World Health Organization
REGIONAL OFFICE FOR Europe

VACCINE SAFETY AND FALSE CONTRAINDICATIONS TO VACCINATION

Training manual

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Abstract

Health professionals are the single most important influence on whether individuals decide to have themselves or their children vaccinated; therefore, information and education for health professionals are essential. The aim of this training manual is to present "state-of-the-art", authoritative, scientifically valid advice to counter common misperceptions of vaccination.

Keywords
IMMUNIZATION
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Acknowledgements

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Abbreviations

AEFI	Adverse effects after vaccination
AIDS	Acquired ImmunoDeficiency Syndrome
BCG	bacille Calmette-Guérin
CIOMS	Council for International Organizations of Medical Sciences
DT	diphtheria and tetanus toxoids
DTP	diphtheria, tetanus and pertussis
DTaP	diphtheria and tetanus toxoids and acellular pertussis
DTwP	diphtheria and tetanus toxoids and whole-cell pertussis
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillian-Barré syndrome
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
Ig	immunoglobulin
IL	interleukin
IPV	inactivated poliovirus vaccine
Men	meningococcus
NK cells	natural killer cells
NRA	National Regulatory Authority
OPV	oral poliovirus vaccine
PCV	pneumococcal conjugate vaccine
PIDM	Programme for International Drug Monitoring
PS23	23-valent pneumococcal polysaccharide vaccine
RV1	rotavirus vaccine RotaTeq®
RV5	rotavirus vaccine Rotarix®
SCID	severe combined immunodeficiency
SIV	Simian Immunodeficiency Virus
TB	Tuberculosis
Td	tetanus and diphtheria toxoids
Tdap	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis
Tdwp	tetanus toxoid, reduced diphtheria toxoid and whole-cell pertussis
TIV	trivalent inactivated vaccine
TST	tuberculin skin test
TT	tetanus toxoid
USA	United States of America
VAEIMS	Vaccine Adverse Event Information Management System
VAERS	Vaccine Adverse Event Reporting System
Vi typhoid	capsular polysaccharide typhoid vaccine
VVM	vaccine vial monitor
WHO	World Health Organization

1. Scope and purpose

Vaccination has been demonstrated repeatedly to be one of the most effective interventions for preventing disease worldwide. Ironically, the fact that vaccines are administered to healthy people to prevent diseases that have become rare, largely thanks to vaccination, contributes to concern about vaccine safety. Because the devastating effects of the diseases are no longer prominent, public attention is focused on side-effects of vaccination. This influences how people weigh up the risks and benefits of vaccination, leading in some instances to reduced vaccination rates and outbreaks of disease; however, the minimal risks associated with vaccination are totally overshadowed by the health risks associated with non-vaccination.

Health professionals are the single most important influence on whether individuals decide to have themselves or their children vaccinated; therefore, information and education for health professionals are essential. The aim of this training manual is to present "state-of-the-art", authoritative, scientifically valid advice to counter common misperceptions of vaccination.

2. Safety of vaccines

2.1. Introduction

The vaccines used in national immunization programmes are safe and effective; however, like other pharmaceutical products, vaccines are not completely risk-free, and adverse events occur occasionally after vaccination. Although most such events are minor (e.g. redness at the injection site, fever), more serious reactions (e.g. seizures, anaphylaxis) can occur at a very low frequency (Annex 1).

The general public has low tolerance for any adverse events after vaccination, because vaccines are given to healthy people to prevent disease. Therefore, vaccines are expected to have a higher standard of safety than the medications used to treat people who are sick (e.g. antibiotics and insulin)[1,2]. The lower public tolerance for risk after vaccination means that a greater effort must be made to detect and investigate any adverse event than is generally expected for other pharmaceutical products.

National regulatory authorities are responsible for ensuring the quality, safety and effectiveness of vaccines and other pharmaceutical products[3]. Before vaccines are introduced into an immunization programme, they are evaluated for their safety and efficacy in clinical trials. Once they are introduced, their manufacturing process undergoes thorough, continuous review, and the national regulatory authorities continue to monitor and investigate adverse events to ensure that the vaccines are safe for the entire population.

2.1.1. Pre-licensure testing

The national regulatory authority of the country in which a vaccine is manufactured tests it before licensing it[3]. First, the vaccine is tested in the laboratory and in computer models that inform

scientists about the disease the vaccine is intended to prevent and its genetic codes. Secondly, it is tested in animals with immune systems that are similar to those of humans to help predict effects in people and to make sure that the vaccine has no major side-effects. Then, a series of clinical trials is performed in humans.

National regulatory authorities set the rules for three phases of clinical trials in order to ensure the safety of the volunteers. Researchers test vaccines in adults first.

- *Phase 1:* 20–100 healthy volunteers are tested to determine whether a vaccine is safe, appears to work and has any serious adverse effects.
- *Phase 2:* Several hundred volunteers are tested to determine the commonest short-term side-effects, whether the size of the dose is related to any side-effects and how the volunteers' immune systems respond to the vaccine.
- *Phase 3:* Hundreds or thousands of volunteers are tested to determine whether the people who receive the vaccine are similar to those who don't, whether the vaccine is safe and effective and the commonest side-effects.

Once a vaccine has been determined to be safe and effective, the regulatory authority grants a license to allow its sale and distribution. It is at this point that post-licensure monitoring of the vaccine begins.

2.1.2. Post-licensure testing

Phase 4 clinical trials, also known as "post-marketing surveillance", involve surveillance of the vaccine for safety (pharmacovigilance) and continuous technical support after it has been licensed for sale. Phase IV studies may be required by regulatory authorities or may be undertaken by a sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug might not have been tested for interactions with other drugs or in certain population groups, such as pregnant women, who are unlikely to volunteer for trials). Surveillance is designed to detect any rare or long-term adverse effects in a much larger patient population and over a longer period than was possible in phases I–III. If harmful effects are detected in phase IV trials, the vaccine might be banned from sale or restricted to certain uses.

