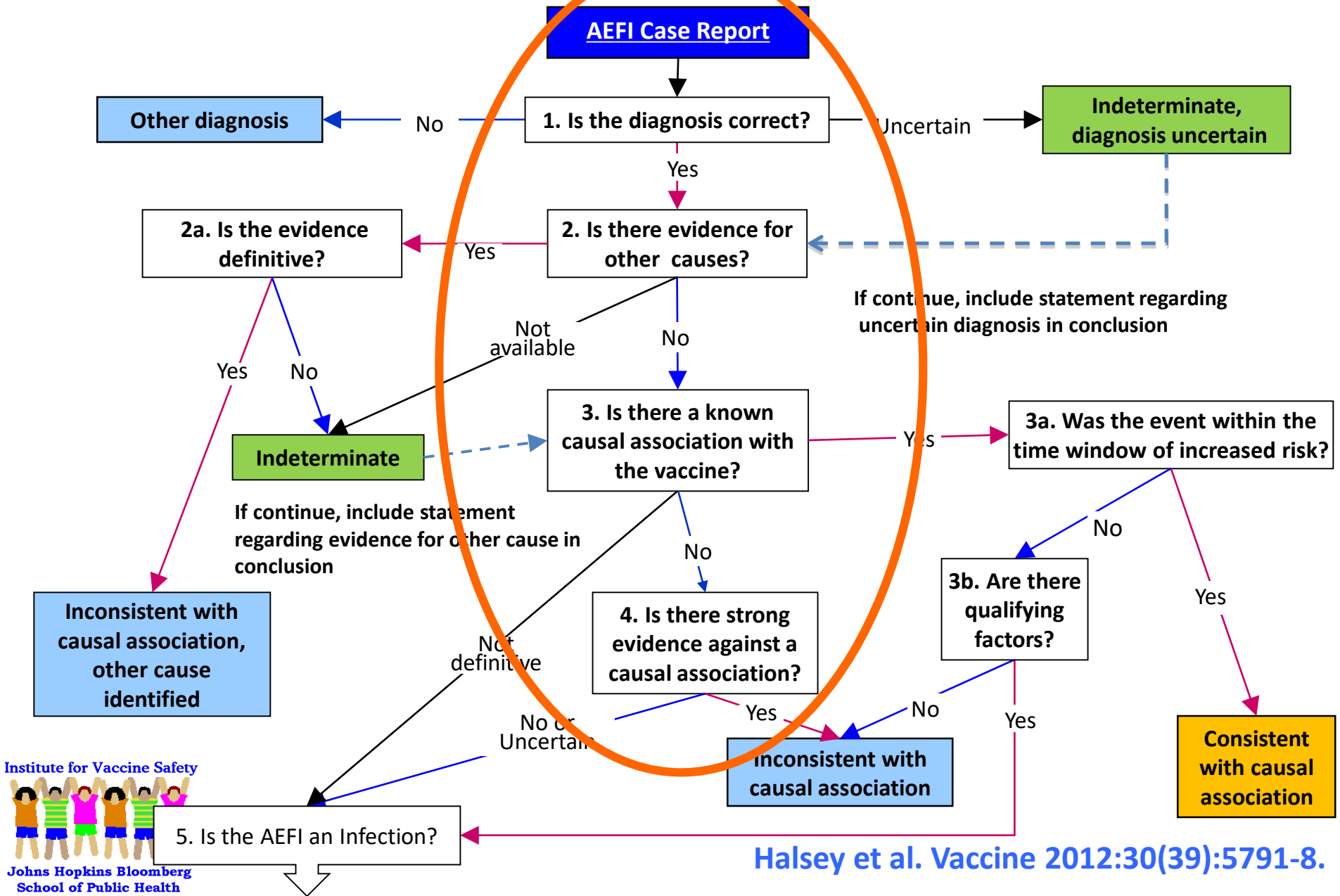
Clinical Immunization Safety Assesment Review of Case Reports of Adverse Events Following Immunizations



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Halsey et al. Vaccine 2012:30(39):5791-8.

Causality assessment of an adverse event following immunization (AEFI)

User manual for the revised WHO classification

http://www.who.int/vaccine_safety/publications/aefi_manual

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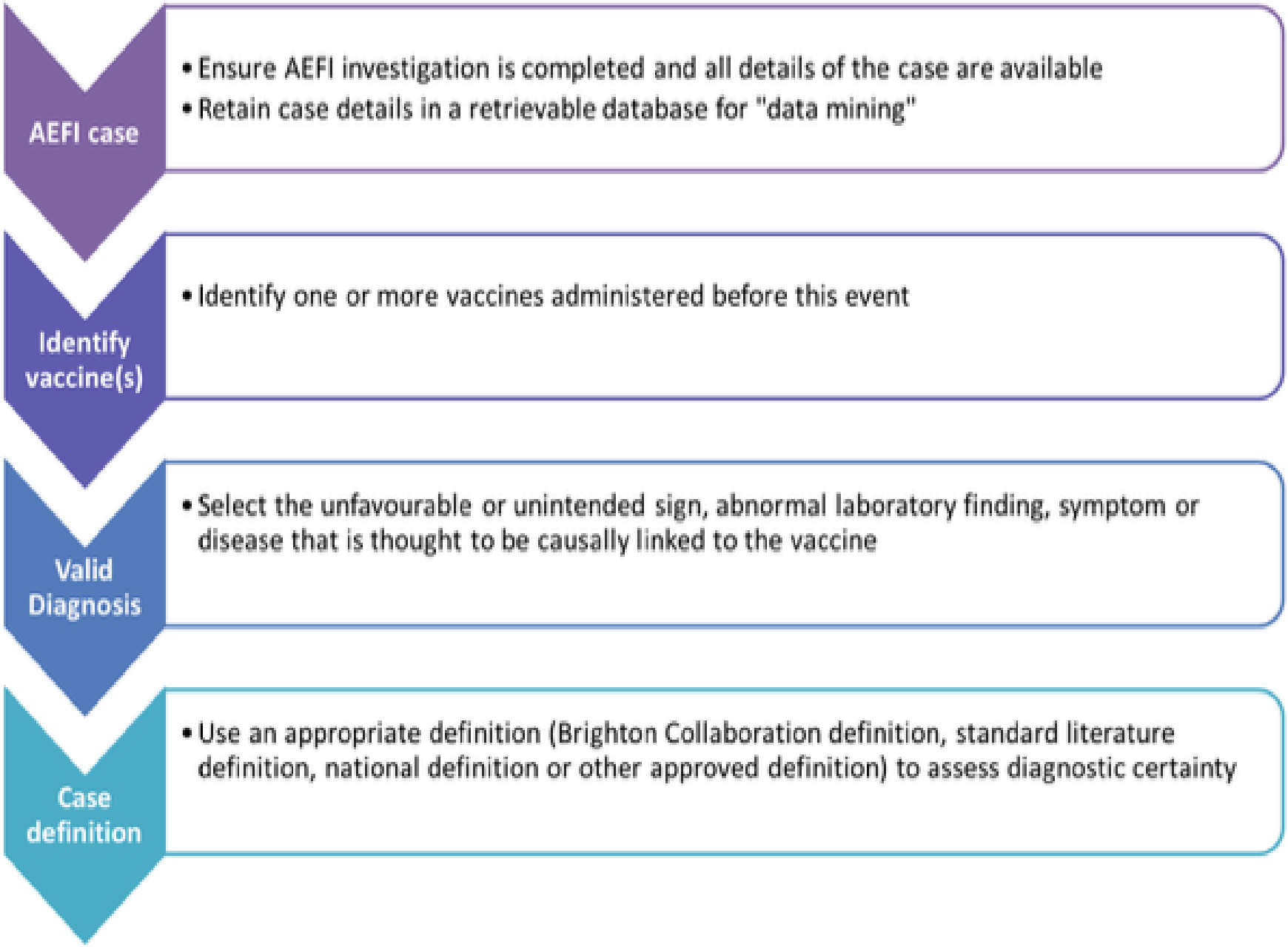
World Health Organization

