Indian Journal of Pediatrics (August 2023) 90(8):817–825
https://doi.org/10.1007/s12098-023-04555-3

REVIEW ARTICLE

Adverse Events Following Immunization- The Known Unknowns and Black Box

Based on 10th Dr. I. C. Verma Excellence Award for Young Pediatricians Delivered as Oration on 9th Oct. 2022

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Received: 3 December 2022 / Accepted: 1 January 2023 / Published online: 26 May 2023

Abstract
Although vaccines are one of the most rigorously tested biological products, the safety concerns persist globally. The vaccine safety concerns linked to measles, pentavalent and human papillomavirus (HPV) vaccines have affected the vaccine coverage significantly in past. While surveillance of adverse events following immunization (AEFI) is part of the national immunization program mandate, it suffers from challenges and biases related to reporting, completeness, and quality. Some conditions of concern, termed as adverse events of special interest (AESI) following vaccination, mandated specialised studies to prove/disprove the association. The AEFIs/AESIs are usually caused by one of the four pathophysiologic mechanisms, but for several AEFIs/AESIs, the exact pathophysiology remains elusive. For the causality assessment of AEFIs, a systematic process with checklists and algorithm are followed to classify into one of the four causal association categories. While the causal association primarily banks on epidemiological observations for several AEFIs, the emerging evidences indicate roles of underlying genetic, gender, age and other pro-inflammatory risk factors for AEFIs and AESIs. The emerging evidences suggest role of antigenic mimicry, autoantibody(ies) and underlying genetic susceptibility for the AEFIs/AESIs. The uncertainty about the frequency, profile, interval, and severity of AEFIs/AESIs and variations across the population, ambiguity about the exact pathophysiology mechanism, absence of definite markers, suggest a possible black box effect of the vaccines. Unless these unanswered questions concerning the AEFIs/AESIs are addressed appropriately and communicated to the stakeholders (professionals, care providers, beneficiaries, general public and media), the anti-vaccine movement shall keep challenging the vaccine and vaccination program.

Keywords Adverse events · AEFI · AESI · Immunization · Vaccines · Vaccine safety

Introduction

Vaccine and vaccination is one of the greatest public health intervention in reducing the morbidities and mortalities. The vaccines against over 27 pathogens are available now and many more are under development. With vaccination, the burden of several childhood diseases and associated deaths have declined by 99% along with eradication of small pox globally and poliomyelitis from most countries [1]. According to estimates, between 2000 and 2019, vaccination has averted over 37 million deaths globally [2]. Vaccination is also estimated to avert US$ 1510.4 billion due to illnesses and assisted in generating US$ 3436.7 billion in benefits, a return of US$ 26.1 for every dollar invested on vaccine [3]. Vaccination against human papillomavirus (HPV) prevents cervical cancer by 59%–87% [4]. Additionally, according to the estimates, COVID-19 vaccination has prevented 14.4–19.8 million deaths during the year 2021 globally [5].

India's Universal Immunization Program (UIP) was launched in 1985 with six antigens, which has expanded to twelve antigens. In 2021, India's Diphtheria-tetanus-pertussis-3 (DTP-3) and measles vaccine coverage stand at 85% and 89%, respectively [6]. According to the concurrent external monitoring of routine immunization program, the reasons for

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non-vaccination included lack of awareness (45%), apprehension about adverse events (24%), vaccine resistance (11%), child travelling (8%), and programmatic gaps (4%) [7]. For the COVID-19 vaccination, till December 2021, the acceptance rates in India varied between 53 and 95% across different states and about 29% of the population showed significant hesitance due to vaccine efficacy and safety related concerns [8]. Although the vaccines are one of the most rigorously tested medicinal/biological products, the safety concerns persist globally.

