Introduction to vaccine safety

Understanding basic concepts

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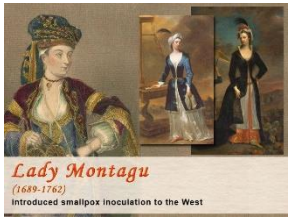
Quiz 1

The history of vaccination – improving safety

Variolation

- Material from a patient with **Small Pox** to induce immunity to **Small Pox**
- Originated in China in the 15th century (India Africa)
  - "nasal insufflation" and scarification (attenuate the scabs)
  - **<u>High mortality - 1 in 30</u>**

- Observed by Lady Mary Wortley Montague, in Turkey, wife of the UK ambassador and introduced into the UK in 1721



Vaccination

- Material from a patient with **Cox Pox** to induce immunity to **Small Pox**
  - **<u>Low mortality < 1 in 100</u>**

1774 first used by a farmer in Dorset called Benjamin Jesty

1796 Introduced by Edward Jenner (published and "efficacy")

1840 variolation banned in the UK

Sacred to the memory of
Benjamin Jesty of Devonshire
who
died on April 16th1816 aged 79 years.

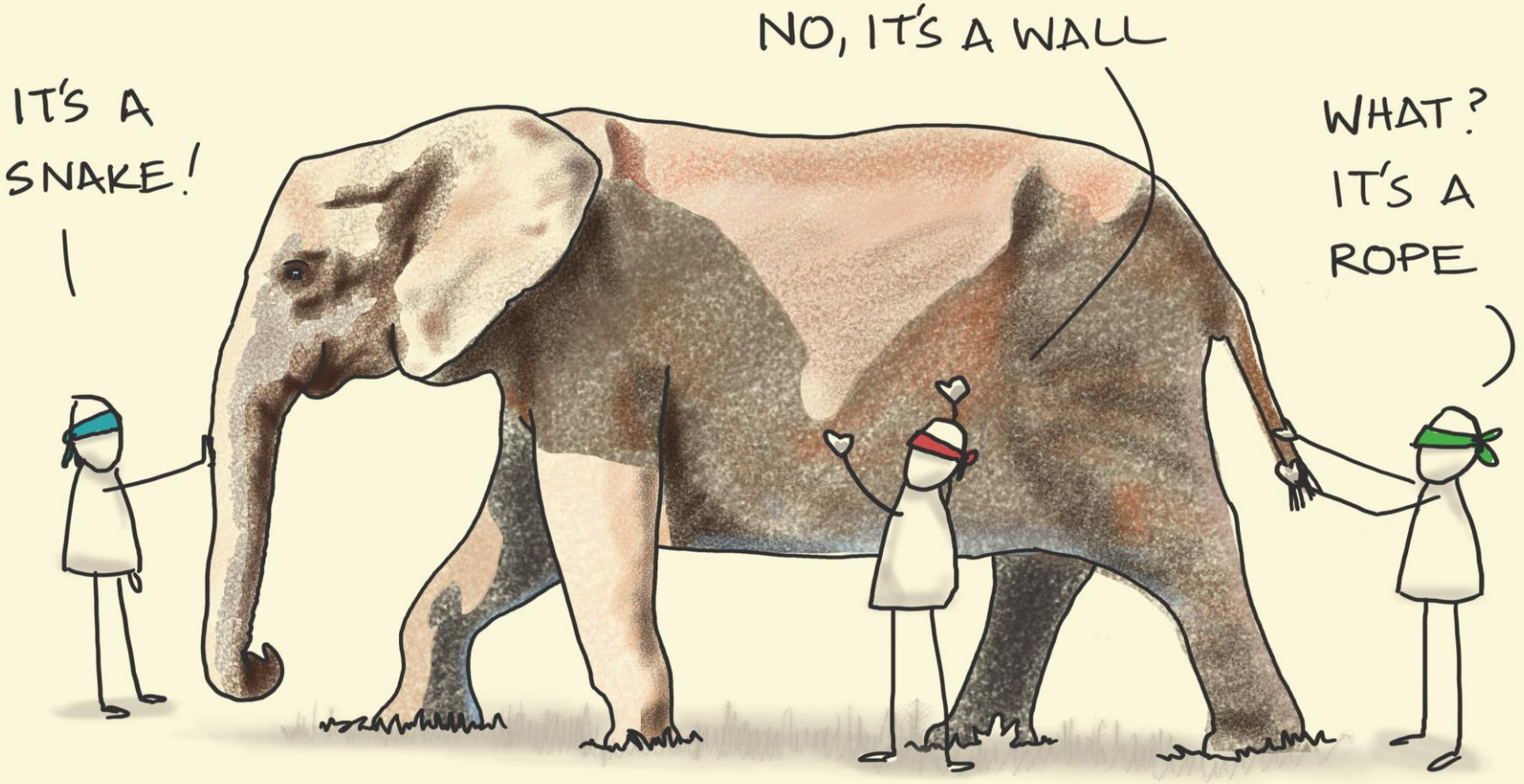
He was born at Westminster in his county an upright honest man
particularly noted for having been the **first person known that introduced the cow pox by inoculation and who from his great strength of mind made the experiment from the cow pox on his wife and two sons in the year 1774**

Outline

- Why is vaccine safety important ?
- How do you know that a vaccine is safe ?
- How do you know that a vaccine has caused a reaction?

THE BLIND AND THE ELEPHANT

OUR OWN EXPERIENCE IS RARELY THE WHOLE TRUTH



sketchplanations

Community concerns are about vaccine safety rather than efficacy

Comparisons of Vaccine Hesitancy across Five Low- and Middle-Income Countries

Vaccines 2019, 7, 155; doi:10.3390/vaccines7040155

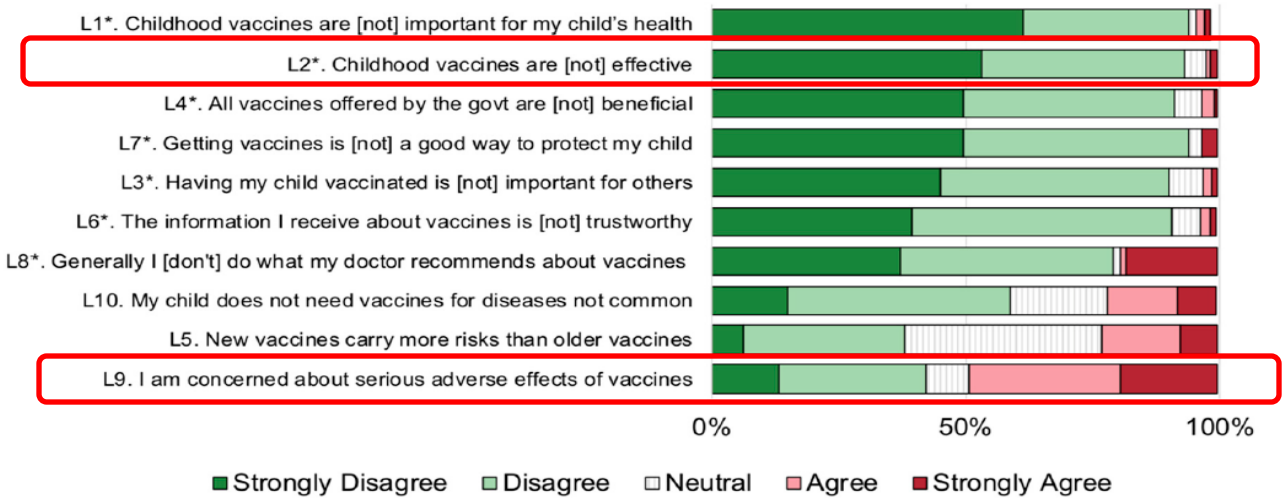


Figure 1. Overall patterns of vaccine hesitancy across the five surveyed Low- and Middle-Income Countries (LMICs), presented by question. Note, questions with a * were reverse coded so that the scale was in the same direction for all questions, with higher scores (1–5, 5 representing 'Strongly Agree', corresponding to higher vaccine hesitancy scores).

COVID-19 Vaccine Hesitancy in South Africa: Lessons for Future Pandemics

Engelbrecht M et al Int. J. Environ. Res. Public Health **2022**, *19*(11),6694; **https://doi.org/10.3390/ijerph19116694**

Variable		n	%
Reasons for not being sure/not taking a COVID-19 vaccine (N = 25,816)	Concerns about side-effects	6732	26.1
	COVID-19 vaccines were developed and approved too rapidly to be trusted	3240	12.6
	Not trusting the government	3052	11.8
	Fear of needles	2728	10.6
	Prefer to acquire natural immunity	2656	10.3
	Don't think it will be effective	2008	7.8
	Against vaccines in general	1836	7.1
	Not at risk for COVID-19	1600	6.2
	COVID-19 vaccines are promoted for commercial gains of pharmaceutical companies	1176	4.6
	Don't have time to go for a vaccine	540	2.1
	Conspiracy theories—reduce the population/kill people	84	0.3
	Pregnant/breastfeeding	68	0.3
	Having co-morbidities	56	0.2
	Religious beliefs	40	0.1

Concerns about vaccine safety affect coverage

Vaccine safety concerns

Loss of confidence in vaccines

Vaccine Hesitancy

Decrease in coverage

The cow pock or wonderful effects of the new inoculation
Publications of ye Anti-Vaccine Society circa 1800
(Jenner's vaccination 1796)

Global resurgence of vaccine preventable disease

Pertussis in UK/Japan in 1970s
Diphtheria in Russia in 1990s
MMR in UK/Ireland in 1998
Polio in Nigeria 2004
HPV in Japan/Denmark 2015
Measles global 2018-23
COVID-19 2022
Polio and VD polio Ongoing

Safety concerns may be about newly introduced vaccines

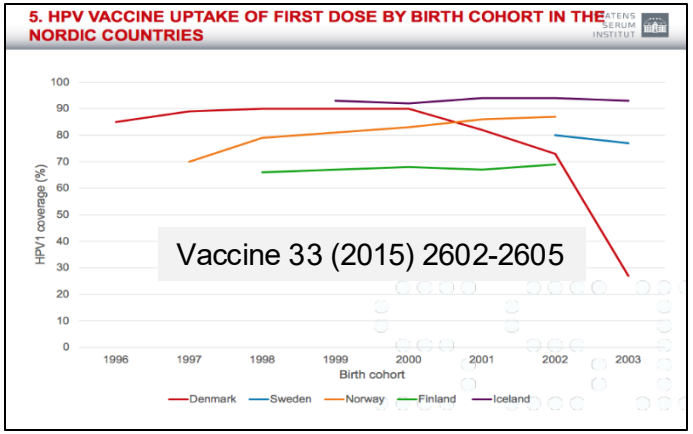
Human Papilloma Virus

OUR GIRLS ARE NOT GUINEA PIGS

Is an upcoming mass inoculation of a generation unnecessary and potentially dangerous?

