Introduction to vaccine safety

Understanding basic concepts



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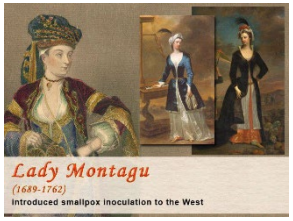
Citation for adaptations: "This is an adaptation of an original *work Causality Assessment to Strengthen AEFI Monitoring (A WHO course) Geneva: World Health Organization (WHO) [2022].* This adaptation was not created by WHO. WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition".

Variolation and vaccination – improving safety

Variolation



- Material from a patient with **Small Pox** to induce immunity to **Small Pox**
- Originated in China in the 15th century
- Attenuated scabs delivered by nasal insufflation / scarification
- **<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>Lower mortality < 1 in 100</u>**



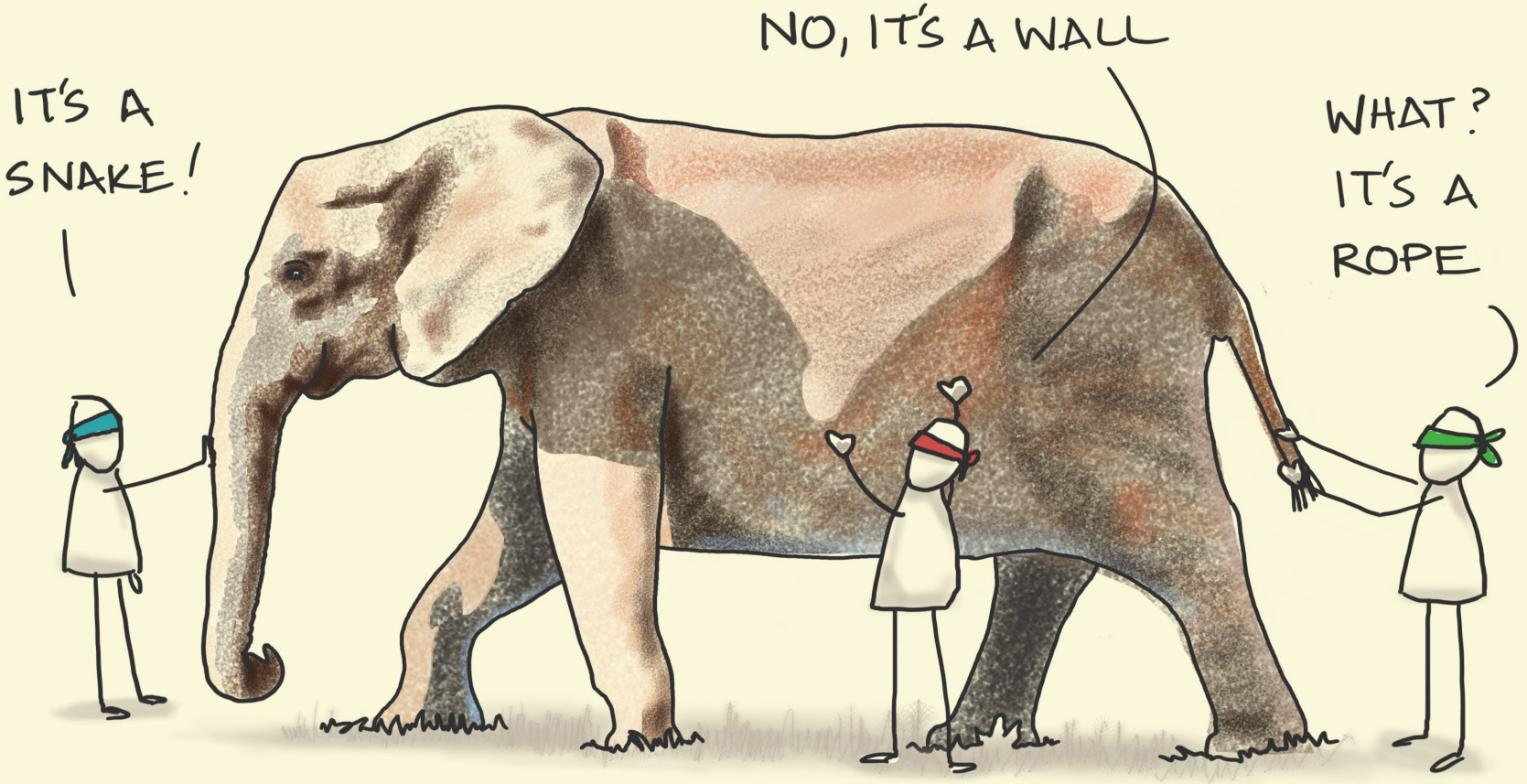
- 1774 `first used by a farmer in Dorset called Benjamin Jesty
  "first person know that introduced the cow pox by inoculation and who from his great strength of mind made the experiment from the cow pox on his wife and two sons"
- 1796 Introduced by Edward Jenner (published and "efficacy")
- 1840 Variolation banned in the UK

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?
  - For an individual
  - Within a population
- For an individual how do we classify adverse vaccine and immunisation reactions ?

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

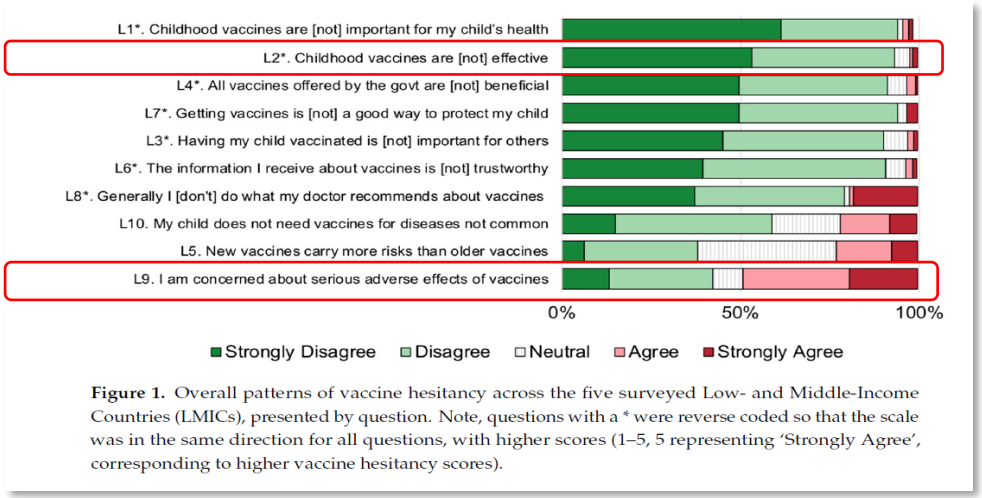


Figure 1. Overall patterns of vaccine hesitancy across the five surveyed Low- and Middle-Income Countries (LMICs), presented by question. Note, questions with a * were reverse coded so that the scale was in the same direction for all questions, with higher scores (1–5, 5 representing 'Strongly Agree',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

Vaccine safety concerns may lead to reduced 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)

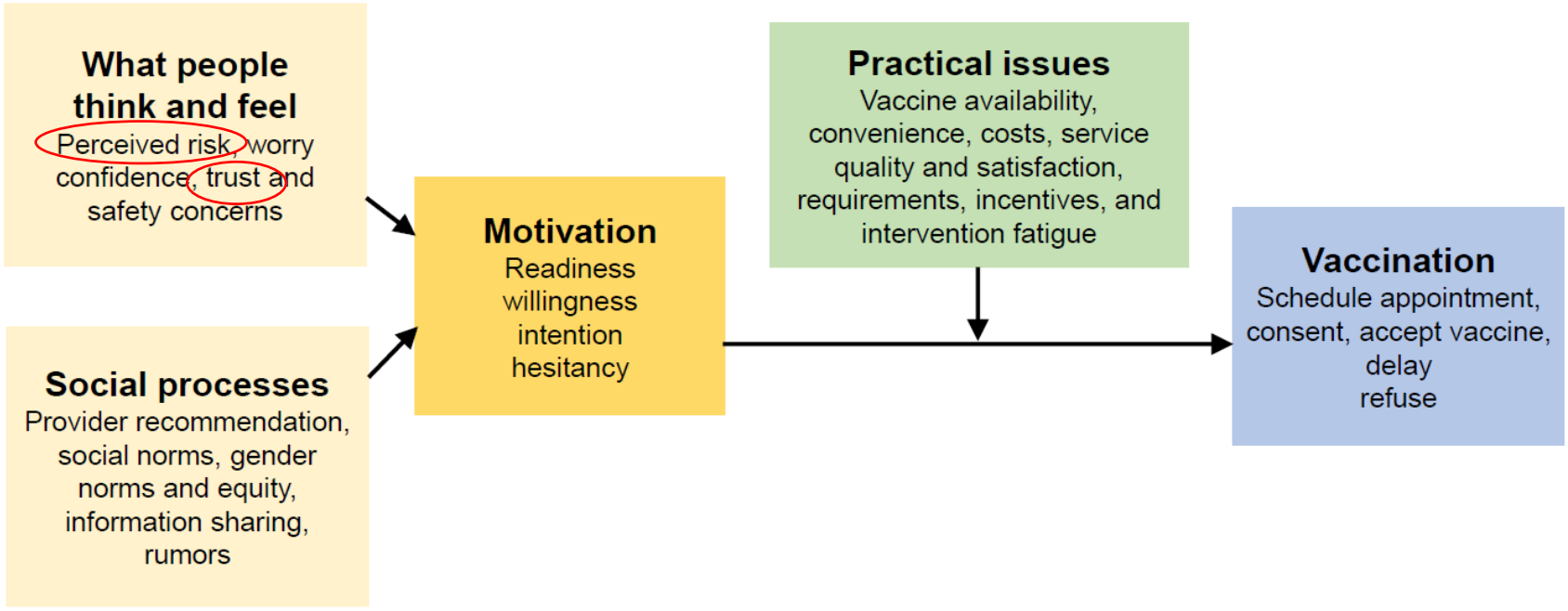
Resurgence of vaccine preventable disease