Fig. 1. Causality assessment – Eligibility



Checklist

Table 1. The causality assessment checklist

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐☐☐☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐☐☐☐	
Immunization error		
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐☐☐☐	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	☐☐☐☐	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
Did the event occur within an appropriate time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	☐☐☐☐	

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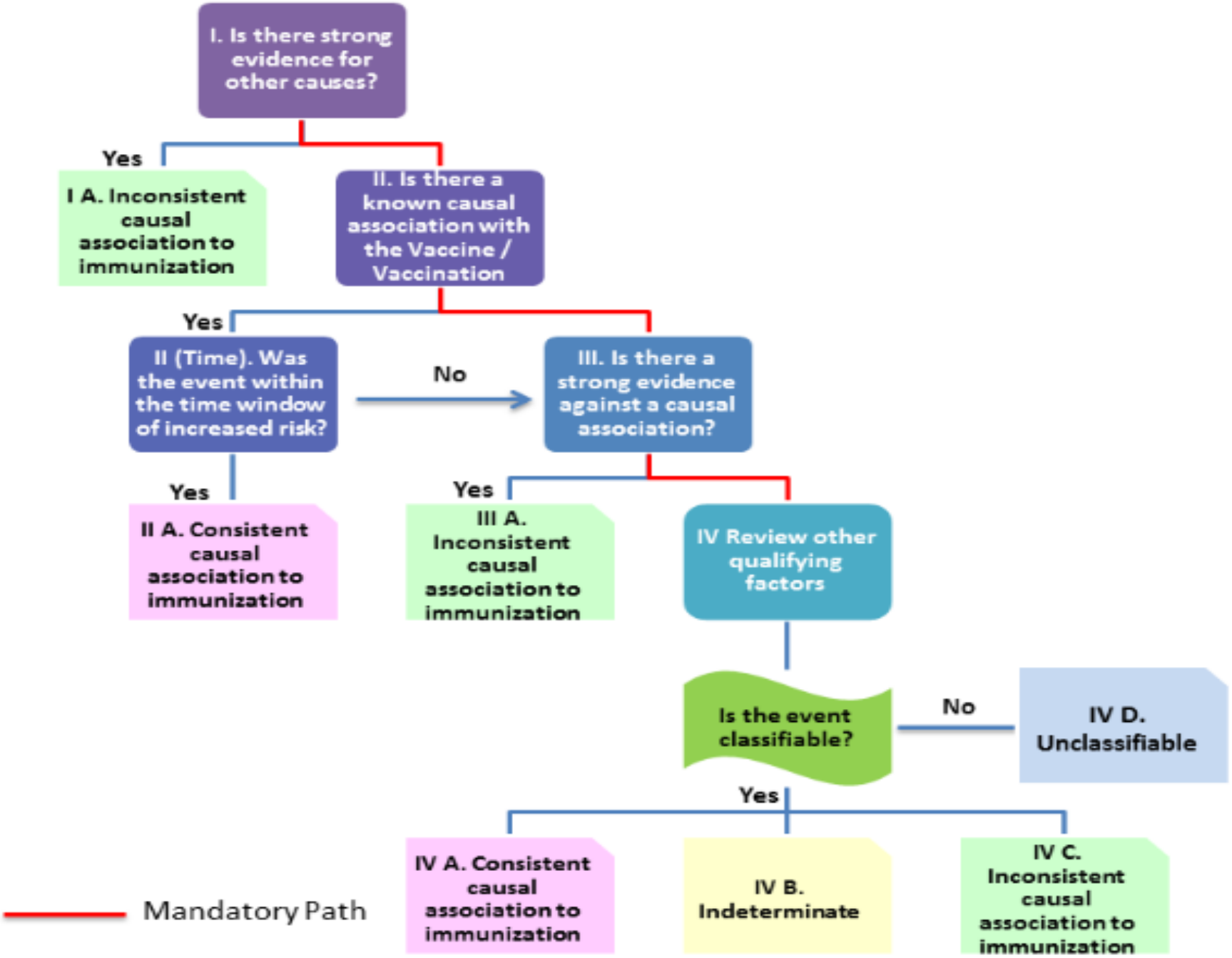
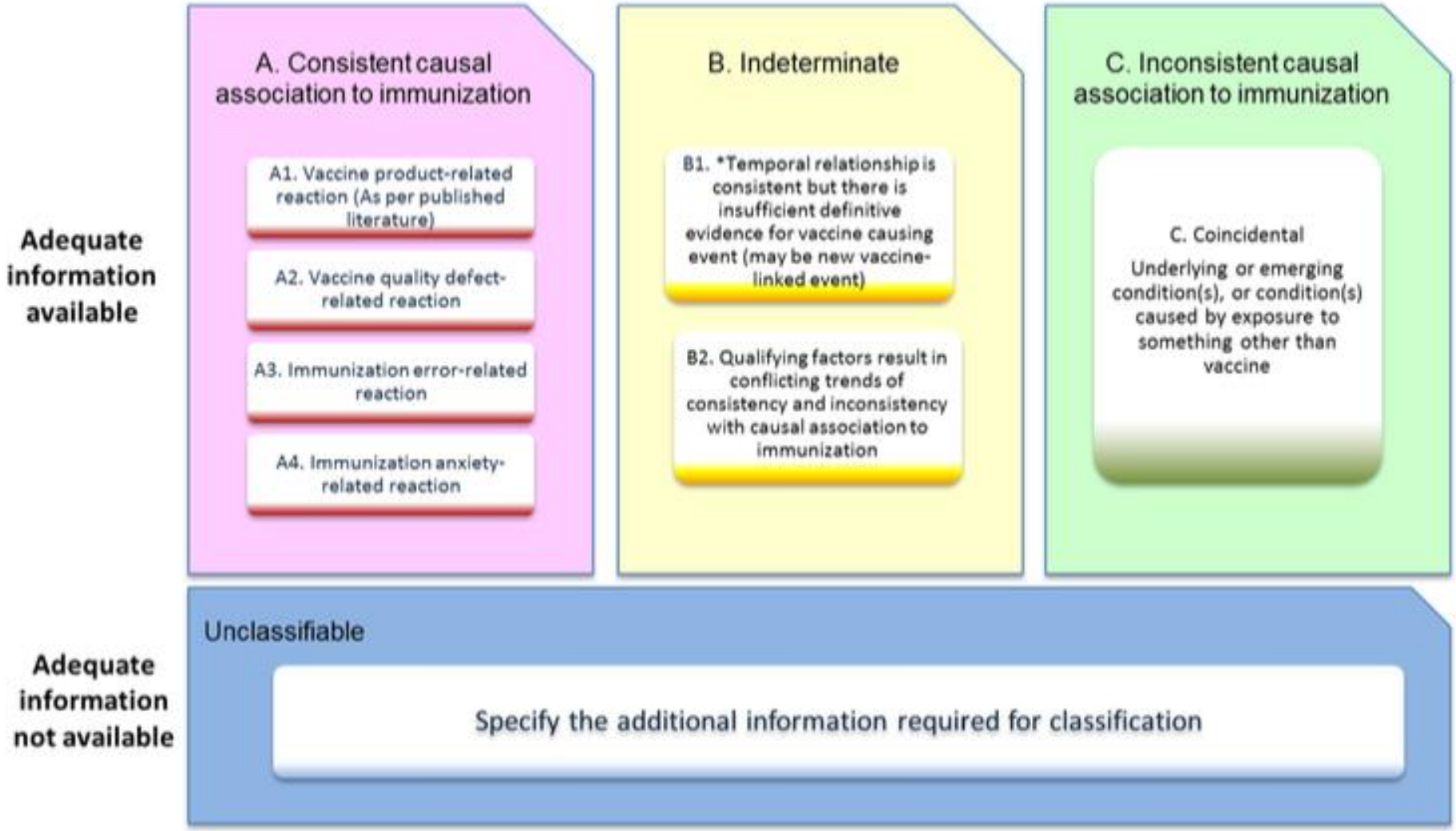
Fig. 3. Causality assessment algorithm



