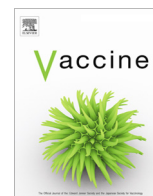


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# Vaccine

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## Vaccine safety evaluation: Practical aspects in assessing benefits and risks

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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.

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**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.

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### 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

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

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

Vaccine reaction or vaccine-induced event	<ul style="list-style-type: none"> <li>• Event caused or precipitated by the vaccine when given correctly (e.g., pain, redness, swelling, fever)</li> <li>• 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)</li> </ul>
Immunisation errors	<ul style="list-style-type: none"> <li>• 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)</li> </ul>
Coincidental event	<ul style="list-style-type: none"> <li>• 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)</li> </ul>
Immunisation anxiety reaction	<ul style="list-style-type: none"> <li>• Event resulting from anxiety about, or pain from, the injection itself rather than the vaccine (e.g., syncope, panic attack)</li> </ul>
Vaccine failure	<ul style="list-style-type: none"> <li>• Event indicating lack of efficacy/effectiveness (e.g., due to failure to respect cold chain requirements)</li> </ul>
Unknown	<ul style="list-style-type: none"> <li>• Cause cannot be determined</li> </ul>

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

information relating to the AEFI, and reporting the event, including any evaluation of risk factors that may have contributed to the event.

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 [46]). 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

**Table 2**  
Examples of how concerns around vaccine safety have impacted on disease control.

Country [ref]	Vaccine	Vaccine concern	Effect on coverage	Incidence before	Incidence after	Outcome
United Kingdom [36]	Whole-cell pertussis	1974: Pertussis immunisation causes permanent neurological illness and death	79% in 1973 31% by 1978	2000 cases nationally in 1972	Three major pertussis epidemics. The first from 1977 to 1979 recorded 102,500 cases and 36 deaths in children	No association identified [4]
Japan [37,38]	Whole-cell pertussis	1974–5: increase in the number of adverse reactions to DTwP reported, including two deaths due to neurologic illness in infants within 24 h	Immunisation briefly suspended, new vaccine schedule proposed in older children, but acceptance remained poor, falling to 10% in 1976	0.4/100,000 in 1974	11.3/100,000 13,000 notifications and 40 deaths	No association identified [4]
England [39–41]	Measles	Late 1990s: Immunisation linked to autism	92% in 1996/7 80% in 2003/04	≤100 cases annually in 1998–2000	>1000 cases annually after 2008 (except 2010)	No association identified [3]
Newly Independent States of the former Soviet Union [42]	Diphtheria	1990–1995s: in children decreasing coverage due to an extensive list of inappropriate contraindications (e.g. allergies, upper respiratory tract infections, low-birth weight, etc.) for immunisation, overall decreased support for immunisation	Reduced to 18–59% in urban areas such as Moscow	0.08/100,000 with 176 cases in 1976	17/100,000 in 1994–95. >157,000 cases and >5000 deaths in Europe between 1990 and 1998	International public health emergency declared. Control strategy included: reduced list of contraindications; renewed emphasis on immunisation [42,43]
Japan and worldwide [44]	Human papilloma virus	Chronic regional pain syndrome, postural orthostatic tachycardia syndrome	Temporary suspension of proactive recommendation of immunisation in Japan	-	-	No association identified [45]

a year, since each individual country's authorities may decide to inspect the facilities at any time.

The safety of an individual vaccine is continuously monitored in humans throughout its clinical development, culminating in large Phase III studies which may be designed to assess specific safety outcomes (Garçon et al. in this issue). Although smaller pre-licensure safety packages may be submitted in settings of public emergency, such as pandemic influenza, or with new vaccine formulations of existing vaccines, most new vaccines are submitted for license approval with an extensive safety data package containing detailed safety information from pre-clinical studies and from the thousands or even tens of thousands of individuals that received the vaccine in clinical trials. Nevertheless, the possible occurrence of extremely rare AEs, AEs with a delayed onset, or AEs in populations that have not been studied during vaccine development, are unlikely to be detected and assessed until the vaccine is used more widely in the general population.