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

Behavioural and social drivers of vaccination

Tools and practical guidance for achieving high uptake

Increasing Vaccination Model



Source: The BeSD expert working group. Based on: Brewer NT, Chapman GB, Rothman AJ, Leask J, and Kempe A (2017). Increasing vaccination: Putting psychological science into action. *Psychological Science for the Public Interest.* 18(3): 149-207

https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/demand

Perceived risk of a newly introduced vaccine

The risk profile for rare reactions are **unknown** but is usually perceived as high

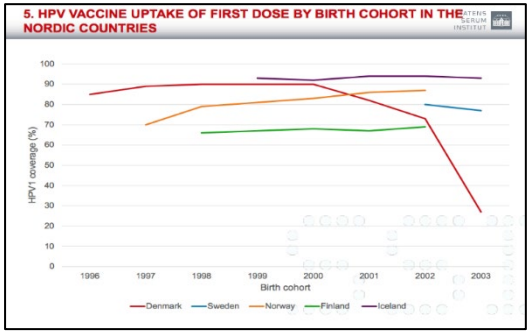
Human Papilloma Virus vaccine



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

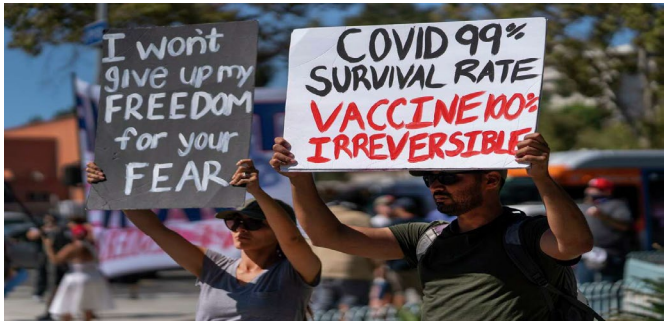
Louise S. Brinth, Kirsten Pors, Ann C. Theibel, Jesper Mehlsen*

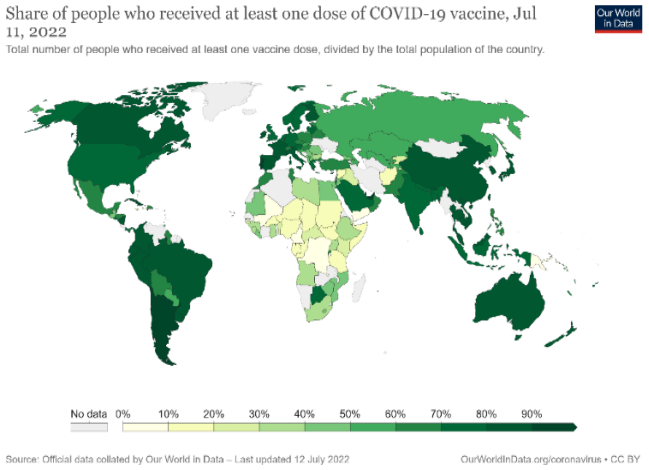
Coordinating Research Centre, Frederiksberg Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark



Vaccine 33 (2015) 2602-2605

COVID-19 vaccine





RSV vaccine



Maternal RSV vaccine is effective, but few women opt for it, new data reveal

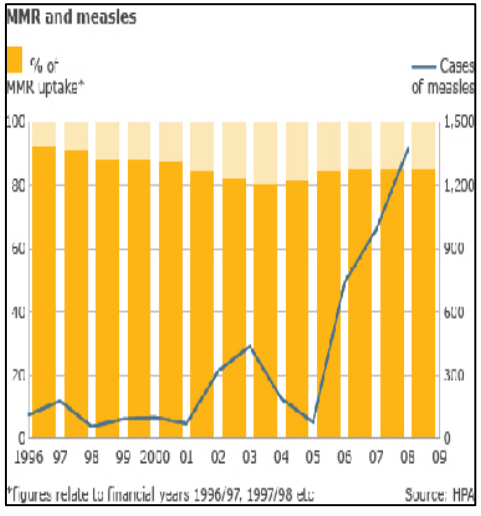
An overall uptake of 27.1% (95% confidence interval (CI): 19.1–37.0; I 2 : 99.9%; N = 1,308,447 pregnancies in 13 studies

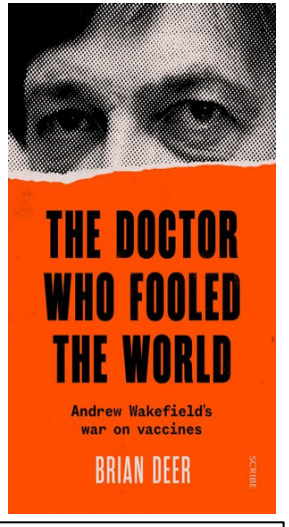
Balsells E el al. **Real-world evidence on maternal RSV vaccination uptake, effectiveness, and safety: a systematic review and meta-analysis.** The Lancet Regional Health 2026

Perceived risk for established vaccines

The risk profile for rare reactions is **known but** is perceived as high due to disinformation motivated by secondary gain (individual or an ideology)

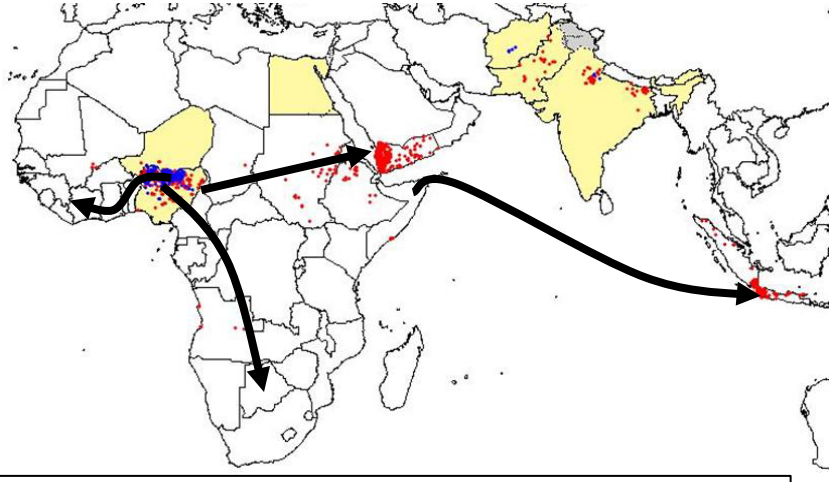
MMR and celebrity





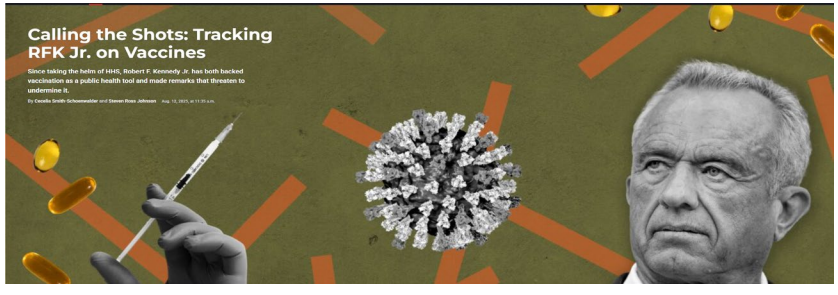
Retraction--Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet retraction. Lancet 2010 Feb 6;375(9713):445.

Polio and politics



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

Vaccines and health beliefs



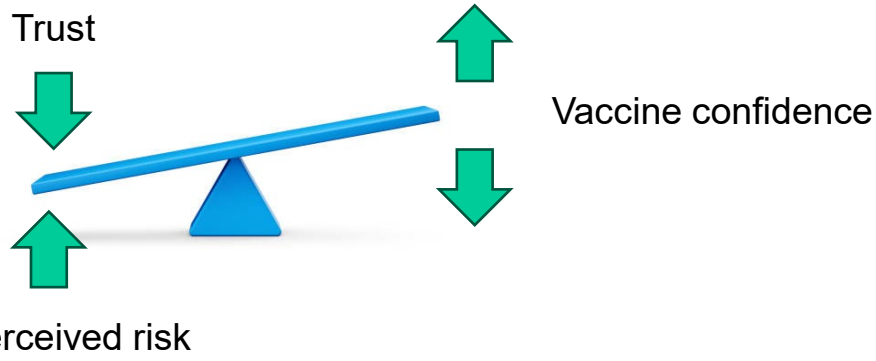
Trust

<u>Trust</u> describes a relationship, based on an aura or feeling, between individuals or between individuals and a system

- The person seeking the trust is vulnerable to potential harm
- Defers a complex decision which is beyond individual knowledge or power to others
- Thus reduces the complexity of the decision (heuristics)

Trust and the perceived risk of vaccination

If perceived risk is high this demands greater trust to promote vaccine confidence

