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Vaccine safety evaluation: Practical aspects in assessing benefits and risks

Alberta Di Pasquale [a,1,*], Paolo Bonanni [b,1], Nathalie Garçon [c], Lawrence R. Stanberry [d], Mostafa El-Hodhod [e], Fernanda Tavares Da Silva [a]

[a] GSK Vaccines, Avenue Fleming 20, Parc de la Noire Epine, B-1300 Wavre, Belgium
[b] Department of Health Sciences, University of Florence, Viale GB Morgagni 48, 50134 Florence, Italy
[c] Bioaster, 40 Avenue Tony Garnier, 69007 Lyon, France
[d] Columbia University College of Physicians and Surgeons and New York-Presbyterian/Morgan Stanley Children's Hospital, New York, NY, USA
[e] Ain Shams University, Faculty of Medicine, Pediatrics Department, Cairo, Egypt

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ABSTRACT

Vaccines are different from most medicines in that they are administered to large and mostly healthy populations including infants and children, so there is a low tolerance for potential risks or side-effects. In addition, the long-term benefits of immunisation in reducing or eliminating infectious diseases may induce complacency due to the absence of cases. However, as demonstrated in recent measles outbreaks in Europe and United States, reappearance of the disease occurs as soon as vaccine coverage falls. Unfounded vaccine scares such as those associating the combined measles-mumps-rubella vaccine with autism, and whole-cell pertussis vaccines with encephalopathy, can also have massive impacts, resulting in reduced vaccine uptake and disease resurgence. The safety assessment of vaccines is exhaustive and continuous; beginning with non-clinical evaluation of their individual components in terms of purity, stability and sterility, continuing throughout the clinical development phase and entire duration of use of the vaccine; including post-approval. The breadth and depth of safety assessments conducted at multiple levels by a range of independent organizations increases confidence in the rigour with which any potential risks or side-effects are investigated and managed. Industry, regulatory agencies, academia, the medical community and the general public all play a role in monitoring vaccine safety. Within these stakeholder groups, the healthcare professional and vaccine provider have key roles in the prevention, identification, investigation and management of adverse events following immunisation (AEFI). Guidelines and algorithms aid in determining whether AEFI may have been caused by the vaccine, or whether it is coincidental to it. Healthcare providers are encouraged to rigorously investigate AEFIs and to report them via local reporting processes. The ultimate objective for all parties is to ensure vaccines have a favourable benefit-risk profile.

1. Introduction

Vaccines are among the most successful and cost-effective public health tools. Not only do vaccines prevent the vaccinated individual from developing a potentially serious illness, but they also help protect entire communities by reducing the spread of infectious agents (herd protection). Vaccines are unique as they are administered to large cohorts of mostly healthy individuals; often infants and small children. Therefore, it is unacceptable for vaccines to induce a significant burden of side effects, even where the illness itself can produce severe or fatal side effects. Acceptance of some side effects in vaccines depends on their frequency and severity, and may vary with time based on how the side-effect

Abbreviations: AE, adverse event; AEFI, adverse event following immunisation; CDC, US Centers for Disease Control and Prevention; DNA, deoxyribonucleic acid; DTPa-IPV-HBV/Hib, combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-hepatitis b-*Haemophilus influenzae* type b conjugate vaccine; MMR, combined measles-mumps-rubella vaccine; MMRV, MMR with addition of varicella vaccine; RMP, Risk Management Plan; RNA, ribonucleic acid; US, United States; VAPP, vaccine-associated paralytic poliomyelitis; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: alberta.di-pasquale@gsk.com (A. Di Pasquale), paolo.bonanni@unifi.it (P. Bonanni), nathalie.garcon@bioaster.org (N. Garçon), lrs2155@cumc.columbia.edu (L.R. Stanberry), moshodhod@med.asu.edu.eg (M. El-Hodhod), fernanda.tavares@gsk.com (F. Tavares Da Silva).
[1] Co-lead authors.

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compares with the symptoms induced by the illness. As first-hand experience of the vaccine-preventable disease fades, even mild side-effects may be viewed as unacceptable by the public and by vaccine providers alike.

No drug, medical procedure or immunisation can be ascribed as totally risk free. If there are known risks (untoward occurrences for which there is a potential or identified association with the medicinal product [1]), these are described in the Prescribing Information. For vaccines, active expansion of the safety information base continues to ensure that the benefits always measurably exceed any potential emerging risks. The balance of benefits and risks is dynamic and may change over time as new data emerge. The benefit-risk balance weighs the benefits of immunisation towards society (such as the prevention of epidemics, reductions in costs associated with treatment, and improved productivity), and benefits to the individual (prevention of disease and its potential sequelae), against the risks to the individual who might suffer an adverse vaccine reaction [2]. To facilitate this assessment, extensive efforts are undertaken to evaluate a vaccine's safety from early development through its entire duration of use. At licensure, surveillance activities are put into place to continue monitoring safety and disease epidemiology, and to supply reliable and up-to-date information to maintain public confidence in immunisation programmes.