Vaccine Safety Concerns and its Impact on Immunization

Following a publication in 1998 linking measles vaccination with autism in children, vaccine safety scepticism led to drop in measles vaccination coverage and rise in measles cases across several countries by mid-2000 [9, 10]. This association was not supported by multiple subsequent studies conducted in the United Kingdom, the United States, Japan, Canada, Denmark and Poland and the article was retracted in 2010 [10]. But, the vaccine safety concern persists in minds of several American parents, even after several years [11].

Sudden infant deaths (SID) has been argued to be increased after the DTP containing vaccines in the United States [12]. This concern gained momentum when infant deaths were reported following pentavalent vaccination across several Asian countries and later in India [13]. To address the concern, a cohort study in India documented no increase in risk of infant deaths following the three primary doses of pentavalent vaccine [14].

HPV vaccine has been documented to be effective in preventing HPV-associated diseases and cervical cancer. Japan introduced HPV vaccination for adolescent girls in 2010 and the coverage reached >70% by 2013. But, based on the reported adverse events (pain and motor dysfunctions), the proactive vaccination was suspended in June 2013. Soon, the vaccine coverage dropped to <1%, despite its availability in the program [15]. With no association of these symptoms with the vaccine/vaccination documented and targeted communication efforts, the coverage started rising 2018–19 onwards and in November 2021, the Japan government decided to resume the proactive HPV vaccination [16]. The vaccine safety concerns have been cited as a key reason for HPV vaccine hesitancy in the United States also [17].

Adverse Events Following Immunization (AEFI)

Vaccines, being biological products, are expected to result in some adverse events. Vaccine safety concerns are not new. With rising number of vaccines for human use, these concerns are also on rise globally. Adverse event following immunization (AEFI) is '*any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine*'. The adverse event may be '*any unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease*' [18]. The characteristics of AEFIs include: temporality, strength of association (epidemiological, statistical significance, not by chance), biologic plausibility, consistency of evidence, specificity, and possible dose response with the vaccine/vaccination.

Types of AEFI

The AEFIs are classified according to the severity, frequency and mechanism (Fig. 1). The *serious* and *severe* AEFI terms are often used interchangeably, they are not same and the *severe* AEFI category includes the *serious* AEFIs. The AEFIs associated with UIP vaccines are summarised in Table 1.

AEFI Surveillance in India

National AEFI surveillance mandates reporting all AEFIs occurring after the vaccination. While the severe and serious AEFIs are individually reported through online portal, the minor AEFIs are recorded in the AEFI register at the facilities. Once reported, the severe and/or serious AEFIs are investigated by the District AEFI committee including invasive autopsy and/or verbal autopsy for deaths. The State and National AEFI committees conduct the causality assessment of these severe/serious AEFIs. The pharmacovigilance program of India, through the adverse drug reaction monitoring centres and the post-marketing safety updates by the market authorization holder or vaccine manufacturers also contribute to the AEFI surveillance. Additionally, for the private pediatricians, Indian Academy of Pediatrics enables contribution to the AEFI surveillance through https://idsurv.org/ portal. Primarily the AEFI surveillance in India is passive in nature, and suffers from challenges including underreporting, reporting biases, incompleteness, investigation quality, and limited contribution from tertiary care hospitals and private practitioners and hospitals.

Adverse Events of Special Interest (AESI)

An AESI is a medically-significant event that has the potential to be causally associated with a vaccine product, which needs to be carefully monitored for confirmation by further studies [19]. The AESIs identified may be relevant for all beneficiaries or population-specific (pregnant women, children, neonates, immunocompromised individuals, *etc.*). Active vaccine safety surveillance and hypothesis testing is