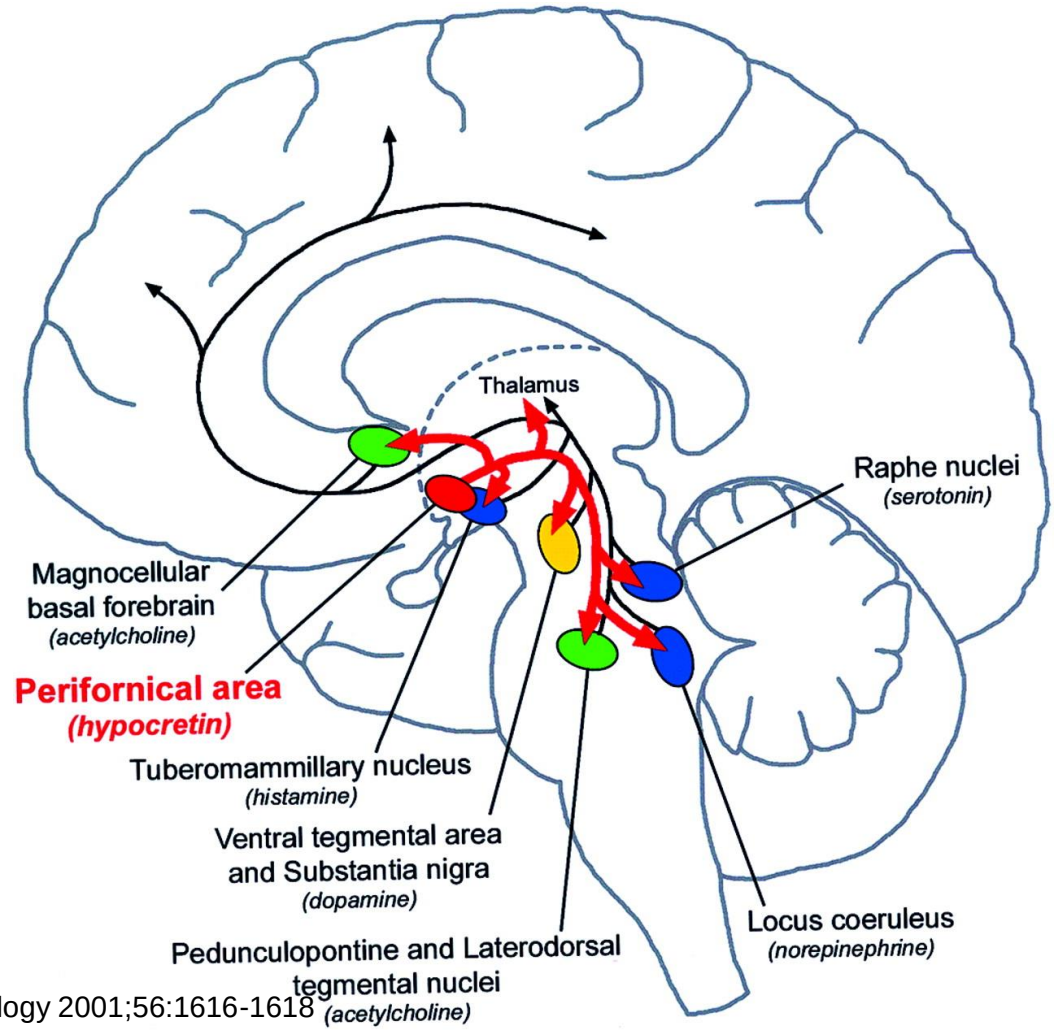
4. Classification



Narcolepsy with Cataplexy
Hypocretin Deficiency

www. wikipedia.org

www.alvaradohospital.com



ber M H , Rye D B Neurology 2001;56:1616-1618

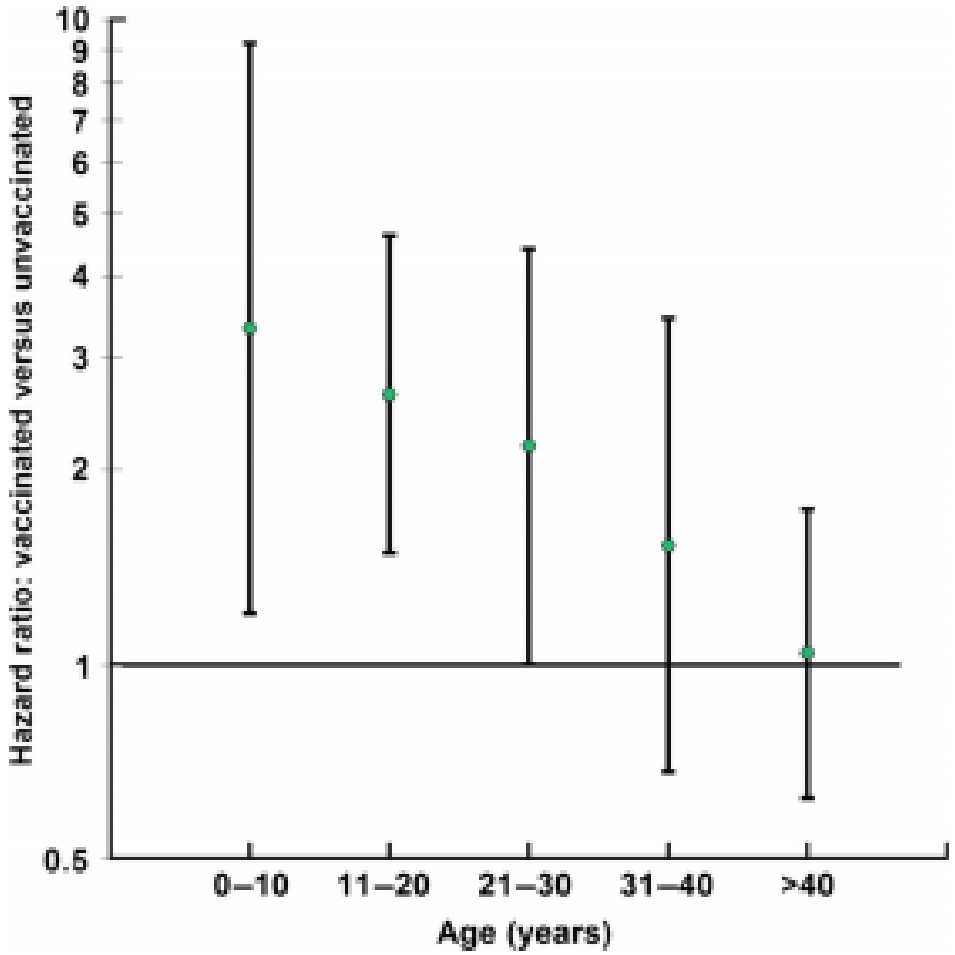
ms & Wilkins

AMERICAN ACADEMY OF NEUROLOGY

Increased Risk of Narcolepsy Following AS03 Adjuvanted Influenza Vaccine

Country	Age Group (yrs)	Study Design	Definition of Onset	Follow up Period	Risk (RR/OR)	95% CI
Finland	4-19	RC	1. contact with HC	1/1/09 - 8/15/10	12.7	6.1 - 30.8
Sweden	≤19	RC	Date of dg G47.4	10/1/09 - 12/31/10	6.6	3.1-14.5
Ireland	<20	RC	1. contact with HC	4/1/09 - 12/31/10	13.9	5.2-37.2
France	<18	CC	Date of Referral MSLT	4/1/09 – 4/30/11	6.5	2.1-19.9
	18+				4.7	1.6-13.9
Norway	4-19	RC	Date of EDS by Patient	10/1/09 - 6/3010	10-20	
UK	4-18	Case-coverage			16.2	3.84.5
