Study protocol – Evaluation of adverse event reports concerning vaccination errors with fatal outcome.

Version 3.2

**Working title** Causality assessment of fatal cases after medication errors with vaccines reported to EudraVigilance

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## 1. Introduction

All medication errors resulting with adverse events need to be reported to the European Adverse Event database, EudraVigilance. In July 2012 the new pharmacovigilance legislation came into effect. As part of the new legislation the definition of an adverse drug reaction (ADR) had been revised as follows; An ADR is a response to a medicinal product which is noxious and unintended (1) (Directive 2001/83/EC, Article 1(11). Consequently not only adverse reactions arising from use of a medicinal product within the terms of marketing authorisation should be reported but also adverse reactions outside the terms of marketing authorisation should be reported (i.e. overdose, off-label use, misuse, abuse and medication errors) (1)(2).

A recent review of spontaneous adverse event reports submitted to Eudravigilance found that in those case reports reporting medication errors, vaccines were most frequently involved (3). Examples of vaccination errors are erroneously administration of different vaccine, administration at the incorrect time interval, and/or using the incorrect dosage. As a result, the patient may be insufficiently protected against the disease for which the vaccine was intended. Similarly, administration of expired vaccines or inappropriately stored vaccines may affect the effectiveness of vaccines (4). Further review of cases reporting vaccination errors showed that 60% of cases were classified as serious, of which 187 cases reported death as outcome (manuscript submitted). Adverse events following immunization (AEFI) due to errors are caused by human factors as opposed to AEFI due to inherent properties or quality defects of the vaccine. It is therefore worth to investigate the factors leading to vaccination errors of the reported fatal outcomes, in order to identify areas for risk mitigation.

Fatal outcome after vaccination has been described in the context of appropriate use (i.e within the terms of marketing authorization). Several studies have investigated death after vaccination administration, especially in the pediatric population (7–11) and for various vaccines case reports have been published of fatalities after immunization. Several studies have ruled out an association with vaccine administration and death, both SIDS and unspecified death (8–11). A recent publication raised concerns with regards to data published in PSURs regarding spontaneously reported deaths in children after receiving hexavalent vaccines (12). The authors argued that there was a temporal association between death after immunization as numbers of death close to the immunization date were higher than several weeks later. However, the authors did not adjust for reporting bias close to the date of immunization, which causes higher rates of reporting.

In 2010 Nakada published data from the Japanese safety system, where a significant number of fatalities were reported after H1N1 influenza vaccine administration (13). The authors noted that the majority of cases occurred within 4 days after administration of the vaccine and concluded that this suggested a strong association between vaccination and death. This publication was criticized by McNeil et al in 2010 as the data was subject to limitations that come with passive surveillance systems (14).
Several publications have described fatalities after immunization using passive surveillance data (15–22). However, in most of these publications other underlying conditions were present that could explain death or limited information was available for causality assessment (15,18–23).
In 2001 Silvers et al published a review on all fatalities reported to VAERS between 1990 and 1997 (24). The authors stated that in approximately half of the cases SIDS was found as causative factor for death. However, there was no clear evaluation on the causality of the other cases. SIDS was also a frequently reported cause for death in children after vaccination with hepatitis B vaccines (17).
Several studies have described immunization errors using passive surveillance data, but none of these publications described immunization errors as a possible causal factor for death (15,18,19,23).
The above discussed publications discuss both immunization errors and death, however the fatalities were not linked to errors. However, in one publication 39 fatalities after hepatitis B immunization were reported with a cause for death coded under the ICD-10 code *injury, poisoning and certain other consequences of external causes*, but it was not clear whether these causes related to errors (17). A publication by Hibbs et al thoroughly discusses immunization errors, but no details were provided on the number or causes of fatal cases (25). An additional publication described use of vaccines stored outside of the recommended temperature (4). According to the authors fatal cases reported within this study were all found to have other causative factors than the vaccine.
Besides data from passive surveillance systems, case reports have been published that describe positive associations between immunization errors and death (26–29).

## 2. Objectives

The aim of this study is to systematically review reported Individual Case Safety Reports with a fatal outcome describing vaccination errors as captured by EudraVigilance using the WHO tool for "Causality assessment of an Adverse Event Following Immunization".