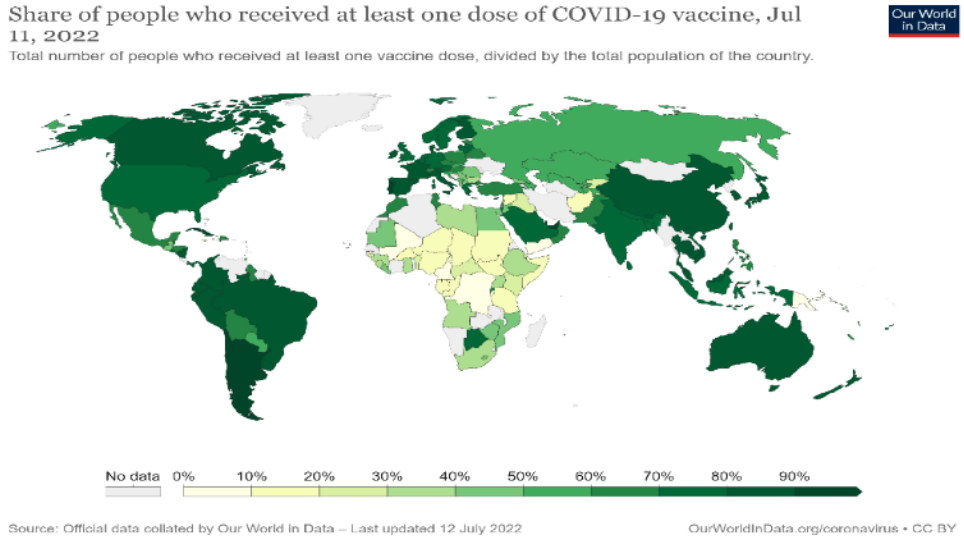
Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus

Louise S. Brinth, Kirsten Pors, Ann C. Theibel, Jesper Mehlsen*



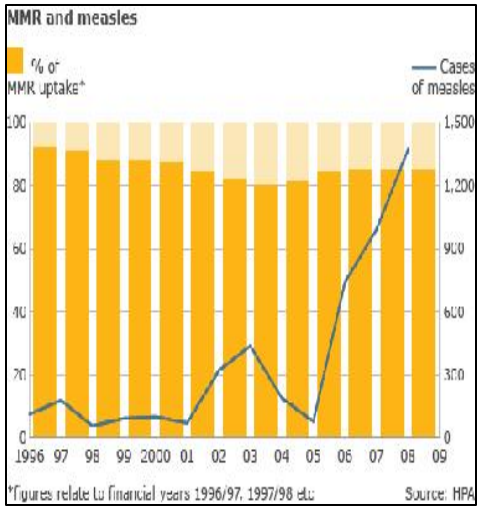
Vaccine 33 (2015) 2602-2605

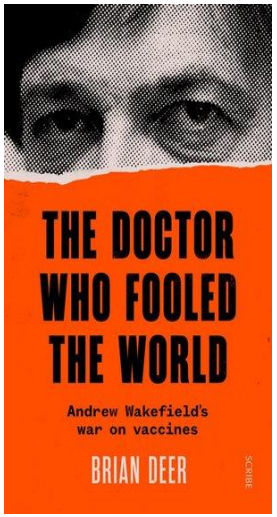
COVID-19



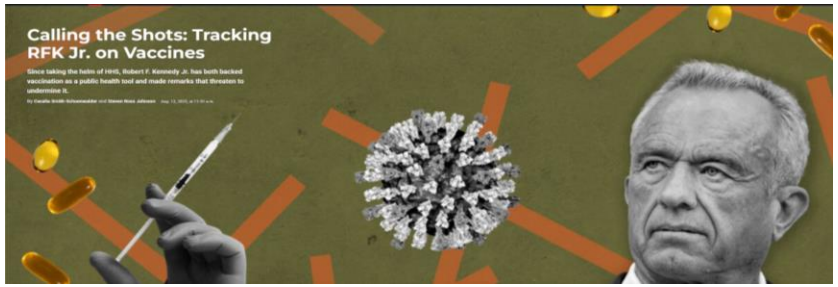
Safety concerns may be about established vaccines

Measles Mumps Rubella

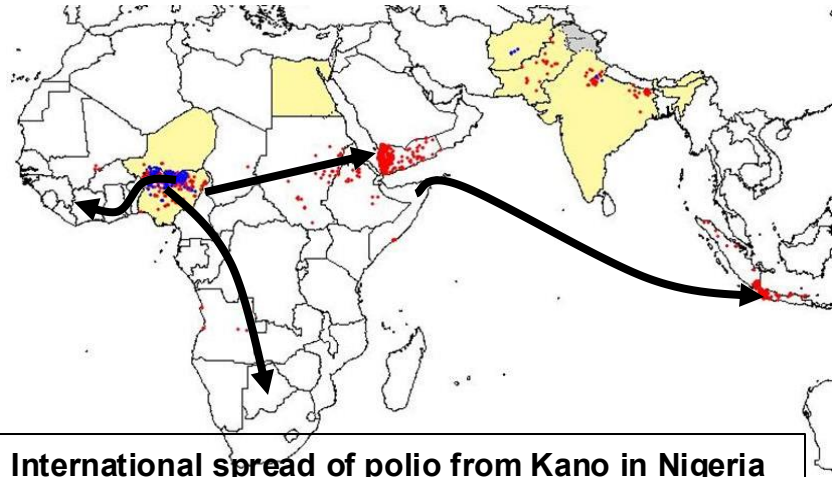




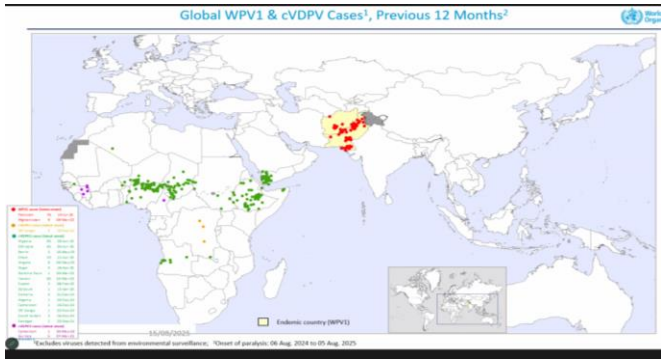
Retraction--Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet retraction.
Lancet 2010 Feb 6;375(9713):445.



Polio



International spread of polio from Kano in Nigeria to 10 countries in Africa and then to Middle East and Asia
Ivory coast Ghana Togo Benin Burkina Faso, Cameroon Central African Republic, Chad, Sudan, Botswana



How do we know ..... is safe ?

Safety inferred because of an absence of **adverse reactions**

Reactions are **adverse** effects that are caused or precipitated (triggered) by;

- **The vaccine (s)**
  What is in the vaccine

- **Immunisation**
  The process of administering the vaccine

Adverse **events** versus **reactions**

Surveillance vs Causality

- Many of the symptoms and signs of an **adverse vaccine or immunisation reaction** also occur in the absence of vaccination
- These events, unrelated to vaccination, are called background or coincidental events
- Surveillance is the detection of **adverse events following immunisation (AEFI),** which are a combination of adverse vaccine reactions and background events
- **Causality assessment** of AEFI is used to differentiate an **adverse reaction** from a **background or co-incidental event**

But …….. there are three unique generalised adverse vaccine reactions that only occur with **vaccination and have no background occurrence**

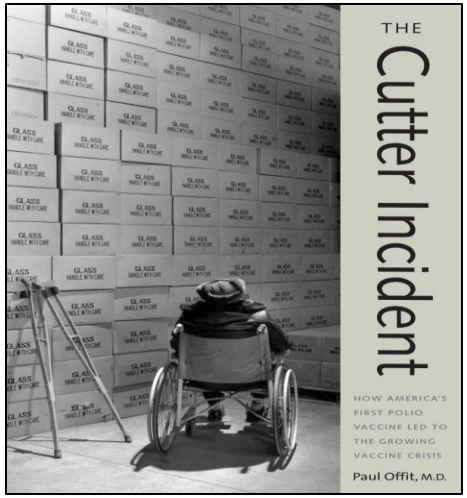
Vaccine	Condition
Yellow Fever	Viscerotropic/Neurotrophic Disease
Attenuated live vaccine disease	BCG Disseminated BCG Measles Vaccine encephalitis Polio (Oral) Vaccine associated paralytic polio (VAPP) VZ Disseminated Varicella-Zoster
COVID-19 viral vector	Vaccine Induced Thrombosis with Thrombocytopenia (VITT)

How do we know a vaccine is safe ?