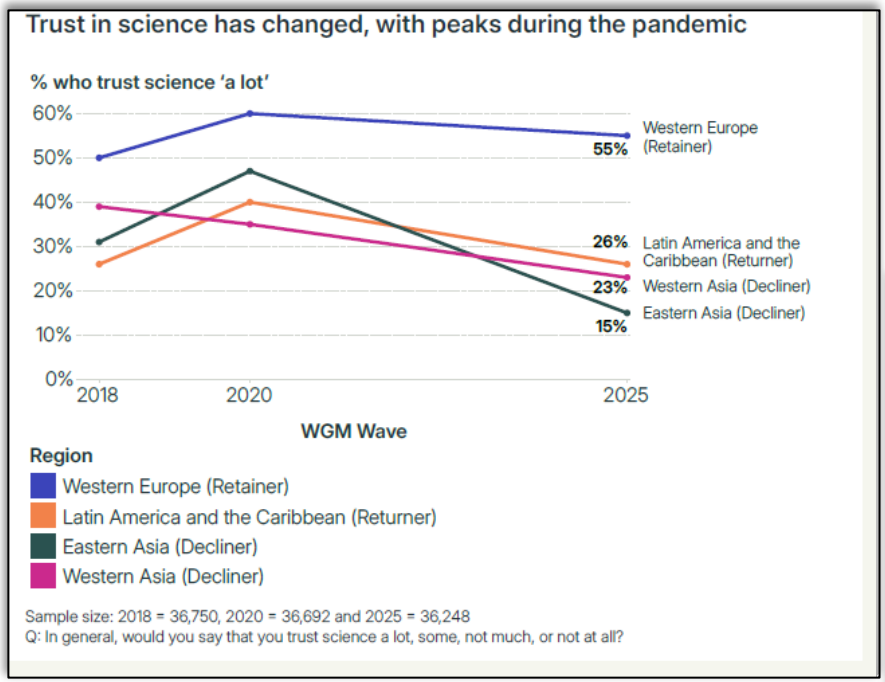


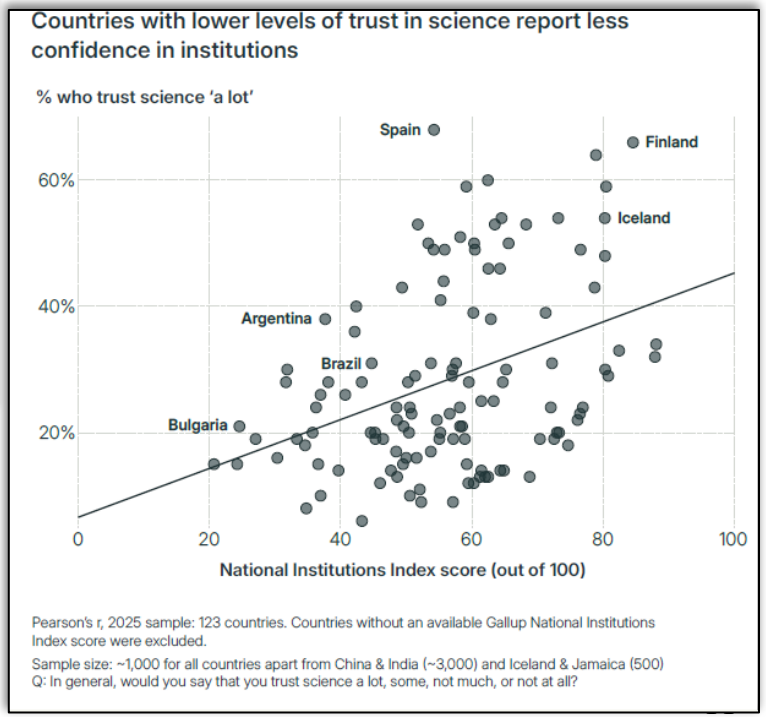
Larson HJ et al.. Measuring trust in vaccination: A systematic review. *Human Vaccines & Immunotherapeutics* 2018; **14**(7): 1599-609

Wellcome Global Monitor

Trust in science under pressure

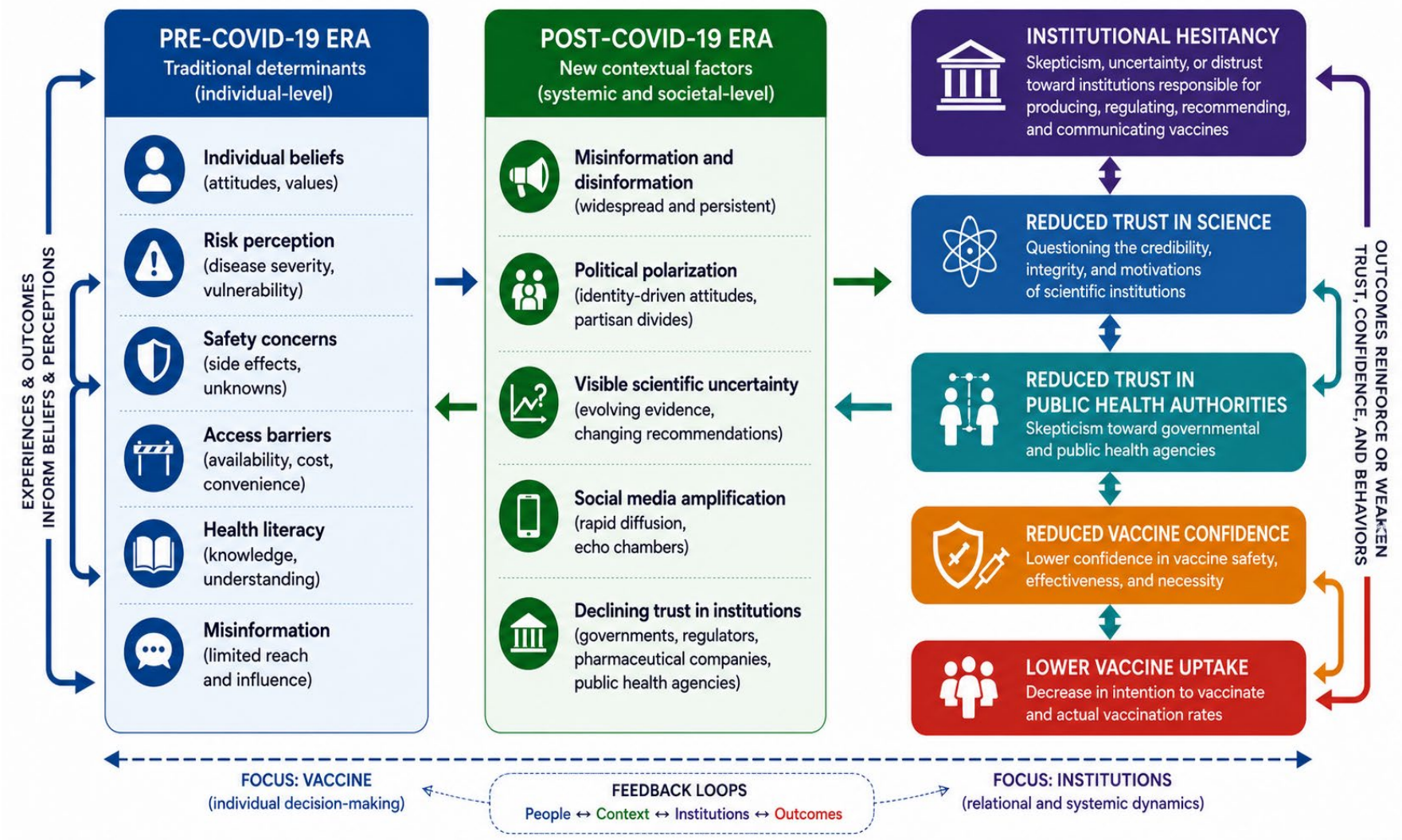
2026





https://wellcome.org/insights/reports/wellcome-global-monitor-2026

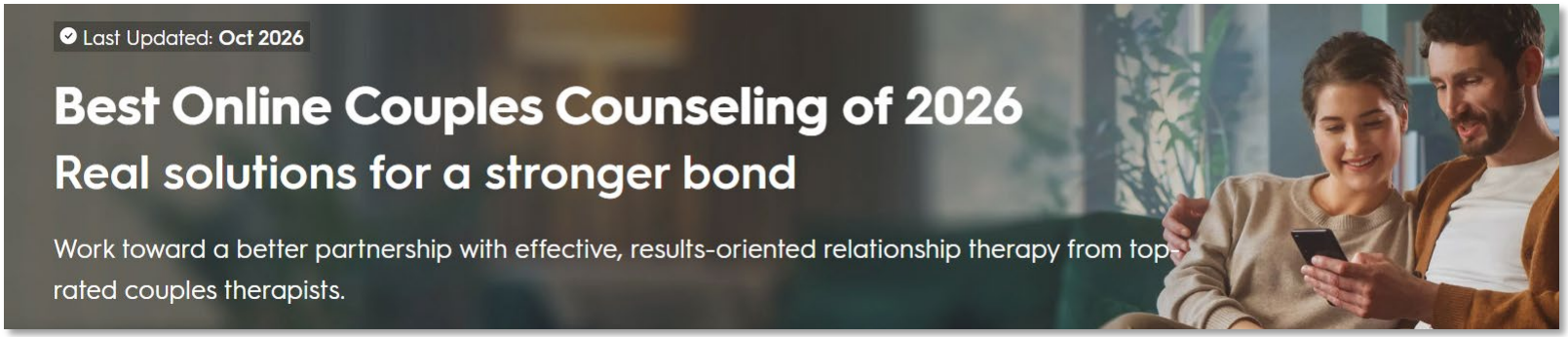
From Vaccine Skepticism to Institutional Distrust: The Post-Pandemic Shift



Maria F et al. From Vaccine Skepticism to Institutional Distrust: The Post-Pandemic Shift. Vaccines (Basel). 2026 Jul 16;14(7):622

Trustworthiness

<u>Trustworthiness</u> is what the <u>individual</u> (you) or the <u>system</u> must earn by demonstrating this repeatedly over time





Trustworthiness



Based on the individual or system behaviors;

• **Shared values**	Health individual or population
• **Competent**	Expert and evidence based
• **Consistent**	Even if uncertain
• **Beneficent**	Individual or community's best interests
• **Transparent**	DOI and COI
• **Empathetic**	Caring
• **Accountable**	Taking responsibility

https://proactsafety.com/blog-posts/behaviors-to-build-strong-trusting-relationships

How do you know ..... is safe ?

Consider what you answer and how you answer

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 product



- **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 coincidental events
- **Causality assessment** of an AEFI is used to differentiate an **adverse reaction** from a **co-incidental event**

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

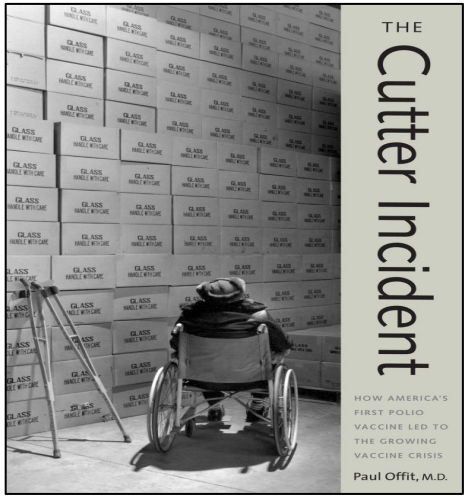
Vaccine	Condition
Yellow Fever	Viscerotropic/Neurotrophic Disease
Attenuated live vaccine disease	BCG Disseminated BCG Measles Vaccine encephalitis Polio (Oral) Vaccine associated paralytic polio (VAPP) VZ Disseminated Varicella-Zoster Generally, in context of immunocompromise or immunosuppression
COVID-19 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 product or the process of immunisation
- Safety surveillance detects AEFI

How do we perform surveillance to **detect** AEFI and then **differentiate** adverse reactions from co-incidental events ?

