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Causality Assessment of AEFI (Part I)

This is the first in a series of two articles on Causality Assessment of Adverse Events Following Immunization (AEFI)

Background

Immunization is among the most successful and cost-effective public health interventions. It has led to the global eradication of smallpox as well as the elimination of poliomyelitis in most parts of the world. Immunization currently averts an estimated 2 to 3 million deaths from diphtheria, tetanus, pertussis (whooping cough) and measles every year in all age groups.

More people than ever before are being reached with immunization. In 2011, in children under the age of one year, about 83% (an estimated 109 million infants) were vaccinated with three doses of diphtheria-tetanus-pertussis (DTP3) vaccine, about 84% (an estimated 110 million) with measles vaccine and about 88% (an estimated 114 million) with the BCG vaccine.

Immunization safety has become as important as the efficacy of the national vaccine preventable disease control programmes. Unlike drugs, the expectations from vaccinations are much higher and problems arising from the vaccine or vaccination are less acceptable to the general public. Vaccines are usually administered to healthy people, including entire birth cohorts of infants and in vast numbers. The settings in which they are administered vary from sophisticated tertiary care hospitals to primitive settings in remote, inhospitable and inaccessible terrain. In many countries, specific vaccinations are mandatory for school admission as well as international travel.

The benefits of immunization are often not visible, particularly if the target disease incidence is low. In contrast, adverse effects that follow immunization are promptly noticeable, especially when the vaccinee was apparently healthy at the time of immunization. Although other factors may have contributed to or even been totally responsible for the event, they may not be considered or investigated. Fear of vaccine reactions, real or perceived, deters many people from undergoing vaccination.

Allegations that vaccines/vaccination cause adverse events must be dealt with rapidly and effectively. Failure to do so can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence long after proof is generated that the adverse event was not caused by vaccine (e.g. autism and MMR, encephalopathy and pertussis). On the other hand it must always be remembered that vaccines are not 100% safe and harm can result from errors in immunization practice. Thus vaccine-associated adverse reactions and error-related immunization events may affect healthy individuals and should be promptly identified for further response. Appropriate action(s) must be taken to respond promptly, efficiently, and with scientific rigour to vaccine safety issues. This will minimize adverse effects to the health of individuals and entire populations and in turn help to maximize the benefits of immunization programmes. Causality assessment of AEFI is thus a vital component of AEFI risk assessment, decision making and the initiation of action.

Definitions of AEFI

General definition-This is defined as 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.

Cause-specific definitions-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.

Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.

Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature, is preventable.

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Immunization anxiety-related reaction: An AEFI arising from anxiety about immunization.

Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

The need for causality assessment of adverse events

Causality is the relationship between two events (the cause and the effect), where the second event is a consequence of the first. A direct cause is a factor in the absence of which the effect would not occur (necessary cause). Sometimes there are multiple factors that may precipitate the effect (event) or may function as co-factors so that the effect (event) occurs.

Causality assessment usually will not prove or disprove an association between an event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

Many challenges are involved in deciding whether an adverse event is actually caused by a vaccine. Vaccines are often administered to children at ages when many underlying diseases become evident. Vaccines administered to adults can also coincide with an entirely different risk factor for an event. The fact that a vaccine was administered within a reasonable time period of the occurrence of an event does not automatically suggest that the vaccine caused or contributed to the event.

The evidence of a link between a vaccine as a potential cause and a specific event is derived from epidemiological studies that follow the scientific method and try to avoid biases and confounders. An example is a patient who is a smoker but also has a family history of breast cancer: is tobacco the cause of the cancer or only a co-factor? In the same way, to perform causality assessment in individual cases after vaccination, even where evidence for a causal link exists for some vaccines and AEFI (e.g. measles vaccine and thrombocytopenia), it is important to consider all possible explanations for the event and the degree of likelihood of each before attributing the event to the vaccine product, a vaccine quality defect, an error in the immunization process, immunization anxiety or coincidence.