- Inferred because of the absence of adverse reactions, which are due to the vaccine or process of immunisation
- Safety surveillance detects AEFI

<u>How do we perform surveillance to detect AEFI and then differentiate adverse reactions from co-incidental events ?</u>

Regulatory framework for drug and vaccine safety evaluation, licensure and surveillance

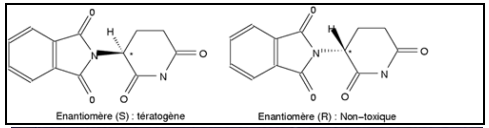


April 1955, **Cutter incident**

- 200,00 children received partially inactivated vaccine
- 40,000 cases of polio
- 200 children paralysed
- 10 deaths

Thalidomide

First introduced October 1, 1957 Withdrawn in 1961



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

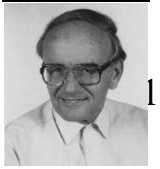
Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

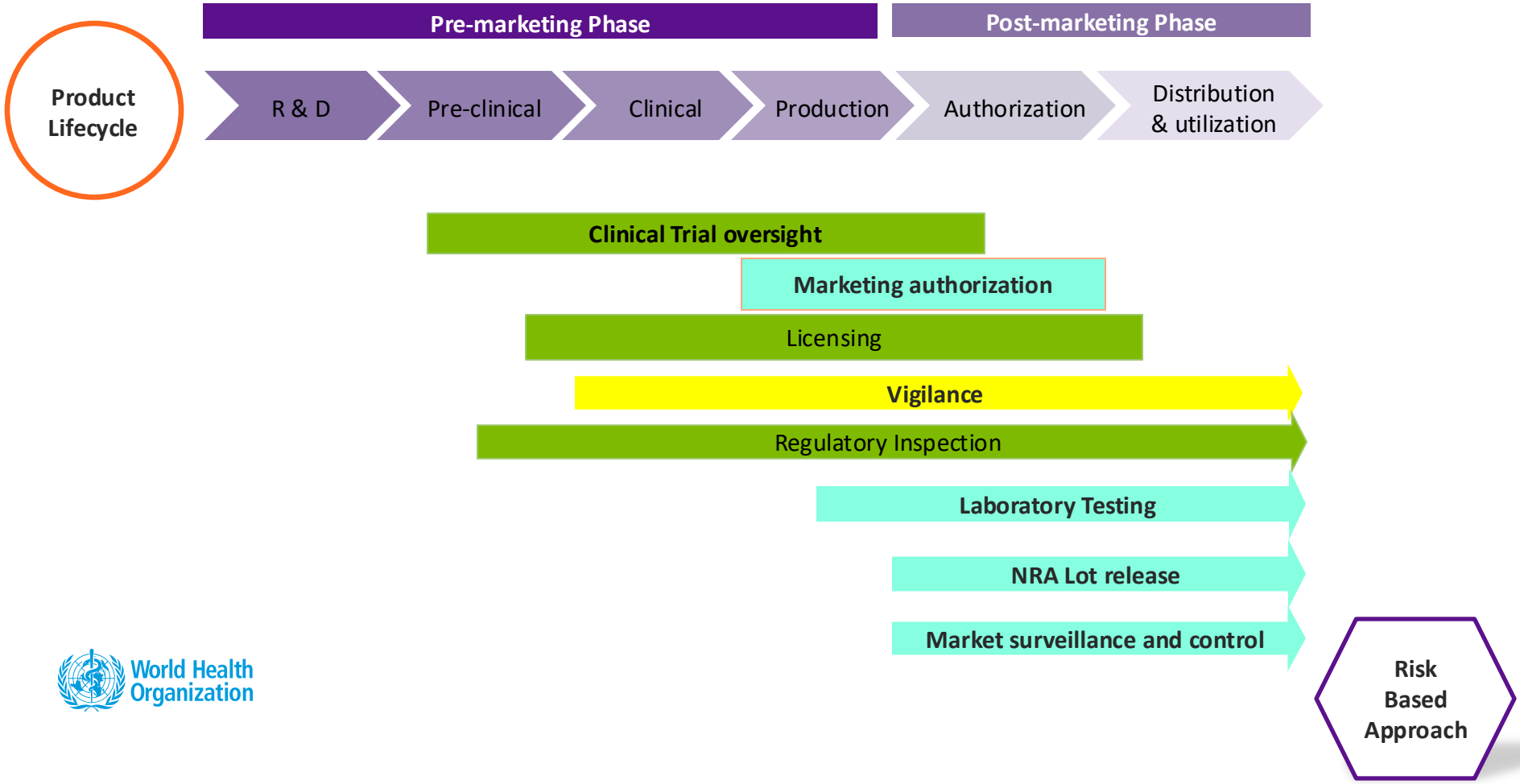
McBride WG. *Thalidomide and congenital abnormalities. Lancet 2:1358. Dec 16 1961*

Widukind Lenz. *Nov 15 1961*
Withdrawn by manufacturer Nov 26 1961- 1,600 reports



WHO Recommended Regulatory Functions Based on Product Lifecycle

National Regulatory System



World Health Organization

Reference: https://apps.who.int/iris/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1&isAllowed

Pre-marketing phase and vaccine safety

	Sample size	Adverse Reactions	
		Common	Rare
Animal trials		+/–	–
Clinical trials			
Phase I	10-100	+/–	–
Phase II	100-1,000	+	–
Phase III	1,000-10,000	+	–

– **Does not detect adverse reactions which are**:
  - rare, delayed, unexpected
  - occur in sub-populations
  - with vaccine combinations

At the time of vaccine licensure safety data is incomplete

Post-marketing Phase
Vaccine Pharmacovigilance

Vaccine pharmacovigilance* the science and activities relating to the **detection, assessment, understanding and communication of Adverse Events Following Immunization (AEFI)** and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

World Health Organization

Reference: * Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012

The differences between **vaccine and drug** pharmacovigilance and safety

Vaccines

- Prevention in healthy, larger population
  - Lower risk tolerance
- Limited number of products
- With single dose, greater potential for temporal “coincidence”

Drugs

- Treatment in ill, smaller population
  - More tolerant of risk
- Large number of products, many classes
- Treatment over time: less “coincidence” after a single dose

Vaccines

- Mass campaigns: many doses in short time, defined population
- Politics of access/safety
  - Collaboration between public health/NIP, NRA and manufacturers

Drugs

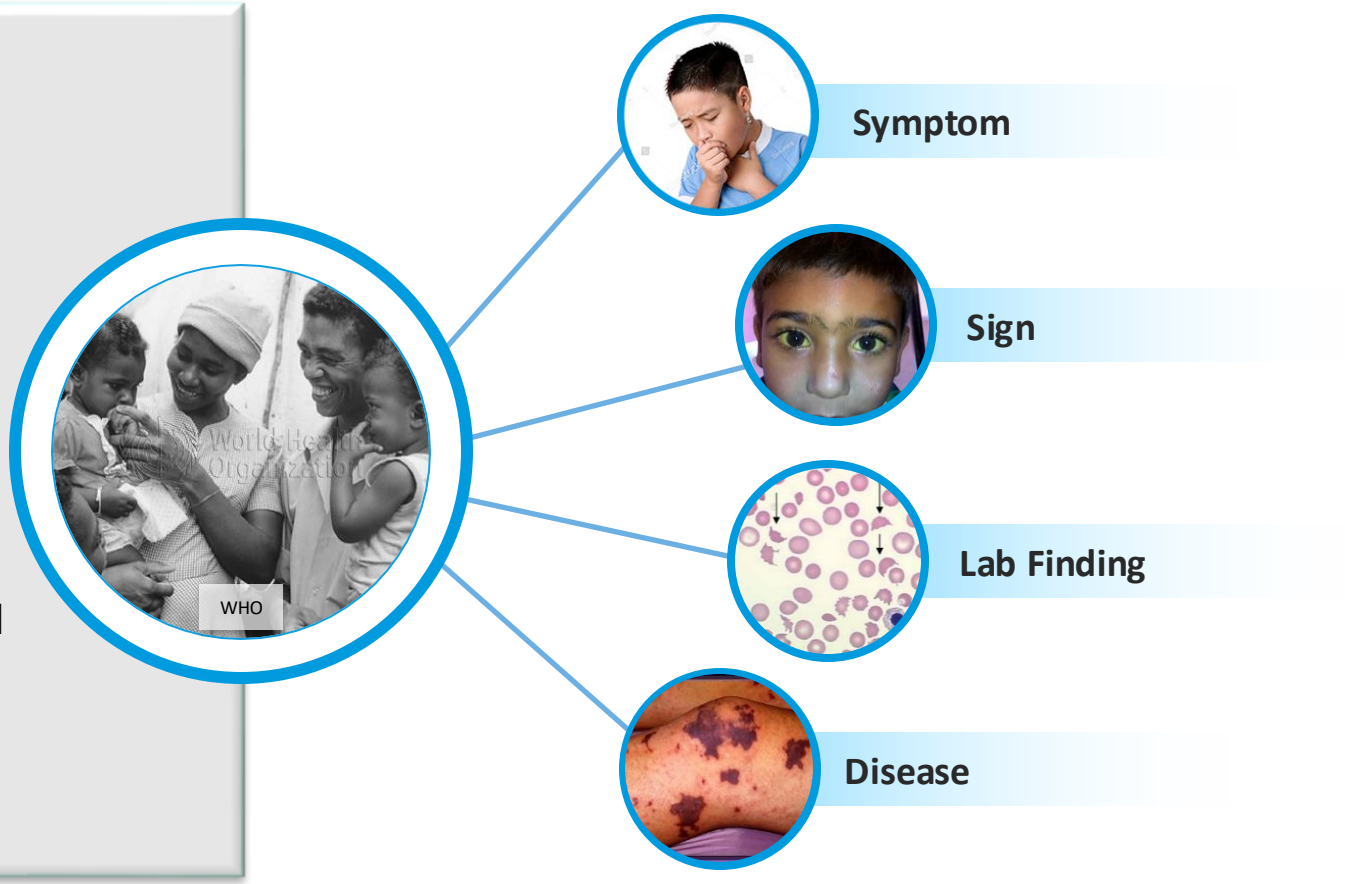
- No mass campaigns – “private” prescribing to less defined population
- Politics of access/safety
  - Less relationship between health system/govt/NRA and manufacturers

Vaccines demand higher safety and more careful quality standards and monitoring.

Adverse Event Following Immunisation (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 unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.