## 3. Methods

### *3.1. Design*

This study will be a case-series analysis of Individual Case Reports (ICSRs)

### *3.2. Data source*

Data will be obtained from individual ICSRs submitted to Eudravigilance by the national drug regulatory agencies and pharmaceutical companies. Eudravigilance is the European system for managing and analysing information from worldwide reporting sources on suspected adverse reaction to medicines which have been authorised or are being studied in clinical trials in the European Economic Area (EEA). Data are obtained from case reports submitted by the national drug regulatory agencies and pharmaceutical companies in accordance with EU legislation. Reporting requirements for the National Competent Authorities and pharmaceutical companies are strictly regulated. Criteria for a valid case report and definitions of the data elements are specified in the International Conference on Harmonization (ICH) guidelines (31). All adverse drug reactions and clinical terms (e.g. diagnostics) reported in the ICSRs are coded by the Medical Dictionary for Regulatory Activities (MedDRA®)

terminology. MedDRA® is the international medicinal terminology developed under the auspices of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

### *3.3. Data extraction*

To facilitate retrieval of MedDRA-coded data, Standardized MedDRA Queries (SMQs) have been developed by the Council for International Organizations of Medical Sciences (CIOMS) working group for SMQs. All ICSRs submitted to EudraVigilance within the study period (1 January 2001 through 31 December 2016) reporting vaccines as a suspect medication and a medication error and death as outcome will be extracted using the narrow Standard MedDRA query (SMQN) from MedDRA version 20.0. Submission date is determined by the ICSR receive date which corresponds with the date when a national competent authority (NCA) or marketing application holder (MAH) received the initial report from the reporter i.e. in case there are multiple versions of the same report, only the latest version will be included. The SMQN is a collection of MedDRA preferred terms (PTs) to identify medication errors cases e.g. 'administration error' or 'product administered to wrong patient'. All PT's listed in the SMQN will be provided in the supplementary table. Reported exposure to active substances of vaccines will be determined by using search terms such as human papilloma, herpes, influenza, et cetera and Anatomical Therapeutic Classification (ATC) code. Only drugs corresponding with ATC code J07 vaccines will be included. ICSR with a fatal outcome will be selected for analysis. No restriction with regards to age, gender or country of origins will be applied.

### *3.4. Data classification*

Data to be collected from the reports (if available):
Patient's age and gender, reporter profession, vaccine involved in error, type of error committed with vaccine (MedDRA PT), Stage of treatment process in which error occurred, adverse events reported, time between vaccine administration and adverse event, time between vaccine administration and death, cause of death (if available).

### *3.5. WHO tool for causality assessment of an AEFI*

Several tools and algorithms are available for causality assessment of adverse events following medication use. However, application to AEFI cases raises problems. Some factors taken into account for most drugs cannot be applied to vaccine use, such as de-challenge/re-challenge, increasing dose levels, or long-term use. Therefore, there was a need for a causality assessment tool specified for vaccines.

In 1994 a tool was developed by the Canadian Advisory Committee on Causality Assessment (ACCA) based on the general WHO causality assessment tool to aid in the causality assessment of AEFI (32). Adaptions to the WHO criteria were proposed to make the tool more applicable for vaccines and for passive surveillance reports (33,34). In 2012 de CISA developed a new algorithm for AEFI causality assessment (35), however, this method is most useful only if complete data is available which is usually not the case for passive surveillance systems. In 2013, a collaboration between the ACCA, EU/VAESCO, CIOMS and CISA, commissioned by the GACVS developed a simple and flexible tool which was derived from the previous WHO classification and the CISA project algorithm (36,37). This method was applied by Singh et al in 2017 on spontaneous reported AEFI. In January 2018 a second edition of the manual was released by the WHO (38). The current tool is the most up to date and specific vaccine specific causality assessment tool available that is suitable for passive surveillance data.

There are no specific tools to assess the causality of adverse events after medication errors. However, in general the same algorithms can be applied as for adverse events after normal administration. WHO defines the causes of AEFI in 5 categories: Vaccine product-related reaction, Vaccine quality defect-related reaction, immunization error-related reaction, immunization anxiety-related reaction, or coincidental event (38). It is important however, to realize that even though an immunization error has occurred, it does not necessary mean that the reported adverse events are caused by the error. It is therefore important to consider three important questions for vaccine safety: *can* the vaccine cause this adverse event? *Did* the vaccine cause this adverse event? *Will* the vaccine cause this adverse event? (38) Further an estimation needs to be made on the likelihood that the adverse event occurred only due to the immunization error, and that it would not have occurred if treatment had been according to protocol.

### 3.6. Data-analysis

All identified cases will be reviewed by two independent reviewers. Cases where differences exist in the assignment of causality categories will be discussed to reach consensus. A kappa coefficient will be calculated to determine the inter-rater agreement.