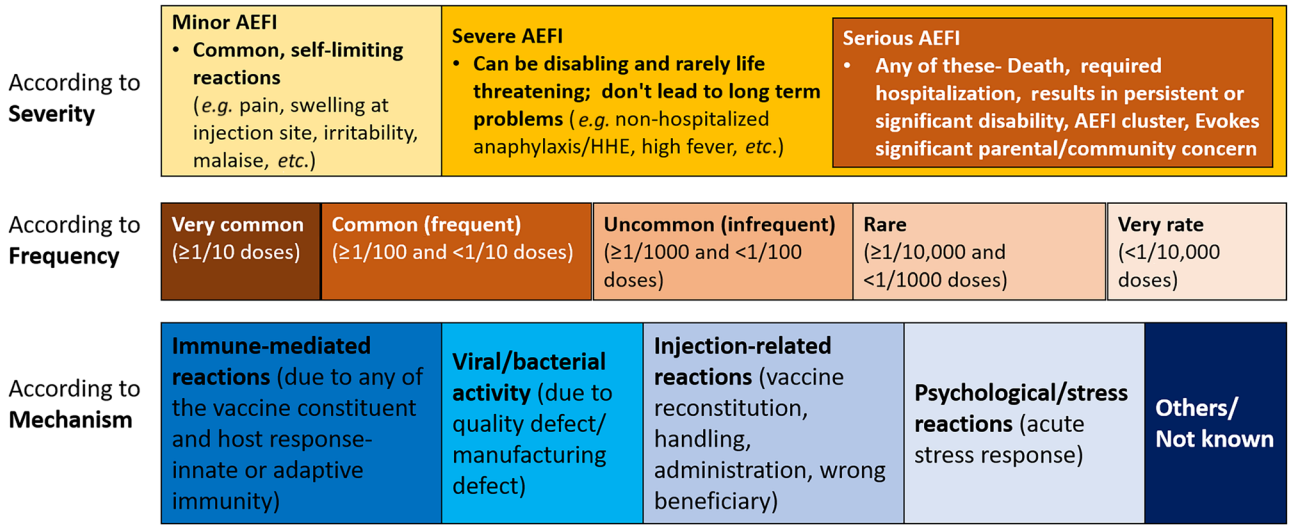

Fig. 1 The taxonomy of adverse events following immunization (AEFI). *Note: Serious AEFIs are part of the severe AEFI. Cluster:* Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered, *AEFI* Adverse events following immunization, *HHE* Hypotonic-hyporesponsive episode

done to establish or refute the causal association of the AESI with the vaccine/vaccination.

Mechanism of AEFIs and AESIs

There are four broad mechanisms for the AEFI and/or AESI including: (1) immune-mediated, (2) viral/bacterial activity, (3) injection-related and (4) psychological/stress reactions (Fig. 1). Additionally, underlying genetic susceptibility (human leukocyte antigen, genetic mutations/deletions, and syndromic states) and pro-inflammatory conditions influence/modulate the occurrence and severity of AEFIs/AESIs.

The vaccines have complex compositions with the active antigen along with variable compositions of adjuvants, stabilisers, antibiotics, preservatives, and traces/residuals of

Table 1 Adverse events associated with the commonly used vaccines

Vaccine	Adverse events	Onset interval	Frequency per doses
BCG vaccine	Suppurative lymphadenitis	2–6 mo	1 in 10,000
	BCG osteitis	1–12 mo	1 in 3,000–100 million
	Disseminated BCG infection	1–12 mo	1 in million
Oral polio vaccine	Vaccine associated paralytic polio	4–30 d	1 in 2.4–3 million
Measles & measles containing vaccines (MR/MMR)	Seizures	6–12 d	1 in 2,000–3,000
	Thrombocytopenia	15–35 d	1 in 30,000–40,000
	Anaphylaxis	0–24 h (0–1 h)	1 in 1 million
	Encephalopathy	6–12 d	<1 in 1 million
Pertussis- whole cell containing vaccines (DTP/ Pentavalent/Hexavalent)	Persistent screaming/crying (>3 h)	0–24 h	1 in 15 to 1000
	Seizures	0–2 d	1 in 1,750 to 12,500
	Hypotonic hyporesponsive episode	0–48 h	1 in 1,500–33,000
	Anaphylaxis	0–24 h (0–1 h)	1 in 0.75–1 million
Hepatitis B vaccine	Anaphylaxis	0–24 h	1 in 0.6 to 0.9 million
Tetanus toxoid	Brachial neuritis	2–28 d	0.5–1 in 100,000
	Anaphylaxis	0–24 h (0–1 h)	1 in 1 million
Rotavirus vaccine	Intussusception	3–14 d	1–2 in 100,000 first dose
Japanese encephalitis vaccine	Allergic reaction	0–10 d	1 in 10,000–100,000
	Seizure	0–7 d	1 in 50,000–1 million
Varicella vaccine	Seizure	7–10 d	1 per 2,500–10,000

