

GUIDE TO THE WHO INFORMATION SHEETS ON OBSERVED RATES OF VACCINE REACTIONS



World Health
Organization

Background

An important part of post-licensure vaccine safety surveillance is to collect and analyse reports of AEFI. An AEFI is defined as any untoward medical occurrence which follows immunization but 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. AEFIs are classified as follows:

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.

Example: Extensive limb swelling following DTP vaccination.

Vaccine quality defect-related reaction

AEFI 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.

Example: Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

Immunization error-related reaction

AEFI is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.

Example: Transmission of infection by contaminated vial.

Immunization anxiety-related reaction

AEFI arises from anxiety about the immunization.

Example: Vaso-vagal syncope in adolescent following vaccination.

Coincidental event

AEFI is caused by something other than the vaccine product, immunization error or immunization anxiety.

Example: A fever occurs at the time of the vaccination (temporal association) but is caused by malaria.

Coincidental events reflect the natural occurrence of health problems in the community with common problems being frequently reported, whereas particularly severe problems cause concern. In most cases unless a specific diagnosis is made, it is usually not possible to definitively determine that the occurrence is not due to the vaccine or the immunization process.

What each information sheet contains

Each information sheet provides details on a single antigen vaccine or combination product. It comprises a short summary of the vaccine products in common use, and the rates of mild and severe adverse events (local and systemic) following immunisation. Where possible the information presented includes an attributable rate, but more often it includes background incidence of the event.

How to use the information sheets

The following steps should be followed when using the information contained in these sheets:

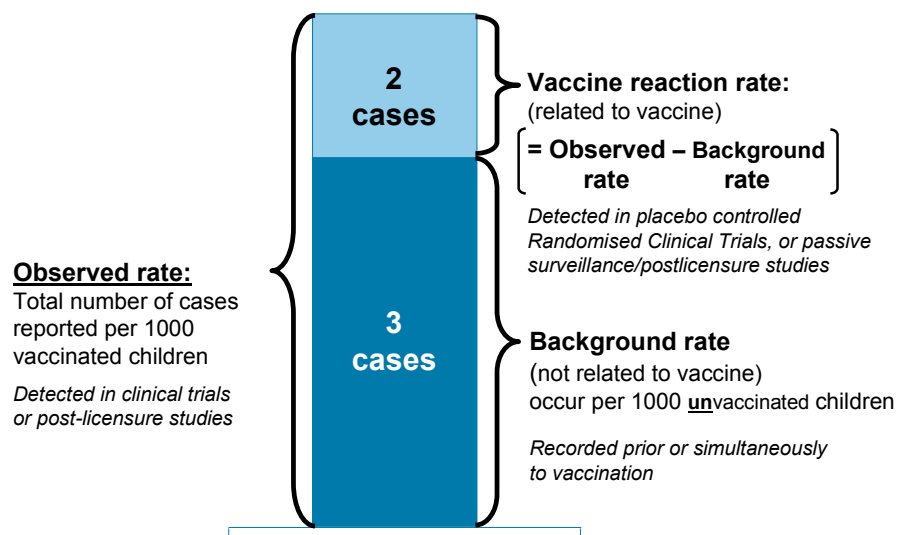
1. Determine the observed rate of an AEFI as ascertained by your surveillance system – define the vaccine, the event, the ages of the vaccinees.
2. If the background rate of that adverse event is known in the same community, then this can be deducted from the observed rate to give an attributable rate.
3. Compare this rate with the “expected adverse event rate” which is contained in the information sheet.
4. If the background rates are **not** known compare the AEFI rate (in your system) with the “expected rate” for that particular event which is contained in this document.
5. Consider what “confounding” factors may influence the determination of these comparator rates (see section *Factors to consider*).
6. Make an assessment as to whether the rate following immunization is greater than expected and if so, whether further investigation or epidemiological studies are required.
7. If the background rate for that particular adverse event is not known in the same community (this is often the case) then one will need to compare the observed rate with the “expected rate” – if this is elevated then this may be due to an increase in the background rate and/or an increase in the vaccine reaction rate. Further studies maybe required to differentiate these two factors.