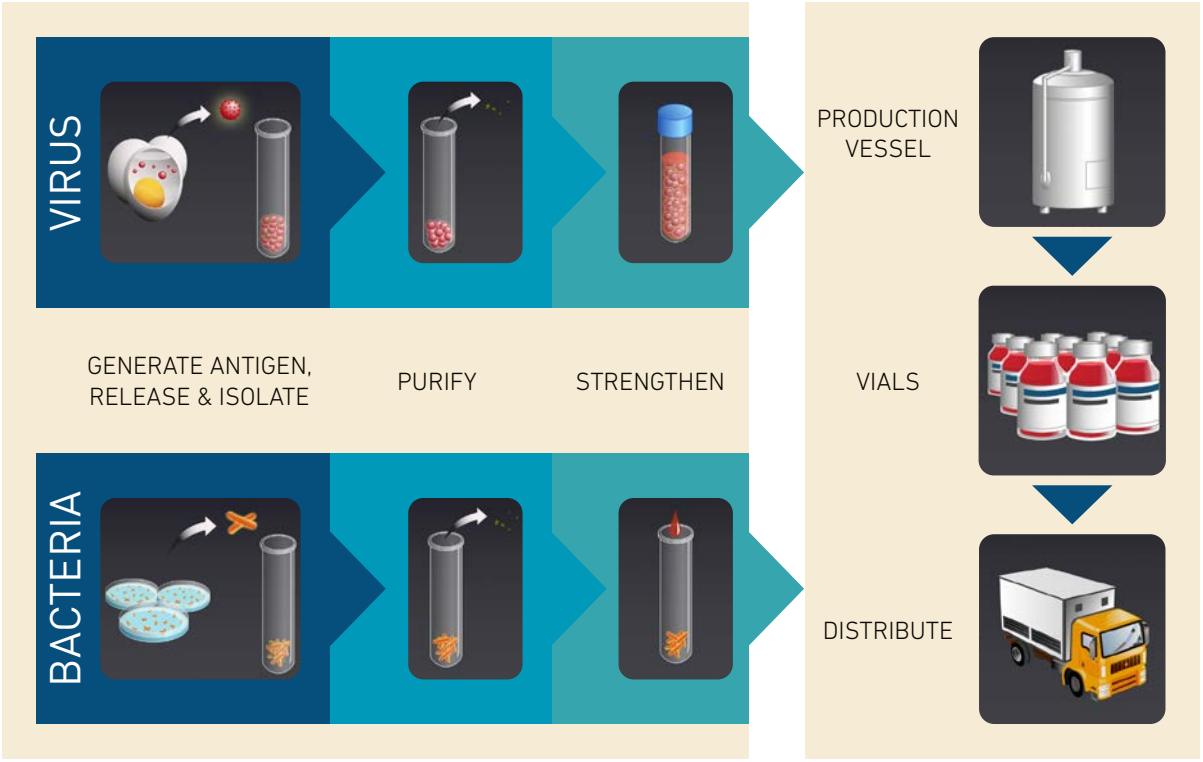
A national regulatory authority licenses a vaccine only if it is safe and effective and if the benefits outweigh the risks1-3. Vaccines are then made in batches, called "lots". Manufacturers must test all lots to make sure that they are safe, pure and potent. Lots can be released only after the national regulatory authority has reviewed their safety and quality by inspecting manufacturing facilities regularly. Every lot of vaccine must be tested and double-checked for safety, potency and purity to assure the uniformity of every dose of vaccine given. Each lot is precisely identified to allow follow-up.

2.1.3. Manufacture of vaccines

Fig. 1 shows the steps in producing and distributing a vaccine. The first step is generation of the antigen used to induce an immune response. This step includes the growth and harvesting of the pathogen itself (for later inactivation or isolation of a subunit) or generation of a recombinant protein (a protein made with DNA technology) derived from that pathogen. Recombinant proteins

can be manufactured in cultures of bacterial cells or yeast. Viruses are grown in cell cultures. Bacterial pathogens are grown in devices with a growth medium designed to optimize the yield of the antigen while maintaining its integrity.

Fig. 1. Stages in vaccine production and distribution



Viruses: For many viral vaccines, the process begins with small amounts of a specific virus that can be grown in cell cultures. Various cell types may be used, such as cells from chicken embryos and cell lines that reproduce repeatedly.

Bacteria: Bacteria can be grown in bioreactors. Some antigens can be manufactured within bacteria or yeast.

The second step is to release the antigen from the cells and isolate it from the material in which it is grown. As proteins and other parts of the growth medium may still be present, they must be removed in the next step. The goal in this stage is to release as much virus or bacteria as possible.

The third step is purification of the antigen. For vaccines that are made from recombinant proteins, this may involve chromatography and ultrafiltration.

The fourth step may be addition of an adjuvant, which is a material that nonspecifically enhances immune responses. Vaccines may also include stabilizers to prolong shelf-life or preservatives to allow safe use of multi-dose vials.

In the final step, all the components of the final vaccine are combined and mixed uniformly in a single vessel. Then, the vaccine is placed into vials or syringe packages, sealed with sterile

stoppers or plungers and labelled for distribution. Some vaccines are freeze-dried and then rehydrated at the time of administration.

Additives are used in vaccines for several reasons, such as to stabilize vaccines in adverse conditions (e.g. extreme temperatures of heat and freeze-drying), to improve the immune response to the vaccine, to prevent the vaccine components from adhering to the sides of the vial and to prevent fungal or bacterial contamination[4, 5]. Examples of additives include lactose and sucrose (sugars), glycine and monosodium glutamate (amino acids or salts of amino acids), human or bovine serum albumin (proteins) and gelatin. These additives ensure that vaccines remain safe and effective.

Some vaccines contain *stabilizers* to maintain the vaccine's safety and effectiveness under various conditions and temperatures. Gelatin and lactose–sorbitol are examples of stabilizers.

Adjuvants are chemicals added to enhance the body's immune response to a vaccine. Various forms of aluminium salts are commonly used. A recent review of all the available studies of aluminium-containing diphtheria, tetanus and pertussis (DTP) vaccines (either alone or in combination) provided no evidence that aluminium salts in vaccines cause any serious or long-term adverse events[6-9].

A *diluent* is a liquid used to dilute a vaccine to the proper concentration. In vaccines, it is usually sterile saline or water.

Preservatives are included in some vaccines to prevent fungal or bacterial contamination, mostly in vaccines that are manufactured in multi-dose vials.

Remnants after manufacture: Often, chemicals are used during vaccine manufacture and then removed from the final product. For example, formaldehyde might be used to kill a vaccine virus, or antibiotics might be used to prevent bacterial contamination while viruses are growing in the laboratory. When these chemicals are removed, trace amounts might remain. While some of these chemicals might be harmful in large doses, the trace amounts left are too small to have any toxic effect[4,5].

2.1.4. Addition of a vaccine to a recommended immunization schedule

A national immunization technical advisory group consists of a group of experts who provide independent, evidence-based advice to ministries of health on the introduction of new vaccines. They include experts in the rea of peadiatrics, infectiouse diseases, public health, epidemiology, immunology, and other disciplins, who carefully review all the available evidence about the vaccine from the clinical trials and other studies and prepare recommendations for use of the vaccine. When making recommendations, they consider how safe the vaccine is at specific ages, how well it works at specific ages, how serious is the disease that the vaccine prevents and how many children would get the disease the vaccine prevents if they were not vaccinated. They also consider pharmaco-economic aspects. Although the national immunization technical advisory group makes recommendations, the ministry of health makes the final decision. The recommendations become part of the national vaccination schedule.

2.1.5. Continuous monitoring of the safety of vaccines

National regulatory authorities such as the European Medicines Agency in Europe and the Food and Drug Administration in the USA, and WHO globally, monitor the safety of vaccines after their introduction[10]. The purpose of monitoring is to detect adverse events and to evaluate possible side-effects, to ensure that any risks associated with the vaccine are identified, especially if the adverse events occur at very low frequency and were therefore not excluded during clinical development. Scientists conduct studies to evaluate the safety of vaccines and determine whether any observed side-effects were actually associated with vaccination. Vaccine recommendations may change according to the results of such safety monitoring.