BCG Bacillus Calmette-Guérin, *d* day, *DTP* Diphtheria-tetanus-pertussis, *h* hour, *MMR* Measles, mumps and rubella, *MR* Measles and rubella

the cell culture materials, several of these change with the vaccine platforms and the presentation form.

Immune-Mediated Reactions

These reactions are induced by the antigen and/or any vaccine constituent through the innate and/or adaptive immunity pathway. Anaphylaxis is an example of type-I (immediate) hypersensitivity reaction, mast cells and basophils activation through the IgE, its high-affinity receptors and FcεRI, which release histamine, tryptase, carboxypeptidase, proteoglycans and other inflammatory markers [20]. The type-II hypersensitivity are mediated through the IgM and IgG antibodies against the vaccine antigens produced by the B lymphocytes, which bind to the antigens/antigen presenting cells (APCs) forming complexes that activate complement activation and release inflammatory mediators that cause cell lysis and death. In another form of type-2 hypersensitivity, Antibody dependent cell mediated cytotoxicity (ADCC), the APCs are tagged with IgG/IgM antibodies, which are destroyed by the Natural Killer cells and macrophages. The type-III hypersensitivity is mediated by soluble immune complexes with aggregations of antigens and IgG/IgM antibodies, which get deposited in various tissues/organs (skin, kidneys, joints, *etc*.) and trigger immune response through complement activation. The reaction may evolve over hours to days and is dependent on the clearance of the antigen–antibody complexes from the blood. The type-IV hypersensitivity usually develops over 2–3 d and is cell-mediated (CD8+ and CD4+ T cells, macrophages) reaction leading to IL-1, interferon-gamma and cytokines mediated target cells destruction. The immune-mediated reactions are influenced/modulated by various factors including vaccine product (antigen, platform, other components, physiochemical properties and dose number), recipient (age, gender, ethnicity, genetic/HLA variations, underlying risk factors/diseases), and vaccine administration (site, and route).

Viral/Bacterial Activity

The inherent property of the live attenuated bacterial and viral vaccines may cause conditions like Bacillus Calmette Guraine (BCG) disease or osteitis and vaccine-derived poliomyelitis. The vaccine manufacturing defects involving incomplete inactivation of the bacteria or virus may lead to the disease or altered manifestation, like the Cutter incident [21].

Injection-Related Reactions

Errors in vaccine storage, handling, preparation/reconstitution, administration and ignoring the contraindications, may cause exaggerated local reaction, cellulitis, abscess, toxic shock syndrome, sepsis, nerve injury, blood-borne infections and even death. These errors are preventable and all efforts must be made to reduce/avoid these.

Psychological Reactions

A range of symptoms related to anxiety may arise around immunization, known as 'immunization anxiety-related reaction' including dizziness, vasovagal syncope, heart racing, nausea, blurred vision, sweating, hyperventilation, pseudoseizure, and conversion reaction. The manifestations are usually seen in adolescents and adults and its severity depends on the recipient's biological, psychological and social factors and the vaccination site environment.