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

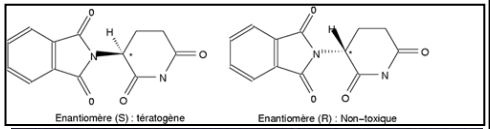


April 1955, **Cutter incident**

- 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.

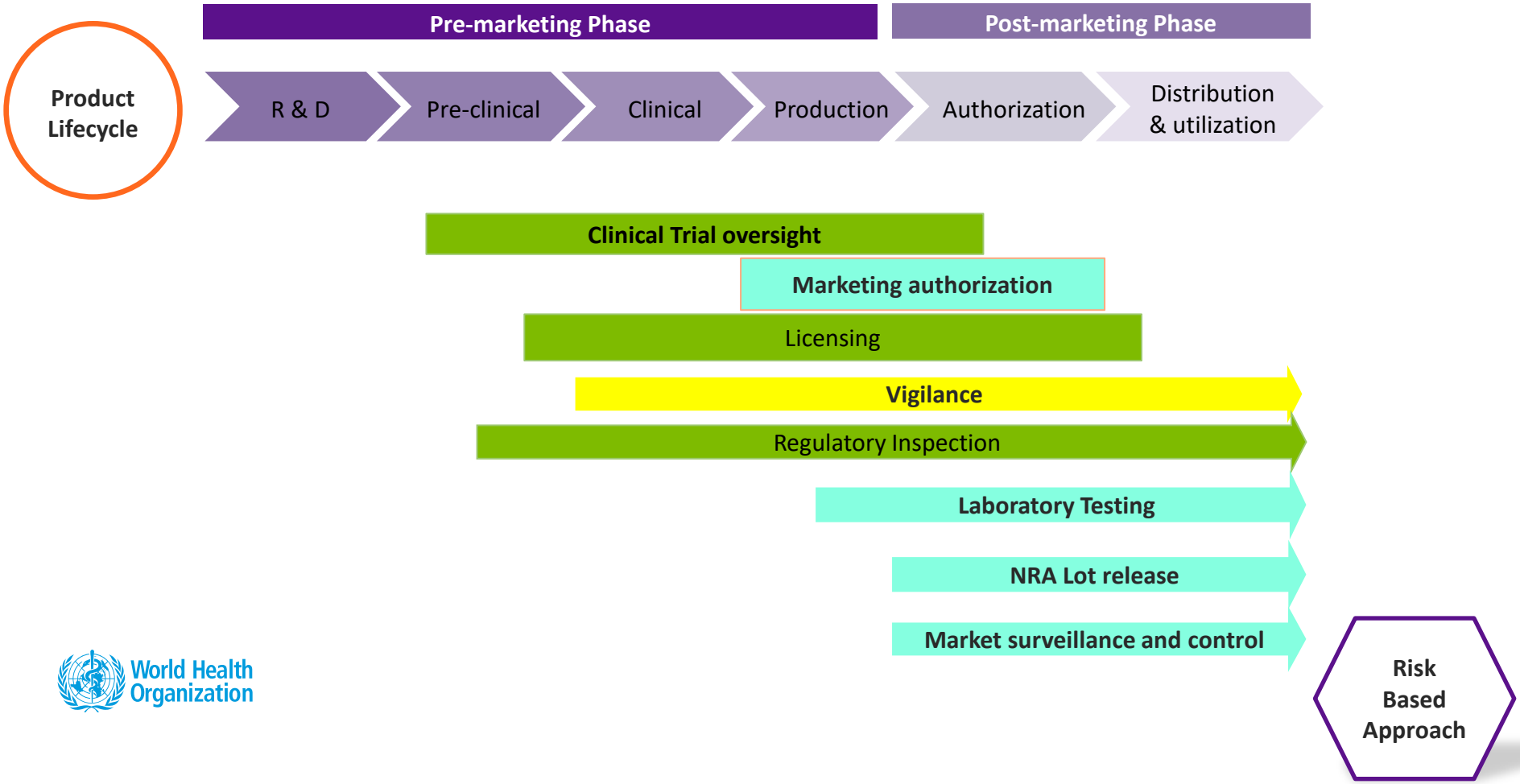
*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided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

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



WHO Recommended Regulatory Functions Based on Product Lifecycle

National Regulatory System



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

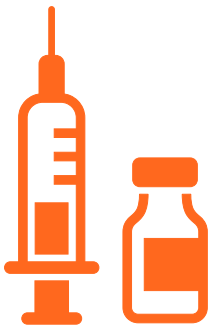
Pre-marketing phase and vaccine safety

	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.

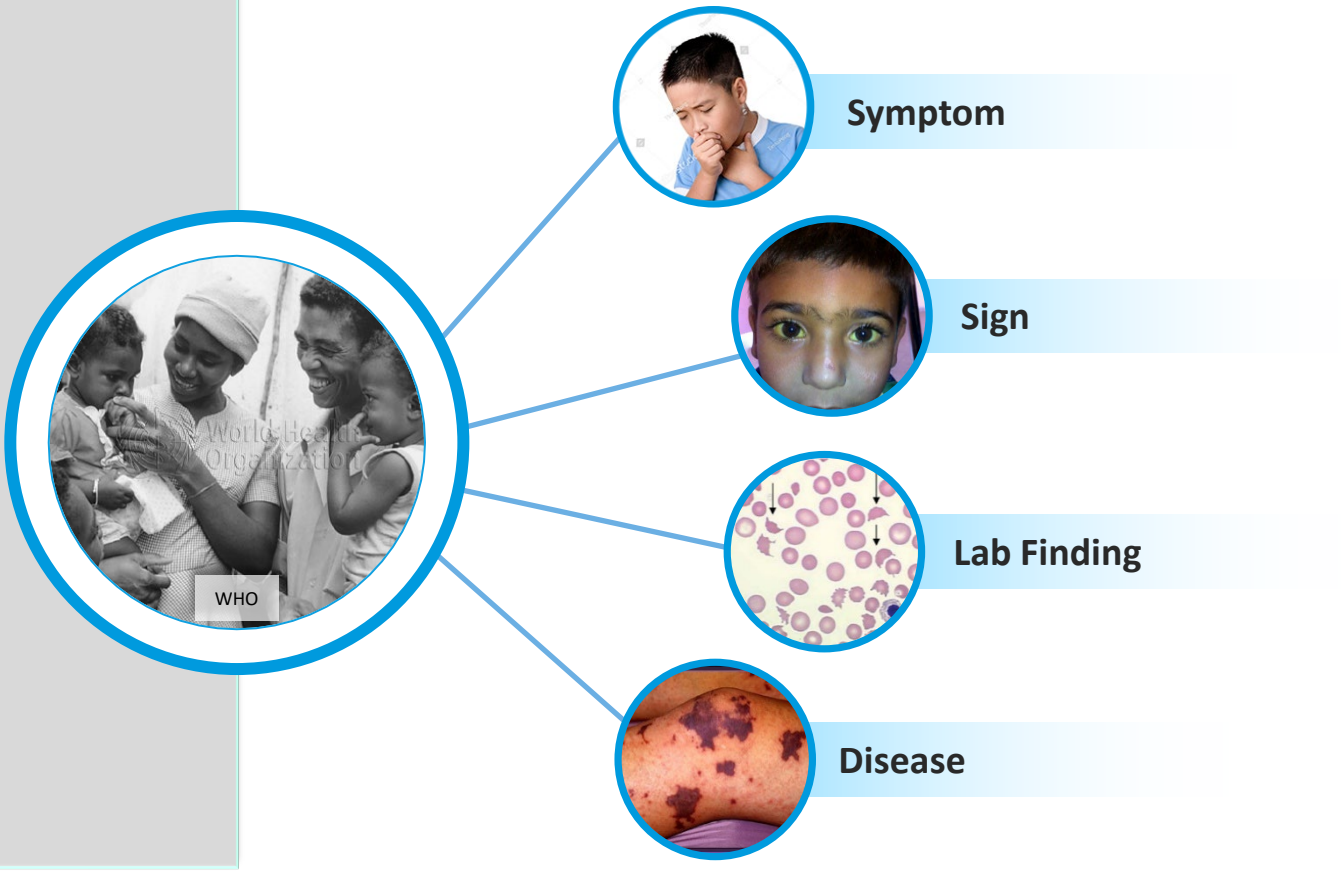
World Health Organization

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

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.

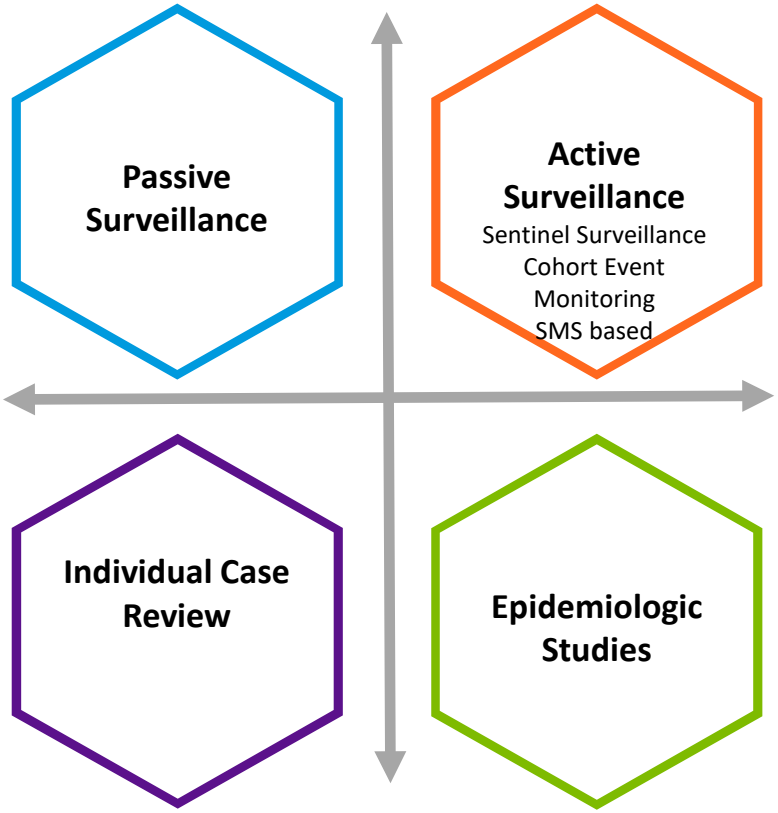
The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.