License applications are supported by the development of a Risk Management Plan (RMP) or Pharmacovigilance Planning [6], in which important safety risks are identified and actions designed to address these concerns [7]. The objectives of the Pharmacovigilance Plan are to specify what is, and is not, known about the safety of a vaccine at the time of license application. This information is intended to help industry and regulators identify any need for specific data collection and to further characterise the safety risks post-authorisation. When necessary, the Pharmacovigilance Plan will define appropriate measures to minimise known (identified) or potential risks to individuals (prevent an AE or reduce its severity, should it occur) and to monitor the success of those measures (Table 3). The Pharmacovigilance Plan can include additional clinical trials, epidemiological studies, database analyses, pregnancy registries and post-authorisation safety studies, any of which may be voluntary or mandated by the licensing authority [8]. Independent studies also add to the wealth of information gathered by authorities and industry [9,10].

### 2.1. Passive safety surveillance

Passive surveillance is an important source of post-licensure safety information [11,12]. Passive surveillance relies on individuals to report AEFI when they become aware of them. Many countries have regional or centralised infrastructure and procedures in place to receive AEFI reports from healthcare providers and the public (Table 4). AEFI reports can also be sent directly to the relevant pharmaceutical company, which receives all reports of AEFI that could concern their products, and holds large safety databases of information that are queried regularly for signal detection and evaluation. Safety signals are assessed using all relevant sources of safety data and are scrutinised to determine if there is sufficient evidence demonstrating causal association to immunisation, or a new aspect of a previously identified association.

Information received through passive AE reporting can be difficult to interpret. Reporting of all AEs after immunisation is encouraged, but whether or not an individual makes a report can be influenced by the severity of the AE, past experience with the product, other similar reports highlighted by media attention, the temporal relationship of the event with immunisation, a pre-conception of a causal association, knowledge of, or ease of access to reporting forms. The quality of information provided may be insufficient to either confirm the diagnosis, or assess the likelihood of a causal association. Underreporting is a well-recognised limitation of passive surveillance systems [13].

Regional, national and supranational organizations, as well as vaccine manufacturers, use a variety of statistical methods to conduct data mining activities searching for potential safety signals [14]. The availability of electronic safety databases has seen the

**Table 3**  
Examples of the goals of safety investigations that can be included in the Risk Management Plan.

Goal	Example	Investigated using
Introduce a new vaccine when there is an identified risk for similar vaccines	Febrile convulsion following quadrivalent measles-mumps-rubella and varicella vaccines	Clinical trials, post-licensure observational studies
Investigate a potential risk identified prior to registration	Risk of spontaneous abortion when adjuvanted human papillomavirus vaccines are inadvertently administered in early pregnancy	Clinical trial adverse event reports, post-licensure observational studies
Investigate a theoretical risk	Immune-mediated diseases following adjuvanted vaccines such as adjuvanted human papillomavirus vaccine, adjuvanted pandemic influenza vaccines	Clinical trials, case-control, retrospective and prospective cohort studies, adverse event reports, post-licensure surveillance activities
Introduce new vaccines to new target populations when safety data are scarce	Adjuvanted pandemic H1N1 influenza vaccine in pregnancy, in immune-compromised	Clinical trial, case-control, retrospective and prospective cohort studies adverse event reports, post-licensure surveillance activities
Introduce new vaccines when available pharmacovigilance infrastructure is limited	Malaria vaccine in Africa. Dengue vaccine in developing countries in Africa, and Asia Pacific	Clinical trials and infrastructure development to allow observational studies to establish rates of adverse events before and after vaccine introduction
Responding to a potential safety signal after authorisation	Narcolepsy reported in temporal association with the use of AS03-adjuvanted pandemic H1N1 influenza vaccine ( <i>Pandemrix</i> <sup>TM</sup> ) Guillain-Barre Syndrome after conjugated meningococcal serogroups ACWY vaccine <i>Menactra</i> <sup>TM</sup> Multiple sclerosis after HBV immunisation	Post-licensure surveillance activities, retrospective and prospective cohort studies

development of sophisticated tools to detect and analyse AEs of special interest. For example, the incidence of specific AEs occurring within a specified timeframe after immunisation can be compared with the incidence of the same AE in the whole surveillance database. Alternatively, when knowledge of the background rates of disease is known (i.e., the incidence of the disease in the general population), ‘Observed-versus-Expected’ analyses can be used to determine if the AEFI is occurring at a higher rate in vaccinees than expected in the general population.