A "vaccine adverse event information management system" (VAEIMS) is used to collect and analyse reports of adverse events after vaccination[11]. For example, in the USA, anyone can submit such a report, including parents, patients and health care professionals. A vaccine safety datalink is a network of health care organizations, through which information is made available to the population.

2.1.6. Role of clinicians in vaccine safety

Clinicians are responsible for proper storage and administration of vaccines, identification of contraindications, providing information and education to patients, reporting and treating any reactions, referring patients as appropriate and following them up.

The vaccinee should be informed or motivated to receive the vaccine and educated by receiving clear facts. The person delivering the vaccine should then screen the vaccinee for potential contraindications, including pre-existing health conditions, allergies, previous adverse events, antecedents of fainting (syncope) and pregnancy. The vaccinee should be asked to sit or lie down and should be observed for at least 30 min. The person giving the vaccine should be ready in advance for common events such as fainting and rare anaphylactic reactions.

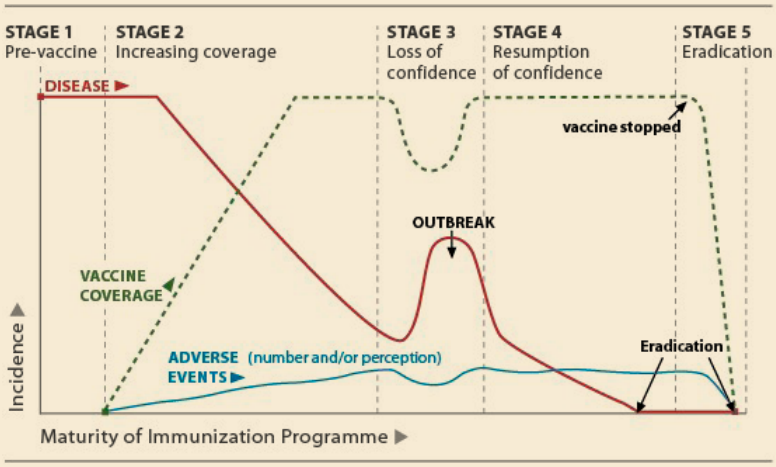
2.1.7. Predictable pattern of behaviour when a new vaccine is introduced

Can vaccines have side-effects? Yes, but very rarely. Reactogenicity (local or systemic) is the usual, expected side-effect of vaccination. Vaccines are, however, often wrongly linked to adverse events: a coincidence in time is commonly misperceived as a causal relation.

The success of vaccination makes it its own worst enemy. Owing to effective vaccination programmes, most people in industrialized countries have never experienced the devastating vaccine-preventable diseases, and many people believe that these diseases no longer pose a threat, as they are no longer visible. Now, some people consider that vaccines are more dangerous than the diseases they prevent. In some countries, such misperceptions have led to decreased coverage and a resurgence of contagious diseases12, as viruses do not respect borders.

Vaccination is a changing science, and, like all aspects of public health, it has social, political and economic implications. The behaviour towards introduction of a new vaccine is cyclical, with a similar pattern observed in the past, the present and probably again in the future (Fig. 2).

Fig. 2. Pattern of perception of vaccination

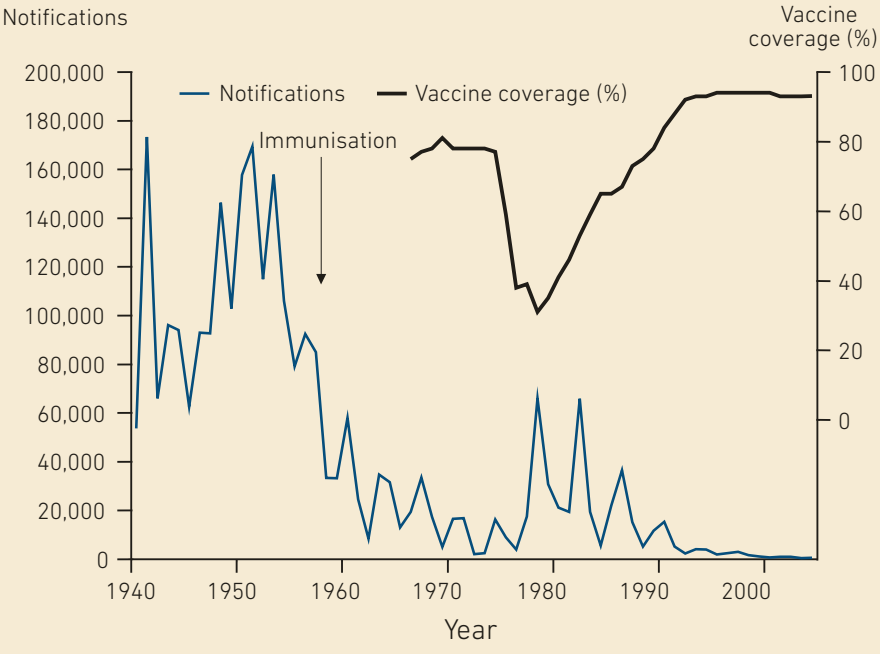


Source: Adapted from Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine. 1994 May;12(6):542-50

As vaccination coverage increases, the prevalence, and thus the fear, of the disease decreases. The rate of adverse events remains constant until very high coverage has been achieved, when more adverse effects are seen globally, with a rapid effect on the mass media, which leads to doubts, fears and finally denial of vaccination. Coverage rapidly decreases, and the disease reappears. Resurgence of the disease usually recalls fear of the disease, and vaccination is resumed. Ideally, the disease is eradicated, and the vaccine is no longer necessary.

Fig. 3 illustrates this pattern. When vaccine coverage is 80%, about 2000 cases may be found; when coverage falls to 20%, the number of cases increases dramatically, to 45 000[13]. Subsequently, vaccination is resumed, and the disease is again controlled.

Fig. 3. Reappearance of pertussis in the United Kingdom due to reduced vaccination coverage

