

CIOMS/WHO Working Group on Vaccine Pharmacovigilance

Vaccination Failure

Position Paper

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I. Background

The development of sustainable immunization programs delivering safe and effective vaccines to human populations has been proven to be highly successful. However, vaccines are neither 100% efficacious nor 100% effective (where efficacy is determined in clinical trials, usually pre-licensure, and effectiveness is determined in practical use, i.e. post-licensure).

Various case definitions for vaccination failure are being used in different settings, e.g. for reporting to regulatory authorities or in epidemiological studies. Vaccination failure can be defined by a variety of endpoint criteria (e.g., disease prevention, disease mitigation or immune response). Different terms are also used inconsistently to designate vaccination failure, e.g. lack of vaccine efficacy or lack of adequate protection. Universally accepted concepts and definitions of vaccination failure are therefore required to assess and compare the benefit of vaccines used in populations.

A major issue regarding any definition of vaccination failure is the question of the clinical endpoint against what a specific vaccine should protect, i.e. infection versus disease versus serious (complicated) disease.

These issues could potentially be solved by proposing general definitions for types of vaccination failure complemented by specific definitions for a given vaccine.

Vaccination failure may be defined based on clinical endpoints or immunological criteria, where surrogate markers for protection exist.

Primary failure (for example lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity).

Reasons for vaccination failure are manifold and include but are not restricted to

1) Vaccinee (host) related

1.1 *immunodeficiency* (leading to suboptimal or even absent immune response after immunization)

1.2 *age related maturation and senescence of immune responsiveness*

1.3 *insufficient or suboptimal immune response* (other than a defined immunodeficiency) to one or more antigenic vaccine components or vaccine strains or serotypes; this may or may not be measurable by standard laboratory tests such as serum antibody tests

1.4 *interference due to other infectious agents* (e.g. wild type enterovirus infection causing interference with the immune response to OPV)

1.5 *waning immunity*

1.6 *suboptimal health status* (e.g. underlying disease, nutrition)

1.7 *immunological interference* (e.g. maternal antibodies, administration of immunoglobulins)

1.8 *preexisting infection* (e.g. with specific HPV genotypes) or *immunization during incubation period* (post exposure)

1.9 *immunosuppressive therapy*

2) Vaccine related

2.1 *vaccine is not 100% efficacious*

2.2 *incomplete coverage* of strains/serotypes/genotypes/antigenic variants/escape mutants that can cause a vaccine preventable disease

2.3 *antigenic interference* or *vaccine-vaccine interactions*

2.4 *manufacturing related* (e.g. lot variations)

3) Compliance and administration related issues

3.1. *administration error* (wrong or suboptimal route, inadequate dose)

3.2 *immunization series incomplete, non-compliance with recommended schedule, including lack of recommended booster immunization(s)* (“failure to vaccinate” rather than “vaccination failure”)

3.3 *storage related (cold chain)*

3.4 *vaccine beyond expiry date* when used

4) Immunization program-related issues

suboptimal recommendations regarding number and time points of immunizations and/or booster doses

Note: One or more of these reasons may lead to individual vaccination failure. They are *not* part of a case definition and may or may not be discovered in the process of analyzing individual suspected vaccination failure.

II. Definitions of vaccination failure

As stated above, each specific vaccine has a specific prophylactic goal or intent. As such, there needs to be a specific definition for vaccination failure which is applicable to that specific vaccine. However, general definitions for vaccination failure can be proposed. *Confirmed* vaccination failure needs to be distinguished from *suspected* vaccination failure.

The following are proposed general definitions:

a) Confirmed Vaccination Failure

The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.

This definition requires clinical and laboratory confirmation (or epidemiological link to a confirmed case) that the actual disease is vaccine preventable, i.e. that the pathogen (including, where appropriate, type, subtype, variant, etc.) and clinical manifestations are specifically targeted by the vaccine.

b) Suspected Vaccination Failure

Suspected vaccination failure is defined as the occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine preventable disease, e.g. invasive pneumococcal disease of unknown serotype in a fully vaccinated person.

c) Immunological Failure

Immunological failure is defined as failure of the vaccinee to develop the accepted marker of protective immune response. This definition requires that there is an accepted correlate or marker for protection, and that the vaccinee has been tested/examined at an appropriate time interval after completion of immunization.

III. Need for vaccine specific definitions of vaccination failure

Circumstances for incomplete protection of an individual after immunization are vaccine specific and therefore vaccine specific definitions are needed. The following items need to be considered in the process of developing such definitions:

- what is the vaccine supposed to prevent (infection? any disease? severe disease?)
- which other known causes may lead to the same or similar clinical endpoints as those caused by vaccine preventable pathogens and how can they be distinguished?
- when is full protection expected during the time course of immunization?
- Are there accepted correlates of protection which can be used to define immunological failure?

A specific vaccine may fail to prevent various degrees of individual disease and therefore clinical relevance of vaccination failure may vary. This could be addressed by the development of definitions for different levels of vaccination failure for specific types of vaccine depending on the immunization goal.

IV Conclusions

The reasons mentioned above require the development of vaccine specific definitions for vaccination failure, where many individual factors need to be taken into account. This position paper shall serve as a guideline for the development of such definitions.

Case definitions for vaccination failures of specific types of vaccine should be prioritized based on public demand and urgency.