Post-licensure safety surveillance allows the assessment of safety when the product is administered to large populations, increasing the ability to detect rare, serious AEs. For example, intussusception is a rare condition that may occur during infancy. A small number of cases of intussusception in young infants occurring during the week after immunisation were reported to a passive surveillance system with the first licensed oral rotavirus vaccine (*Rotashield*<sup>®</sup>, Wyeth). In response to these reports, the immunisation programme with this vaccine was suspended pending further investigations. The US Centers for Disease Control and Prevention (CDC) performed two large investigations; they estimated that *RotaShield*<sup>®</sup> vaccine increased the risk for intussusception by one or two cases per 10,000 infants vaccinated [15]. The manufacturer voluntarily withdrew the vaccine from the market [16]. These data informed the design of subsequent clinical trials of new rotavirus vaccines. These trials required large sample sizes to be able to rule out an intussusception risk of the same magnitude. Several years after these studies, post-licensure active safety surveillance data of the two available rotavirus vaccines from international settings identified a lower intussusception risk of currently available rotavirus vaccines; estimated at 1 to 2/100,000 vaccinated infants [17].

### 3. The healthcare provider’s role in monitoring vaccine safety

Industry, regulatory agencies, academia, the medical community and the public have a shared responsibility in monitoring vaccine safety. However, early detection and management of an AEFI will most often fall first to frontline general practitioners and other vaccine providers. Healthcare professionals have a key role in preventing AEFI: for example, syncope-related injuries, vaccine administration errors and serious allergic reactions to vaccine components can usually be prevented through careful history-

taking and by having adequate procedures in place before and during vaccine administration. Healthcare professionals also need to recognise individuals for whom certain vaccines are contraindicated: such as live viral vaccines in severely immunocompromised patients or during pregnancy. Some AEFIs may occur well after the immunisation event (for example the risk of intussusception may increase slightly for up to 31 days after immunisation with oral rotavirus vaccine), requiring additional vigilance to identify the event as an AEFI. Other AEFI such as anaphylaxis frequently occur rapidly after exposure to the allergen and are anticipated to have an onset <1 h after immunisation, requiring observation of vaccine recipients. Anaphylaxis needs to be differentiated from other acute events that may also occur soon after immunisation with similar presenting symptoms and signs; such as vasovagal reactions, psychogenic or conversion symptoms.

Healthcare providers are encouraged to report AEFIs via local reporting processes (Table 4). All AEFI reports from all sources worldwide are sent to the relevant manufacturer and entered into the central safety database. All serious AEFIs are individually assessed and more information may be requested from the individual who reported the AEFI. All efforts are made to obtain a complete medical record of the AEFI including the results of diagnostic tests and treatments administered. It is important that medical information of high quality is collected to allow diagnostic certainty and to perform causality assessment of individual cases. While a temporal relationship to immunisation or a series of similar AEFIs in vaccinated individuals may suggest causality, proving causality is much more difficult and other evidence is required [18].

#### 3.1. Cause or coincidence? How to assess the true relationship between vaccines and events occurring after immunisation

Since many events may occur in temporal association with vaccine administration, it is important to know and perform all the steps needed to investigate whether an event was causally associated with vaccination or if the association was merely coincidental (i.e., another factor occurring at the same time was the real cause). Sometimes the aetiology remains unknown or very hard to determine.