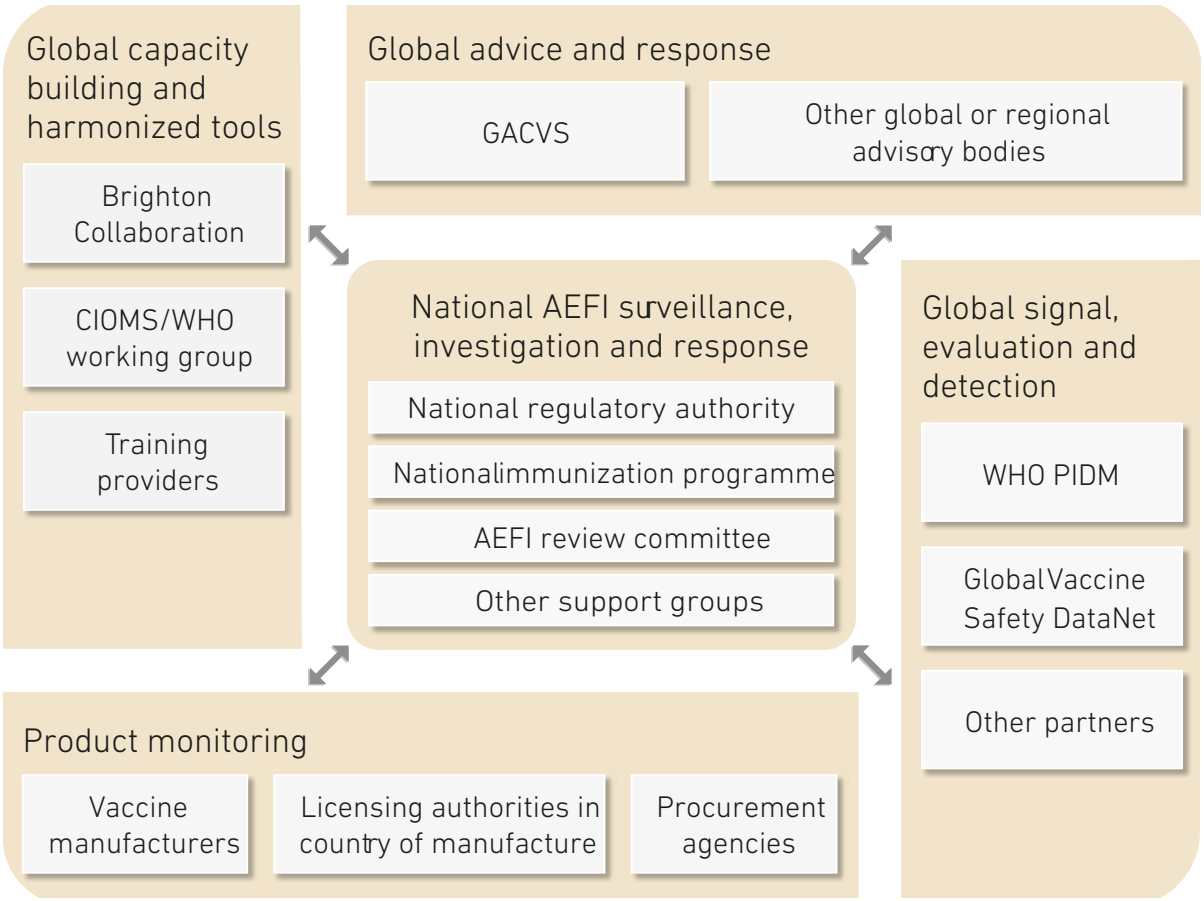


Source: Immunisation against infectious disease 1996, Eds. Salisbury DM and Begg NT. En: Edward Jenner, Bicentenary Edition

2.2. Vaccine safety institutions and mechanisms

The general principles for the surveillance of adverse events after vaccination are similar in all countries, although the approaches may differ due to factors such as the organization of immunization services and the resources available. Different organizations serve different purposes in vaccine safety and in monitoring and supporting national responses to adverse events (Fig. 4).

Fig. 4. Components of a global vaccine safety monitoring, investigation and response system



GACVS, Global Advisory Committee on Vaccine Safety; CIOMS, Council for International Organizations of Medical Sciences; AEFI, adverse effects after vaccination; PIDM, Programme for International Drug Monitoring

2.2.1. National regulatory authorities

The safety of vaccines is assured by national regulatory authorities[3]. All countries should have such an authority to ensure that all medicines, including vaccines, used in the country are safe, effective and of good quality. The authority must abide by the principles of transparency, fairness and accountability (Figs 5–7). After a vaccine has been licensed and introduced, the authority is responsible for strong surveillance for adverse events to ensure its safety and to ensure exchange of information with the system of vaccination delivery or the national immunization programme[10,11].

The national regulatory authority and the national immunization programme together are responsible for seting up and maintaining a national surveillance system for adverse events after vaccination, often with a review committee and other support groups, such as academic institutions and technical agencies[1-3, 10, 11]. In countries that produce their own vaccines, vaccine manufacturers and national control laboratories may be part of the surveillance system.

Fig. 5. Functions of a national regulatory authority, depending on the source of vaccines[15]

<table>
<tr><th rowspan="2">Vaccine-specific NRA functions needed</th><th colspan="3">Areas of activity by NRA (or WHO) depending on source of vaccines</th></tr>
<tr><th>Vaccine procured by United Nations agency</th><th>Vaccine procured by NRA</th><th>Vaccine manufactured in country</th></tr>
<tr><td>FUNCTION 1
Marketing authorization and licensing activities</td><td>✔</td><td>✔</td><td>✔</td></tr>
<tr><td>FUNCTION 2
AEFI surveillance</td><td>✔</td><td>✔</td><td>✔</td></tr>
<tr><td>FUNCTION 3
NRA lot release</td><td rowspan="4">NRA functions undertaken by WHO on behalf of United Nations agencies or producing countries.</td><td>✔</td><td>✔</td></tr>
<tr><td>FUNCTION 4
Laboratory access</td><td>✔</td><td>✔</td></tr>
<tr><td>FUNCTION 5
Regulatory inspections</td><td rowspan="2">NRA functions undertaken by producing country.</td><td>✔</td></tr>
<tr><td>FUNCTION 6
Oversight of clinical trials</td><td>✔</td></tr>
</table>

Fig. 6. Functions of national regulatory authorities relating to vaccines[15]