Canada	0.5-20	RC	Date of EDS by Patient	1/1/09 – 12/31/10	2.96	0.71-12.39

Hazard Ratios and 95% Confidence Intervals for Diagnosed Narcolepsy 2009-2011 by Age at Vaccination: Sweden



Persson I, et al. J Intern Med 2014;275(2):172.

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Proportion of Population with HLA Type Associated with Narcolepsy

DQB1*0602

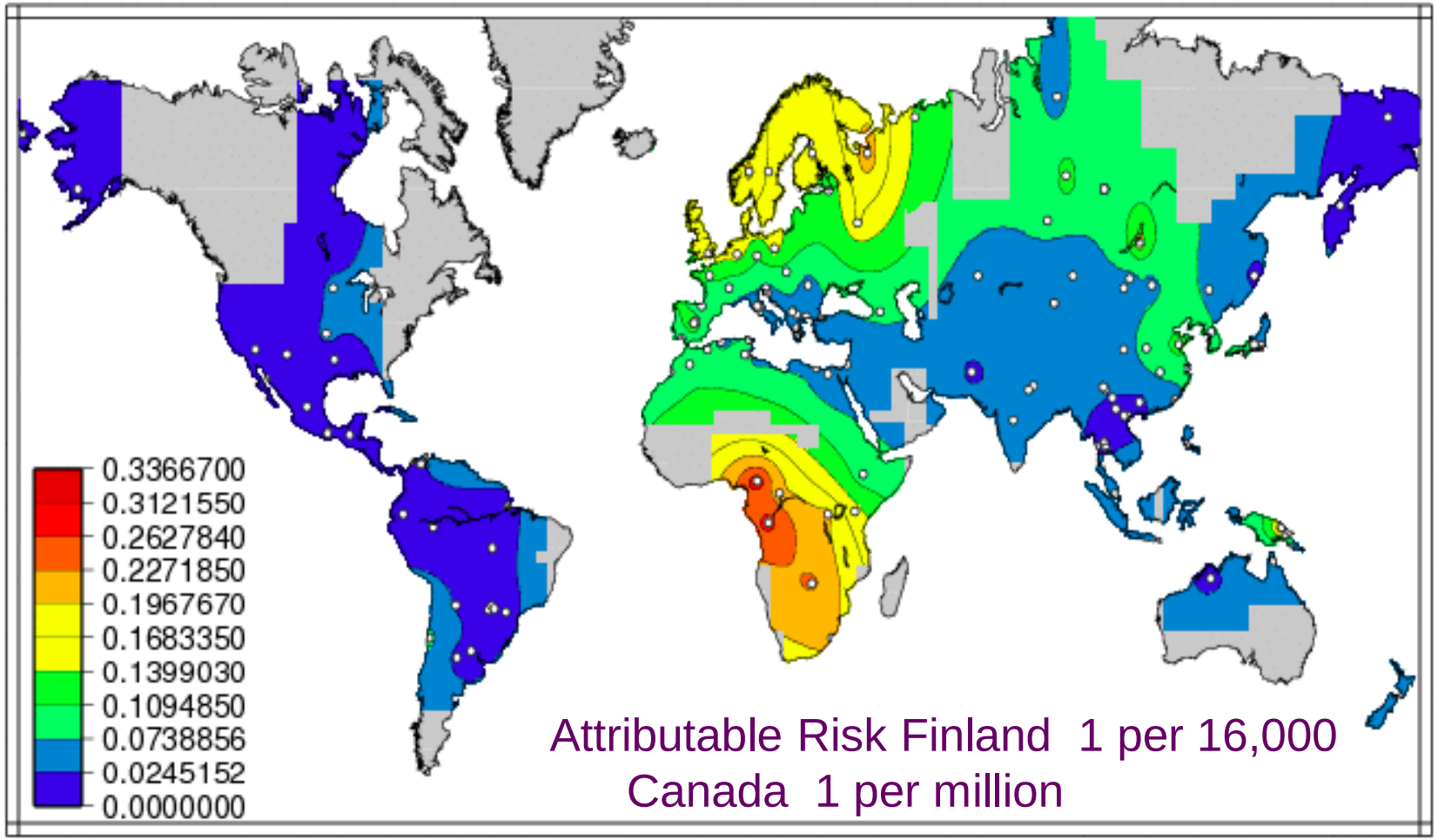

Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.

http://www.pypop.org/popdata/2008/maps/DQB1-0602.gif.

No Increase in Narcolepsy after Other H1N1 Influenza Vaccines

- US 127 million doses (no adjuvant), no signal
  - 2 studies no increased risk
- No increase in Europe with other vaccines, including LAIV and MF59 adjuvanted
- Difference in virus presentation? Structurally altered viral nucleoprotein in Pandemrix?