Safety surveillance systems are correctly intended to be as sensitive as possible to detect signals that trigger further

**Table 4**  
Examples of national infrastructure for reporting adverse events following immunisation.

Country	Surveillance system	Organization	Link
United States	Vaccine Adverse Event Reporting System (VAERS)	Centers for Disease Control and Prevention; Food and Drug Administration	<a href="http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html">http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html</a>
Canada	Canadian Adverse Events Following Immunisation	Public Health Agency of Canada	<a href="http://www.phac-aspc.gc.ca/im/aeefi-essi-form-eng.php">http://www.phac-aspc.gc.ca/im/aeefi-essi-form-eng.php</a>
United Kingdom	Yellow Card Scheme	Medicines & Healthcare products Regulatory Agency	<a href="https://yellowcard.mhra.gov.uk/">https://yellowcard.mhra.gov.uk/</a>
Australia	Australian Adverse Drug Reaction Reporting System	Therapeutic Goods Administration	<a href="https://www.tga.gov.au/reporting-medicine-and-vaccine-adverse-events">https://www.tga.gov.au/reporting-medicine-and-vaccine-adverse-events</a>
Belgium	Belgian Centre for Pharmacovigilance for Medicines for Human Use	Federal Agency for Medicines and Health Products	<a href="http://www.fagg-afmps.be/en/items-HOME/notification_adverse_reactions/">http://www.fagg-afmps.be/en/items-HOME/notification_adverse_reactions/</a>
Italy	Italian Pharmacovigilance Adverse Event Spontaneous Reporting System	Italian Medicines Agency	<a href="http://www.agenziafarmaco.gov.it/it/content/rete-nazionale-di-farmacovigilanza">http://www.agenziafarmaco.gov.it/it/content/rete-nazionale-di-farmacovigilanza</a>
Singapore	Health Sciences Authority	Health Sciences Authority	<a href="http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Report_Adverse_Events_related_to_health_products.html">http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Report_Adverse_Events_related_to_health_products.html</a>
Hong Kong	Pharmacovigilance Unit	Drug Office, Department of Health	<a href="http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/adr_reporting/reporting_guideline.html">http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/adr_reporting/reporting_guideline.html</a>
China	China Adverse Drug Reaction Monitoring System	China Food and Drug Administration	<a href="http://eng.sfda.gov.cn/WS03/CL0756/">http://eng.sfda.gov.cn/WS03/CL0756/</a>
Thailand	National Adverse Product Reaction Monitoring Centre	Thai Food and Drug Administration	<a href="http://www.fda.moph.go.th/eng/index.stm">http://www.fda.moph.go.th/eng/index.stm</a>
Japan	Pharmaceuticals and Medical Device Agency	Ministry of Health, Labor, and Welfare	<a href="http://www.pmda.go.jp/english/">http://www.pmda.go.jp/english/</a>
Israel	Pharmacology Department	Ministry of Health	<a href="http://www.health.gov.il/English/Topics/PharmAndCosmetics/Pages/side_effects_reports.aspx">http://www.health.gov.il/English/Topics/PharmAndCosmetics/Pages/side_effects_reports.aspx</a>
Turkey	Turkey Pharmacovigilance Centre	Ministry of Health General Directorate for Pharmaceuticals and Pharmacy	<a href="http://beta.titck.gov.tr/UnitsPageDescription.aspx?BirimId=qNbDt1uv/1w=">http://beta.titck.gov.tr/UnitsPageDescription.aspx?BirimId=qNbDt1uv/1w=</a>
Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	Polish Regulatory Authority	<a href="http://www.urpl.gov.pl/pl">http://www.urpl.gov.pl/pl</a>
Russia	Federal Service for the Supervision of Public Health	Russian Ministry of Health	<a href="http://www.roszdravnadzor.ru/en/drugs/monitpringlp">http://www.roszdravnadzor.ru/en/drugs/monitpringlp</a>
Brazil	Consumer Accidents Information System	Ministry of Health	<a href="http://siac.justica.gov.br/">http://siac.justica.gov.br/</a>

investigations to confirm or refute a possible causal association between the AEFI and the vaccine administration.