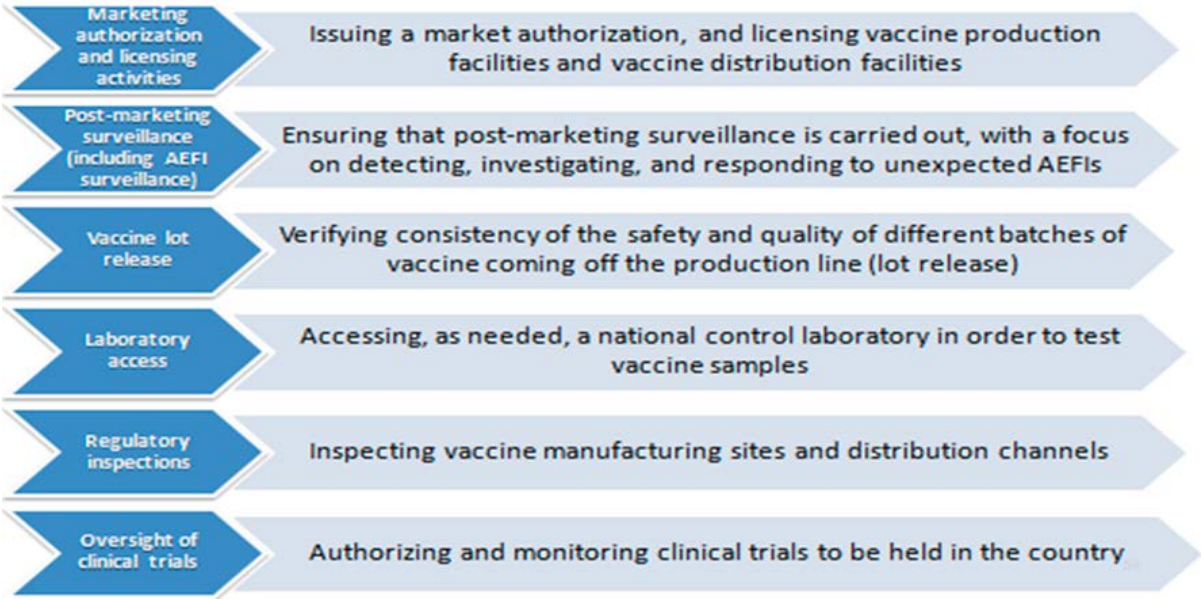
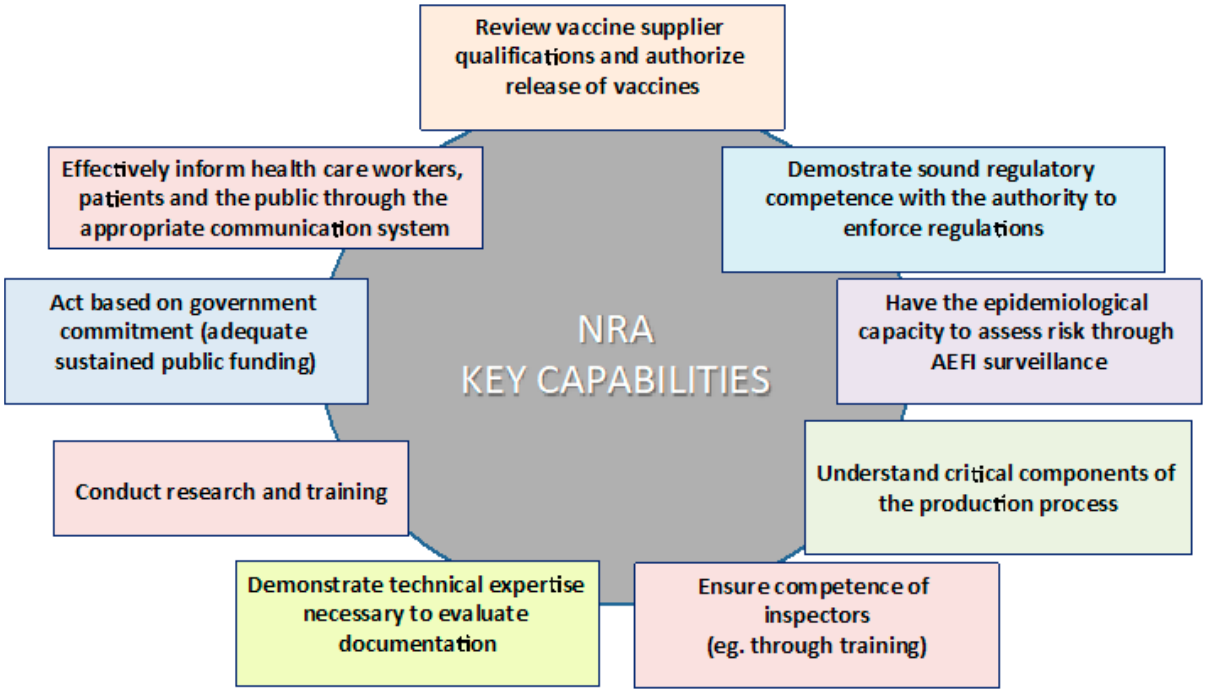


Fig. 7. Key functions of a national regulatory authority[15]



2.2.2. Immunization safety surveillance system

Immunization safety involves ensuring and monitoring the safety of all aspects of immunization, including vaccine quality, adverse events, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste[14]. Vaccination safety may be monitored by:

- *passive surveillance*, or reporting all spontaneous adverse events after vaccination. Its main strength is early detection of previously undetected serious adverse events (signals), but it has many limitations, including underreporting.
- *active surveillance*, used primarily to characterize the rates of adverse events and risk factors. Countries may conduct active surveillance for only selected adverse events at selected institutions (sentinel sites) or in the community (e.g. cohort event monitoring).
- *ad hoc studies*, in which epidemiological studies are conducted to extend specific aspects of vaccination safety surveillance, such as testing hypotheses of causality.

2.3. Adverse events after vaccination

An adverse event after vaccination is any untoward medical occurrence that follows vaccination, which is not necessarily causally related to administration of the vaccine. The event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease[16]. Although all vaccines used in national immunization programmes are safe and effective if used correctly, no vaccine is completely risk-free, and some adverse events will occasionally occur after vaccination. The frequency of adverse reactions of commonly used vaccines is listed in Annex 1.

Adverse events after vaccination are grouped into five categories[17], depending on whether they are due to:

- *the vaccine product:* an adverse event caused or precipitated by a vaccine due to one or more of its inherent properties. Example: extensive limb swelling after administration of DTP vaccine
- *quality:* an adverse event caused or precipitated by a vaccine with one or more defects, including the administration device provided by the manufacturer. Example: paralytic poliomyelitis due to failure by a manufacturer to completely inactivate a lot of poliovirus vaccine
- *vaccination error:* an adverse event due to inappropriate handling, prescription or administration of a vaccine. Example: transmission of infection from a contaminated multidose vial
- *anxiety:* an adverse events arising from anxiety about the procedure. Example: vasovagal syncope in an adolescent during or after vaccination
- *a coincidental event:* an adverse event caused by an event other than the vaccine, vaccination error or anxiety. Example: a fever occurring at the time of vaccination (temporal association) that is in fact due to a viral infection

2.3.1. Vaccine reactions

A vaccine reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly (Table 1).

Table 1. Main minor and severe reactions associated with vaccination

Minor reaction	Severe reaction
Usually occurs within a few hours of injection	Usually does not result in long-term problems
Resolves after a short time, and poses little danger	Can be disabling
Local, including pain, swelling or redness at the site of injection	Includes seizures and allergic reaction of the body to a component of the vaccine
Systemic, including fever, malaise, muscle pain, headache or loss of appetite	

Vaccine reactions are due to either the vaccine product or the quality of the vaccine quality. Vaccination induces immunity by causing the recipient's immune system to react to the antigens contained in the vaccine. Local and systemic reactions such as pain or fever may be part of the immune response. Other vaccine components (e.g. adjuvants, stabilizers and preservatives) can also trigger reactions[17]. In a successful vaccine, even minor reactions are kept to a minimum while the best possible immune response is elicited.

Vaccine reactions likely to be observed with some of the most commonly used vaccines, their frequency and their treatment are listed in Table 218. Reactions typically occur within 1–2 days of vaccination (except for rash reactions after measles vaccination, which can arise 6–12 days after vaccination) and persist for 1–2 days[19].