Establishing Causality Association

The association between the event/AEFI and the vaccine/vaccination is determined by systematic review of the available data from AEFI investigation, known as 'causality assessment (CA)'. Multidisciplinary experts review the available information related to the event (clinical), epidemiological, programmatic aspects and published literature/fact sheets, follow the checklist and algorithm to classify the AEFI under one of the four categories and the specific subcategories, as given in Fig. 2 [18]. These AEFI categories include: A - consistent causal association to immunization; B - indeterminate; C - inconsistent causal association to immunization (coincidental); and D - case without adequate information for causality conclusion (unclassifiable). The AEFI CA classification differs from the adverse event classification in the clinical trials (certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable). For standardization in AEFIs diagnosis, Brighton Collaboration case definitions are usually followed (https://brightoncollaboration.us/).

AEFIs and AESIs- Special Case Scenarios

Infant Deaths

Infant deaths following pentavalent vaccine were reported in several South-Asian countries (2009–2013), which led to transient interruption of the vaccination program, although resumed later as no association was found in the investigations [13]. Similar infant deaths were also reported in India following pentavalent vaccine introduction in 2011. A cohort study in India found no increased risk of serious AEFIs (deaths and hospitalisations) in infants with the pentavalent vaccination [14].

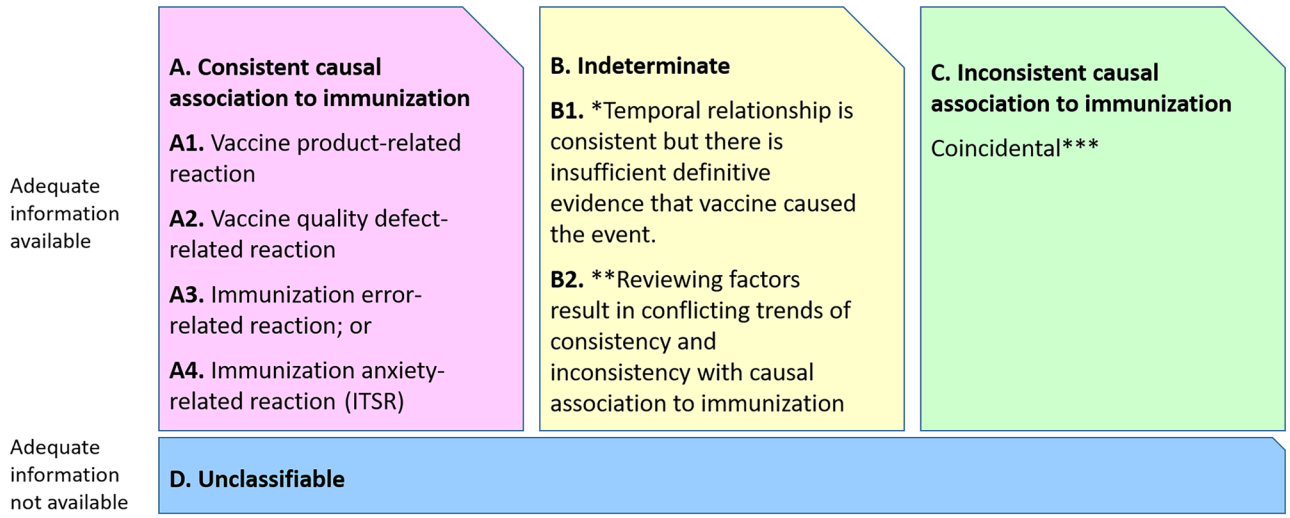

Fig. 2 Adverse events following immunization (AEFI) causality assessment classification. *ITSR: Immunization triggered stress response-Stress response to immunization that can be triggered and may manifest just prior to, during, or after immunization. *It may be a new vaccine-linked event or potential signal and needs to be considered for further investigation. **It may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other. ***It could be due to underlying or emerging condition(s) or conditions caused by exposure to something. Adapted from Causality Assessment of an Adverse Event Following Immunization (AEFI): User Manual for the Revised WHO Classification* [18]

