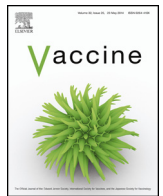




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Review

An approach to death as an adverse event following immunization

Michael S. Gold^{a,*}, Madhava Ram Balakrishnan^b, Ananda Amarasinghe^c,
Noni E. MacDonald^d

^a University of Adelaide, Discipline of Paediatrics, Women's and Children's Health Network, 72 King William Road, Adelaide 5000, Australia

^b World Health Organization, 20 Avenue Appia, 1211 Genève 27, Switzerland

^c Epidemiology Unit, Ministry of Health, Sri Lanka

^d Department of Paediatrics, Dalhousie University and IWK Health Centre, Canada

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ABSTRACT

Co-incidental death occurring proximate to vaccination may be reported as an adverse event following immunization. Such events are particularly concerning because they may raise community and health provider concerns about the safety of the specific vaccine and often the immunization programme in general. Coincidental events need to be differentiated from vaccine reactions, such as anaphylaxis, which may very rarely result in death. In 2013, the World Health Organization (WHO) released an updated manual for the Causality Assessment of an AEFI. The purpose of this review is to apply the WHO causality methodology to death when this is reported as an AEFI. The causality assessment scheme recommends a four step process to enable classification of the AEFI and to differentiate events which are causally consistent from those that are inconsistent with immunization. However, for some events causality maybe indeterminate. Consistent causal reactions that may result in death are very rare and maybe related to the vaccine product (e.g. anaphylaxis, viscerotropic disease), vaccine quality defect (e.g. an incompletely attenuated live vaccine agent) or an immunization error (e.g. vaccine vial contamination). Events that are inconsistent with immunizations are due to co-incidental conditions that may account for infant and childhood mortality. In countries with a high infant mortality rate the coincidental occurrence of death and immunization may occur not infrequently and a robust mechanism to obtain information from autopsy and perform an AEFI investigation and causality assessment is essential. Communication with the community and all stakeholders to maintain confidence in the immunization programme is critical.

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1. Introduction

An adverse event following immunization (AEFI) is defined as “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 unfavourable or unintended sign, abnormal laboratory finding, symptom or disease” [1]. An AEFI is considered serious if this results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect [1]. Because co-incidental death occurs in all communities and in the age groups being immunized, it should not be unexpected that death, unrelated to immunization, is reported as an AEFI. Deaths following

immunization, especially if this occurs in the first 48 h following immunization, are particularly concerning because they may raise community and health provider concerns about the safety of the specific vaccine and often the immunization programme in general [2]. This is most problematic for low and middle income countries where infant and child mortality rates are high and where coincidental death proximate to vaccination may occur not uncommonly (Table 1).

Furthermore, given that the vaccine safety surveillance systems and expertise in causality assessment may not be available, or may be inadequate in these countries, such coincidental deaths can undermine trust in the immunization programme if not well investigated. Unfortunately, experience has shown that when there is an inability to collect timely clinical and laboratory case data and to perform a quality causality assessment (to ascertain the relationship between the immunization and death) this may lead to an immunization programme crises. For example, reported coincidental deaths post-immunization with a whole-cell pertussis

* Corresponding author.

E-mail address: michael.gold@adelaide.edu.au (M.S. Gold).

Table 1

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 ^a in		
			A month	A week	A day	A month	A week	A day
Bhutan	42	15,000	53	12	2	3233	746	106
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
Uzbekistan	42	589,000	2062	476	68	126,959	119,986	4174

Source: Infant mortality and births from 2011 immunization summary. New York (NY) and Geneva: United Nations Children's Fund and World Health Organization, 2013. (<http://www.unicef.org/videoaudio/PDFs/EN-ImmSumm-2013.pdf> [accessed 07.12.13]).

Note: Assumes uniform distribution of deaths and immunization over the time period.

^a The assumption here is a three-dose schedule for either DTP or PVV, with 90% coverage for each dose.

Pentavalent vaccine in Sri Lanka and Vietnam have resulted in a temporary cessation of the national immunization programmes for the implicated vaccine [2].