Table 2. Commonly observed vaccine reactions, frequency and treatment

Vaccine	Local reaction (pain, swelling, redness)	Specific reaction	
		Fever > 38 °C	Irritability, malaise and systemic symptoms
BCG	90–95%	None	None
Hepatitis B	Adults, ≤ 15% Children, ≤ 5%	1–6%	None
Haemophilus influenza type b	5–15%	2–10%	None
Measles, mumps and rubella	10%	5–15%	5% (rash)
Oral poliovirus	None	< 1%	< 1%
Pertussis (DTP)	≤ 50%	≤ 50%	≤ 55%
Pneumococcal conjugate	20%	20%	20%
Tetanus, diphtheria toxoids adsorbed	10%	10%	25%
Treatment	Cold cloth on injection site Paracetamol	Extra oral fluids Cool clothing Tepid sponge or bath Paracetamol	Extra oral fluids

BCG, bacille Calmette-Guérin

Severe vaccine reactions include seizures, thrombocytopenia, hypotonic hyporesponsive episodes and prolonged crying (Table 3), all of which should be reported. Most severe vaccine reactions do not result in long-term problems. Anaphylaxis, while potentially fatal, is treatable without long-term effects.

Table 3. Frequency and delay to onset of severe reactions to commonly used vaccines

Vaccine	Reaction	Delay to onset	Frequency per no. of doses given person
BCG[20]	Fatal dissemination of BCG infection	1–12 months	0.19–1.56/1 000 000
Oral poliovirus vaccine[21]	Vaccine-associated paralytic poliomyelitis	4–30 days	2–4/1 000 000
DTP[22]	Prolonged crying and seizures	0–24 h	< 1/100
	Hypotonic hyporesponsive episodes	0–24 h	< 1–2/1000
Measles[23]	Febrile seizures	6–12 days	1/3000
	Thrombocytopenia	15–35 days	1/30 000
	Anaphylaxis	1 h	1/100 000

BCG, bacille Calmette-Guérin; DTP, diphtheria and tetanus toxoids and pertussis

2.3.2. Reactions associated with defective vaccine quality

These adverse events are caused or precipitated by a vaccine that has one or more defects, including the administration device provided by the manufacturer. An example would be failure by the manufacturer to completely inactivate a lot of poliovirus vaccine. If the reaction is related to a particular lot or batch, the distribution of the lot or batch should be ascertained and instructions provided on its use. The national regulatory authority and the marketing authorization holder should be notified about the adverse event, and these bodies should communicate the information to the manufacturer[18].

2.3.3. Reactions due to vaccination errors

Vaccination errors result from errors in vaccine preparation, handling, storage or administration (Table 4)[18,24]. These errors are preventable. As they detract from the overall benefit of an immunization programme, identification and correction of these practices are of great importance.

Table 4. Vaccination errors resulting from errors in vaccine preparation, handling, storage or administration

Vaccination error	Possible adverse event
Non-sterile injection Reuse of disposable syringe or needle, resulting in contamination of a vial, especially in the case of a multi-dose vial Improper sterilization of a syringe or needle Contaminated vaccine or diluent	Local injection-site reaction (e.g. abcess, swelling, cellulitis) Sepsis Toxic shock syndrome Bloodborne transmission of disease (e.g. hepatitis B, HIV infection) Death
Reconstitution error Inadequate shaking of vaccine vial Use of incorrect diluent Drug substituted for vaccine or diluent Reuse of reconstituted vaccine at subsequent session	Local abcess Vaccine ineffective Effect of drug (e.g. insulin, oxytocin, muscle relaxant) Toxic shock syndrome Death
Incorrect injection BCG given subcutaneously Diphtheria, tetanus and/or pertussis vaccine given too superficially Injection into buttocks	Abcess or other local reaction Damage to sciatic nerve
Vaccine transported or stored incorrectly	Local reaction to frozen vaccine Vaccine ineffective
Contraindication ignored	Avoidable severe reaction

Vaccination errors can result in a cluster of events, i.e. two or more cases of the same adverse event related in time, place or the vaccine administered. Clusters are usually associated with a particular provider or health facility or a vial of vaccine that has been inappropriately prepared or contaminated. Errors may affect many vials; for example, freezing vaccine during transport may increase the number of local reactions.

To avoid programme errors[24]:

- vaccines must be reconstituted only with the diluent supplied by the manufacturer;
- reconstituted vaccines must be discarded at the end of each vaccination session and never kept longer than 6 h;
- no other drugs or substances should be stored in the refrigerator containing the vaccine; and
- vaccination workers must be adequately trained and closely supervised.

2.3.4. Reactions due to anxiety about vaccination

Individuals may react in anticipation and as a result of any injection. Such reactions are not related to the vaccine itself or its components but to fear of the injection. The four main reactions are listed below[18].

- *Fainting* is relatively common, mainly among older children and adults. This vasovagal reaction may lead to loss of postural tone and consciousness. Patients recover spontaneously, and the main risks are related to falling and not to the underlying mechanism or syncope. Fainting can be prevented by adequate explanation, vaccination of a patient when he or she is seated or lying down (to avoid injury caused by falling) and placing patients in a recumbent position after the injection, particularly if they are prone to fainting (such as adolescents and people with a previous history of fainting).
- *Hyperventilation* due to anxiety about vaccination can cause light-headedness, dizziness and tingling around the mouth and in the hands.
- *Vomiting:* Vomiting is a common anxiety symptom in young children. Breath-holding spells may occur, which can result in brief unconsciousness, during which breathing resumes.
- *Convulsions:* An anxiety reaction to injection can, on rare cases, include convulsions. Convulsions usually occur in the context of a vasovagal reaction and syncope, soon after or with the loss of postural tone and consciousness that characterizes syncope. Such seizures are due to anoxia, are usually self-limited and benign and do not require antiepileptic drug therapy.

Mass vaccination events can generate a **mass psychogenic reaction**[25], which is the collective occurrence of symptoms (e.g. headache, dizziness, loss of consciousness) suggestive of organic illness in a group with shared beliefs about the cause of the symptoms. Adolescents are particularly prone, resulting in fainting, sometimes accompanied by tonic–clonic seizure-like movements (not seizures). Clear explanation of vaccination and calm, confident delivery will decrease the level of anxiety and reduce the likelihood of an occurrence.

2.3.5. Coincidental events

The majority of problems thought to be related to the administration of a vaccine are actually not due to the vaccine itself[17,18]. Many are events that occur at the same time as vaccination. For example, if a 6-month-old infant has a seizure starting 1 h after a vaccination, it would naturally be considered differently from one that started 1 h before the vaccination.

Coincidental events are inevitable when children in these age groups are vaccinated, especially during mass campaigns. The commonest mistake is to establish a causal link between vaccination and the coincidental event because of the temporal relation. Individual case ascertaiment is not always easy for a frontline physician, and epidemiological surveillance is essential. The expected numbers of coincidental events after vaccination can be obtained by comparing the normal incidences of disease and death in these age groups with the coverage and timing of vaccination.

2.4. Case definitions and treatment of adverse events after vaccination

Health workers should know how to recognize and treat adverse events after vaccination, immediately if they are serious. Common adverse events and their treatment are listed below[17,18,24,25].

- **Fever**

Fever can be classified (on the basis of rectal temperature) as mild (38–38.9 °C), high (39-40.4 °C) and extreme (≥40.5°C). Fever on its own need not be reported. Treatment is symptomatic with paracetamol.