World Health Organization

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



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

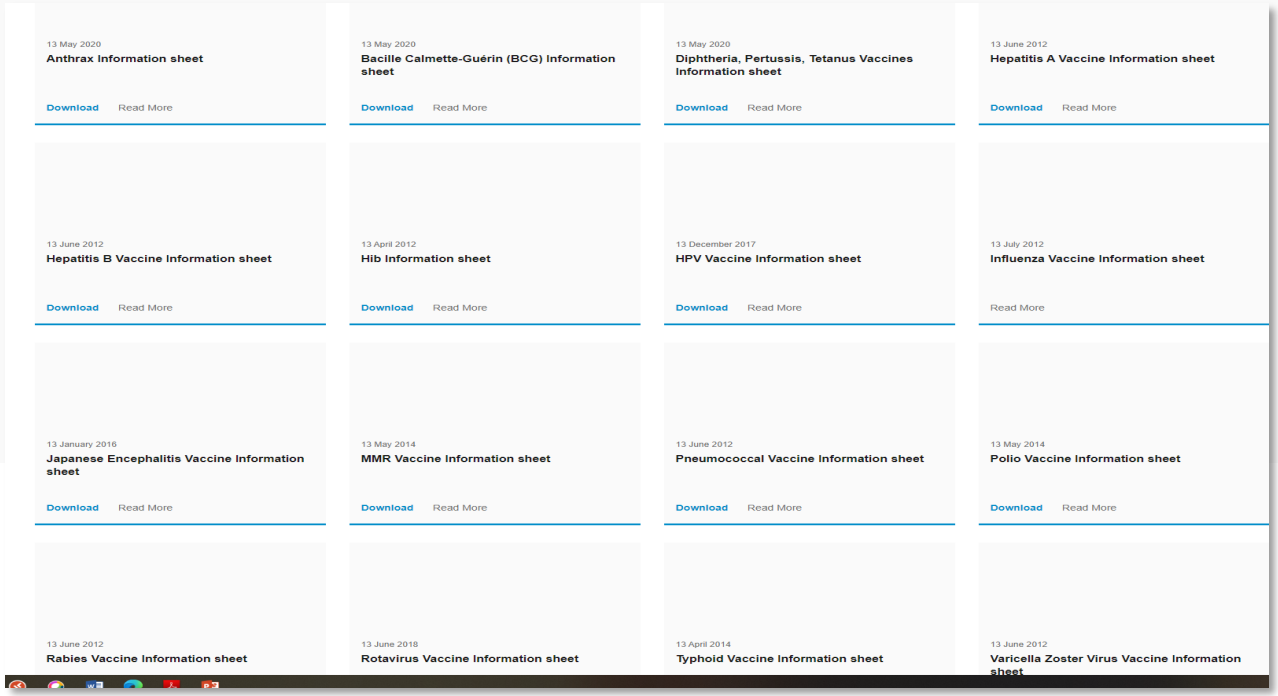
Global Vaccine safety
Essential Medicines & Health Products
20, Avenue Appia, Ch- 1211 Geneva 27

INFORMATION SHEET

OBSERVED RATE OF VACCINE REACTIONS

HUMAN PAPILLOMA VIRUS VACCINE

December 2017



World Health Organization

02

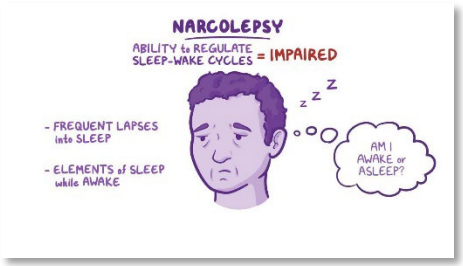
To detect a vaccine safety signal

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

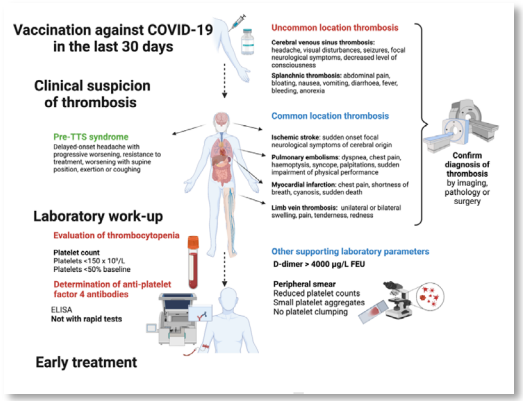
A safety signal is a cluster of AEFIs that may require further investigation to determine if this is a newly described adverse reaction or a co-incidental event



Intussception and Rotaviral vaccine



Narcolepsy and adjuvanted pH1N1 influenza vaccines



Viral vector COVID-19 vaccine and VITT

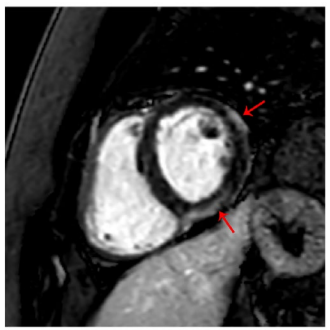


Fig. 2. Short axis late gadolinium enhancement image. Mid-myocardial enhancement of the middle inferolateral and anterolateral wall consistent with myopericarditis. (Red arrows point to LGE). (For interpretation of the references to

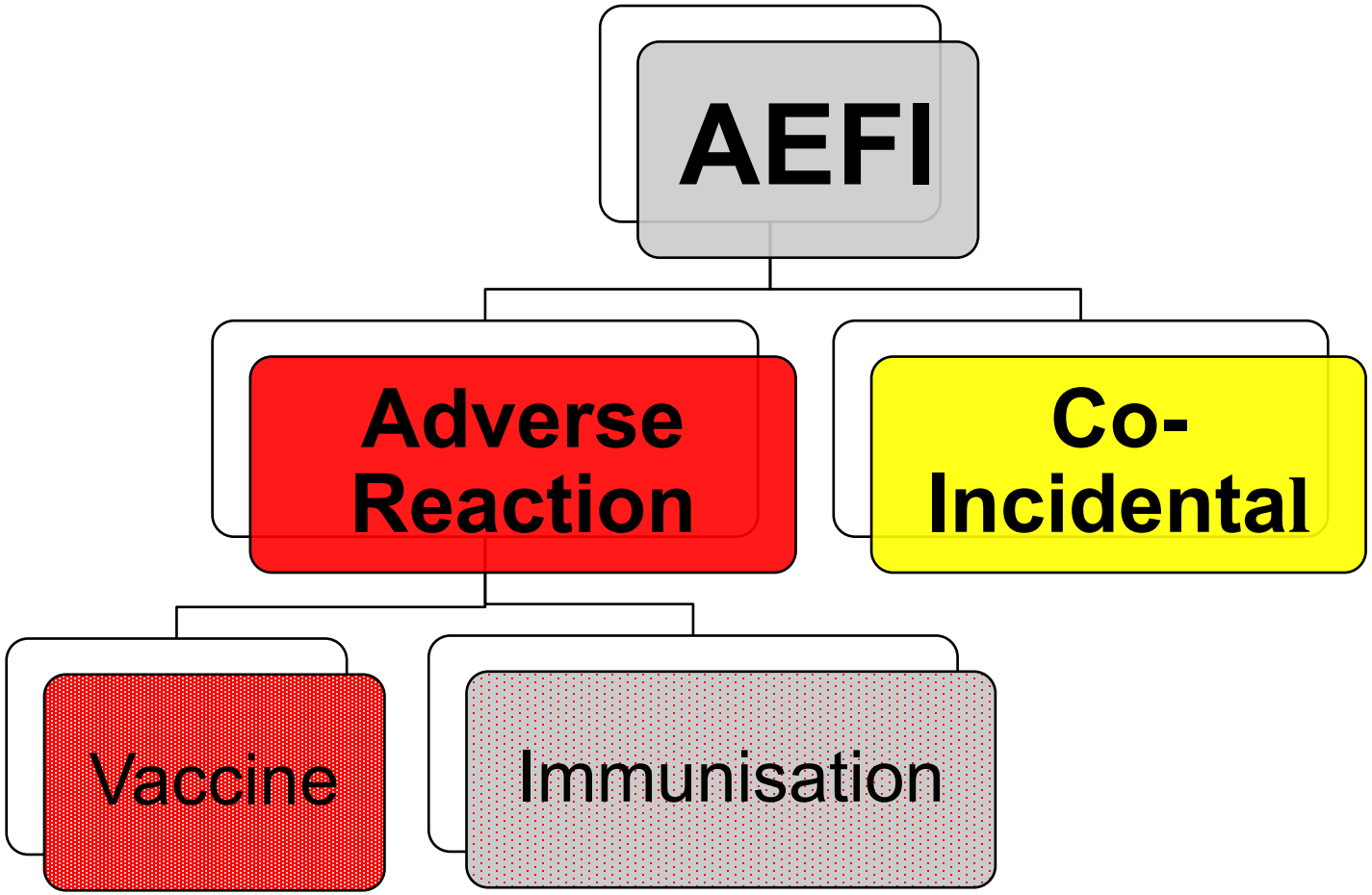
mRNA COVID-19 vaccine and myopericarditis

03

To detect immunization errors

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

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?