AEFI causality assessment in practice

Causality assessment is the systematic review of data about an AEFI case; it aims to determine the likelihood of a causal association between the event and the vaccine(s) received. For individual cases, one tries to apply the evidence available on the basis of the history and time frame of the event to arrive at a causal likelihood. The quality of the causality assessment depends upon:

- the performance of the AEFI reporting system in terms of responsiveness, effectiveness and quality of investigation and reports
- the availability of adequate medical and laboratory services and access to background information
- the quality of the causality review process.

With inadequate or incomplete data, an AEFI can be deemed unclassifiable. However, it should also be noted that AEFI causality may be indeterminate due to lack of clear evidence for a causal link, or conflicting trends, or inconsistency with causal association to immunization. It is nevertheless important not to disregard the above reports of AEFI because at some point they may be considered a signal and may lead to hypotheses regarding a link between a vaccine and the event in question, with specific studies designed to test for a causal association. Pooling of data on individual cases is very helpful in generating hypotheses. The case of rotavirus vaccine and intussusception is a good example.

In 1998 a rotavirus vaccine was licensed for use in the USA. Initial clinical trials with the vaccine showed that it had been effective in preventing severe diarrhoea caused by rotavirus A, and researchers had detected no statistically significant serious adverse effects. After the vaccine was licensed, however, some infants vaccinated developed intussusception. At first it was not clear if the vaccine or some other factor was causing the bowel obstructions. The results of investigations showed that the vaccine caused intussusception in some healthy infants younger than 12 months of age who normally would be at low risk for this condition. The United States Advisory Committee on Immunization Practices (ACIP) voted on 22 October 1999 to no longer recommend use of the Rota Virus vaccine in infants because of an association between the vaccine and intussusception.

Levels of causality assessment and their scientific basis

Causality assessment of AEFI should be performed at several different levels. The first is the population level, where it is necessary to test if there is a causal association between the use of a vaccine and a particular AEFI in the population. Secondly, at the level of the individual AEFI case report, one should review previous evidence and make a logical deduction to determine if an AEFI in a specific individual is causally related to the use of the vaccine. The third level of assessment is in the context of the investigation of signals.

The population level

At the population level the aim is to answer the question "Can the given vaccine cause a particular adverse event?" Several criteria are relevant to establishing causality but only the first criterion is absolutely essential.

- Temporal relationship: The vaccine exposure must precede the occurrence of the event.
- Strength of association: The association should meet statistical significance to demonstrate that it was not simply a chance occurrence.
- Dose–response relationship: Evidence that increasing exposure increases the risk of the event supports the suggestion of a causal relationship. However, one should keep in mind that, in the case of vaccines, dose and frequency tend to be fixed.
- Consistency of evidence: Similar or the same results generated by studies using different methods in different settings support a causal relationship.
- Specificity: The vaccine is the only cause of the event that can be shown.
- Biological plausibility and coherence: The association between the vaccine and the adverse event should be plausible and should be consistent with current knowledge of the biology of the vaccine and the adverse event.

One should also consider the presence of systematic bias (analytic bias) in study methods as this weakens conclusions that a causal association exists.

Source-Causality assessment of AEFI following Immunization-available from *http://www.who.int/vaccine_safety/publications/aevi_manual.pdf*

Compiled by Dr. Madhava Gunasekera of the Epidemiology Unit

Table 4: Selected notifiable diseases reported by Medical Officers of Health 28th Sept-04th Oct (40th Week)