#### *3.6.1. Eligibility of cases*

As death is an outcome and not an adverse event, it is required to identify the underlying cause of death from the report. The underlying cause can be specified or derived from information in the ICSR. A diagnosis or case definition may be obtained using laboratory values, diagnoses, or symptoms as described in the ICSR. Cases without sufficient information for causality assessment will be reported separately.

#### *3.6.2. Analysis of cases with sufficient information for causality assessment*

Eligible cases will be reviewed using the WHO tool for "Causality assessment of an Adverse Event Following Immunization" (38). This tool classifies causality of AEFIs in three main categories and 7 sub-categories (see appendix). The three main categories are defined as consistent causality, indeterminate, or inconsistent causality. Consistent causal cases are assigned one or more of the sub-categories Vaccine product related reaction, vaccine quality defect-related reaction, immunization error-related reaction, or immunization anxiety related reaction. Indeterminate cases are assigned to one of the following categories: 1) temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event, 2) reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization. Inconsistent cases are coincidental cases where the underlying or emerging condition(s), or conditions caused by exposure or something other than the vaccine.

*Medical literature:*

For some vaccines fatal cases have been identified and assessed as causally related. Examples are anaphylaxis following vaccination, immunocompromised persons receiving live vaccines and intussusception after rotavirus vaccine. A publication by Miller et al, provides an overview of death following vaccinations and may provide useful background information supporting the case analysis (5).

#### *3.6.3. Estimation of error contribution*

After categorization an subjective estimation will be made by both reviewers of the impact of the error on the chance of the outcome occurring. This estimation will be applied for all elligble cases. The main question to ask is: would death have occurred if the error had not occurred? Cases will be categorized as 'yes', 'no' or 'uncertain'. Cases where differences exist in the assignment of causality categories will be discussed to reach consensus. A kappa coefficient will be calculated to determine the inter-rater agreement.

### *3.6.4. Description of cases*

Descriptive analysis will be presented. The review will be concluded with description of cases for which death is potentially related to the vaccine.

### 3.6.5 Data management and quality control

Data management and quality control for EudraVigilance is done by the European Medicines Agency. Case review and analysis and independent review of the cases and results are taking place in the secured working environment of the Dutch Medicines Evaluation Board.

## 4. Limitations

Although a few studies have been published using the same causality assessment tool, the tool has not been tested for reliability, reproducibility and consistency (37). However, the tool is based on previous algorithms developed both for general medicines and vaccines (37). Another limitation of the tool is that the final assessment is based on the judgement of the case reviewer, which may lead to inter-reviewer differences. A limitation of this study is that these cases are collected via passive surveillance systems. Therefore, information for full causality analysis may lack.

## 5. Advantages

This tool has been specifically designed for vaccines as opposed to the majority of adverse event causality assessment algorithms available. The tool utilizes standard CIOMS/WHO definitions and vaccine terminology. Advantages of this approach, instead of a scoring system is the fact that it allows the reviewer to assess all information of the cases, rather than separate segments.

## 6. Reporting of study results

This study is aimed to result in submission for publication to a scientific peer-reviewed journal by the end of 2018. The data in this study is confidential as per GDPR, therefore, sensitive data cannot be shared. As per the rules of EudraVigilance, data from ICSRs cannot be shared to third-parties on request.

**Funding**

No external funding was received for this study.

## 7. Amendments to protocol

| Section | Changes | Date of change |
|---|---|---|
| | | |
| | | |
| | | |

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## Appendix: Causality assessment form

### Step 1 (Eligibility)

| Name one of the vaccines administered before this event | What is the Valid Diagnosis? | Does the diagnosis meet a case definition? |
|---|---|---|
| | | |

Create your question on causality here

Has the _____ vaccine / vaccination caused _____(The event for review in step 2 - valid diagnosis)