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McCarthy, et al Vaccine 2013. 31:5975-5982
Ahmed, et al J. Autoimmunity 2014. 50:1-11
Vaara et al. *PLOS 1 Dec 15 2014*

Biologicals 44 (2016) 276–280

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Meeting report

Where are we in our understanding of the association between narcolepsy and one of the 2009 adjuvanted influenza A (H1N1) vaccines?☆

K. Johansen [a], D. Brasseur [b], N. MacDonald [c], H. Nohynek [d], J. Vandeputte [e], D. Wood [f], P. Neels [e, g, *], on behalf of the Scientific Committee

- Pathological mechanism not identified
- Observational studies meet at least 4 of the Bradford Hill causality criteria; strength, consistency, specificity and temporality

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Johansen et al. 2016

Hypothesized Bias in Narcolepsy Studies

Computer Simulations

RESEARCH ARTICLE

Application of Probabilistic Multiple-Bias Analyses to a Cohort- and a Case-Control Study on the Association between *Pandemrix*™ and Narcolepsy

Kaatje Bollaerts[1]*, Vivek Shinde[2], Gaël Dos Santos[3], Germano Ferreira[4], Vincent Bauchau[4], Catherine Cohet[4], Thomas Verstraeten[1]

EXPERT REVIEW OF VACCINES, 2016
VOL. 15, NO. 5, 573–584
http://dx.doi.org/10.1586/14760584.2016.1164045

Taylor & Francis
Taylor & Francis Group

PERSPECTIVE

OPEN ACCESS

Pandemic influenza vaccine & narcolepsy: simulations on the potential impact of bias

Leonoor Wijnans[a,b#], Caitlin Dodd[a#], Maria de Ridder[a], Silvana Romio[a,c], Daniel Weibel[a], Sebastiaan Overeem[d], Gert Jan Lammers[e,f], Jan Bonhoeffer[g,h], Steve Black[i] and Miriam Sturkenboom[a]

[a]Department of Medical Informatics Erasmus MC Rotterdam, The Netherlands; [b]Pharmacotherapeutic group IV, Medicines Evaluation Board, Utrecht, The Netherlands; [c]Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, Laboratory of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy; [d]Sleep Medicine Center Kempenhaeghe, Heeze, The Netherlands; [e]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands; [f]Sleep Wake Center SEIN Heemstede, Heemstede, The Netherlands; [g]Brighton Collaboration Foundation, Basel, Switzerland; [h]University Children's Hospital, Basel, Switzerland; [i]Center for Global Health, Cincinnati Children's Hospital, Cincinnati, OH, USA

IABS meeting to review data
March 2018

CYD-TDV Dengue Vaccine

- Some experts believe vaccine caused enhancement

Halstead SB Vaccine 2016;34:1643-7.

Hadinegoro SR N Engl J Med 2015;373:1195
SAGE Working Group on Dengue Vaccines

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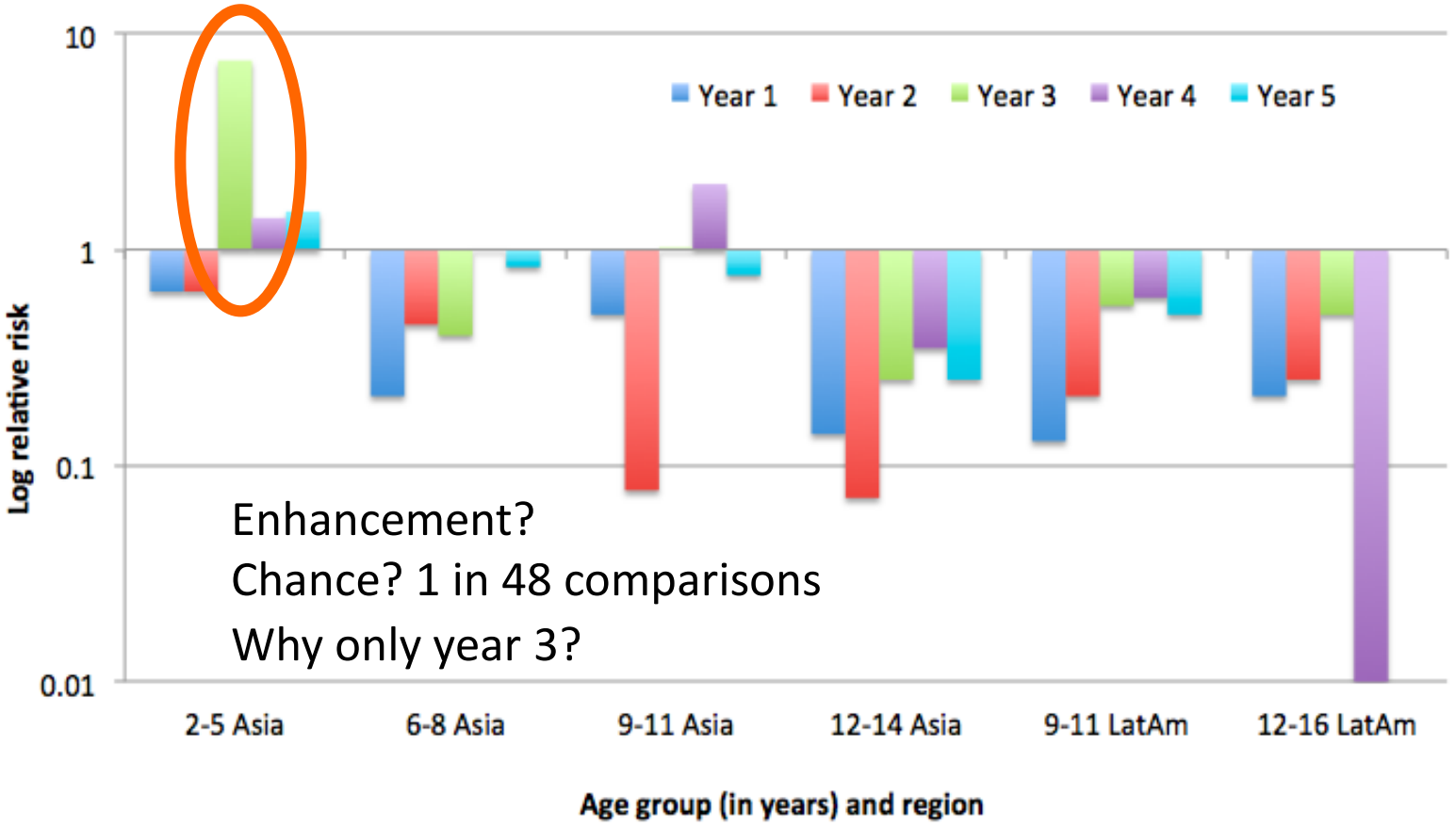
Relative risk of dengue hospitalization in vaccinated vs. control populations, by follow-up year



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Gessner and Halsey Vaccine. 2017 Jun 14;35(27):3452-3456

Cumulative hospitalizations by year for confirmed dengue in vaccinated and control* children: Asia

Figure 2a. Children enrolled at age 2-5 years.