Many methods have been proposed to assess the potential relationship between a medicine and an AE in a given patient, ranging from short questionnaires, guidelines and algorithms, which have been developed to promote systematic and standardised assessment of causality [19,20]. A standardised algorithm has been developed by Neal Halsey et al. (Clinical Immunisation Safety Assessment network, US) to assist in data collection, interpretation, and in assessing causality after individual AEFIs ([http://jhsph.co1.qualtrics.com/SE/?SID=SV\\_OffGju4La9Hjf8h](http://jhsph.co1.qualtrics.com/SE/?SID=SV_OffGju4La9Hjf8h)) [20,21]. The first step is to establish a firm diagnosis of the AEFI using accepted clinical case definitions. A fundamental contribution to this end is the ongoing work of the Brighton Collaboration, a network of scientists whose aim is to establish clear case definitions for individual AEFIs so that reports from all parts of the world are comparable and reporting consistency is ensured [22,23]. The second step is the determination of whether the time that elapsed between the administration of the vaccine and the onset of symptoms is consistent with current knowledge about possible causal relationships. For example, if an immunological mechanism is thought to be implicated in an AEFI (for instance, Guillain-Barré syndrome), and the event is reported 1–2 days after the administration of the first dose of a vaccine, the time interval is not compatible with a causal relationship with immunisation simply because more time (several days or even several weeks) is needed to induce the immune-pathological condition. Similarly, a concomitant infection should be investigated as the most likely cause of febrile seizures occurring 2 days after the administration of a MMR/MMRV vaccine, since it is well known that live-attenuated viruses are much

more likely to be responsible for febrile seizures 5–12 days after administration.

The possibility of contamination of the vaccine lot by chemicals, toxins or infectious agents should be considered in certain contexts. In these cases, it is expected that the event would be reported in a considerable number of recipients of the suspected contaminated vaccine lots. Moreover, if contamination is investigated, the responsible organism or substance should be detected in the residual content of the vaccine vial. If an attenuated vaccine agent is responsible for an AEFI, the agent or its nucleic acid should be found in the damaged tissues, and the sequencing of its deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) should correspond to the vaccine strain.

Even when the time interval is compatible with a possible role of the vaccine, all alternative potential causes of the event need to be investigated (step 3). This is of critical importance on two counts: firstly, in order to decide whether the next vaccine dose can be administered; secondly, although often difficult, to determine what was the likely cause. A ‘temporal factor’ may prejudice the conclusion that the vaccine is the cause, simply because it preceded the event. By failing to look for alternative explanations, potentially treatable causes may go unrecognised, patients may not receive the full immunisation series, and the vaccine will be inappropriately blamed for the AE.

Finally, healthcare providers are encouraged to report all AEFIs to their local surveillance systems because these reports are fundamental to generate hypotheses for further investigation. Timely reporting and a complete evaluation of AEFI are critical in order to maintain public confidence in vaccines, and to highlight the true rare AEFIs when they occur. Vaccines have an excellent safety

record and are of paramount importance in infectious disease prevention. Accurate and complete safety information puts vaccine attributable AEFIs into perspective, thus allowing health providers to correctly weigh the benefits and risks of their implementation.

### 3.2. When causality is not established

The perception of a relationship between a vaccine and serious AE can have profound effects on vaccine confidence, leading to widespread rejection of some vaccines, with devastating consequences (Table 2). Changing these perceptions is highly challenging and requires the communication of up-to-date and detailed information to providers and their patients, for maintaining trust in vaccines. For example, a gastroenterologist claimed a causal association between MMR immunisation and autism when he investigated a series of patients with autism of whom 8 out of 12 had onset of symptoms within 2 weeks of immunisation [24,25]. This assertion was made in 1998 and since then, dozens of studies and several data reviews by independent organizations have all concluded that there is no evidence to support a causal association between MMR immunisation and autism. However, 17 years later there are still fears within the public that MMR immunisation will cause autism.