- **Local infection**

A fluctuant or draining fluid-filled lesion at the site of injection is of bacterial origin if there is evidence of infection (e.g. purulent, inflammatory signs, fever, culture) and a sterile abscess if not. Treatment involves incision and drainage; antibiotics should be given if the infection is bacterial.

- **Severe local reaction**

Redness and/or swelling at the site of injection and one or more of the following:

- swelling beyond the nearest joint;
- pain, redness and swelling of more than 3 days' duration;
- requires hospitalization.

Local reactions of lesser intensity occur commonly and and need not be reported. They resolve spontaneously within a few days to a week, and symptomatic treatment with analgesics or antibiotics is inappropriate.

- **Seizures**

These comprise generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures occur if the rectal temperature is >38°C (rectal) and afebrile seizures if the temperature is normal. Seizures are self-limiting; supportive care with paracetamol and cooling may be given if the patient is febrile. Anticonvulsants are rarely required.

- **Encephalopathy**

Acute onset of major illness characterized by any two of the following:

- seizures,
- evere alteration in the level of consciousness lasting for ≥ 1 day,
- distinct change in behaviour lasting ≥ 1 day.

If it is related to vaccination, it should occur 7–12 days after administration. No specific treatment is available; supportive care should be given.

- **Thrombocytopenia**

Serum platelet count < 50 000/mL, leading to bruising and/or bleeding. The condition is usually mild and self-limiting; occasionally, steroids or platelet transfusion is required.

- **Anaphylactic reaction (acute hypersensitivity reaction)**

Exaggerated acute allergic reaction, within 2 h of vaccation, characterized by one or more of the following:

- wheezing and shortness of breath due to bronchospasm,
- laryngospasm or laryngeal oedema,
- skin manifestations, e.g. hives, facial or generalized oedema.

Less severe allergic reactions need not be reported. Self-limiting; antihistamines may be helpful.

- **Anaphylaxis**

Anaphylaxis is very rare (estimated as once every million doses of vaccine given) but is a severe, potentially life-threatening allergic reaction. When anaphylaxis occurs, it must be diagnosed properly and the patient treated and managed urgently by trained staff and transferred to hospital. Health workers who lack training are highly likely to misdiagnose fainting (vasovagal syncope) and dizziness after vaccination as the onset on anaphylaxis; most episodes of malaise or fainting that occur immediately after vaccination are not due to the onset of anaphylaxis.

Programme managers must take these aspects into consideration before deciding at which level of the health system treatment for anaphylaxis will be provided during a campaign. Once a decision is made, the appropriate staff should receive training and equipment for the management of anaphylaxis. Vaccinators should be able to distinguish anaphylaxis from fainting, anxiety and breath-holding spells, which are common benign reactions (Table 5). A person who is fainting suddenly becomes pale, loses consciousness and collapses (unless supported). Fainting is sometimes accompanied by brief clonic seizure activity (i.e. rhythmic jerking of the limbs), which requires no specific treatment or investigation. Fainting is relatively common after vaccination of adults and adolescents but very rare in young children. It is managed by simply placing the patient in a recumbent position. Consciousness is recovered within 1–2 min, but the patient may take more time to recover fully.

An anxiety spell can lead to a pale, fearful appearance and symptoms of hyperventilation (light-headed, dizziness, tingling in the hands and around the mouth). Breath-holding occurs in young children, leading to facial flushing and cyanosis, and may end in unconsciousness, during which breathing resumes.

Table 5. Differential diagnosis of fainting and anaphylaxis

	Characteristic	Fainting (syncope)	Anaphylaxis
	Onset	Usually during or soon after injection	Usually after 5–30 min
Symptoms	Skin	Pale, sweaty, cold and clammy	Generalized red, raised, itchy rash; swollen eyes and face
	Breathing	Normal-to-deep breaths	Noisy breathing (wheeze or stridor) due to airway obstruction
	Cardiovascular	Bradycardia Transient hypotension	Tachycardia Hypotension
	Gastrointestinal	Nausea and vomiting	Abdominal cramps
	Neurological	Transient loss of consciousness; good response when prone	Loss of consciousness; little response when prone

Recognition of anaphylaxis

Anaphylaxis is a severe reaction of rapid onset (usually 5–30 min after the injection), characterized by circulatory collapse. The early signs of anaphylaxis are generalized erythema and urticaria and upper and/or lower respiratory tract obstruction. In more severe cases, limpness, pallor, loss of consciousness and hypotension are also seen.

Vaccinators should be able to recognize the signs and symptoms of anaphylaxis. In general, the more severe the reaction, the more rapid the onset. As most life-threatening reactions begin within 10 min of vaccination, recipients should be kept under observation for at least 30 min after the injection[18,24,25]. The clinical progression of anaphylaxis from mild, early-warning signs to late, life-threatening symtoms is as follows:

- urticaria, rash and swelling around the injection site;
- dizziness and a general feeling of warmth;
- painless swelling, e.g. of the face or mouth;
- flushed, itchy skin, nasal congestion, sneezing and tears;
- hoarseness, neausea and vomiting;
- swelling in the throat, difficulty in breathing and abdominal pain; and
- wheezing, noisy, diffult breathing, collapse, low blood pressure and an irregular, weak pulse.

Unconsciousness is rarely the sole manifestation of anaphylaxis and occurs only as a late event in severe cases. A strong central pulse (e.g. in the carotid) is maintained during a faint but not in anaphylaxis. Although anaphylaxis usually involves multiple body systems, symptoms may be seen in only one body system (e.g. skin), leading to delayed diagnosis. Occasional reports have been made of symptoms recurring 8–12 h after the onset of the original attack and of prolonged attacks lasting up to 48 h[18,25].

Treatment of anaphylaxis

Once anaphylaxis has been diagnosed, the patient should be considered as having a potentially fatal condition, regardless of the severity of the symptoms. Treatment should be started immediately and plans made to transfer the patient swiftly to hospital (if he or she is not already in hospital). Adrenaline stimulates the heart, reverses spasm in the lung passages and reduces oedema and urticaria, thus countering anaphylaxis. This very potent agent can, however, cause an irregular heartbeat, heart failure, severe hypertension and tissue necrosis if used at an inappropriate dose. Administration of adrenaline for fainting is not only contraindicated but is very dangerous.

Vaccinators trained in the treatment of anaphylaxis should have rapid access to an emergency kit with adrenaline and be familiar with its dosage and administration[24,25]. The expiry date of the adrenaline should be written on the outside of the emergency kit, and the whole kit should be checked three or four times a year. Adrenaline that has a brown tinge must be discarded[18].

2.5. Reporting of adverse events after vaccination

Case detection is the first step in surveillance of adverse events after vaccination. The person who first reports an adverse event may be a field health worker, clinic or hospital staff, a volunteer, a

parent or another person. Suspicion alone is a valid reason for reporting: the primary reporter is not expected to assess causality. Rapid detection and evaluation of a possible link to the vaccine is essential to ensure its continued safety. Thus, a report on a suspected adverse event after vaccination should preferably be submitted rapidly to a suitable technical authority rather than waiting until all aspects of the investigation are completed, particularly if the event is serious[17,24,25]. In many settings, the primary reporter submits a report to the immediate authority, which is generally a local public health authority. The report is then transferred through the intermediate level to national level and to the central immunization programme and/or national regulatory authority. Recipients at each level may seek clarification or request additional information before sending the report onwards. The chain depends on the government structure.