In addressing community vaccine concerns and expectations when a death occurs following immunization, knowing whether this was coincidental or causally related to the vaccine or immunization is crucial as this may have implications at the local, national, regional and global levels. In 2013 WHO released the updated manual for "Causality Assessment of an Adverse Event Following Immunization" [3]. The purpose of this review is to apply the WHO causality methodology when death is reported as an AEFI to help inform AEFI investigation data collection and causality assessment. This need for a review of AEFI deaths and potential causality has been requested by low and middle income countries [4].

2. Cause specific classification of death as an AEFI

The causality assessment scheme (Fig. 1) recommends a four step process to enable classification of an AEFI [5]. The first step is to ascertain if all eligibility criteria are met enabling a causality question to be framed. If adequate information is available the AEFI check list is completed, the causality algorithm completed and an attribution category assigned. Causality assessment will assign one of seven possible outcomes as outlined in the final step. The AEFI may be found to be consistent with a vaccine reaction in which case this could be related to one of four sub-categories – vaccine product, vaccine quality defect, and immunization error or immunization anxiety (the latter not a primary category when the AEFI is death – see below). The event maybe classified as inconsistent or coincidental. Lastly, the event maybe classified as indeterminate in which case there are two sub-categories; firstly, when the temporal relationship is consistent but there is insufficient definitive evidence for a vaccine(s) causing the event (may be new vaccine signal) or when qualifying factors result in conflicting trends of consistency and inconsistency with a causal association to immunization. If despite formulating an eligibility question adequate information is not available, to establish causality, then the event is listed as unclassifiable. With such events it is important to specify the additional information that is required to enable classification of the event.

3. Establishing a causal (eligibility) question when death is an AEFI

The first step in causality assessment is to formulate an eligibility question. In order to do this one needs to clearly identify the exposure (one or more vaccines), a valid diagnosis (or case

definition) and determine if the exposure preceded the event. Given that death is an outcome and not a diagnosis (or case definition) a case will not be eligible, for classification, unless there is sufficient clinical information from which the possible or likely underlying cause of death can be derived. Sometimes, even after a comprehensive and timely autopsy is performed, the "exact cause" of death may not always be evident. However, taking the pre-morbid history, examination, investigations, available post-mortem autopsy and/or verbal autopsy evidence into account a "diagnosis" may be arrived at based upon "sign(s), abnormal laboratory finding(s), symptom(s) or disease(s)".

If insufficient information is available to meet eligibility criteria all attempts should be made to obtain further information. Regardless of fulfilling the eligibility criteria all cases should be stored in a repository so that the report can be accessed should additional information or cases become available. Ineligible or unclassifiable cases may still be useful for identification of potential vaccine safety signals. Whilst it is recognized that in some countries the majority of death cases maybe ineligible or unclassifiable this does not distract from the importance that these cases for further case investigation, epidemiological review (for example, for inclusion in a case vs control study) and for corrective action (see below).

4. Vaccine product-related reaction and death

A vaccine product-related reaction is an AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. The documented causes of death that could possibly occur due to the inherent properties of a vaccine are limited and include: (a) anaphylaxis [6]; (b) viscerotropic disease following yellow fever vaccine [7–10]; (c) disseminated attenuated live vaccine agent infection in severely immune-compromised individuals [11,12]; and (e) death from intussusception following rotaviral vaccine, based on two case reports, from passive surveillance data [13].

(a) Anaphylaxis: studies show that the reported rate of anaphylaxis following vaccination varies widely because of differences in anaphylaxis case definitions, surveillance methodology, vaccine antigens and the demographic characteristics of the vaccinated individuals [14–17]. In general, anaphylaxis is regarded as a rare event with accepted ranges of rates being between 1 event per 100,000 to 1 million vaccine doses [12]. The case fatality rate of vaccine anaphylaxis is unknown but it would be reasonable to hypothesize that this would be similar to drug anaphylaxis (approximately 10%) and thus would be in the region of 1 death per 1–10 million vaccine doses. Frequently any unexpected serious event following

Check ✓ all boxes that apply

Adequate
information
availableA. 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 anxiety-related reaction

B. Indeterminate

- ☐ B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
- ☐ B2. Reviewing 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 conditions caused by exposure to something other than vaccine

Adequate
information
not available☐ UnclassifiableSpecify the additional
information required
for classification :