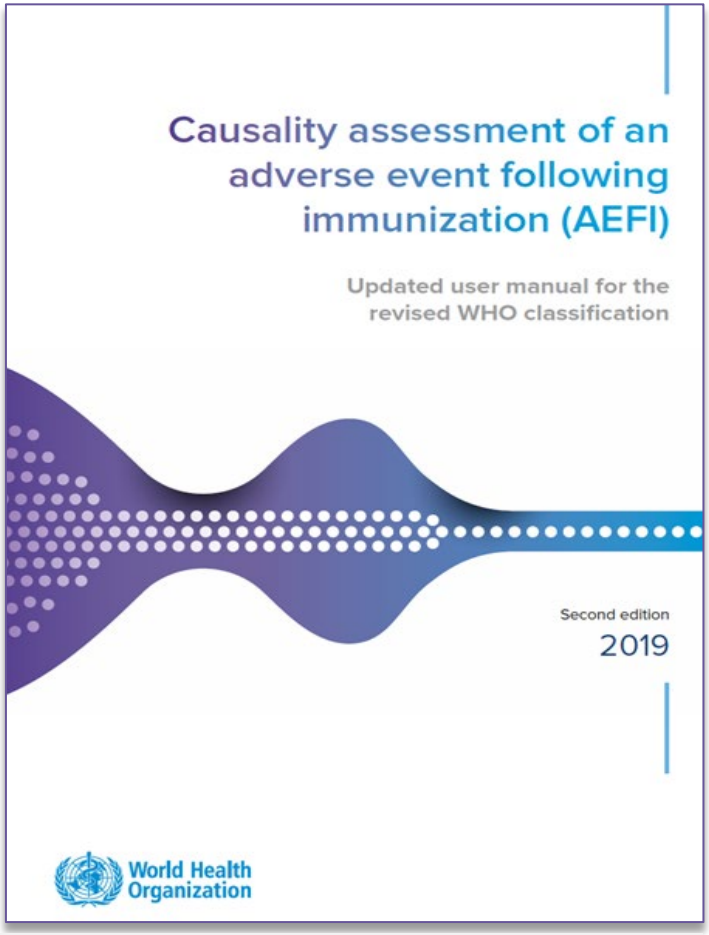
Individual (Did it?)

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

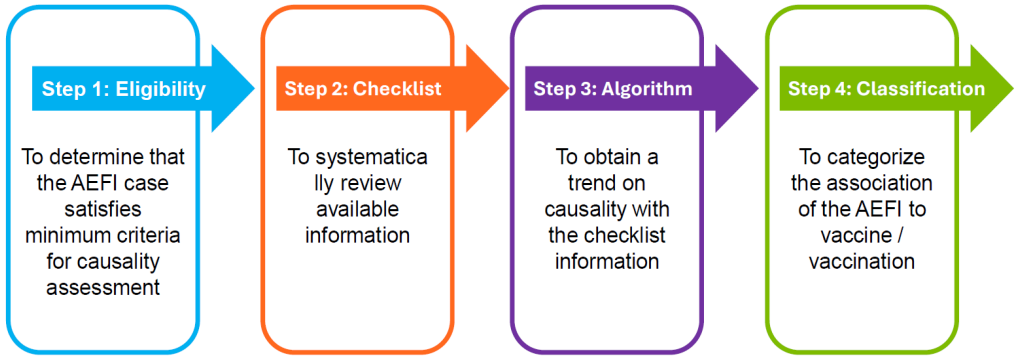
World Health Organization

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

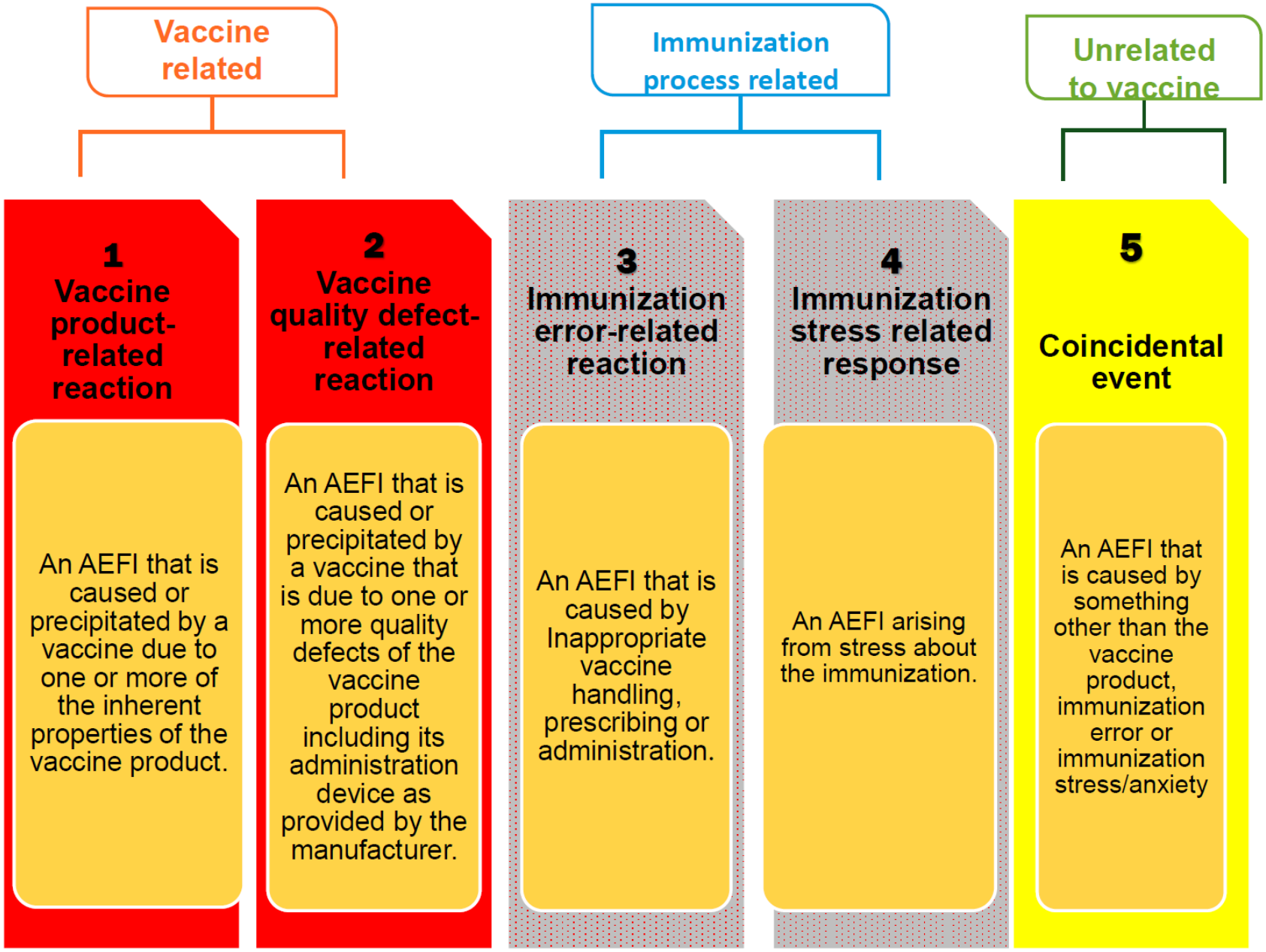
Adequate information not available

Unclassifiable

Specify the additional information required for classification

World Health Organization

*B1 : Potential signal and maybe considered for investigation


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









4 months of age	8 years of age	3 months of age	4 years of age
Infanrix hexa Onset 6 hours Progressive over 48 hours	BCG Onset 2-3 months	BCG Onset 2-3 months Cluster of BCG adenitis	DTaP Onset after 24 hours







5 years of age	12 months of age	12 years of age
DTaP Immediate onset of pain rt knee Progressive swelling and pain	MMR Hib Onset 1-2 days	HPV (LHS) Onset over 1 week and persisted



4 months of age
Infanrix hexa Onset 6 hours Progressive over 48 hours
Inflammatory non-infective
Immunisation Error Likely superficial injection



8 years of age
BCG Onset 2-3 months
BCG Adenitis
Immunisation error Subcutaneous administration



3 months of age
BCG Onset 2-3 months Cluster of BCG same
BCG adenitis – cluster
Vaccine quality defect Cluster same batch-different providers



4 years of age
DTaP Onset after 24 hours
Extensive Limb Swelling
Vaccine product



5 years of age
DTaP Immediate onset of pain Progressive swelling and pain
Bursitis right knee
Immunisation Error Injection into knee bursa



12 months of age
MMR Hib Onset 1-2 days
Inflammatory non-infective
Co-incidental Contact dermatitis Chlorhexidine



12 years of age
HPV (LHS) Onset over 1 week and persisted
Complex Regional Pain Syndrome (CRPS)
Co-incidental (Trigger)

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

Vaccine attributable 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)

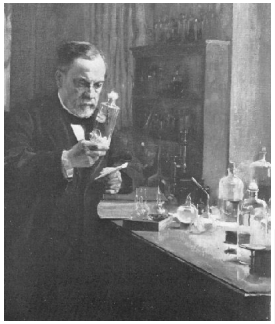
Kathleen Stratton, Andrew Ford, Erin Rusch, and Ellen Wright Clayton, Editors; Committee to Review Adverse Effects of Vaccines; Institute of Medicine

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



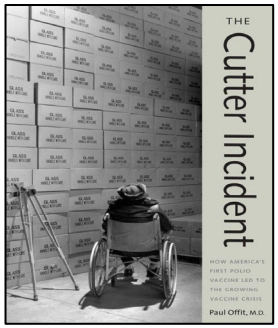
1800
Rabies
1 in 230
seizures,
paralysis coma



1930
BCG
Lubeck
252 vaccinated
72 died



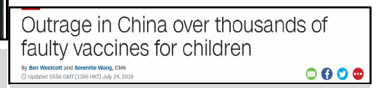
1942
YF vaccine
Hep B, 330,000
infected, 50,000
hepatitis,
62 died