For other purported vaccine-AEFI associations, it is frequently the case that despite extensive efforts and large investigative studies, a causal association between an AEFI and immunisation can neither be proven nor ruled out. This may be due to very low frequency of the AEFI, inability to exclude alternative causes, or both. Under these circumstances, attempts are made to quantify the level of certainty of any potential association using statistical methods.

### 3.3. Steps once causality is established

When a causal association between an AEFI and immunisation is established, or if a causal association is suspected but not established and the AEFI is potentially serious, the benefit versus risk is re-assessed. Decisions are made regarding AEFI management and whether future vaccine doses should be administered. Risk management and risk minimisation strategies, such as changes to the Prescribing Information, identification of measures to reduce the risk to vaccinees, product suspension or withdrawal, are under-

taken. National Technical Advisory Groups and National Regulatory Agencies also play a key role in evaluating and acting upon new safety information after it is received. Accurate safety information and risk minimisation strategies are communicated in a timely manner to healthcare providers through changes to the Prescribing Information or by direct communications to doctors.

The evaluation of AEFIs is continuous. There is a constant circular process of gathering safety data, analysing the data for signals, determining if signals impact the benefit-risk profile of the vaccine and taking actions as appropriate (Fig. 1). This feedback mechanism works to change immunisation practices and has led to improvements in vaccine safety (Fig. 2).

### 3.4. The Prescribing Information

The safety information that appears in the Prescribing Information represents a summary of data obtained from clinical trials and post-marketing surveillance reports. In clinical trials, all symptoms that occur at the vaccine injection site are considered to be vaccine-related, while the investigator running the trial independently assesses the causal association between all other AEFI that are reported. All AEFI reported in clinical trials that are considered to be at least possibly related to the vaccine, that are biologically plausible (for example, fractures are a common occurrence in childhood but it is not biologically plausible that they are directly caused by immunisation), and that are reported after at least 0.1% of doses, are included in the Prescribing Information. Similarly, series' of AEFI reports from global sources are included if a causal relationship is biologically plausible and reported after at least 0.1% of doses. AEFIs are described in the Prescribing Information as “very common” if they are reported after at least 1 in every 10 doses (such as pain and redness at the infection site), “common” between 1 in every 10–100 doses, “uncommon” between 1:100–1000 doses, “rare” between 1:1000–10,000 doses and “very rare” if reported less frequently than 1:10,000 doses (such as Vaccine-associated-paralytic-poliomyelitis after live oral polio virus vaccine which has an overall risk of 1:1,000,000 [26]).

The Prescribing Information and accompanying patient information sheet are updated as required to reflect the most recent safety information (Fig. 1). Events that might trigger an update of the safety information in the Prescribing Information include the availability of new data that allow the removal of contraindications