*B1: This is a potential signal and maybe considered for investigation

Fig. 1. WHO causality assessment scheme.

immunization with or without death is ascribed to vaccine anaphylaxis. This occurs because a standardized case definition has not been applied. Anaphylaxis is an acute onset rapidly progressive allergic disorder with multisystem (dermatologic or mucosal, cardiovascular, respiratory and/or gastrointestinal) involvement and a clearly defined case definition according to Brighton collaboration criteria [16]. For death where anaphylaxis is the presumed cause once the Brighton case definition is met the causality assessment process can be followed. The timing of onset of the first symptom(s) is usually between 15 and 120 min [17]. Since the post mortem findings of anaphylaxis maybe non-specific especially if the mechanism of death is sudden hypotension resulting in cardiac arrhythmia and arrest, attention to the reported pre-morbid symptoms and signs is critical [10]. A careful verbal autopsy can help. However, less than 10% of anaphylactic events present with sudden onset hypotension without respiratory manifestations and/or rash (urticaria or angioedema). In such events, diagnosis may clearly be problematic and pre or post-mortem (within 6 h) elevation of mast cell tryptase is supportive in the correct clinical context [20,21]. Access to this test maybe difficult in some settings and the timing of specimen collection affects the test's validity but this could be addressed by establishing national or regional reference laboratories. Another point for consideration is that the mechanism of anaphylaxis is idiosyncratic (i.e. particular to specific immune or non-immune mechanisms) in an individual vaccine recipient hence clusters of deaths following immunization are highly unlikely to be due to anaphylaxis and other causes of death should be considered.

- (b) Viscerotropic disease is defined as an acute multi-organ system dysfunction that occurs following vaccination and was first described following yellow fever (YF) vaccine [7]. The condition has not been described after other vaccines or as a co-existing condition and is very rare. The estimated rates are 0.3–0.4 per 100,000 YF vaccines although lower rates have been reported in mass campaigns [10]. Since the YF vaccine is live and attenuated and vaccine virus strain can be isolated from post-mortem tissue in affected individuals the likely pathogenesis is disseminated infection with an altered host immune response. The case fatality rate is thought to be as high as 60% and risk factors have

included first dose, age greater than 65 years, thymus disease and a thymectomy. Initial symptoms, occur after 1 week and are non-specific (e.g. fever, malaise) but progression to multi-organ failure (liver, renal and pulmonary) can be rapid [10]. The mean day of onset of symptoms is 4.1 days [22] i.e. not in the first 48 h. Rarely YF may be associated with a neurological disease but this is rarely fatal [10].

- (c) Severely immune-compromised individuals may succumb to disseminated attenuated live vaccine agent disease. This has been documented for the BCG, measles, varicella and polio vaccines [11,12,23–25]. Although severe rotaviral vaccine gastroenteritis has been reported in infants with severe combined immunodeficiency disorder no death have been documented [26]. Fatal disseminated live vaccine agent associated disease occurs in the in the context of both a primary or acquired immunodeficiency disease. The primary immunodeficiency disorders of concern are those that effect lymphocyte function (such as Severe Combined Immunodeficiency Disorder) or antibody production (such as X-linked agammaglobulinaemia). Importantly, vaccination may occur prior to the diagnosis of an immunodeficiency disorder since neonatal screening for primary immune-deficiency disorders is limited even in highly developed countries and maternal screening for HIV is not universally performed. The mechanism of death is due to disseminated disease and hence is not likely to occur acutely (within 48 h) of immunization as time is required for the vaccine viral or bacterial agent to incubate and then disseminate. If an infant or child is identified as being severely immunocompromised and then accidentally immunized with a live vaccine (s) this should be classified as an immunization error because such conditions are a contra-indication to immunization with these live attenuated vaccines.
- (d) Intussusception is a recognized vaccine reaction that occurs following both licensed rotaviral vaccine products. The risk is highest after the 1st dose and within 7 days of vaccination [27]. Untreated intussusception may be fatal. Two deaths from intussusception and following the rotaviral vaccine have been reported to VAERS, however, given the passive nature of reporting the causal association to vaccination has not been established [13].