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 prescribing



Error administration



BRIEF REPORTS

Toxic Shock Syndrome: An unforeseen Complication Following Measles Vaccination

M.A. Pbadke

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

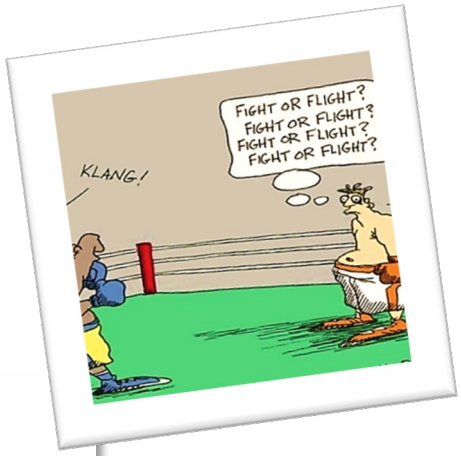
Mass psychogenic illness following tetanus-diphtheria toxoid vaccination in Jordan

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

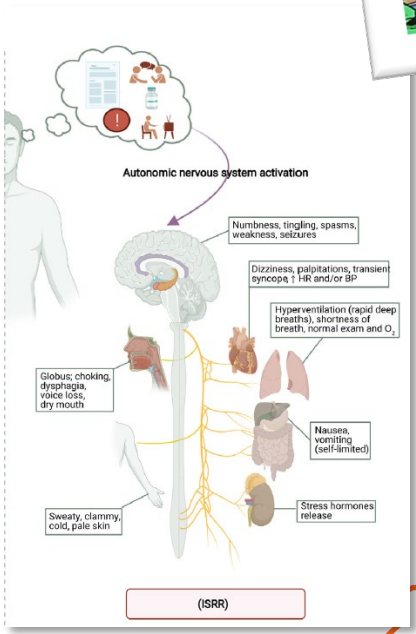
- Acute breath holding (Infants)
- Acute Stress Response
- Hyperventilation syndrome
- Vocal Cord Dysfunction / Inducible Laryngeal Obstruction

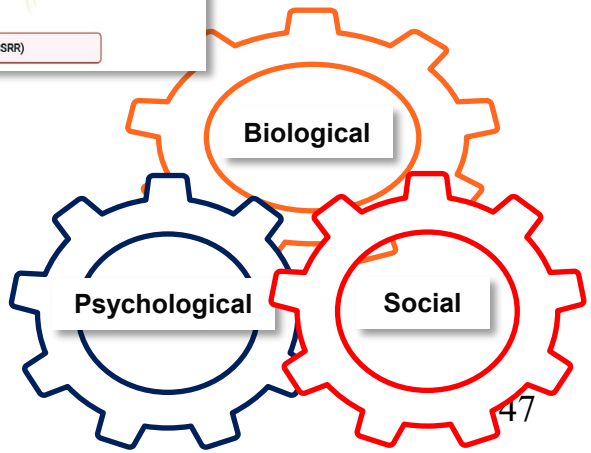
Cardiovascular

- Vasovagal syncope

Neurological

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





Differential diagnosis and ISRR

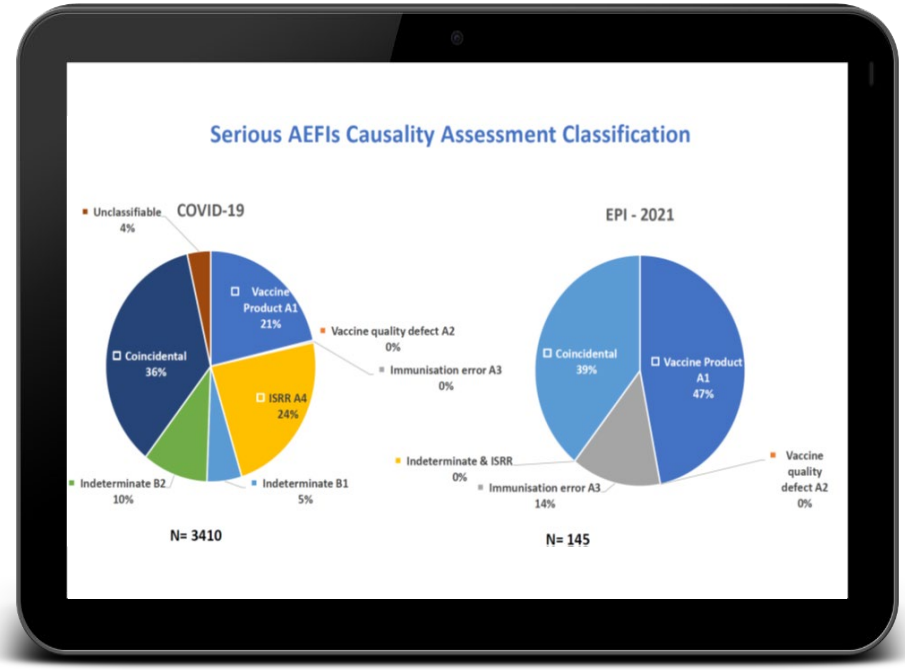
Dissociative neurological reactions / anaphylaxis

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)

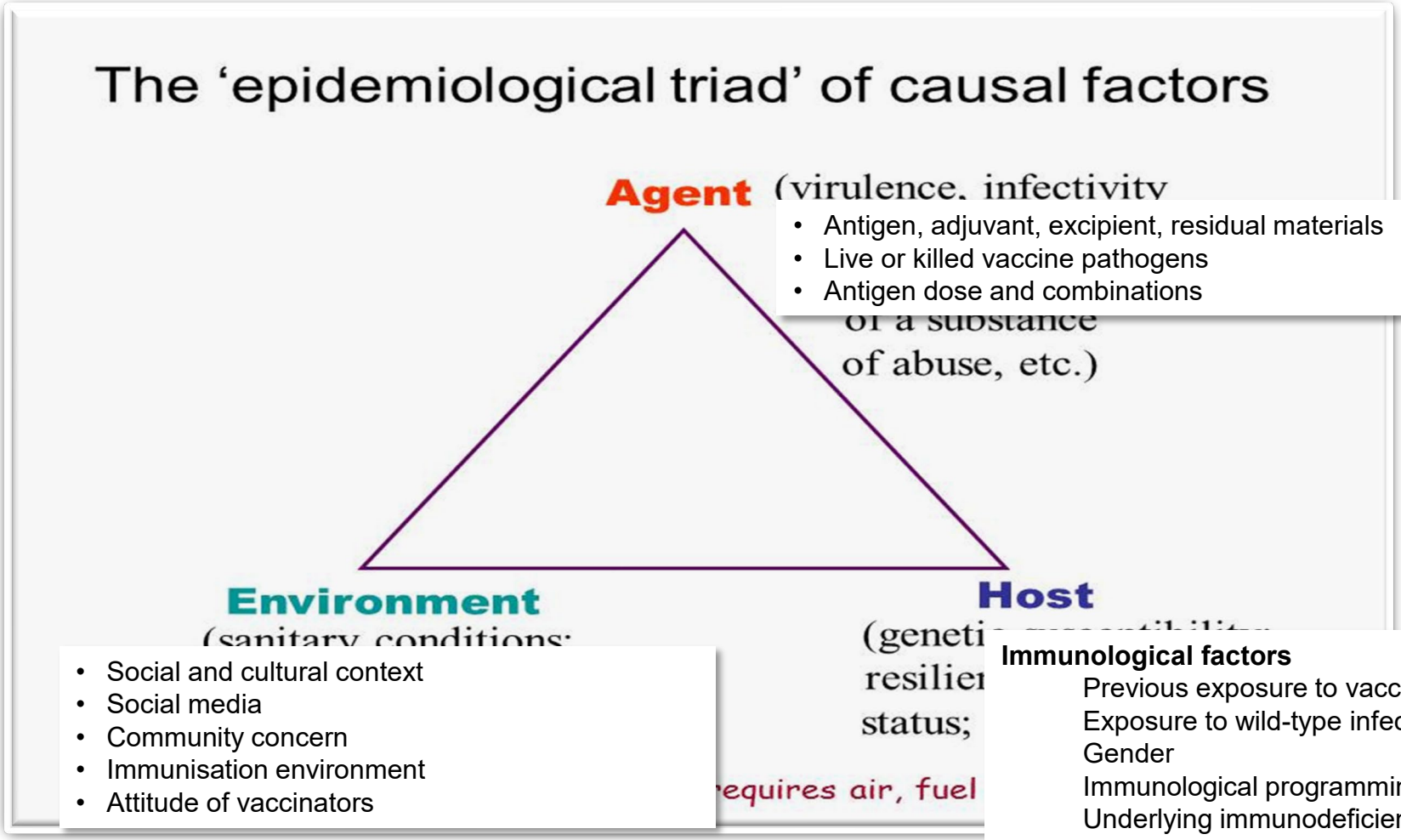
Co-incidental event

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

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



- Antigen, adjuvant, excipient, residual materials
- Live or killed vaccine pathogens
- Antigen dose and combinations

- Social and cultural context
- Social media
- Community concern
- Immunisation environment
- Attitude of vaccinators

Immunological factors

Previous exposure to vaccine
Exposure to wild-type infection
Gender
Immunological programming
Underlying immunodeficiency

Non-immunological factors

Underlying or predisposing conditions
Febrile seizures
Genetic determinants – Narcolepsy, Dravet's


FARSIDE '83
Victoria Times Colonist-dist. by Kopypress Inc. · farsidecartoon. com
DOCTORS LINK MERCURY IN VACCINES TO AUTISM.
THIS VACCINATION BUSINESS IS GETTING OUT OF CONTROL!
IT'S TIME I DID SOMETHING.
I WANT HIM VACCINATED AGAINST MERCURY.