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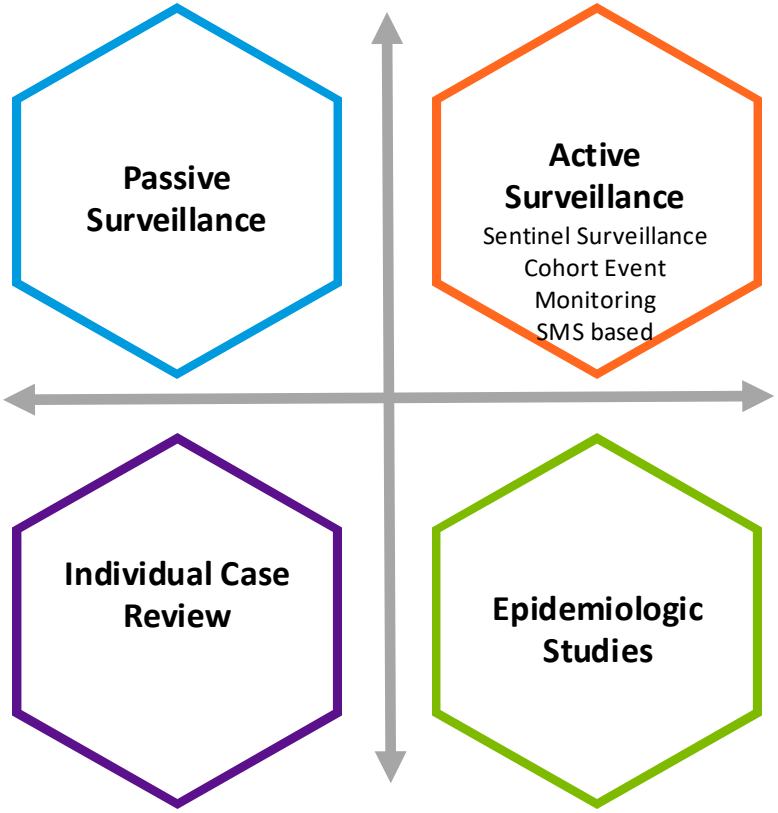
Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012

How is post-marketing surveillance undertaken?



Passive (spontaneous) reporting by health providers, consumers, manufacturers of

Adverse Events Following Immunization (AEFI)

World Health Organization

AEFI Surveillance Cycle

STRATEGIC PRIORITY 1.

Monitoring vaccine safety: Ensure that national immunization programmes can detect and respond to any concern about vaccine safety by continuous monitoring and coordination among relevant stakeholders.

World Health Organization

Why do we do post-licensure AEFI surveillance ?

01

To monitor the rates of **known adverse vaccine reactions** and compare the **observed** with the **expected** rates

World Health Organization

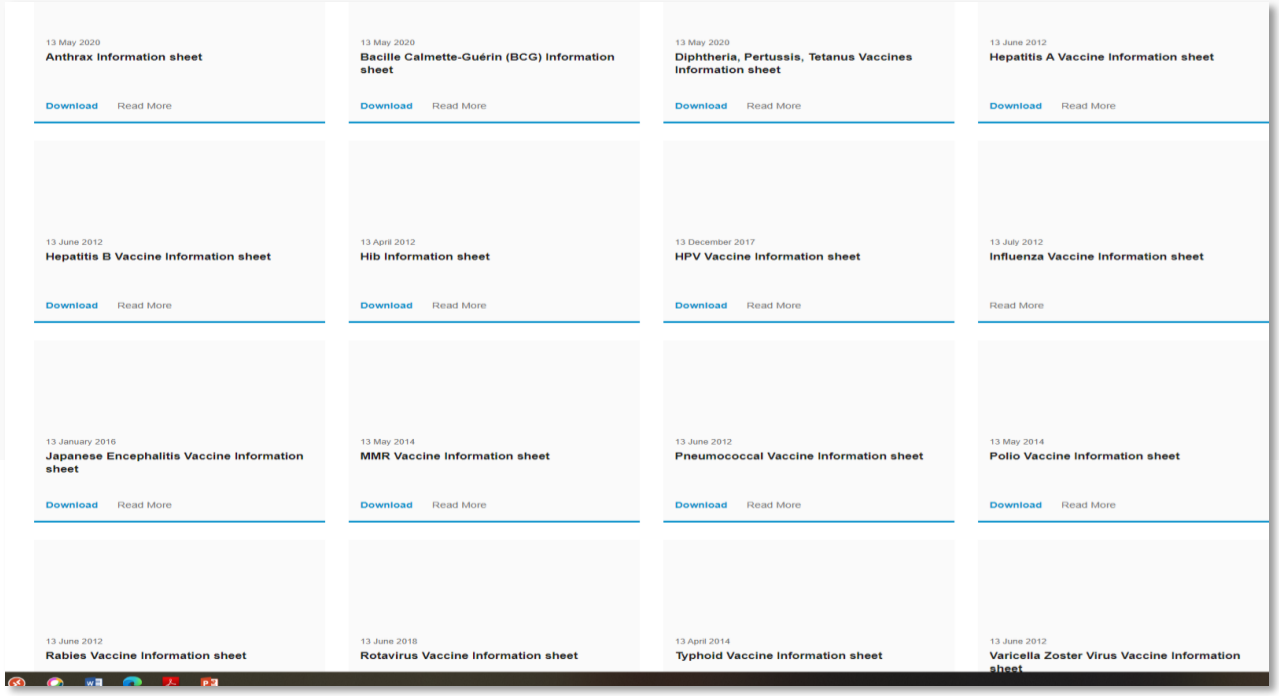
Global Vaccine safety
Essential Medicines & Health Products
20, Avenue Appia, Ch- 1211 Geneva 27

INFORMATION SHEET

OBSERVED RATE OF VACCINE REACTIONS

HUMAN PAPILLOMA VIRUS VACCINE

December 2017



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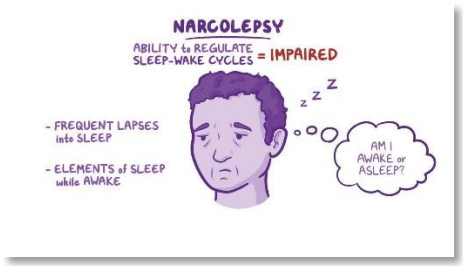
02

To detect a vaccine safety signal

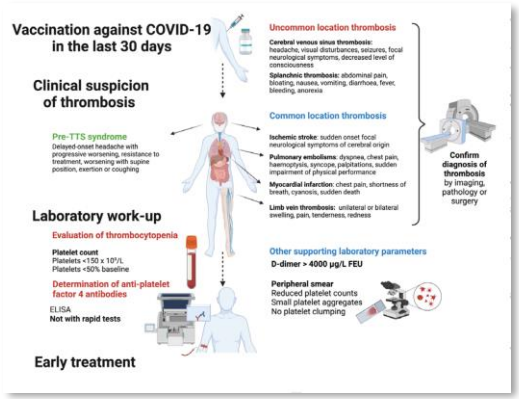
An adverse vaccine reaction which is **unknown** at the time of licensure.

A safety signal is a cluster of AEFIs that may require further investigation to determine if this is a newly described adverse reaction or a co-incidental event

Intussception and Rotaviral vaccine



Narcolepsy and adjuvanted pH1N1 influenza vaccines



Viral vector COVID-19 vaccine and VITT

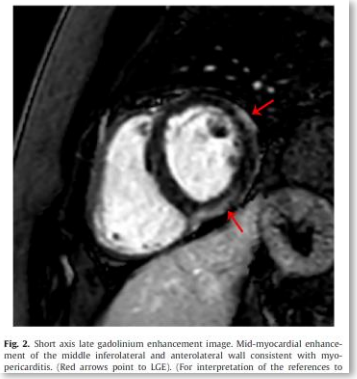


Fig. 2. Short axis late gadolinium enhancement image. Mid-myocardial enhancement of the middle inferolateral and anterolateral wall consistent with myopericarditis. (Red arrows point to LGE). (For interpretation of the references to

mRNA COVID-19 vaccine and myopericarditis

03

To detect immunization errors

Vaccine handling

14 deaths following Measles vaccine

	Age (approximate)	Sex	Time of vaccination (approximately)	Time of onset of symptoms	Symptoms presented (from primary informant)	Time of deaths
1	> 5 years	M	Morning	Shortly after	Fever, ask for water, Vomiting, No diarrhoea	Early afternoon around 2 PM
2	1-5 years	F	Morning	Shortly after	High fever , Very tired, vomiting, no talking, No diarrhoea	Early afternoon
3	2 – 3 years	M	Morning	Around mid-day	Felt very tired, vomiting, sleepy, passed urine. No diarrhoea	Late afternoon around 6 PM
4	>5years	M	Morning	Shortly after	Very high fever, big swelling at the site of injection (still visible), fainted and rolled her eyes up.	Survived
5	>5 years	M	Morning	Shortly after	Red eyes, tired, Diarrhoea and vomiting, complaint of headache and pain in the chest	Mid-afternoon
6	6 years	F	Morning	Shortly after	Pain at site of vaccination, then diarrhoea not vomiting , big swelling on site of injection extending to the arm up to the neck, frosting and convulsion (rolling eyes up)	Mid-afternoon
7	>5 years	F	Morning	Very shortly after	Headache, fever, convulsion and comatose	Mid-day
8	>5 years	M	Morning	Shortly after	Weakness, unable to walk, fever and fits and died	Mid-day
9	>5 years	F	Morning	Shortly after	Fever, fits, saliva in mouth, loss of consciousness and dead	Mid-day
10	2 years	M	Morning	Shortly after	Vomiting, diarrhoea, fever	7 PM
11	1-5 years	F	Morning	Mid-day	Vomiting, diarrhoea, fever	7 PM
12	9 years	M	Morning	Mid-day	Vomiting, diarrhoea, fever	Evening (9PM)
13	8-9 years	M	10 AM?	Early afternoon	Vomiting diarrhoea, fever	Late evening
14	2 years	M	Morning	Mid-afternoon	Vomiting Diarrhoea	No known
15	8 years	M	Morning	Mid-day	Fever vomiting , diarrhoea	Mid-afternoon
16	1 years	F	Morning	Mid-day	Fever, vomiting, Diarrhoea	3 PM? Mid-afternoon