Adverse events (AEs) occurring after immunisation, regardless of whether they were or were not caused by the vaccine, are referred to as 'adverse events following immunisation' (AEFI) (Table 1). Most vaccines are provided as injections and the most common AEFI are symptoms that occur at the injection site (pain, redness, swelling), or common systemic symptoms such as fever or myalgia. These events are reported as side-effects of most injected vaccines and are generally mild and self-limiting. Occasionally, unexpected AEs or rare serious AEs may occur. Some events, such as anaphylaxis, usually occur rapidly after immunisation and require swift recognition and management. Others may occur days or weeks after immunisation; these require comprehensive investigation to distinguish those events that can be potentially causally related to immunisation, and those which are merely coincidental to immunisation. If the possible cause of an AEFI is not clearly identified, or if the event occurred in temporal association with immunisation, the patient who experiences the event may assume that the vaccine was the cause. Allegations that vaccines may cause an AEFI must be dealt with diligently and either confirmed or refuted based on scientific evidence. Misleading data can rapidly undermine confidence in an individual vaccine, or can lead to groundless suspension or withdrawal of the product from the market; ultimately having dramatic consequences for public health including decreased coverage and disease resurgence (Table 2). In some cases it takes a long time after an AEFI is reported to generate sufficient scientific data to determine that the AEFI was not caused by the vaccine; such as the unfounded fears that measles-mumps-rubella vaccine (MMR) caused autism or that whole-cell pertussis vaccines caused encephalopathy [3,4].

Vaccine safety is monitored and assessed by multiple parties and at many levels. For example, there is a constant effort made from a programmatic/public health perspective by authorities such as the World health Organization (WHO) and its safety committee (GACVS), and other supranational and national organizations to strengthen National Regulatory Authorities, favouring the establishment of National Immunisation Advisory Groups, safety surveillance, etc. Moreover, large epidemiologic studies and post-marketing surveillance are increasingly targeted to refine the benefits versus risk of vaccines. However, these aspects will not be the focus of this review.

Among all stakeholders, healthcare providers play an important role which includes identifying AEFI, collecting all available clinical information relating to the AEFI, and reporting the event, including any evaluation of risk factors that may have contributed to the event.

Table 1
Classification of adverse events following immunisation (AEFI).

Vaccine reaction or vaccine-induced event	• Event caused or precipitated by the vaccine when given correctly (e.g., pain, redness, swelling, fever) • Caused by inherent properties of the vaccine (e.g., presence of an adjuvant inducing injection site reactions due to activation of local inflammatory response, or replicating live attenuated viruses such as MMR vaccines inducing mild fever and/or rash about 10 days after immunisation, or paralytic polio following live-attenuated poliovirus vaccines)
Immunisation errors	• Event caused by an error in vaccine preparation, handling, or maladministration (e.g., for the DTPa-IPV-HBV/Hib vaccine, injecting a fully liquid pentavalent DTPa-IPV-HBV part without reconstituting it with a lyophilised Hib, or oral rotavirus vaccine injected intramuscularly)
Coincidental event	• Event that happens shortly after immunisation but is not caused by the vaccine (chance association, e.g., flu-like symptoms due to a rhinovirus infection after influenza immunisation)
Immunisation anxiety reaction	• Event resulting from anxiety about, or pain from, the injection itself rather than the vaccine (e.g., syncope, panic attack)
Vaccine failure	• Event indicating lack of efficacy/effectiveness (e.g., due to failure to respect cold chain requirements)
Unknown	• Cause cannot be determined

DTPa-IPV-HBV/Hib – combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-hepatitis b-*Haemophilus influenzae* type b conjugate vaccine.

Here we review the procedures that are in place for monitoring vaccine safety and establishing causality, focusing on the healthcare provider's role in these processes. We also examine difficulties in AEFI reporting faced by healthcare providers in some parts of the world, and propose improvements in vaccine safety monitoring for the global community.

2. Infrastructure for monitoring vaccine safety

Before a vaccine is administered to humans, vaccine manufacturers undertake extensive safety evaluation of individual vaccine components and of the final formulation to be administered. Raw materials must be of the highest possible purity and quality (or 'clinical grade'), their origin must be properly traced and their ongoing supply must be guaranteed [5]. The vaccine components and the final product are tested in the laboratory for purity, sterility, potency, consistency, activity and stability (described in more detail by Cunningham et al. in this issue). Many of these tests are conducted in the laboratory, and many, such as tests for efficacy, toxicity, safety and effects on reproductive health, are conducted in animal models.

After licensure, all vaccine lots must pass a rigorous array of quality control tests that are agreed on by regulatory agencies (both the authority responsible for the jurisdiction where the manufacturer is based, and the authority [or authorised delegate] on the receiving country), before they can be released. During manufacturing an individual vaccine will undergo multiple non-clinical, toxicology and safety tests (sometimes numbering in the hundreds) before being released for use in humans. New production sites need to be inspected and approved before starting their activities, after which they are regularly inspected and audited by regulatory agencies. Production sites can undergo many inspections in

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