Intussusception

Increased risk of intussusception in infants after the RotaShield™ (Wyeth-Lederle Laboratories) vaccine led to its withdrawal. Subsequent rotavirus vaccine trials included larger sample sizes (60,000–70,000) to document the risk of intussusception. Although no significant increased risk of intussusception was observed in pre-licensure clinical trials; post-licensure studies in the North American, South American and European countries observed some increased risk during the 1–7 d after the first (relative risk, RR 5.4–5.5) and second doses (RR 1.7–1.8) of the rotavirus vaccines [22]. Three post-licensure studies in India did not observe any increased risk of intussusception following the Rotavac™ (Bharat Biotech) vaccination [23–25]. The observed risk of intussusception following the rotavirus vaccine is lower in India, Brazil and some African countries compared to several developed countries [23]. Although the exact reason of intussusception following rotavirus vaccine and variations across the countries are not known, genetic, immune, microbiome, diet, and other infections have been proposed as the potential modifiers.

Thrombocytopenia

Thrombocytopenia has been reported following several vaccines including measles containing vaccine (MCV), varicella, diphtheria-tetanus-pertussis (DTP)/diphtheria-tetanus- acellular pertussis (DTaP), hepatitis B, hepatitis A, influenza, meningococcal and pneumococcal vaccines, with variable frequency. Usually the thrombocytopenia manifests between 1–6 wk after the vaccination and is proposed to be immune mediated (a combination of antigen mimicry, B-cell and T-cell mediated platelet destruction and production suppression) [26].

Seizure

Increased risk of seizures with/without fever have been reported after vaccination with whole-cell pertussis, MCV, Japanese encephalitis, influenza and varicella vaccines, at variable intervals (Table 1). For the pertussis vaccine, the risk of seizure is higher after the first (day 0, RR 6.49; days 1–7, RR 1.47), than the second (day 0, RR 3.97; days 1–7, RR 1.52) and third (day 0, RR 1.07; days 1–7, RR 0.89) doses [27]. The risk of seizure was higher (RR 2.75) during second week following MCV vaccination [28]. High proportion of unrecognised genetic pre-disposing conditions like *SCN1A* mutation-Dravet syndrome, protocadherin-19 (PCDH19) mutation, 1qter microdeletion, neuronal migration disorders, and monogenic familial epilepsy have been documented in children with seizure following vaccination [29].

Guillain-Barré Syndrome (GBS)

About 500 cases of GBS were reported following A/New Jersey/76 vaccination during the swine flu epidemic in the United States in 1976 [30]. Following that, GBS is considered as a potential AEFI/AESI for influenza vaccines and also other vaccines, including MCV, hepatitis B, DTP and polio.

Although GBS is rare, studies and metaanalysis revealed the risk of GBS to be mildly increased (RR 1.15–4.4) following the influenza vaccination [31, 32]. A combination of antigenic mimicry, cross-reacting antibody triggered by vaccination with underlying genetic susceptibility have been proposed as the mechanism for GBS [33].

Narcolepsy

Narcolepsy (excessive day sleepiness) in children, adolescents and young adults were reported following H1N1 vaccination campaign (2009) in Finland, Sweden, France, Norway, the United Kingdom (UK), Ireland and Germany, mostly with the Pandemrix vaccine [34]. Genetic pre-disposition with presence of HLA-DQB1*06:02 (OR 39.4), antigenic mimicry with enhanced T-cell immunity against the viral epitopes (neuraminidase 175–189 and nucleoprotein 214–228) brain self-epitope (protein-O-mannosyltransferase-1), along with the up-regulation of IFN-γ, perforin-1 and granzyme B, have been observed as the possible mechanisms [35, 36].