RDHS	Dengue Fever		Dysentery		Encephaliti		E Fever		F Poisoning		Leptospiro		T Fever		V Hepatitis		H Rabies		Chickenpox		Meningitis		Leishmania-		WRCD %	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	T*	C**
Colombo	112	7713	7	168	0	17	3	124	1	52	7	178	0	7	0	68	0	1	10	359	3	56	0	0	**85**	**15**
Gampaha	40	2913	2	170	1	15	1	45	0	29	7	325	0	16	3	164	0	0	7	141	2	81	0	5	**93**	**7**
Kalutara	7	1430	2	151	0	19	1	69	0	23	1	328	0	5	0	20	0	0	14	225	1	61	0	0	**77**	**23**
Kandy	18	1504	6	132	0	11	1	24	0	8	0	65	0	92	5	88	0	0	4	112	1	14	1	4	**78**	**22**
Matale	6	392	3	83	0	4	0	24	0	7	1	57	0	4	0	39	0	0	0	42	0	33	0	11	**46**	**54**
NuwaraEliya	6	212	1	136	0	2	2	11	0	217	1	24	0	57	0	20	0	0	1	101	0	12	0	0	**92**	**8**
Galle	17	744	3	99	1	19	1	5	1	81	4	193	0	51	0	13	0	2	6	275	1	45	0	0	**89**	**11**
Hambantota	8	281	1	48	0	3	0	15	0	32	0	159	0	61	4	83	0	0	4	91	0	44	2	274	**92**	**8**
Matara	7	402	1	69	1	12	0	28	0	27	3	132	0	77	0	134	0	2	4	231	3	69	1	78	**100**	**0**
Jaffna	5	584	25	296	0	10	3	297	0	96	0	8	2	328	0	17	0	1	0	131	2	53	0	0	**100**	**0**
Kilinochchi	0	57	4	33	0	0	0	14	0	5	0	9	0	16	0	0	1	2	0	2	0	7	0	11	**75**	**25**
Mannar	0	63	0	63	0	2	0	59	0	36	0	14	0	19	0	2	0	0	0	11	0	5	0	4	**20**	**80**
Vavuniya	0	63	2	48	1	13	2	12	0	19	0	50	0	2	0	3	0	2	0	22	0	32	1	9	**100**	**0**
Mullaitivu	0	107	1	19	0	2	0	8	3	38	0	37	0	6	0	1	0	2	0	8	1	6	0	14	**80**	**20**
Batticaloa	8	498	12	263	0	5	2	10	2	72	2	33	0	2	1	13	0	3	0	39	0	7	0	0	**79**	**21**
Ampara	8	165	9	137	0	1	1	5	0	10	0	33	0	1	1	8	0	0	2	78	1	17	0	3	**71**	**29**
Trincomalee	1	183	0	57	0	3	0	5	0	3	0	59	1	13	0	3	0	1	1	37	0	4	0	28	**75**	**25**
Kurunegala	27	2475	4	151	2	35	0	38	0	23	6	274	1	40	0	49	0	1	12	314	0	94	0	40	**89**	**11**
Puttalam	6	790	1	63	0	7	0	16	0	36	1	41	0	12	0	6	0	1	2	76	0	31	0	8	**69**	**31**
Anuradhapur	8	457	2	90	0	16	0	3	2	40	2	301	0	22	1	24	0	2	2	157	1	88	1	342	**84**	**16**
Polonnaruwa	2	372	5	69	0	1	0	14	0	62	2	157	0	3	0	28	0	2	0	119	0	17	1	143	**71**	**29**
Badulla	4	437	6	168	1	5	0	17	0	10	1	53	2	74	0	43	0	0	3	108	1	57	0	7	**82**	**18**
Monaragala	3	210	1	102	0	4	0	22	0	25	1	196	0	53	2	152	0	1	1	47	0	23	0	10	**55**	**45**
Ratnapura	9	1562	4	318	0	83	0	37	0	16	6	303	3	62	9	392	0	1	5	145	0	74	0	12	**83**	**17**
Kegalle	8	946	4	110	0	15	1	26	0	11	10	185	0	69	2	189	0	0	2	276	0	98	0	1	**91**	**9**
Kalmune	1	490	0	135	0	2	0	3	1	117	0	8	0	2	0	5	0	0	1	82	1	9	0	1	**69**	**31**
SRI LANKA	**311**	**25050**	**106**	**3178**	**07**	**306**	**18**	**931**	**10**	**1095**	**55**	**322**	**09**	**1094**	**28**	**1564**	**01**	**24**	**81**	**322**	**18**	**1037**	**07**	**1005**	**81**	**19**

Source: Weekly Returns of Communicable Diseases (WRCD).