5. Vaccine quality defect-related reaction and death

A vaccine quality defect-related reaction is 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 [5]. Death due to a vaccine quality defect has been only infrequently found through the course of history, primarily due to incomplete inactivation of a live vaccine. For example, in 1929 in the city of Lubeck, Germany, 72/252 infants vaccinated with BCG died because of contamination of the vaccine with a live human tuberculosis strain [28]. In 1955, in the Cutter Incident in the United States incomplete activation of the oral polio vaccine resulted in 56 cases of paralytic polio and 5 deaths [29].

Fortunately, the quality control for the manufacture of vaccines is now highly regulated within a framework of good manufacturing practice (GMP) and appropriate batch to batch testing and lot release ensures that mechanisms are in place to prevent vaccines with major quality defects from being used [30]. Although no known deaths due to manufacturing quality defects have been reported in the past 5 decades there are two recent examples where quality defects have affected the seasonal trivalent influenza vaccine resulting in the oculo-respiratory syndrome and febrile seizures [31,32]. Both episodes occurred in high income countries with post-marketing surveillance systems in place able to detect these AEFI and emphasizing the importance of a functional surveillance system. Global pharmacovigilance programmes need strengthening particularly in low and middle income countries. It is important to note that WHO has taken a greater role in ensuring GMP of vaccines through strengthening of National Regulatory Authorities and the prequalification process.

6. Immunization error-related reaction and death

An immunization error-related reaction is an AEFI that is caused by inappropriate vaccine handling, prescribing or administration. Fortunately, severe immunization errors resulting in death have rarely been reported. One of the common immunization error-related reactions and death occurs due to improper vaccine handling which results in bacterial contamination (usually with *Staphylococcus aureus*) of a vaccine vial and can lead to toxic shock syndrome (TSS) and death [33]. TSS is toxin mediated and presents with the sudden onset of fever, vomiting, diarrhoea, skin and mucosal changes and progression to multi-organ failure. To prevent TSS, the cold chain and multi-dose protocols must be strictly adhered to ensure vial sterility. Monitoring of the cold chain is a key element in ensuring vaccine safety. Because the toxin is preformed in the contaminated vial, symptoms and signs occur rapidly after injection and may proceed to death in less than 24–48 h. Aggressive treatment can change the outcome.

Immunization error related death may also occur as a result of drugs, such as an anaesthetic agent, muscle relaxant or insulin being given inadvertently instead of a vaccine or diluent [34]. The cause is often system error as a result of poor training of staff administering immunization, co-storage of drugs with vaccines and/or diluents, failure to follow standard protocols, inadequate local supervision and monitoring leading to a failure to differentiate a vaccine or diluent from a medication vial. To avoid such episodes, a number of preventative strategies can be implemented including separating vaccine from medication or drug refrigeration.

When immunization errors occur they frequently result in a cluster of deaths localized to a single immunization site or single vaccine storage/distribution site. Rapid notification and analysis of these AEFI's is required to prevent further events.

7. Immunization anxiety-related reaction – not a direct cause of death

Immunization anxiety-related reaction is an AEFI arising from anxiety about the immunization. Injury secondary to syncope has been documented, most commonly after the HPV vaccine in adolescent girls and there is a single death reported to VAERS attributed to trauma secondary to a vaso-vagal syncopal episode following immunization [35]. Steps should be taken to decrease both the risk of syncope and injury from syncope following immunization. For example, Canadian Guidelines on pain mitigation at the time of immunization note that for those over age 7 years increasing muscle tension e.g. squeezing a rubber ball at the time of injection can decrease vaso-vagal syncope [36].

8. Coincidental event

A coincidental event is an AEFI that is caused by something other than the vaccine product, immunization error or secondary to immunization anxiety. Coincidental deaths following immunization occur in all countries. The number of such potential deaths occurring on each day of immunization can be estimated (Table 1). A clear documentation of presenting symptoms and signs combined with details about any medical interventions and investigations (including a formal autopsy or verbal autopsy) enables a vaccine reaction to be differentiated from a co-incidental cause. A detailed AEFI investigation involving the community of patient (near his residence/place of vaccination), verification of travel prior to vaccination and reviewing the morbidity and mortality patterns in local hospital admissions (e.g. malaria, meningitis, encephalitis, dengue, etc.) at the time of occurrence of the death(s) can provide further clues for probable coincidental events. Unfortunately in many low and middle income countries (LMIC) formal autopsy is unavailable or specific technical expertise maybe lacking to make it useful. In such situations a verbal autopsy with specimen collection may be possible and should be undertaken [37].