AEFIs and AESIs Following COVID-19 Vaccination

To curtail the COVID-19 pandemic, the vaccine was developed at record speed using various new platforms. The COVID vaccine was administered to a large number of adults and later to children through mass vaccination campaign across countries. Considering limited experience, WHO advised surveillance for AESIs following COVID vaccination, (Table 2) which were categorised under tier one (serous and observed) and tier two (non-serious and theoretical concerns) and proposed to conduct active vaccine safety surveillance to document [19]. Some of the AESIs of concern include vaccine-induced immune thrombotic thrombocytopenia (VITT)/thrombosis with thrombocytopenia syndrome (TTS), myocarditis, pericarditis, GBS, acute disseminated encephalomyelitis (ADEM), multisystem inflammatory syndrome and vaccine associated enhanced disease (VAED). VITT/TTS cases were reported following the adenovirus-vector COVID-19 vaccine (ChAdOx1-S, Astra-Zeneca, Vaxzevira™ and Covishield™; and Ad26.COV2.S, Janssen/Johnson & Johnson, Jcovden) with mean interval of 7 d (usually 4–27 d) with thrombocytopenia and thrombosis of cerebral venous sinus, intracerebral, pulmonary, deep veins, and others [37]. Higher risk of VITT/TTS was observed in younger adults [38]. VITT is caused by the anti-platelet factor-4 antibodies (anti-PF4) that bind to the receptors on platelets to form immune complexes that activate the clotting cascades coupled with thrombocytopenia [39]. It is proposed to be mediated by antigenic mimicry with potential genetic predisposition or prior exposure to heparin. GBS has been reported following COVID-19 vaccination, more with the adenovirus-vector vaccines compared to the mRNA vaccines (1–21 d, RR 20.56; and 1–42 d, RR 11.46) [40]. Myocarditis and/or pericarditis have been reported following the COVID-19 vaccination, more after the mRNA vaccines and especially in the young adults [41]. Formation of antigens

Table 2 The adverse events of special interest (AESIs) for COVID-19 vaccines

Tier One	Tier Two
Vaccine associated enhanced disease	Acute kidney injury
Multisystem inflammatory syndrome in children and adults (MIS-C/A)	Acute liver injury
Myocarditis	Anosmia/ageusia
Pericarditis	Bell's palsy
Thrombosis with thrombocytopenia syndrome (TTS) or Vaccine-induced immune thrombotic thrombocytopenia (VITT)	Chilblain like lesions
Thrombosis	Erythema multiforme
Thrombocytopenia	Acute pancreatitis
Acute disseminated encephalomyelitis (ADEM)	Rhabdomyolysis
Encephalitis	Subacute thyroiditis
Myelitis	
Acute respiratory distress syndrome (ARDS)	
Anaphylaxis*	
Toxic shock syndrome (TSS)	
Injection site cellulitis/abscess*	

Tier One AESIs are serious; and have been observed or associated with a COVID-19 or other coronavirus vaccines in animal models, clinical trials, or post-introduction pharmacovigilance, or are specific to immunization errors

Tier Two AESIs are non-serious, and theoretical concerns as seen with COVID-19 disease.

Adapted from Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) list (https://brightoncollaboration.us/wp-content/uploads/2021/01/COVID-19-updated-AESI-list.pdf)

*Cases of anaphylaxis and infection site cellulitis/abscess may not be hospitalized

from some components of the mRNA and antigenic mimicry that activates the T and B cells producing cross-reacting cardiotropic antibodies, has been proposed as the pathogenesis [42]. VAED is a rarely-observed phenomenon documented with vaccines against measles, respiratory syncytial virus, and dengue is also anticipated with the COVID-19 vaccines. VAED is characterised by augmentation of the pathological and clinical manifestations in vaccinated individuals with subsequent infection with the associated pathogen. VAED is mediated through either antibody-dependent enhancement, antibody-enhanced disease or Th2-mediated responses, with immune complexes triggering the pathogenesis [43].