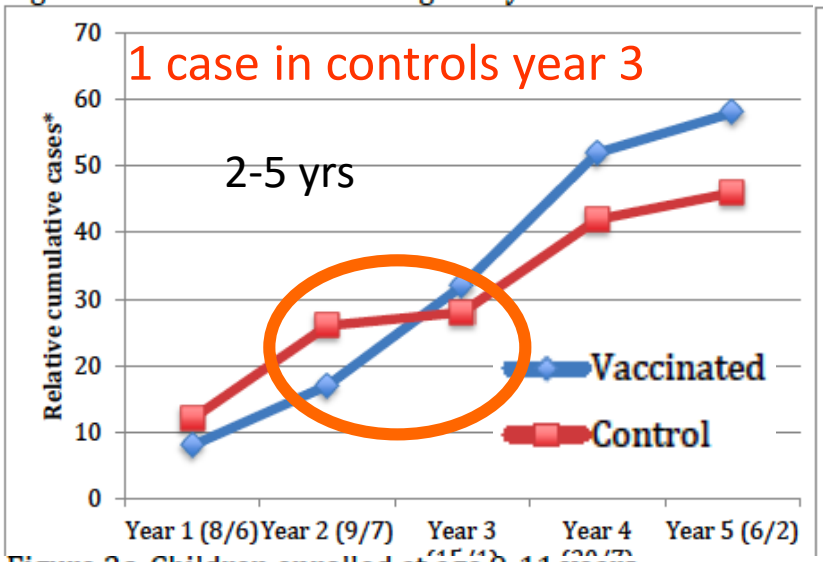


Figure 2b. Children enrolled at age 6-8 years.

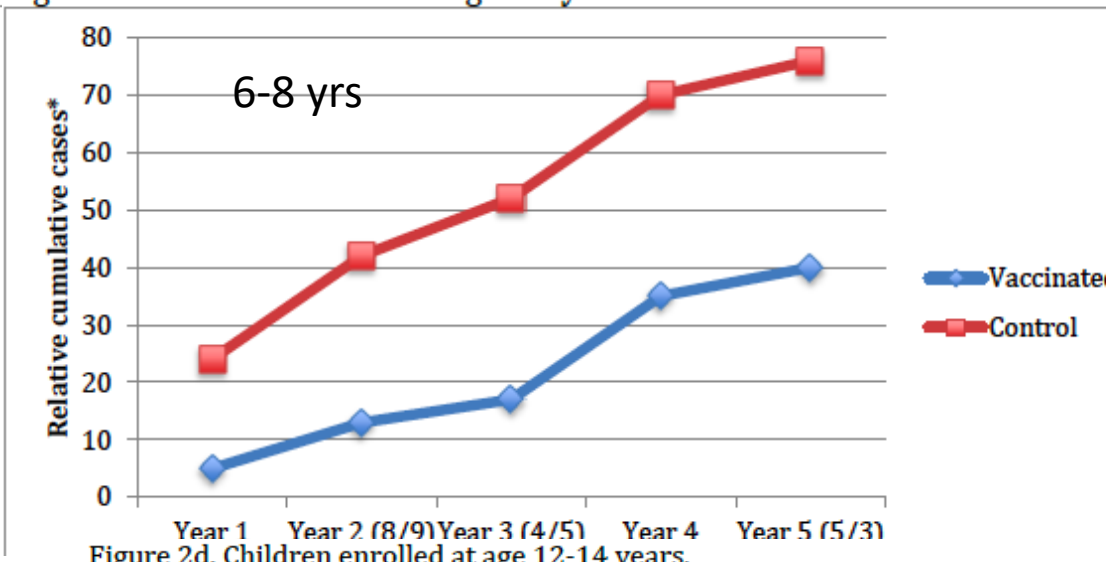


Figure 2c. Children enrolled at age 9-11 years.

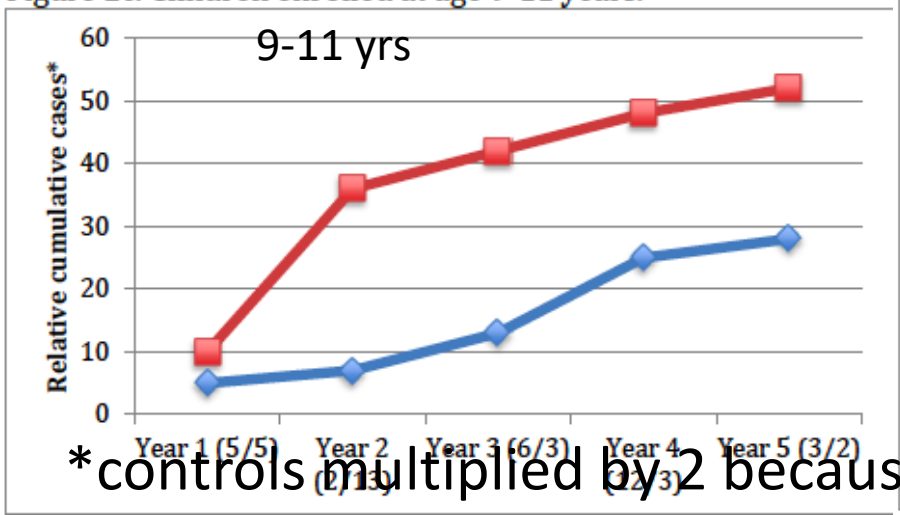
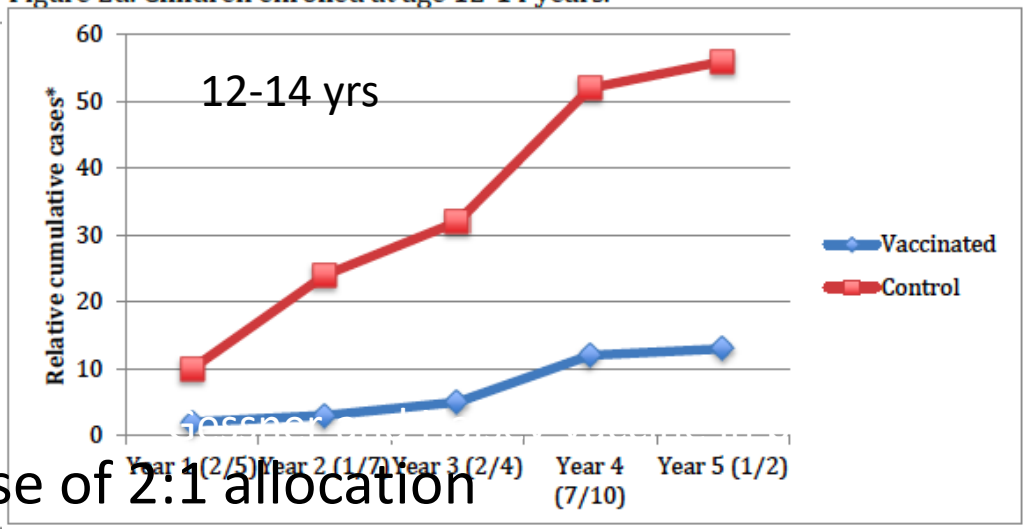


Figure 2d. Children enrolled at age 12-14 years.