Analysis of multiple AEFI reports -

Determination of AEFI rate & vaccine attributable rate

When AEFI data is analysed it is important to understand what rates are being determined. The graphic below displays the different rates using a hypothetical example of observed rate, background and vaccine reaction rate (see also table on p.3).

Example: Fever following vaccination



Analysing multiple AEFI reports helps determine if the observed reaction rate to a specific vaccine is higher than the expected vaccine reaction rate which is often determined from published studies or trials¹. If a vaccinated group and a placebo group have identical background rates of an event any differences between groups can be attributed to the vaccine. **CAVEAT:** Background, observed and vaccine reaction rates of events can vary considerably for specific AEFI's due to the way the data is collected and analysed but also in relationship with the epidemiology of diseases in each community. When comparing one rate with another it is therefore important to take into account the factors described in the next section.

¹ Randomised placebo controlled trials serve best to determine vaccine reaction rates. In reality, most clinical trials that are performed pre-licensure are often not placebo controlled or do not have the statistical power to determine the vaccine reaction rate of uncommon or rare reactions. Therefore, vaccine reaction rates are usually determined from post-licensure studies.

Factors to consider

when comparing one observed AEFI rate with another

Vaccines

Although two vaccines may have the same antigens they may differ substantially in their composition, including the presence of an adjuvant or other excipients. Each of these factors may modify the reactogenicity of individual products. This will affect the vaccine attributable rate.

Ages

The same vaccine given at different ages may result in different vaccine attributable rates. For example, MMR vaccine given to infants may result in febrile convulsions but this may not occur in adolescents who are given the same vaccine.

Vaccine doses

The same vaccine given as a “primary dose” may have a different reactogenicity profile to that given as a “booster dose”. For example, the DAP vaccine given as primary doses is less likely to result in extensive limb swelling when compared with this same vaccine given as a booster dose.

Case definitions

How an adverse event is defined – the case definitions - may differ between studies and this will change the AEFI rate (e.g. fever defined as >38°C or >39°C).

Surveillance methods

The way that the surveillance data is collected may alter the rate – surveillance data may be collected using pre or post-licensure clinical trials and may involve active or passive surveillance.

Background conditions

The background rate of certain events may differ between communities and across age groups. Thus, these may influence the observed rate even though the vaccine attributable rate is the same in both communities. Reports of death post-vaccination may be higher in a country with a high mortality.



World Health
Organization

Geneva, 12 April 2012

Immunization, Vaccines and Biologicals
Department
Global Vaccine Safety
vaccsafety@who.int

Terminology and definitions

Terminology	Definition	How is this measured	Example (see also graphic)
Background rate	Rate of an event (occurring/reported/measured) due to all cases fitting the case definition, which are expected to occur in the community in the absence of the putative vaccine.	Background rates can be determined in a population prior to the introduction of a new vaccine or simultaneously in non-vaccinated people.	If we measured the temperatures of a population of 1,000 unvaccinated children during one week, some children would present a fever (defined as >38°C) during the time of observation (e.g., infections). For example, a rate of 2 cases of fever per 1000 children per week.
Observed (reported) rate	This is the background rate PLUS the additional effect of the vaccine.	The observed rate can be measured in pre-licensure clinical trials or post-licensure studies	If we observe the same population of 1000 children but we now vaccinate all children and measure their temperatures daily there will be greater rate of fever. Thus, the rate of fever may increase to 5/1000 children per week, with the increase concentrated in the 72 hours that follow vaccination.
Vaccine reaction rate (attributable rate).	This is the rate of an event that is caused by the vaccine – that is a vaccine reaction.	Randomised clinical trials which are placebo controlled. Post-licensure studies - passive surveillance.	Thus, the vaccine attributable rate of fever will be 3/1000 vaccinated children (that is the observed rate minus the background rate)