Pregnancy- Special Case for Adverse Events

Immunization during pregnancy is being explored as an opportunity to prevent infections in the infants apart from maternal benefits. The dynamism of cell-mediated immunity (Th1-Th2 balance), immune-tolerance along with hormonal levels and lower immune response to vaccines during pregnancy is likely to be associated with a different AEFI/AESI context [44]. Occurrence of several events during pregnancy, which are considered as AEFI/AESI further complicate the risk association with vaccines. The initial observations do not reflect any increased risk of adverse pregnancy outcomes with COVID-19 vaccines, it requires further documentation [45].

Vaccine and AEFIs/AESIs– The Black Box Effect

Although the AEFIs/AESIs are uncommon or rare, the frequency, their profile, interval, and severity varies across the beneficiaries and the underlying cause(s) and modulators are not clear. This can be considered as a black box effect and the explanations for many of these still remain elusive. Several questions related to AEFI/AESI remain unanswered (Box 1).

Box 1 The unanswered questions related to AEFIs/AESIs

- Why some develop serious AEFIs/AESIs?
- What are the biological mechanisms and triggers of these AEFIs/AESIs?
- What is/are the influence of antigen combinations and/or concomitantly administered vaccines on AEFIs/AESIs?
- Are there population level variations in these AEFIs/AESIs?
- How to prove or disprove the causal linkages with greater confidence?
- How to predict the risk of AEFIs/AESIs?
- What are the conditions and/or factors that influence occurrence and severity of the AEFIs/AESIs?
- What is/are the specific biological markers that confirm(s) vaccine association?

AEFI Adverse events following immunization, *AESI* Adverse events of special interest

Anti-Vaxxers and Anti-Vaccine Movement

Although the anti-vaccine movement is not new, with the rising number of vaccines and identification of new AEFIs/AESIs, the safety concerns are also growing. The past experiences with measles/measles mumps rubella (MMR), polio, pentavalent, HPV and recent COVID-19 vaccination, the risk for vaccine hesitance/resistance remains sizable. The social and electronic media has the potential to fuel the anti-vaccine movement, much faster than in the past.

Role of Hospitals and Health Professionals

While the routine vaccines are administered mostly in the public health system, the new vaccines are usually administered in the private sector. With the low sensitivity and biased reporting under the passive AEFI surveillance, the role of secondary- and tertiary-care hospitals, especially the medical colleges becomes important. Apart from the pediatricians, the roles of medicine/cardiology/respiratory/neurology specialists and obstetricians are becoming important with expanding vaccination horizon. Unless, the specialists suspect, investigate, elicit the vaccination history, and document, most of these AEFIs/AESIs are likely to be missed.

Way Forward

India and developing countries are challenged with the surveillance sensitivity, reporting quality, investigation and research to document vaccine safety. Unless the AEFI reporting becomes part of routine service delivery monitoring, the detection and establishment of association with vaccine/vaccination in India shall be dependent on targeted studies, which have their own limitations. There is a need to invest and undertake comprehensive research to better understand the pathophysiology and manifestation related questions. While an ideal vaccine with no AEFI appears to be unreal, appropriate AEFI/AESI surveillance is essential to document the vaccine safety and retain public confidence.

Conclusions

The recent gains in vaccine development, especially during the COVID times are likely to be sustained in future. While India is gaining a leadership position in vaccine development

and manufacturing, there is a need for investments in vaccine safety surveillance to improve report and document the AEFIs/AESIs. Appropriately designed epidemiological, bio-mechanistic, immunological and multi-omics framework studies are necessary to better understand the black-box effect of the vaccines/vaccination. Vaccines are one of the most important invention in medicine and it could be even more effective with better documentation of the science and transparent communication to maintain the public confidence.

Acknowledgements The author expresses his gratitude to Dr. Narendra K. Arora for his constant guidance and mentorship. He acknowledges the investigators and partners of INCLEN AEFI research network supporting the researches conducted. He appreciates the National AEFI Committee for the support.

Author's Contribution MKD: Conceptualisation, literature search, data collation, manuscript drafting and finalisation.

Declarations

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Conflict of Interest None.

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