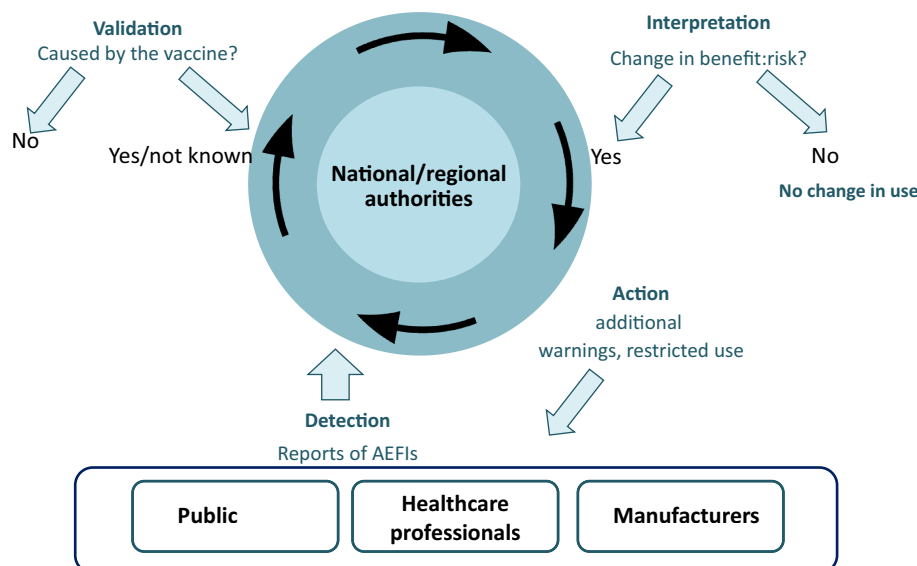


Fig. 1. Continual evaluation of adverse events reported by authorities.

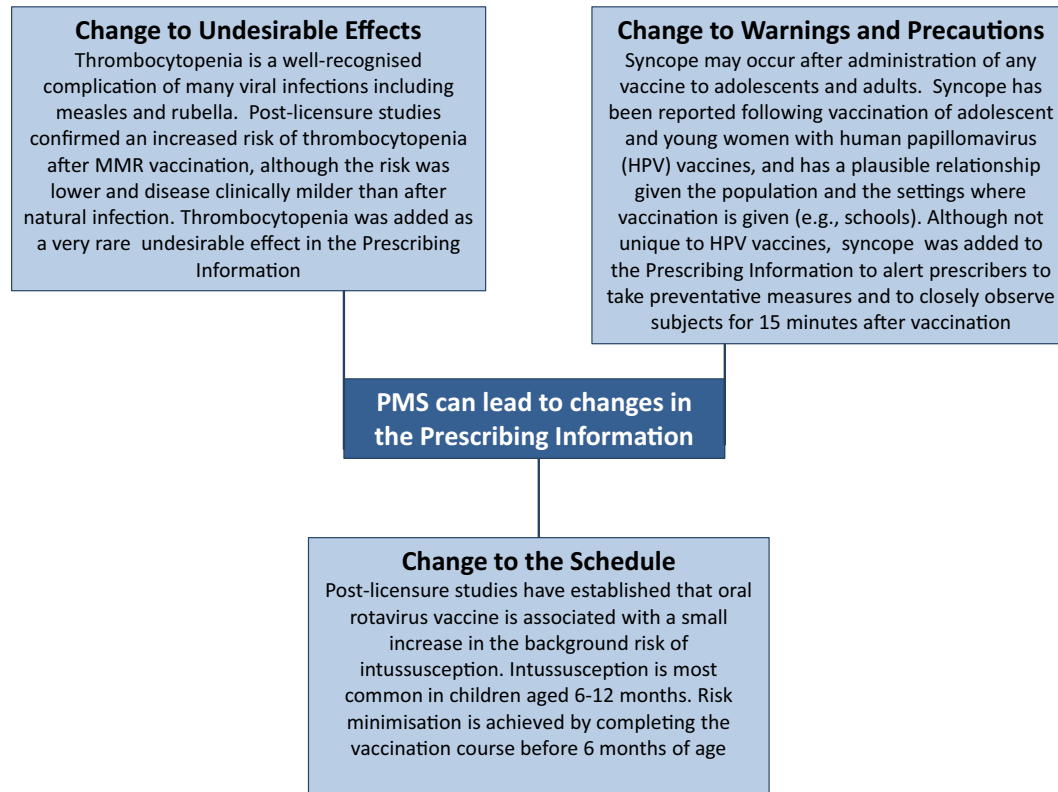


Fig. 2. Recent examples where post-marketing surveillance (PMS) has led to updates of the Prescribing Information.

in place because of a previous lack of data; the addition of AEs reported through post-marketing surveillance mechanisms; or the addition of warnings or strategies to minimise risk to vulnerable populations (Fig. 2). Sometimes the Prescribing Information will be updated because of the existence of a ‘class effect’ (the effect is observed in all vaccines or similar vaccines).