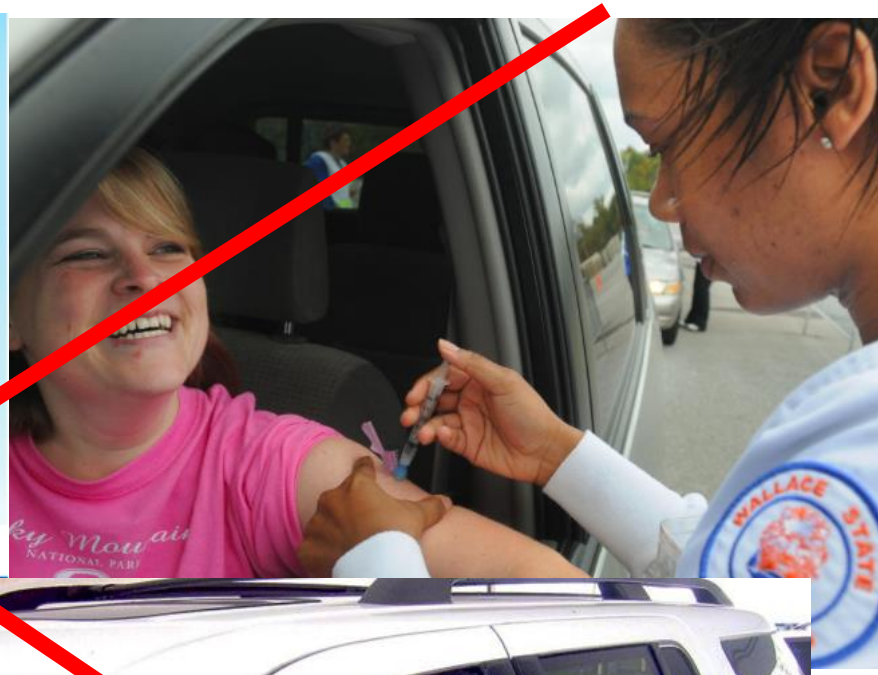


*controls multiplied by 2 because of 2:1 allocation

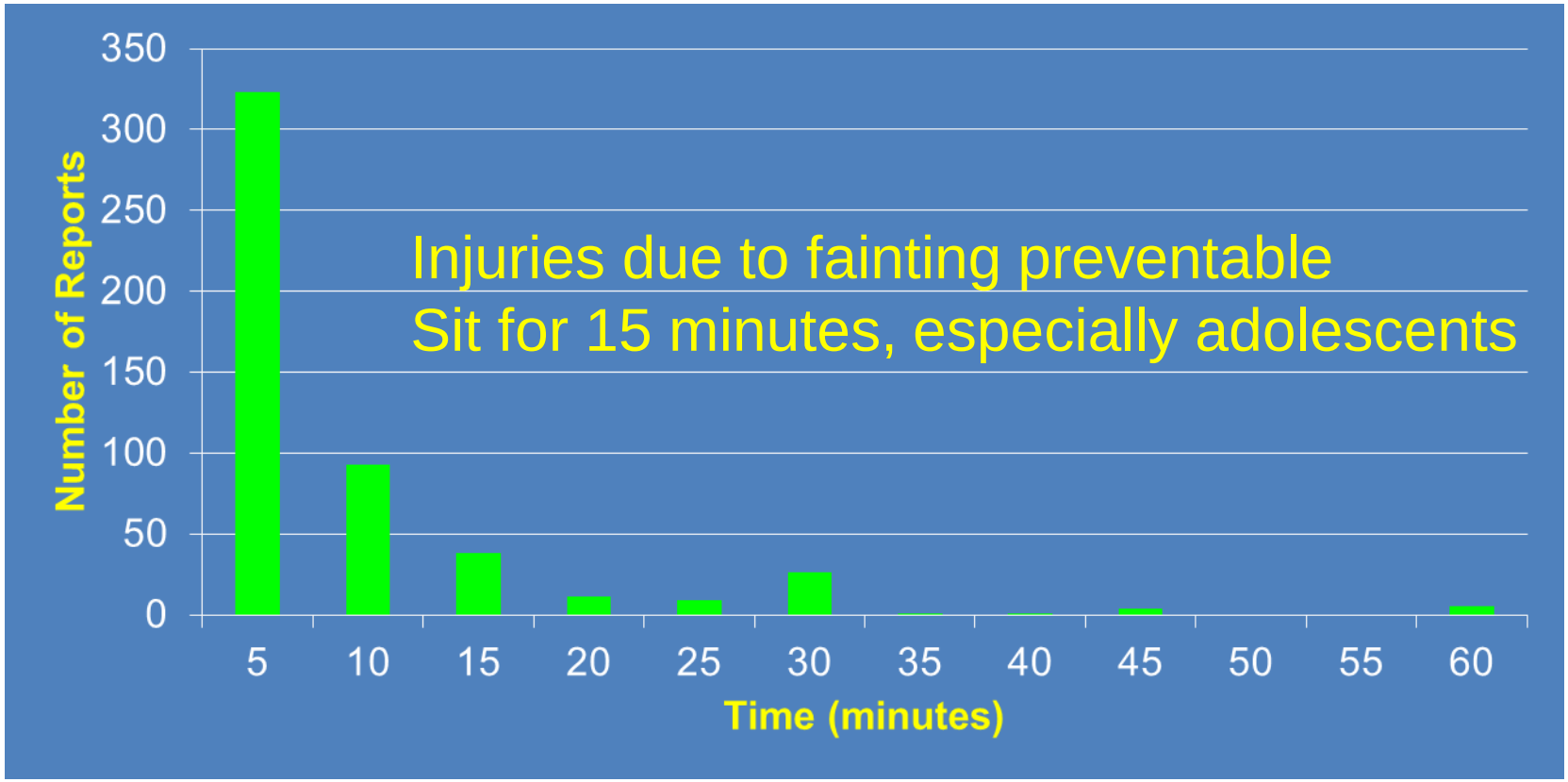
Preventable Serious Adverse Events

- Fainting
  - Head injuries
  - Auto accidents
- Administration errors
  - Shoulder injury
  - Drugs mistaken for vaccine diluent
  - Sepsis from contaminated multi-dose vials of vaccine

Drive through Vaccine Clinics
NOT a good idea



Time from Vaccination to Syncope



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Braun MM, et al. Arch Ped Adol Med 1997;151:255.