*T=Timeliness refers to returns received on or before 04th October , 2013 Total number of reporting units 339. Number of reporting units data provided for the current week:266 C** Completeness

A = Cases reported during the current week. B = Cumulative cases for the year.H Rabies*= Human Rabies, E Fever*=Enteric Fever, F Poison* =Food Poisoning, T Fever*=Typhus Fever, V Hepatitis*=Viral Hepatitis

Table 1: Vaccine-Preventable Diseases & AFP 28th September – 04th October 2013 (40th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2013	Number of cases during same week in 2012	Total number of cases to date in 2013	Total number of cases to date in 2012	Difference between the number of cases to date in 2013 & 2012
	W	C	S	N	E	NW	NC	U	Sab					
AFP*	00	00	00	02	00	00	01	00	00	03	01	71	61	+ 16.4 %
Diphtheria	00	00	00	00	00	00	00	00	00	-	-	-	-	-
Mumps	01	02	00	00	02	04	02	01	00	13	48	1237	3781	- 67.3 %
Measles	20	04	18	01	02	03	02	01	23	74	02	3080	49	+ 6185.7 %
Rubella	00	00	00	00	00	01	00	00	00	01	-		-	-
CRS**	00	00	00	00	00	00	00	00	00	00	-	06	-	-
Tetanus	00	00	00	00	00	00	00	00	00	00	01	19	10	+ 90.0 %
Neonatal Tetanus	00	00	00	00	00	00	00	00	00	00	-	00	-	-
Japanese Encephalitis	00	00	00	00	00	00	00	00	00	00	-	66	-	-
Whooping Cough	00	01	01	00	00	00	00	00	00	02	04	68	86	- 20.9 %
Tuberculosis	02	00	05	04	07	00	06	00	00	24	273	6386	6687	- 04.5 %

Key to Table 1 & 2

Provinces: W: Western, C: Central, S: Southern, N: North, E: East, NC: North Central, NW: North Western, U: Uva, Sab: Sabaragamuwa.

RDHS Divisions: CB: Colombo, GM: Gampaha, KL: Kalutara, KD: Kandy, ML: Matale, NE: Nuwara Eliya, GL: Galle, HB: Hambantota, MT: Matara, JF: Jaffna, KN: Killinochchi, MN: Mannar, VA: Vavuniya, MU: Mullaitivu, BT: Batticaloa, AM: Ampara, TR: Trincomalee, KM: Kalmunai, KR: Kurunegala, PU: Puttalam, AP: Anuradhapura, PO: Polonnaruwa, BD: Badulla, MO: Moneragala, RP: Ratnapura, KG: Kegalle.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Neonatal Tetanus, Whooping Cough, Chickenpox, Meningitis, Mumps., Rubella, CRS,

Special Surveillance: AFP* (Acute Flaccid Paralysis), Japanese Encephalitis

CRS** =Congenital Rubella Syndrome

AFP and all clinically confirmed Vaccine Preventable Diseases except Tuberculosis and Mumps should be investigated by the MOH

Dengue Prevention and Control Health Messages

Thoroughly clean the water collecting tanks bird baths, vases and other utensils once a week to prevent dengue mosquito breeding.

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Comments and contributions for publication in the WER Sri Lanka are welcome. However, the editor reserves the right to accept or reject items for publication. All correspondence should be mailed to The Editor, WER Sri Lanka, Epidemiological Unit, P.O. Box 1567, Colombo or sent by E-mail to chepid@sltnet.lk. **Prior approval should be obtained from the Epidemiology Unit before publishing data in this publication**

ON STATE SERVICE

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