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Review

The concept of vaccination failure

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ABSTRACT

Despite remarkable success of immunization programmes on a global perspective, vaccines are neither 100% efficacious nor 100% effective. Therefore, vaccination failure, i.e. occurrence of a specific disease in an individual despite previous vaccination, may occur. Vaccination failure may be due to actual vaccine failure or failure to vaccinate appropriately.

Universally accepted concepts and definitions of vaccination failure are required to assess and compare the benefit of vaccines used in populations. Here we propose general definitions for types of vaccination failure. In the future, these should be complemented by specific definitions for specific vaccines as needed depending on public health considerations.

Contents

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1. Introduction

The development of sustainable immunization programmes delivering safe and effective vaccines to human populations has been proven to be highly successful [1–4]. 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) [5–7].

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) [8–11]. Different terms are also used inconsistently to designate vaccination failure, e.g. lack of vaccine efficacy or lack of adequate protection [12,13]. Universally accepted concepts and definitions of vaccination failure are therefore required to assess and compare the benefit of vaccines.

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. Here we provide general vaccinee- and vaccine-related causes as well as vaccine usage and vaccine programme related causes that can lead to vaccination failure. They should be considered by stakeholders who aim for the development of vaccine specific definitions of vaccination failure, for which a general concept of stratification by clinical versus immunological and suspected versus confirmed vaccine failure will be provided.

2. Vaccination failure: vaccine failure or failure to vaccinate

Vaccination failure may be defined based on clinical endpoints or immunological criteria where correlates or surrogate markers for disease protection exist [14,15].

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

Vaccination failure can be due to (1) vaccine failure or (2) failure to vaccinate, i.e. that an indicated vaccine was not administered appropriately for any reason (Fig. 1).

Causes for vaccination failure are manifold and include but are not restricted to the following:

2.1. Vaccine failure

Vaccinee-related (host-related)

2.1.1 *Immunodeficiency* (leading to suboptimal or even absent immune response after vaccination)

2.1.2 *Insufficient or suboptimal immune response* (other than a defined immunodeficiency) to one or more antigenic vaccine components or vaccine strains or serotypes (e.g. non-responders or low-responders to hepatitis B vaccine).

2.1.3 *Age-related maturation and senescence of immune responsiveness*

2.1.4 *Waning immunity*

2.1.5 *Suboptimal health status* (e.g. underlying disease, nutrition)

2.1.6 *Interference due to other infectious agents* (e.g. wild type enterovirus infection causing interference with the immune response to oral poliomyelitis vaccine, OPV)

2.1.7 *Immunological interference* (e.g. maternal antibodies, administration of immunoglobulins)

2.1.8 *Pre-existing infection with pathogen targeted by the vaccine* (e.g. with specific HPV genotypes) or immunization during incubation period (after exposure to pathogen)

Vaccine-related

2.1.9 *Vaccine is not 100% efficacious against included antigens*

2.1.10 *Incomplete coverage* of strains, serotypes, genotypes, antigenic variants, or escape mutants that can cause a vaccine preventable disease

2.1.11 *Antigenic interference* or other *vaccine–vaccine interactions in case of co-administered vaccines*

2.1.12 *Manufacturing-related* (e.g. batch variations, quality defect)

2.2. Failure to vaccinate

Usage issues

2.2.1 *Administration error* (wrong or suboptimal route, inadequate dose, wrong diluent)

2.2.2 *Vaccination series incomplete, non-compliance with recommended schedule, including lack of recommended booster vaccination(s)* ("failure to vaccinate" rather than "vaccine failure")

2.2.3 *Storage-related* (e.g. cold chain)

2.2.4 *Vaccine beyond expiry date* when used

Immunization programme-related issues

2.2.5 *Suboptimal recommendations* regarding number and time points of primary and/or booster vaccinations

2.2.6 *Shortage of vaccine* leading to no or incomplete vaccination (see also 2.2.2).

One or more of these causes listed under 2.1 and 2.2 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 (see Appendix "Data Collection Checklist for Suspected Vaccination Failure").

3. Definitions of vaccine failure

As stated above, each specific vaccine has a specific prophylactic goal and is used with a specific intent which may be country- or programme-specific. As such, there needs to be a specific definition for vaccine failure which is applicable to that specific vaccine. However, general definitions for vaccine failure can be proposed and confirmed vaccine failure needs to be distinguished from suspected vaccine failure.

The following are proposed general definitions:

3.1. Confirmed clinical vaccine 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.

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

Example (consistent with clinical vaccine failure). Report of a 60-year-old patient who received one dose of 23-valent pneumococcal polysaccharide vaccine and who is diagnosed with bacteraemic pneumonia with *S. pneumoniae* Type 19F 6 months later. In this case the patient was appropriately vaccinated, and he got sick at a time when he should have mounted an immunologic response to the vaccine. In addition, his exposure would have been at a time