Short communication

Shoulder injury related to vaccine administration (SIRVA)☆

S. Atanasoff[a,*], T. Ryan[a], R. Lightfoot[b], R. Johann-Liang[a]

Vaccine 2010:28; 8049

[a] U.S. Department of Health and Human Services, Health Resources and Services Administration, National Vaccine Injury Compensation Program, United States
[b] The Division of Rheumatology and Women's Health, University of Kentucky School of Medicine, United States

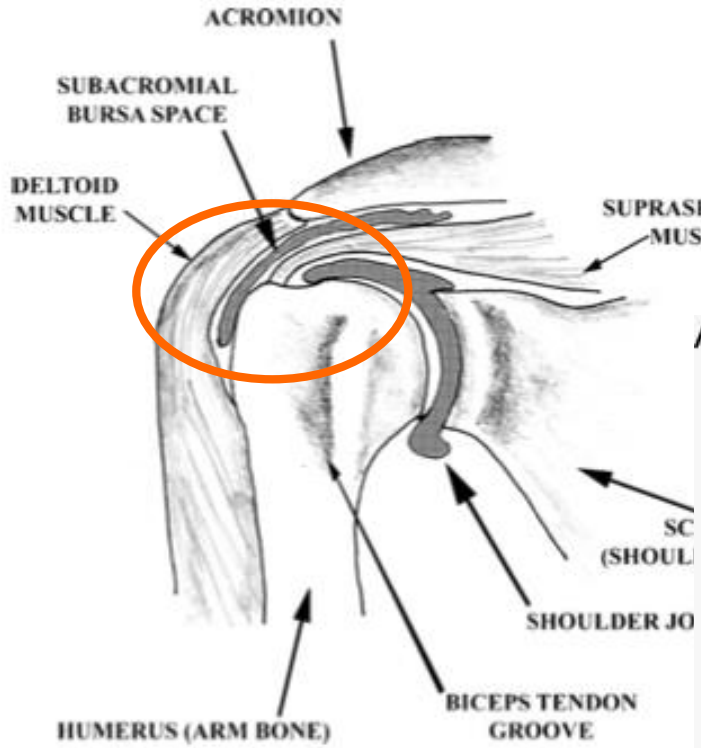
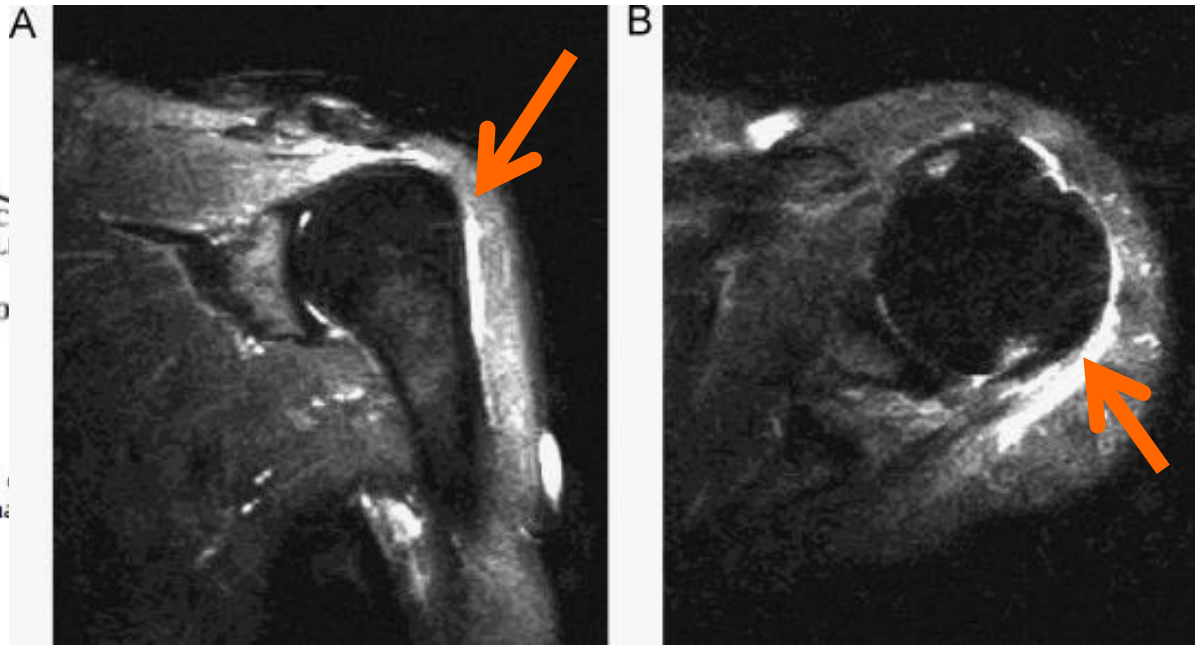


Fig. 1. Anatomy of the shoulder girdle. The relationships toid/subacromial bursa and shoulder joint space to the supraspina to the greater tuberosity on which it inserts.

US VICP: 492 patients with shoulder injury compensated Wadman Science 2017



Bursitis after HPV vaccine Uchida Vaccine 2012

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Safest Deltoid Muscle Injection

1. Hand on hip
   - Abduct 60^{o}
   - Moves axillary nerve
2. Index finger on acromian process
3. Thumb on tuberocity
4. Inject at mid point

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Cook IF. Human Vaccine 2011;7(8):845.

Administration Errors
Measles Vaccines and Diluent

10 dose vials

Single dose

Vaccine refrigerated
Diluent stored room temperature

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Respiratory Arrest and Deaths Following Measles and BCG Vaccines

- Paralyzing agents mistaken as vaccine diluent

Weekly Epi Record

1996;71(32):239.

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15 Deaths in Syria 2014

Atracurium used to reconstitute measles vaccine

World Report

Campaign suspended for months

Contaminated vaccine deaths a serious setback for Syria

Experts say that the deaths of several children from a contaminated measles vaccine will have a devastating effect on future immunisation and health efforts in Syria. Sophie Cousins reports.

Flo Smith/NurPhoto/Corbis

At least 15 children died last week after being vaccinated against measles in northern Syria, an incident that is likely to have serious ramifications for future vaccination campaigns in opposition-held areas.

According to a preliminary investigation by a Syrian opposition group, the vaccine was accidentally mixed with atracurium, a muscle relaxant

of the Syrian American Medical Association, said.

Parents initially accused medics of incorrectly storing the vaccines or using out-of-date ones while some doctors accused the Syrian Government of sabotaging the vaccination campaign.

The campaign was suspended after the deaths. WHO said it had sent

catastrophe", said Annie Sparrow, public health expert and deputy director of the Human Rights Program at Icahn School of Medicine, NY, USA. "It's hard to see any parent letting their child be vaccinated in Syria ever again. It is just awful on so many levels."

She added that whatever the outcome of the investigation, it wouldn't address the fear the incident

Bacterial Contamination of Measles Vaccines

More than 30 clusters of deaths associated with contamination of vials after opening

Reuse of same syringe for reconstitution. Then storage of partially used vials for > 6 hours.

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Weekly Epi Record 1996;71(32):239.

Lahore Pakistan
October 13, 2017

DAWN

'Poorly-handled' vaccine blamed for three minor girls' death

Asif Chaudhry | Tariq Saeed | Updated October 13, 2017

TOBA TEK SINGH/LAHORE: Three minor girls died allegedly hours after they were administered anti-measles vaccine at a rural health centre at Chak 262-GB, Marthan Wala, in Rajana area.

According to locals, a health department team on Wednesday vaccinated around a dozen children at the village's rural health centre (RHC) against different diseases.

They said six of the children who were vaccinated against measles started vomiting and had fever after vaccination.

Two of them -- nine-month-old Hafsa Nasir and 14-month-old Ayeena Nawaz died in the night, they added.

Bacterial Contamination of Multi-dose vials Associated with Severe Disease

- Measles
- Yellow fever
- BCG
- DTP

Institute for Vaccine Safety

Johns Hopkins Bloomberg School of Public Health

Summary

- Vaccines are generally safe
- All countries need dedicated teams to investigate SAEs and address problems
- There is poor understanding of causality assessment
- Training and supervision of all health personnel administering vaccines