Vaccine 34 (2016) 212–217

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

ARTICLE INFO

Article history:
Received 12 August 2015
Received in revised form 4 November 2015
Accepted 6 November 2015
Available online 19 November 2015

Keywords:
Adverse event following immunization
Death
Vaccine
Immunization

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, viscerotrophic 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.

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).

http://dx.doi.org/10.1016/j.vaccine.2015.11.018
0264-410X/

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) viscerotrophic 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