Sudden infant death syndrome: The most troublesome of the coincidental causes to differentiate from a vaccine reaction is sudden infant death syndrome (SIDS). The use of the term “sudden infant death syndrome” or “SIDS” should be restricted to deaths in the first and second year of life, which remain unexplained after autopsy and meet the Brighton case definition [38]. SIDS occurs in all countries including LMIC although the rates may vary according to population, location and ethnicity. For example, the rate of SIDS in the Hong Kong population is estimated to be 0.05/1000 live births compared with a rate of 6.7/1000 live births in the American Indian population [38]. The diagnosis is established by comprehensive autopsy and fulfilment of a case definition [39]. The level of detail required to fulfil a case definition may not always be available, especially in LMIC with scant resources. The use of the standard verbal autopsy method may be especially helpful in communities where resources for testing and for formal autopsy are non-existent or precluded by religious tenets.

SIDS maybe associated with specific pathological medullary changes as well as genetic and environmental determinants [40]. Importantly, a number of studies in different settings have found no association between immunization and SIDS [41–45]. In LMIC it is likely that underlying and undiagnosed congenital disease, particularly congenital heart disease or immunodeficiency disease (primary or secondary), maybe unrecognized prior to immunization and may be the cause of sudden and coincidental death. Without access to an autopsy these underlying conditions may not be readily diagnosed in some instances. Careful history from birth and a careful verbal autopsy may help.

9. Indeterminate

There are two different classifications in-order to ascribe an indeterminate causal association to immunization. The first is when there is a temporal relationship consistent (with immunization) but there is insufficient definitive evidence for a consistent event or secondly, when qualifying factors result in conflicting trends of consistency and inconsistency with a causal association to immunization. Information from indeterminate cases should be kept in a repository for identification because these may be a new vaccine-linked event. It should be decided if reports of deaths following immunization indicate a potential safety signal for identification and investigation.

10. Vaccine safety response to death as an AEFI

Understandably, death following immunization will always result in public and health provider concern and could precipitate a crisis. An effective response requires that countries establish standard investigation and communication procedures prior to the occurrence of deaths following immunization. The WHO have developed global manual for the surveillance of AEFI and these should be implemented in all countries as an effective response to a death following immunization requires a functional system [46]. Importantly, comprehensive AEFI investigation needs to be conducted using established resources such as the AEFI Investigation form [47] and WHO verbal autopsy guidelines [37].

Communication with all stakeholders should occur early and frequently and will often need to occur when the investigation is still ongoing and findings are unknown. The principles of communication are to provide clear messages that promote and sustain public confidence in the investigation process and subsequent outcome. Timely and appropriate communication on the cause of death to the relevant stakeholders is critical to maintain confidence of the end users (recipients and immunization staff), the public, health staff/programme managers and other stakeholders and could prevent the repercussions that could occur due to a poorly managed vaccine safety crisis. If at all possible clear information on the cause of death, even when coincidental, is more helpful than simply saying the death was not vaccine or the immunization programme related. In publically disclosing the cause of death, the patient's right to privacy must also be respected but working with the family may make public disclosure of the cause possible. If the cause is vaccine or immunization programme related, the communication must also state how this is being corrected.

11. Conclusions

As vaccine safety surveillance systems in LMIC are being strengthened it can be expected that more deaths will be reported as an AEFI as has happened in the WHO South East Asia Region [4]. With few very rare exceptions (anaphylaxis, viscerotropic disease, disseminated vaccine disease in the immunocompromised or quality or administration related defects such as toxic shock syndrome) vaccines do not cause death. Thus, a reported death following immunization is more likely to be due to a co-incidental cause. The challenge is in differentiating a co-incidental cause (likely) from a vaccine reaction (highly unlikely) whilst maintaining public confidence in the immunization programme. This requires a functional vaccine safety surveillance system, a meticulous and thorough AEFI investigation, a dedicated team with expertise on vaccine safety and a clear and articulated communication strategy.

Conflict of interest statement

No conflicts of interests are declared by any of the authors.

Uncited references

[18,19].

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