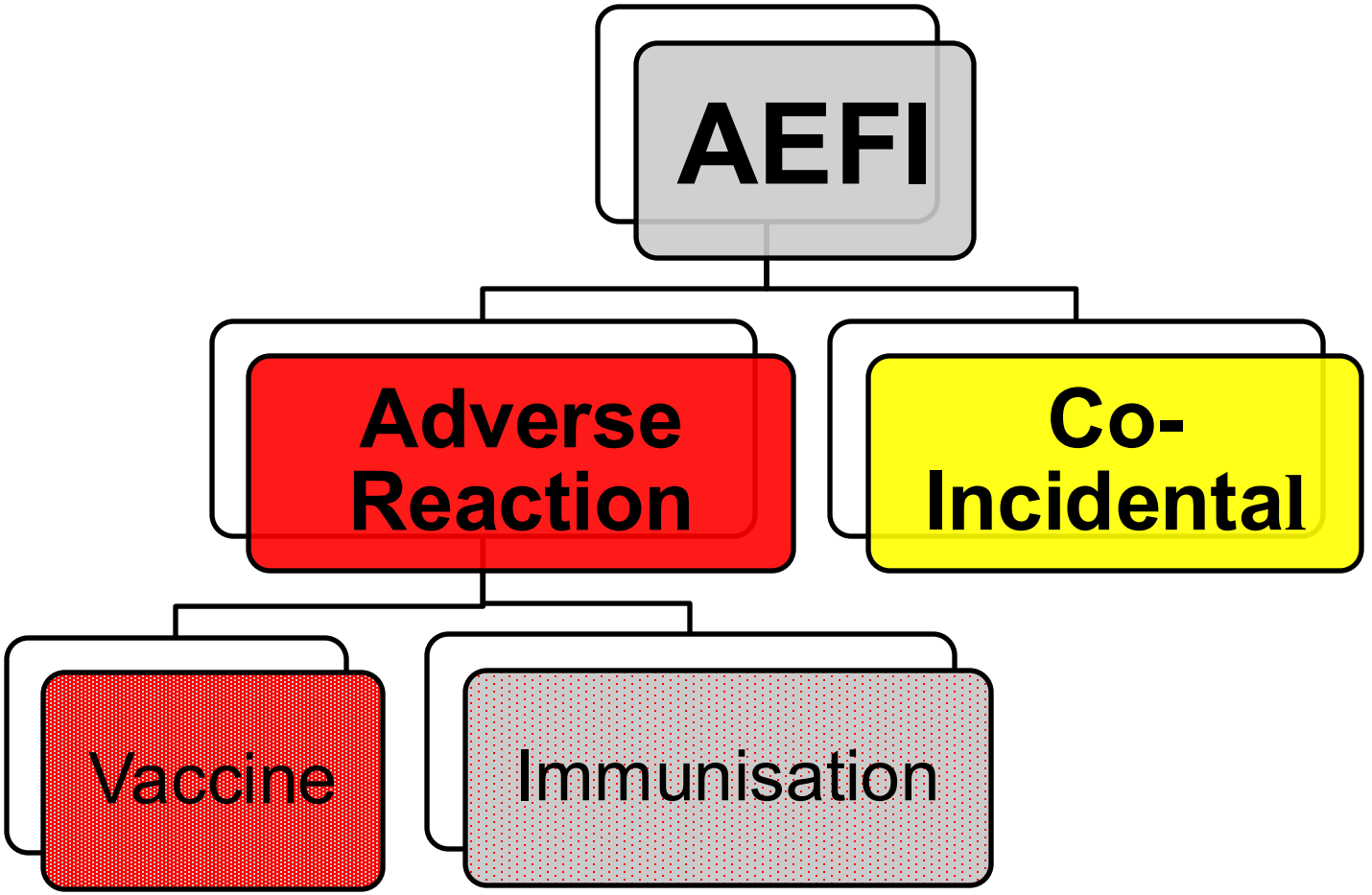
REPUBLIC OF KENYA

MINISTRY OF HEALTH

PRESS RELEASE ON DEATH OF TWO CHILDREN FOLLOWING MEASLES IMMUNIZATION IN KERIO VALLEY, MARAKWET EAST SUB COUNTY, ELGEYO MARAKWET COUNTY

The Ministry of Health wishes to shed light on the incidence of death following measles immunization of two children in Kotut village of Endo Ward near Kapetwa Health Centre, Kerio Valley, Marakwet East Sub-county in Elgeyo Marakwet County. The incidence occurred during routine outreach health services targeting the local population at Kotut Village by staff from Kapetwa Health Centre.

How do you differentiate an adverse reaction from a co-incidental event ?



Causality and causality assessment

CAUSE

EFFECT

Causality*

Is the relationship between two events (the cause and the effect), where the second event is a consequence of the first

Causality Assessment

Determining if such a relationship exists and if so to what extent

***A direct cause is a factor in absence of which the effect would not occur**

***Sometimes, there are multiple factors that can precipitate or function as co-factors for the effect (event) to occur.**

How do we know that a vaccine has caused a reaction ?

Population (Can it ?)

Does vaccination increase the risk of occurrence of the event in the community?

Individual (Did it?)

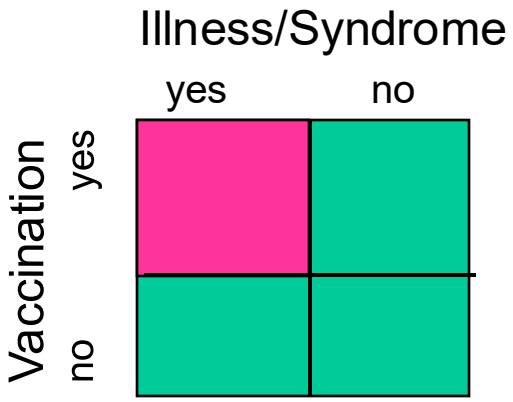
Was the vaccine a factor in the individual developing the event?

Reference: *Causality assessment of an AEFI: User manual for the revised WHO classification (2nd edition), https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf;jsessionid=8C9A85696A36FD04B549A6DCDE268075?sequence=1

World Health Organization

Population (Can it ?)

Passive surveillance does not establish causality



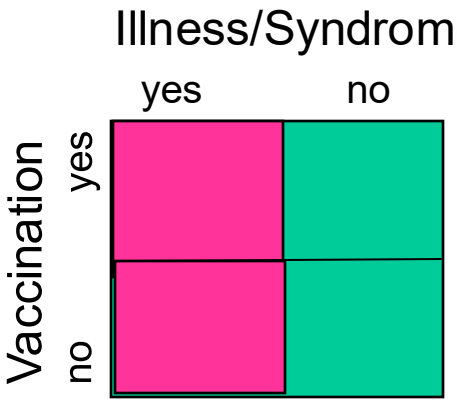
Except for …….

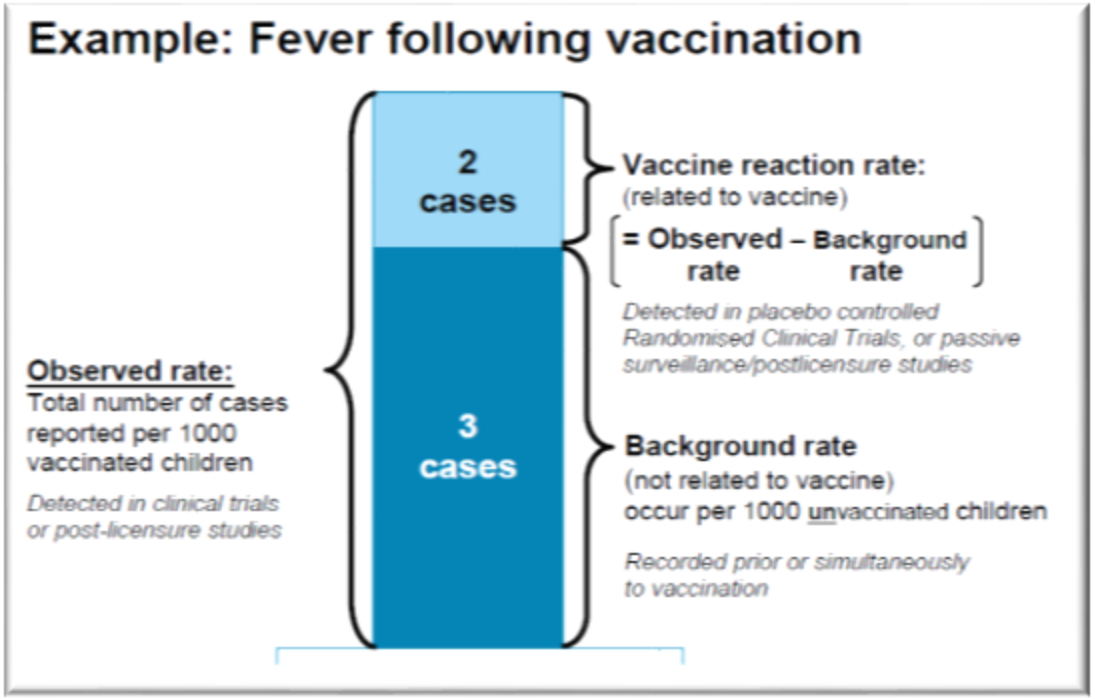
Unique vaccine reactions

Viscerotrophic disease post –Yellow fever vaccine
Attenuated vaccine disseminated disease- MMR/BCG/Zoster/Varicella/VAPP
Vaccine Induced Thrombotic Thrombocytopenia (VITT) –VV COVID-19

Population (Can it ?)

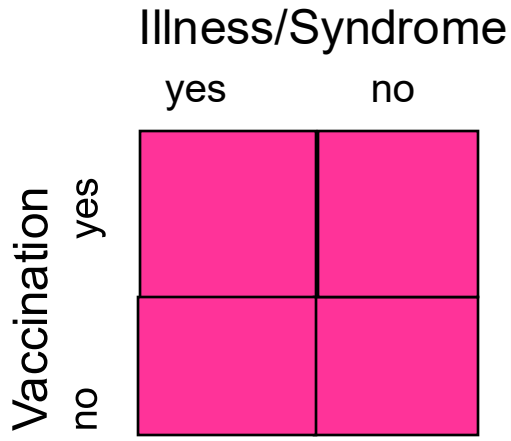
Background rates to establish causality





Population (Can it ?)