#### 4. Adopting a global approach to vaccine safety

Over the last 10–15 years there have been many initiatives undertaken and infrastructure developed to improve assessment of vaccine safety [12]. Collaborative projects monitor and evaluate vaccine safety independently of industry: for example, the Vaccine Safety Datalink is a collaboration between the US CDC and 9 healthcare organizations [27]; the Institute of Medicine is a non-government Organization in the US [28]; the Vaccine Adverse Event Surveillance & Communication is a collaboration of regulatory agencies, public health institutes and scientists that aims to improve safety monitoring including the conduct of safety studies within Europe [29]; the Global Advisory Committee on Vaccine Safety is an independent expert clinical and scientific advisory body that advises the World Health Organization on vaccine safety issues of potential global importance [30]; and there are other systems in place in North America, Europe and parts of Asia [31]. Conversely, the importance of surveillance of AEFI has not always been widely recognised in low- and middle-income countries. For example, in April 1998, AEFI following diphtheria-tetanus-pertussis vaccine in one governorate in Egypt were reported by the media before medical authorities were informed, resulting in panic over immunisation and a reduction in coverage of all vaccines in the immunisation programme. A surveillance program was subsequently established in July 1998 [32]. The program has received 2000 reports until 2015 and the consequences appropriately man-

aged (personal communication from unpublished reports by the Ministry of Health in Egypt).

In addition, regulatory agencies provide guidelines for safety monitoring of vaccines at all stages of their development and for the entire duration of their use [33].

Nonetheless, it is estimated that the majority of low-and-middle income countries do not have post-marketing safety surveillance infrastructure in place, and there remains a need to build a global platform for vaccine safety monitoring and communication efforts [34]. Such a platform would facilitate detection of rare AEFIs across countries and rapid deployment of risk minimisation measures. In resource-poor settings where the establishment of safety monitoring infrastructure is not immediately possible, global infrastructure has an important role to play, particularly for new vaccines intended primarily for use in resource-poor countries (such as malaria and dengue vaccines). In 2011 the World Health Organization launched the Global Vaccine Safety Blueprint, a project to achieve effective vaccine pharmacovigilance systems in all countries [30] and which is developing standardised tools such as the Global Manual On Surveillance Of Adverse Events Following Immunisation [35], to build vaccine pharmacovigilance capacity in low- and middle-income countries.

#### 5. Conclusions

The benefit-risk profile of each vaccine is assessed constantly during the entire duration of its use. Increased knowledge of the safety surveillance processes that are in place to collect, analyse and communicate around AEFI can increase confidence of healthcare providers and the public in immunisation. Healthcare providers have a central role in enhancing knowledge of vaccine safety by ensuring AEFI are identified quickly, that high-quality data is collected to allow thorough assessment of the AE, and to

determine the likelihood that immunisation may have been (or not) the cause of the event. Ultimately these events should be reported via national pathways. The ability to detect and communicate AEFI is not adequate in all countries, but could be improved with a global approach to vaccine safety monitoring. Prescribing information leaflets are regularly updated to inform the healthcare provider and vaccine recipients about the most recent assessment of benefits and AEFI. These activities help to maintain public trust in vaccines, the ultimate objective being to have vaccines with the most favourable benefit-risk profile.

## Trademarks

Pandemrix is a trademark of the GSK group of companies. RotaShield is a trademark of Wyeth. Menactra is a trademark of Sanofi Pasteur.

## Contributorship

All authors were involved in the development of this manuscript and gave final approval before submission.

## Disclosures

ADP and FTDS are employees of the GSK group of companies and report ownership of stock/restricted shares/shares in the GSK group of companies. PB has received grants and personal fees from Pfizer, and personal fees from GSK, Novartis, and Sanofi Pasteur MSD, unrelated to the present work. NG was previously an employee of the GSK group of companies, declares stock ownership and is also inventor on patents owned by the GSK group of companies. LRS reports consulting fees from Vical, Genocera, and Janssen Pharmaceuticals, and is a member of the scientific advisory board of Abivax. MEL-H has received a speaking honorarium from the GSK group of companies, unrelated to the present work.

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