Conclusion

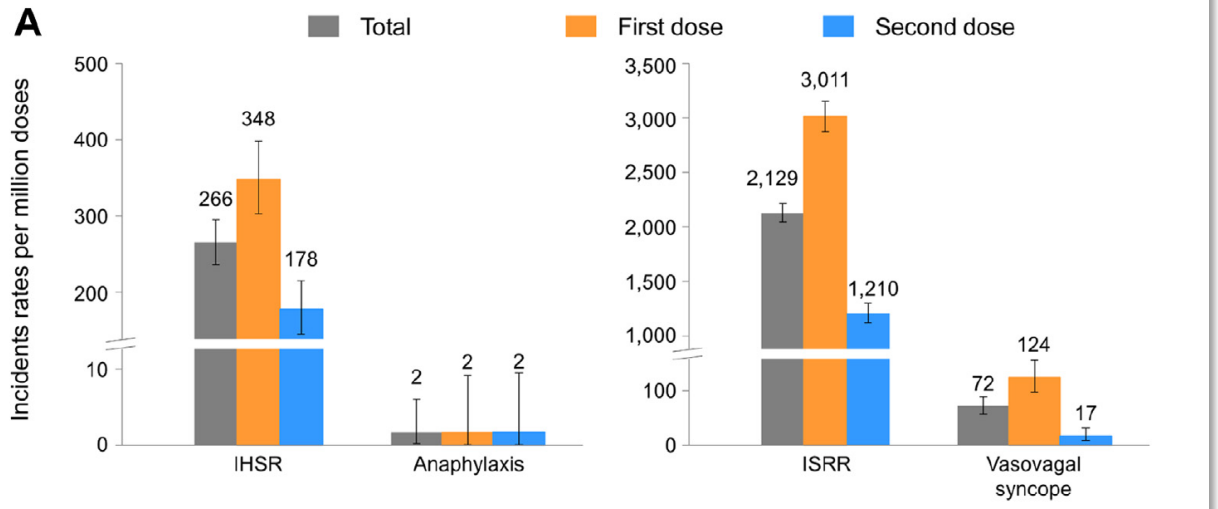
- Concerns about vaccine safety affect vaccine coverage
- Safety is inferred because of the absence of a vaccine or immunisation reaction
- Pre and post-licensure surveillance of Adverse Event Following Immunisation is the basis of pharmacovigilance
- Causality assessment can be performed at a population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

Additional Slides

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.

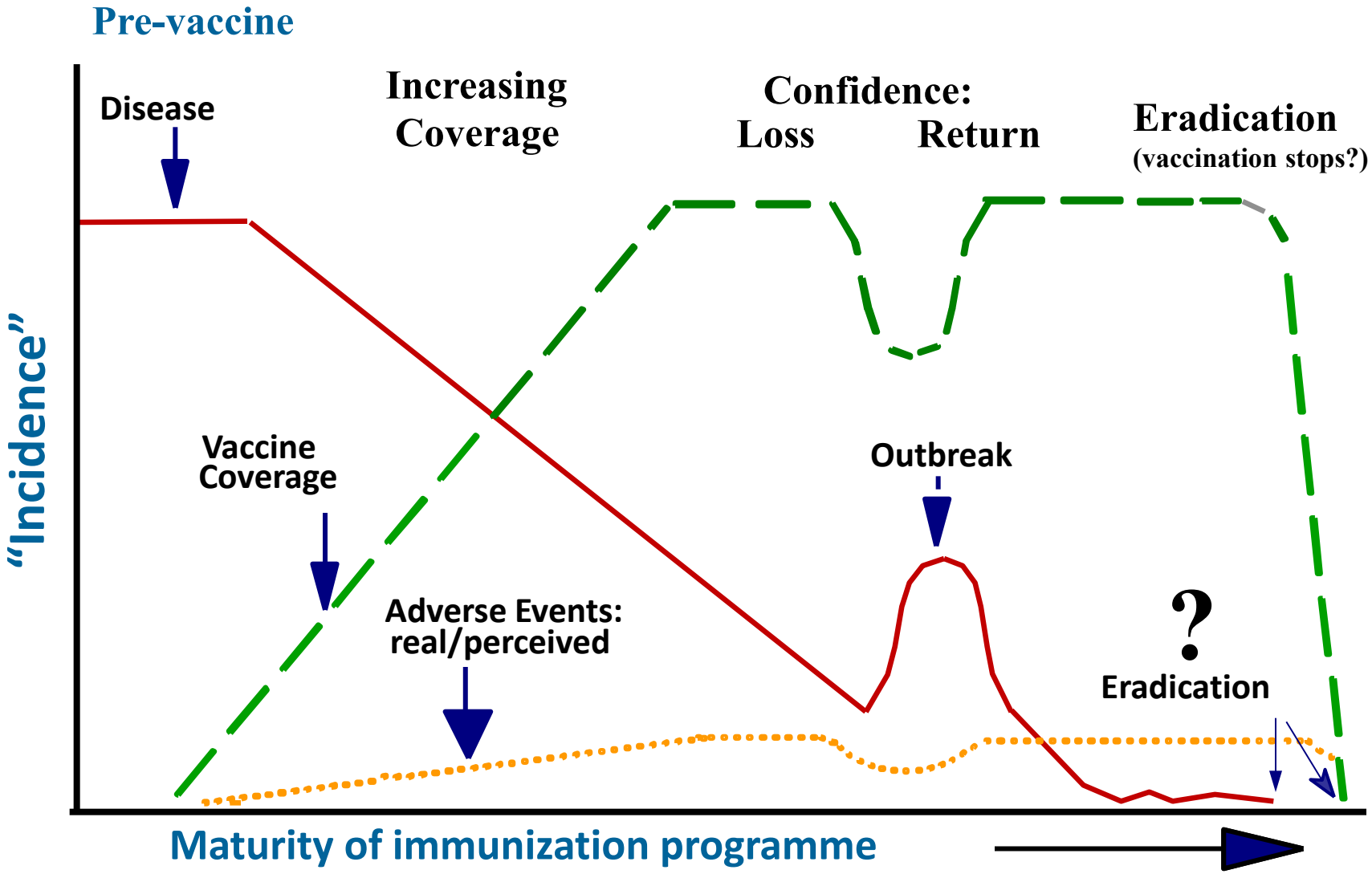
Risk factor	Answer	Univariate analysis of risk factors[a]				
		OR	95% CI			p-value
Administration	First dose	Ref.				
	Second dose	0.872	0.636	,	1.197	0.397
Sex	Male	Ref.				
	Female	1.256	0.874	,	1.805	0.218
Age	per 1 year	0.996	0.984	,	1.009	0.549
Any allergies	No	Ref.				
	Yes	1.594	1.137	,	2.235	**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.



Vaccine safety cycle



Adapted from: Chen RT et al, Vaccine 1994; 12:542-50



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?

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

What did the COVID-19 pandemic teach us about vaccine safety?

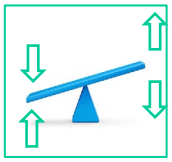
- **Difficulty in establishing confidence in the safety of a novel vaccine**
  - Accelerated development of novel platforms, Emergency Use Licensure, Waiver of legal liability, mandated vaccination, punitive measures, false assurance of complete safety of the vaccines, poor risk/benefit advice, loss of trust in government (transparency, perceived/real COI), social media and influence, LMIC vs HIC

- **Expect rare adverse reactions following licensure and use**
  - Knowledge of vaccine safety incomplete at time of licensure

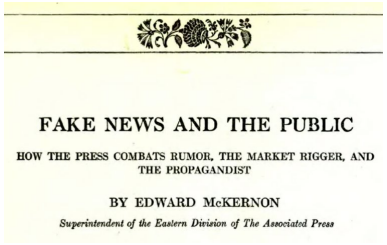
- **Adverse Event Following Immunisation (AEFI) pharmacovigilance**
  - Passive surveillance can be enhanced, case definitions are important, causality assessment critical

- **Differences in adverse event profiles between LMIC and HIC**
  - Safety data from HIC, differences between LMIC and HIC remain unexplained - ? Reactogenicity or surveillance

Why trust and trustworthiness have been eroded



- Governments
- Institutions
  - Regulators
  - Health Departments
  - Expert Advisory Groups
- Source of information
  - Traditional media
  - Social media
    - Fake news – misinformation and disinformation
    - Attracts our attention 6 times faster on social media compared with
    - Dominated by “super-sharers” 70% of fake news during DT campai people
- Artificial Intelligence
  - Evidence currency
  - Sourse traceability
  - Honest uncertainty

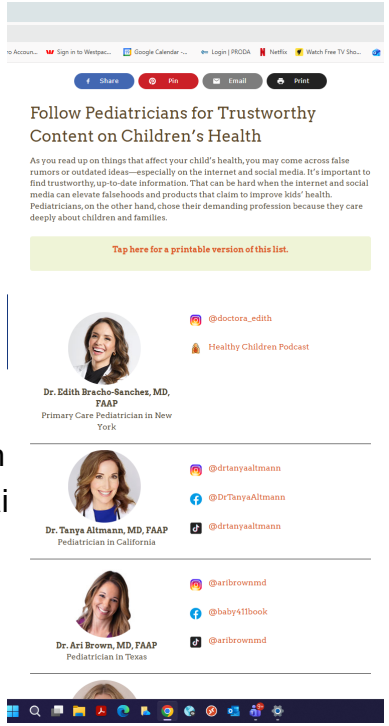


FAKE NEWS AND THE PUBLIC

HOW THE PRESS COMBATS RUMOR, THE MARKET RIGGER, AND THE PROPAGANDIST

BY EDWARD McKERNON

Superintendent of the Eastern Division of The Associated Press



Follow Pediatricians for Trustworthy Content on Children’s Health

As you read up on things that affect your child’s health, you may come across false rumors or outdated ideas—especially on the internet and social media. It’s important to find trustworthy, up-to-date information. That can be hard when the internet and social media can elevate falsehoods and products that claim to improve kids’ health. Pediatricians, on the other hand, chose their demanding profession because they care deeply about children and families.

Tap here for a printable version of this list.

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McKernon E October 1926. Harper’s Magazine
Soroush V Science 369 (2018) 1146-1151
Gringerg Science 2019
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