Epidemiological studies to establish causality



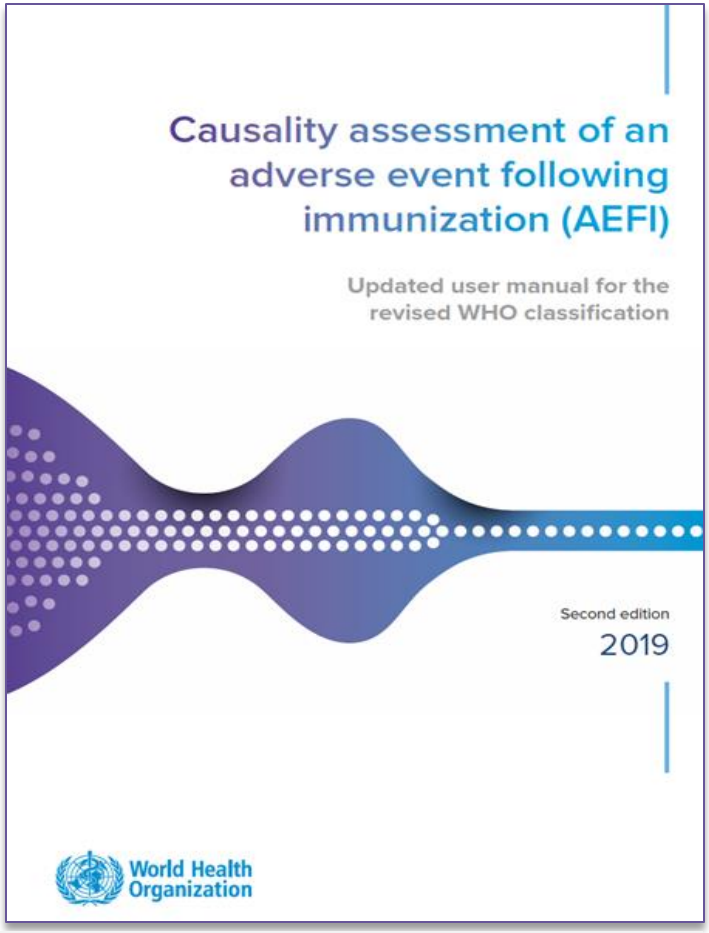
Randomised Placebo Controlled Trials

Observational studies

- Cohort
- Case-control
  - Self controlled case series
    (only requires vaccinated cases)

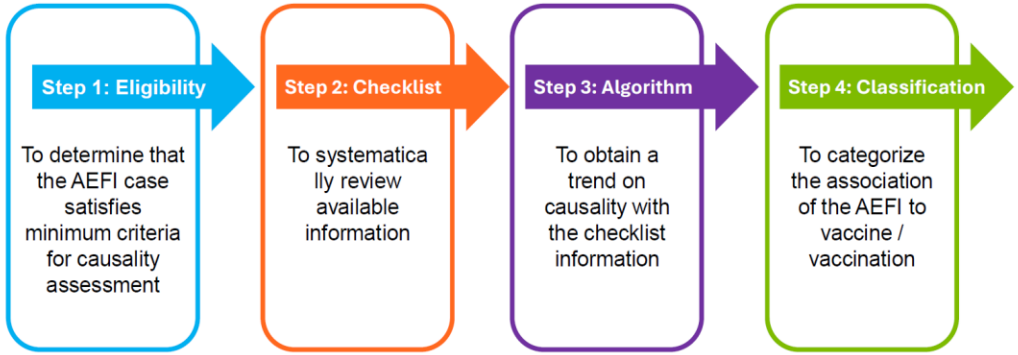
Needed for previously unrecognized reactions

Individual (Did it?)
Causality assessment



https://apps.who.int/iris/handle/10665/340802
https://gvsi-aefi-tools.org/

Four steps to classification



Final causal assessment classification of AEFI

Adequate information available

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 stress related response (ISRR)

B. Indeterminate

- B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
- B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent causal association to immunization

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

Adequate information not available

Unclassifiable

Specify the additional information required for classification

World Health Organization

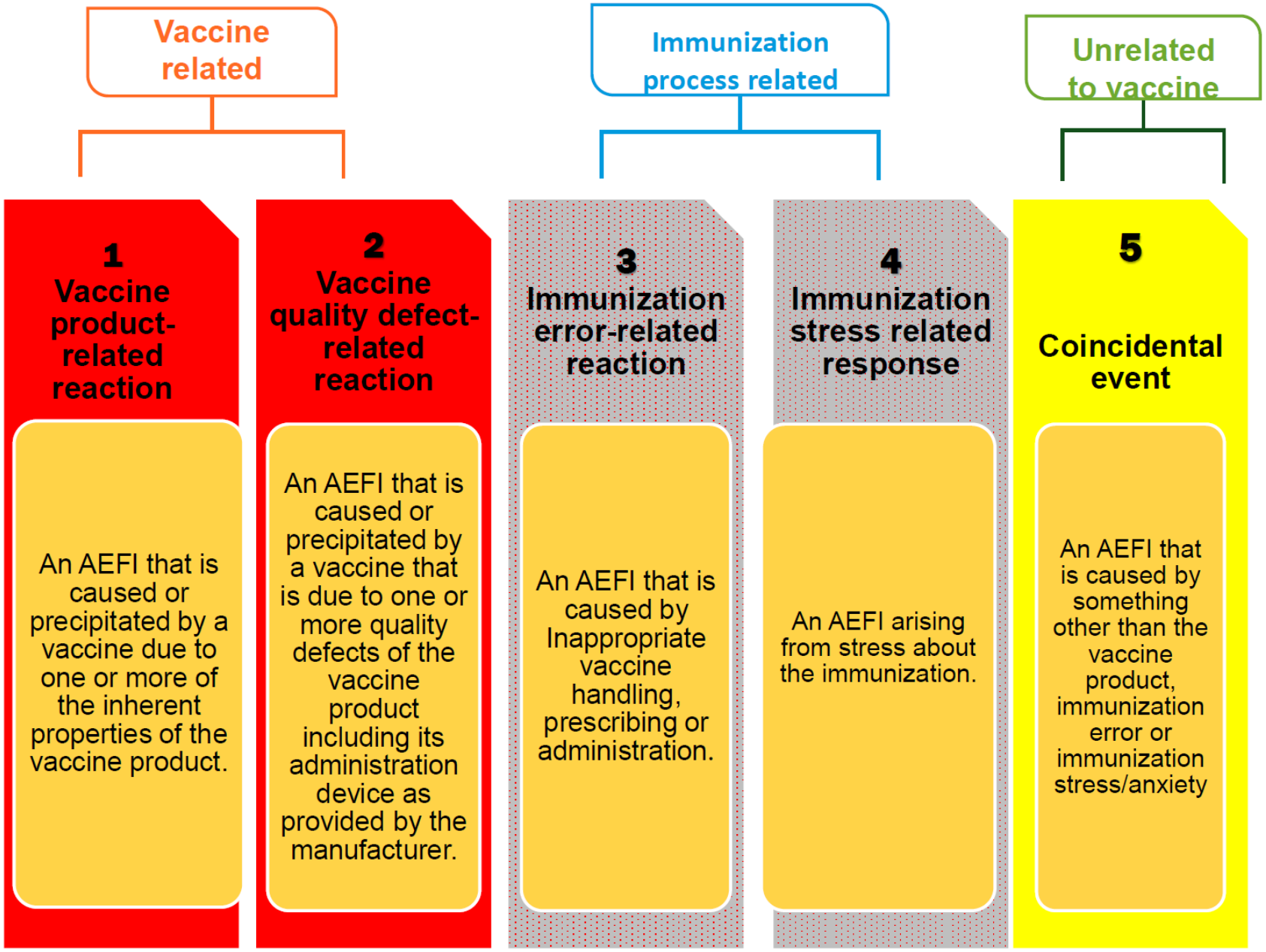
*B1 : Potential signal and maybe considered for investigation

Conclusion

- Concerns about vaccine safety affect vaccine coverage
- Safety is inferred because of the absence of a vaccine or immunisation reaction
- Pre and post-licensure surveillance of Adverse Event Following Immunisation is the basis of pharmacovigilance
- Causality assessment can be performed at a population or individual level to differentiate a reaction(s) from co-incidental event(s)
- AEFI can be classified further into adverse vaccine or immunisation reactions or co-incidental events

Outline

- How do vaccines or immunisation cause reactions?
- Why do some individuals have a reaction?
- What is the clinical approach to management of an AEFI?


Vaccine related
Immunization process related
Unrelated to vaccine
1
Vaccine product-related reaction
An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
2
Vaccine quality defect-related reaction
An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
3
Immunization error-related reaction
An AEFI that is caused by Inappropriate vaccine handling, prescribing or administration.
4
Immunization stress related response
An AEFI arising from stress about the immunization.
5
Coincidental event
An AEFI that is caused by something other than the vaccine product, immunization error or immunization stress/anxiety

Quiz 2

Vaccine **Product Related** Reaction

An AEFI that is caused or precipitated by a vaccine due to one or more of the **inherent properties** of the vaccine product

- Known vaccine reaction
- Due to vaccine antigen/adjuvant/excipient/residual substance (s)

Mild reaction **Side effect/reactogenicity**	**Moderate or severe reaction**	
Common > 1% and < 10%	**Rare** >0.01% and < 0.1%	**Very rare** < 0.001% and<0.0001
Expected	**Unexpected**	
Examples		
Fever Injection Site Reactions Rash	Febrile convulsion BCG adenitis Extensive limb swelling Urticaria/Angioedema	Thrombocytopenia Hypotonic Hyporesponsive Episodes (HHE) Anaphylaxis

Adverse vaccine product reactions

http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

REVIEW ARTICLE

Comparison between the safety of the HPV vaccine versus placebo: a systematic review and meta-analysis of randomized clinical trials

Swelen Aparecida dos Santos [a,b,c,#], Mariane Yoshie Sato [a,b,#],

This PDF is available from The National Academies Press at http://www.nap.edu/catalog.php?record_id=13164