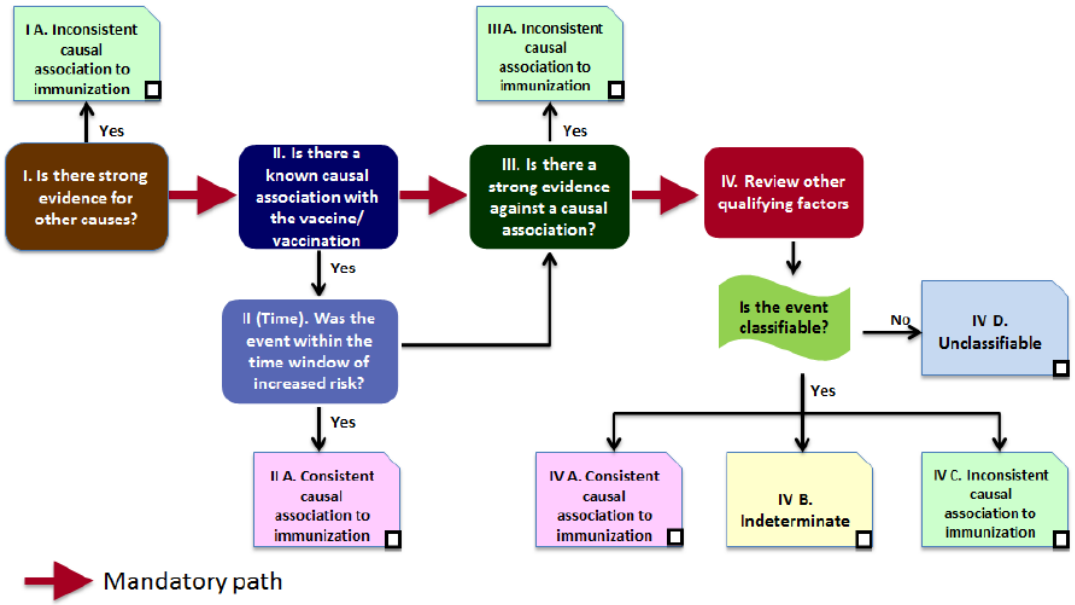
Is this case eligible for causality assessment? Yes/ No; If, "Yes", proceed to step 2

### Step 2 (Event Checklist) ✓ (check) all boxes that apply

| I. Is there strong evidence for other causes? | Y N UK NA | Remarks |
|---|---|---|
| 1. In this patient, does the medical history, clinical examination and/ or investigations, **confirm** another cause for the event? | ☐☐☐☐ | |
| **II. Is there a known causal association with the vaccine or vaccination?** | | |
| *Vaccine product* | | |
| 1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly? | ☐☐☐☐ | |
| 2. Is there a biological plausibility that this vaccine could cause such an event? | ☐☐☐☐ | |
| 3. In this patient, did a specific test demonstrate the causal role of the vaccine ? | ☐☐☐☐ | |
| *Vaccine quality* | | |
| 4. Could the vaccine given to this patient have a quality defect or is substandard or falsified? | ☐☐☐☐ | |
| *Immunization error* | | |
| 5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)? | ☐☐☐☐ | |
| 6. In this patient, was the vaccine (or diluent) administered in an unsterile manner? | ☐☐☐☐ | |
| 7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered? | ☐☐☐☐ | |
| 8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)? | ☐☐☐☐ | |
| 9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)? | ☐☐☐☐ | |
| 10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)? | ☐☐☐☐ | |
| *Immunization anxiety (Immunization Triggered Stress Response - ITSR)* | | |
| 11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)? | ☐☐☐☐ | |
| **II (time). If "yes" to any question in II, was the event within the time window of increased risk?** | | |
| 12. In this patient, did the event occur within a plausible time window after vaccine administration? | ☐☐☐☐ | |
| **III. Is there strong evidence against a causal association?** | | |
| 1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event? | ☐☐☐☐ | |
| **IV. Other qualifying factors for classification** | | |
| 1. In this patient, did such an event occur in the past after administration of a similar vaccine? | ☐☐☐☐ | |
| 2. In this patient did such an event occur in the past independent of vaccination? | ☐☐☐☐ | |
| 3. Could the current event have occurred in this patient without vaccination (background rate)? | ☐☐☐☐ | |
| 4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event? | ☐☐☐☐ | |
| 5. Was this patient taking any medication prior to the vaccination? | ☐☐☐☐ | |
| 6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)? | ☐☐☐☐ | |

**Y: Yes N: No UK: Unknown NA: Not applicable or Not** available

## Step 3 (Algorithm) review all steps and ✓ all the appropriate boxes




**Notes for Step 3:**

## Step 4 (Classification) ✓ all boxes that apply

**Adequate information available**

**A. Consistent with 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 (ITSR**)

**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 with 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**

- ☐ **Unclassifiable**

Specify the additional information required for classification :

*B1: This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

**Summarize the classification logic in the order of priority:**

With available evidence, we could conclude that the classification is _____ because:

With available evidence, we could **NOT** classify the case because:_____