Adverse Effects of Vaccines: Evidence and Causality

IOM INSTITUTE OF MEDICINE

ISBN
978-0-309-21435-3

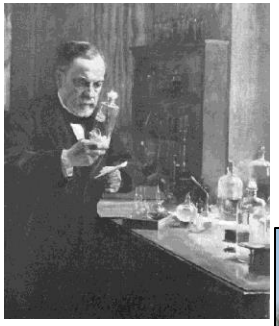
800 pages
6 x 9
HARDBACK (2011)

Kathleen Stratton, Andrew Ford, Erin Rusch, and Ellen Wright Clayton, Editors; Committee to Review Adverse Effects of Vaccines; Institute of Medicine

http://www.cdc.gov/vaccinesafety/research/iomreports/index.html

https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi

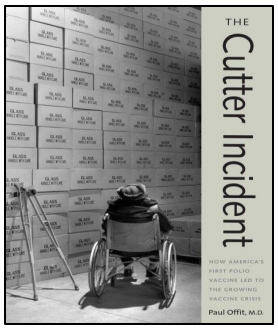
Vaccine **Quality Defect-related** Reaction



1800
Rabies
1 in 230
seizures,
paralysis coma

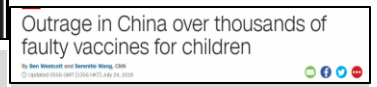
1930
BCG
Lubeck
252 vaccinated
72 died

1942
YF vaccine
Hep B, 330,000
infected, 50,000
hepatitis,
62 died



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

2010
Fluvax
Australia
Hyperpyrexia
Febrile
seizures 1 in
200



2018
China
Changchun
Changsheng
DTaP and Rabies
vaccine
Efficacy not safety

An AEFI that is caused or precipitated by a vaccine that is due to one or more **quality defects** of the **vaccine** product including its **administration device** as provided by the manufacturer.

Immunization **Error-Related** Reaction

An AEFI that is caused by inappropriate vaccine **handling, prescribing or administration**.

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 or 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

Vaccine handling

Error administration

BRIEF REPORTS

Toxic Shock Syndrome: An unforeseen Complication Following Measles Vaccination

M.A. Phadke

Error prescribing

REPUBLIC OF KENYA

MINISTRY OF HEALTH

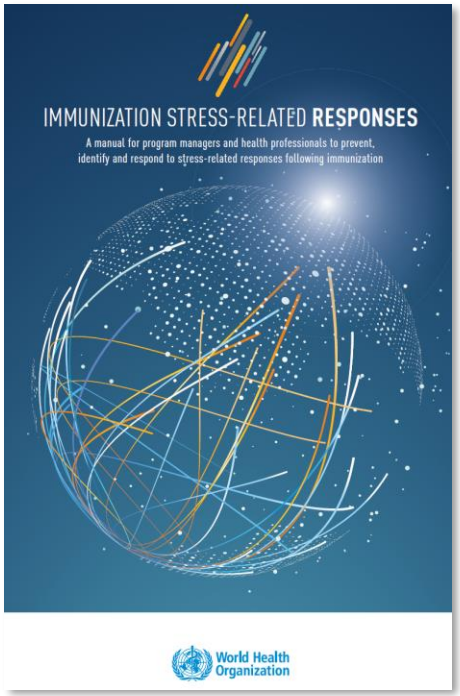
PRESS RELEASE ON DEATH OF TWO CHILDREN FOLLOWING MEASLES IMMUNIZATION IN KERIO VALLEY, MARAKWET EAST SUB COUNTY, ELGEYO MARAKWET COUNTY

The Ministry of Health wishes to shed light on the incidence of death following measles immunization of two children in Kotut village of Endo Ward near Kapetwa Health Centre, Kerio Valley, Marakwet East Sub-county in Elgeyo Marakwet County. The incidence occurred during routine outreach health services targeting the local population at Kotut Village by staff from Kapetwa Health Centre.

Vaccine/ Diluent	Mechanism
Diluent (M or MR)	Pancuronium Insulin

Immunization Stress Related Responses (ISRR)

Responses to the pain and stress of the **process of immunisation** not caused by the **vaccine product**



2019
https://www.who.int/publications/i/item/9789241515948

PUBLIC HEALTH

Mass psychogenic response to human papillomavirus vaccination

Jim P Buttery, Simon Madin, Nigel W Crawford, Sonja Elia, Sophie La Vincente, Sarah Hanieh, Lindsay Smith and Bruce Bolam

Policy and Practice

Mass psychogenic illness following tetanus-diphtheria toxoid vaccination in Jordan

Saad Kharabsheh,[1] Haidar Al-Otoum,[2] John Clements,[3] Adnan Abbas,[4] Najwa Khuri-Bulos,[5] Adel Belbesi,[6] Taky Gaafar,[7] & Nora Dellepiane[8]

Gold MS et al. Immunization stress-related response - Redefining immunization anxiety-related reaction as an adverse event following immunization. Vaccine. 2020 Mar 23;38(14)

Immunization Stress Related Responses
Manifestations

Skin

- Skin flushing (adolescent and young females, infants)

Respiratory

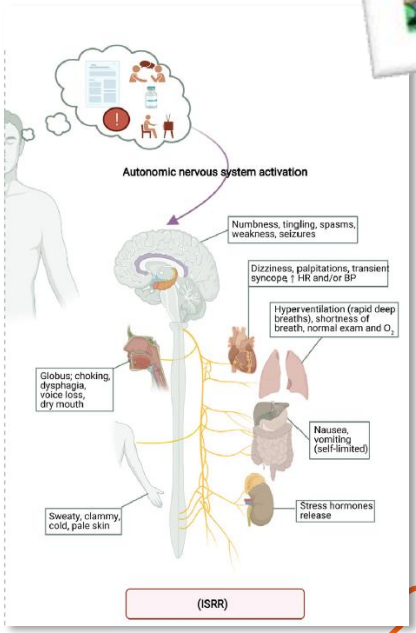
- Acute breath holding (Infants)
- Acute Stress Response
- Hyperventilation syndrome
- Vocal Cord Dysfunction / Inducible Laryngeal Obstruction

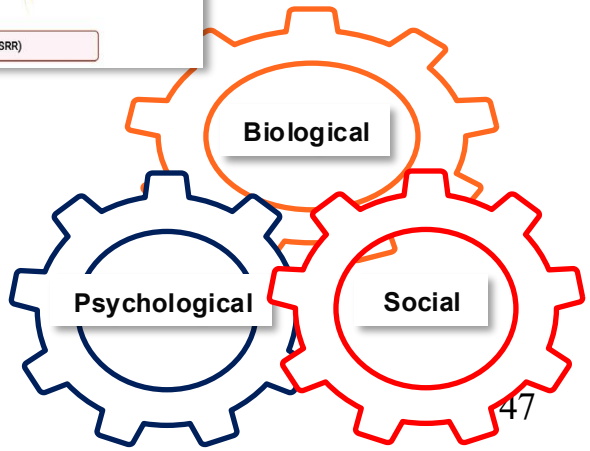
Cardiovascular

- Vasovagal syncope

Neurological

- Dissociative Neurological Reaction (Conversion syndromes/Functional Disorders)
  - Includes Non-Epileptic seizures
- Hypotonic Hyporesponsive Episodes (HHE) – infants immediate





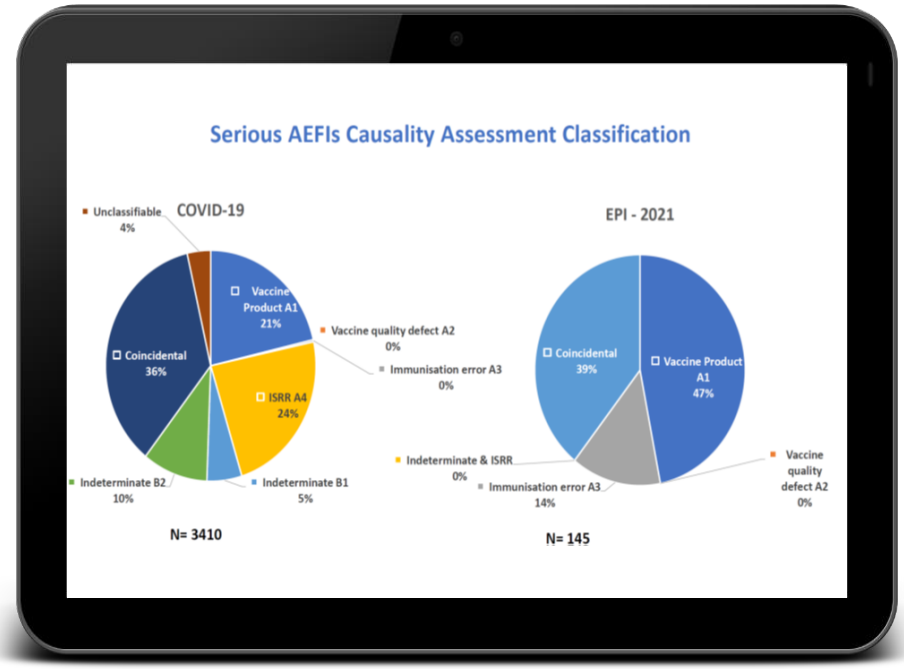
Differential diagnosis and ISRR – CNS ALLERGY

Table 4.2: Clues to the diagnosis of a conversion reaction [adapted from Evens, Vendetta et al. 2015[47]]

General	• Disappearance of symptoms or signs when patient distracted • Signs or symptoms which are not consistent with known disorders • Symptoms or signs may not respond to pharmacological interventions (for example, no response to a bronchodilator which could be given for shortness of breath due to bronchospasm) • Symptoms and signs maybe intermittent and vary between presentations.
Dystonia	• Inconsistent sustained movements over time • Unusual postures
Gait	• Fluctuation of gait and stance • Normal limb power and sensation lying down but inability to stand and walk • Sudden buckling of knees without falls
Myoclonus	• Changing pattern of frequency, amplitude and anatomical distribution
Sensory	• Loss of sensory function which is not anatomically consistent with any known sensory disorders.

	Acute Stress Response		Anaphylaxis
	General	**Vasovagal Syncope**	
Onset	Before, During After <5min	Before, During, After <5min (less if pt. moves)	After >5min (usually < 60min)
Skin	Pale, Sweaty, Cold, Clammy	Pale, Sweaty, Cold, Clammy	Red itchy skin & eyes
Respiratory	Hyperventilation	Normal or Deep Breaths	Cough, Wheeze, Stridor
Cardio	Increased HR Normal or Elevated BP	Decreased HR +/-Transient Decreased BP	Increased HR Decreased BP
GI	Nausea	Nausea, Vomiting	Nausea, Vomiting, Abdominal Cramps
Neuro / Other	Fear, Dizzy, Numb, Weak, Tingling lips, Spasm in hands and feet	Transient LOC, respond well once supine, rarely +/- tonic-clonic seizure	Unease, restless, agitated, LOC, little response to lying supine

Post marketing surveillance for COVID-19 vaccines and ISRR



April 21, 2021
9:51 PM GMT+9:30
Last Updated a year ago

Asia Pacific

Thailand sticks with Sinovac vaccine after cases of 'stroke-like' side effects

Reuters

RESEARCH ARTICLE

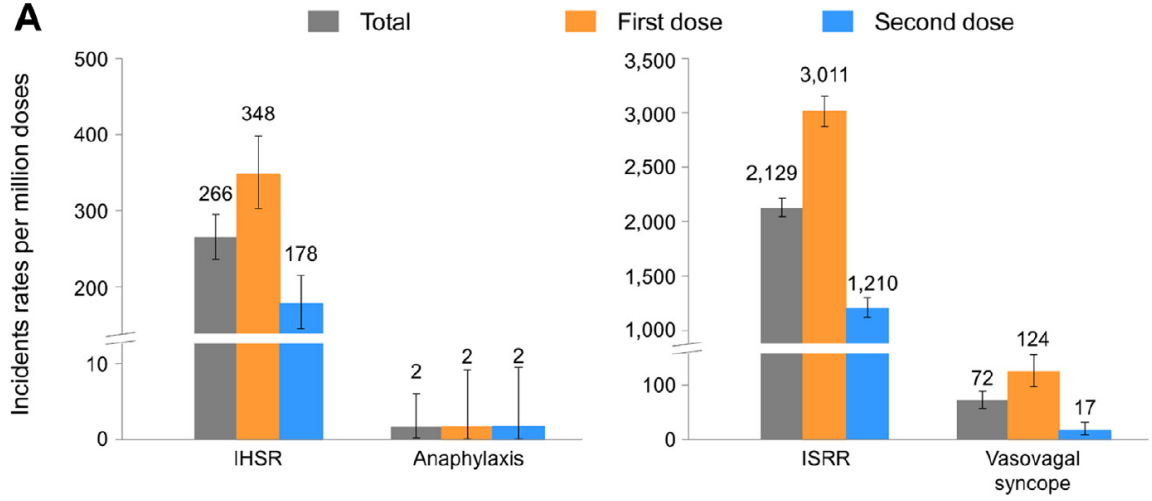
Good recovery of immunization stress-related responses presenting as a cluster of stroke-like events following CoronaVac and ChAdOx1 vaccinations

Apiwattanakul M et al. Good recovery of immunization stress-related responses presenting as a cluster of stroke-like events following CoronaVac and ChAdOx1 vaccinations. PLoS One. 2022 Aug 25;17(8)

Incidence and Risk Factors of Immediate Hypersensitivity Reactions and Immunization Stress-Related Responses With COVID-19 mRNA Vaccine

Moderna vaccine 614,151 recipients, 1,202,688 vaccine doses

Risk factors case control methodology



Odds ratios for each risk factor.

Risk factor	Answer	Univariate analysis of risk factors[a]				
		OR	95% CI			p-value
Administration	First dose	Ref.				
	Second dose	0.872	0.636	,	1.197	0.397
Sex	Male	Ref.				
	Female	1.256	0.874	,	1.805	0.218
Age	per 1 year	0.996	0.984	,	1.009	0.549
Any allergies	No	Ref.				
	Yes	1.594	1.137	,	2.235	**0.007**
Epilepsy or taking any antiepileptic drugs	No	Ref.				
	Yes	1.201	0.221	,	6.524	0.832
Anxiety	I did not feel anxious	Ref.				
	I felt a little anxious	1.279	0.890	,	1.839	0.183
	I had a very strong anxious feeling	2.317	1.303	,	4.120	**0.004**

Imai K et al. Incidence and Risk Factors of Immediate Hypersensitivity Reactions and Immunization Stress-Related Responses With COVID-19 mRNA Vaccine. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2667-2676

Takano T et al. Investigation of the incidence of immunisation stress-related response following COVID-19 vaccination in healthcare workers. J Infect Chemother. 2022 Jun;28(6):735-740.

Co-incidental event

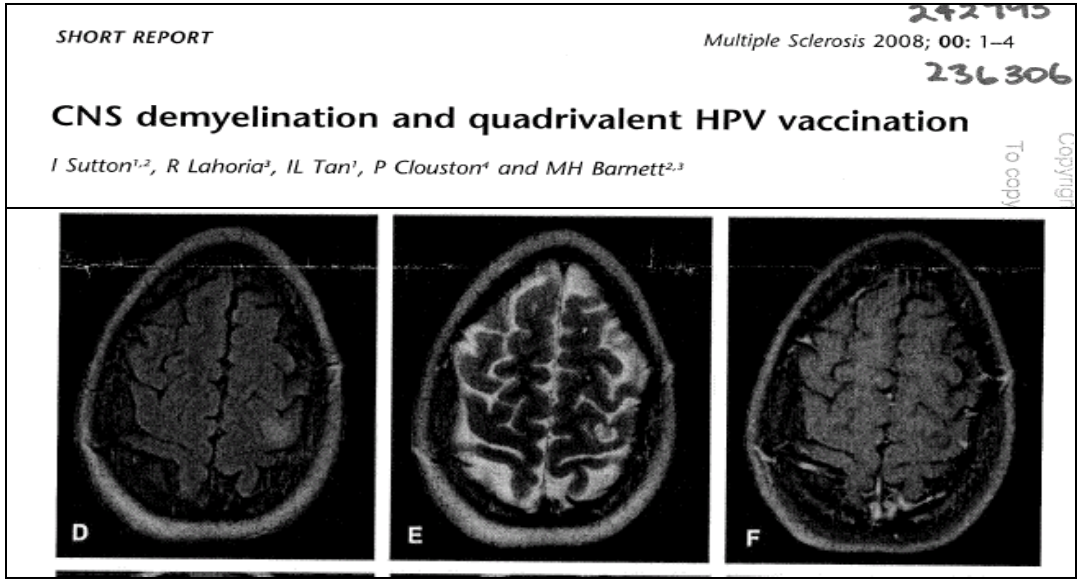
An AEFI that is caused by something other than the vaccine product, programme error or injection reaction

TABLE 5. ESTIMATED NUMBER OF COINCIDENTAL INFANT DEATHS THAT COULD BE TEMPORALLY LINKED TO IMMUNIZATION (E.G. WITH DPT/PVV) IN THE MONTH, WEEK AND DAY AFTER IMMUNIZATION IN SELECTED COUNTRIES

Country	Infant mortality rate per 1000 live births (IMR)	Number of births per year (N)	Estimated number of infant deaths 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	3233	746	106
Canada	5	388 000	162	37	5	86 864	20 045	2856
China	13	16 364 000	17 728	4091	583	3 634 035	838 624	119 475
Indonesia	25	4 331 000	9023	2082	297	950 113	219 257	31 237
Iran	21	1 255 000	2196	507	72	276 445	63 795	9089
Mexico	13	2 195 000	2378	549	78	487 455	112 490	16 026
Sudan	57	1 477 000	7016	1619	231	313 382	72 319	10 303
United Kingdom	4	761 000	254	59	8	170 540	39 355	5607

Co-incidental or causal event ?

SIGNAL with newly introduced vaccines



SHORT REPORT

Multiple Sclerosis 2008; **00**: 1–4

CNS demyelination and quadrivalent HPV vaccination

I Sutton[1,2], R Lahoria[3], IL Tan[1], P Clouston[4] and MH Barnett[2,3]

D E F

AEFI reports

- Pancreatitis (2)
- Multiple sclerosis (2)
- Acute Disseminated Encephalomyelitis (1)
- Ascending neuropathy (1)
- Nephrotic syndrome (1)
- Vaginal blistering (6)
- Macularetinopathy (1)
- ITP (1),
- Hemolytic aneamia (1),
- Pancytopenia (1)
- Deep Vein Thrombosis (2)
- Brachial neuritis (1)

Why do some individuals have an adverse reaction to a vaccine ?

Underlying immunodeficiency

Non-immunological factors

Underlying or predisposing conditions

Febrile seizures

Genetic determinants – Narcolepsy, Dravet's

Clinical approach to AEFI

❖General Approach

Communication skills – empathy and trust
Don't dismiss possible causative role of the vaccine or immunisation
Understand the context

❖Accurate history

- Event
  - Clearly define symptoms and signs (verify from Ambulance notes, providers, ED notes etc).
  - Vaccine (s) administered
  - Sequence of events – relationship to vaccination-onset time
  - Alternate causative factors
  - Management of the event
  - Attitude and knowledge of health care providers
- Past history
  - Vaccine, medical and family history, co-morbid

❖ Establish the diagnosis / case definition

Do not focus on causative association with the vaccine or immunisation

❖ Consider causality

- **Known** adverse vaccine reaction, a**lternate explanation** (co-incidental), none (unknown)

❖ Outcome

- Vaccine or immunisation reaction
  - Diagnosis, prognosis
- Implications for re-vaccination
  - Risk Benefit
  - Same or different vaccine
  - Contra-indications or precautions
  - Support post-vaccination
- Post exposure prophylaxis if non-immune

Conclusion

- Adverse Events Following Immunisation can be classified into vaccine product reactions, immunisation quality defects, immunisation errors, immunisation stress related responses or co-incidental events
- The mechanism of adverse vaccine and immunisation reactions are determined by the vaccine properties, the host and the environment
- Management of an individual who has had an AEFI needs to determine if this was a vaccine or immunisation reaction ascertain the risks and benefits of re-vaccination