To improve detection of adverse events, the primary reporter should have good knowledge of the types of events and the purpose of surveillance. Regular orientation, training and awareness programmes can be used to update knowledge and maintain willingness among primary reporters[24,25].

Parents of infants and children to be vaccinated, health workers in vaccination facilities and the staff of hospital accident and emergency departments are most likely to recognize or detect adverse events after vaccination when they first occur. Health workers are responsible for detecting adverse events after vaccination and reporting them when appropriate; they are also responsible for treating or referring patients[17,24,25]. All vaccination staff and medical workers must be capable of diagnosing adverse events. This requires effective training and education to ensure accurate diagnosis based on clear case definitions, which can be included on the reporting form and in national guidelines for adverse events after vaccination.

2.5.1. Events to be reported

Any adverse event that is of concern to parents or health care workers must be reported, in particular[24,25]:

- serious adverse events,
- signs and events associated with a newly introduced vaccine,
- events after vaccination that might be due vaccination error,
- significant events of unexplained origin that occur within 30 days of vaccination and
- events that raise significant concern for parents or the community.

Reporting of minor adverse events, such as high fever and minor local reactions, is optional. These are expected vaccine reactions; if all were reported, the reports would overwhelm the system with information of limited value[17]. It is nevertheless helpful to record crude numbers of events and compare them with background rates, which might indicate a product quality defects, vaccination errors or even increased susceptibility for vaccine reactions in a particular population.

Table 6 lists suggested reportable events[24,25]. Each country should decide which events should appropriately be included in its reporting system; however, they are encouraged to include a broad range of events for the purposes of global harmonization of data.

Table 6. Adverse events after vaccination that it is suggested be reported

Adverse event after vaccination	Onset after vaccination
Acute flaccid paralysis in a recipient of oral poliovirus vaccine	4–30 days
Acute flaccid paralysis after contact with a recipient of oral poliovirus vaccine	4–75 days
Anaphylaxis (after any vaccine)	Within 48 h
Brachial neuritis in a recipient of a tetanus-containing vaccine	2–26 days
Disseminated BCG infection in a recipient of BCG vaccine	1–2 months
Encephalopathy in a recipient of	
measles or MMR vaccine	6–12 days
DTP vaccine	0–2 days
Hypotonic hyporesponsive episode in a recipient of DTP or pentavalent vaccine	Median, 3–4 h; range, immediate to 48 h; even after 48 h
Bacterial or sterile injection-site abscess in a recipient of any injectable vaccine	Not specific; commonly within first 14 days
Intussusception in a recipient of rotavirus vaccine	Commonly within 21 days; risk increased after the first 7 days and usually the first dose
Lymphadenitis, osteitis or osteomyelitis in a recipient of BCG vaccine	1–12 months
Persistent (> 3 h) inconsolable screaming in a recipient of DTP or pentavalent vaccine	Common immediately and up to 48 h; can occur after 48 h
Sepsis in a recipient of any injectable vaccine	Within 7 days
Seizures, including febrile seizures in a recipient of	
measles or MMR vaccine	6-12 days following imunization
DTP vaccine	0-2 days following immunization
Severe local reaction in a recipient of any injectable vaccine	Within 7 days
Thrombocytopenia in a recipient of measles or MMR vaccine	Median, 12–25 days; range, 1–83 days
Toxic shock syndrome in a recipient of any injectable vaccine	Commonly within 72 h

BCG, bacille Calmette-Guérin; MMR, measles, mumps and rubella; DTP, diphtheria, tetanus toxoids and pertussis

The interval between vaccination and the onset of an event may not always be precise or well established. Consequently, an interval is included in case definitions only for selected adverse reactions. Case definitions should be simple. Those of the Brighton Collaboration provide different levels of diagnostic certainty and are widely used[27]. Countries that find it difficult to adapt them to their situations can, however, adopt other, valid case definitions for reporting purposes. Local reactions that occur at increased frequency, even if they are not severe, should also be reported, as they may indicate vaccination errors or inadequate quality of specific lots.

2.5.2. Timing of reporting

Immediately. A report must be made as quickly as possible so that an immediate decision can be made on action and investigation. When there are many cases or widespread community concern, a telephone call, fax or e-mail to the administrative or operational level at which a decision can be made is appropriate.

2.5.3. Mode of reporting

Reports should be made on a standard form (Table 7)17,24,25, which should be supplied by the immunization service. The form should be simple but should ensure that health workers provide the essential information: the minimum required information must be entered onto the reporting form, as it is the basis for decisions about further investigation.

Table 7. Example of a standard form for reporting adverse events after vaccination

Identity	Date report first received at the national centre Country in which the event was reported Location (address)
Case	Patient identification Date of birth or age at time of onset or age group at time of onset Sex Medical history
Vaccine	Primary suspected vaccine (generic name) Other vaccines given just before the adverse event Batch number and expiry date Vaccine dose number
Event	Date and time of vaccination Date and time of onset of adverse event Adverse event Outcome
Reporter	Name of first reporter of adverse event Institution and location Position and department E-mail address Telephone number
Other	Comments (if any) by a national officer before the report is sent to the global database

For optimal monitoring of vaccine safety and meaningful analysis of adverse events after vaccination, systematic, standard collection of critical data is essential. A limited number of variables are required to manage adverse events properly, including the unique identifier of the report, the primary source of information, patient characteristics, details of the event, the vaccine(s) of interest and the possibility for collecting additional information if needed.

2.5.4. Reporting adverse events during immunization campaigns

In a campaign, a large number of doses are given during a short period, so that there will be more vaccine reactions and coincidental events[26]. The rate of events remains unchanged, but the increased number is readily apparent to both staff and the public, particularly when injectable vaccines are used and especially at a time of intensive social mobilization[26]. Programme errors may also increase during campaigns.

Careful planning will limit negative publicity about an adverse event after vaccination. During a mass or a special vaccination programme, it is of utmost importance to ensure that adverse events are reported, for two reasons[26]:

- Unless an event that occurs during a mass vaccination campaign is properly investigated and analysed, it may raise concern in the public and may affect the vaccination programme.
- In special immunization programmes, a new vaccine may be introduced for which there is no prior experience of or little information on adverse reactions. Signs can be detected by strengthening surveillance during such programmes and may be used to improve the quality of the vaccine.

Even if a national programme does not yet have a functioning adverse events surveillance system, some form of monitoring is essential in mass campaigns. Otherwise, the public is likely to hear of an adverse event before the programme manager does, and the situation may become difficult to control. Surveillance should be simple, flexible and rapid.

One person should be assigned overall responsibility for surveillance of adverse events, who should be the focal point and the spokesperson. The person may be the manager of the Expanded Programme on Immunization, the person in charge of surveillance at national level or a staff member at the national regulatory authority. This is particularly important if surveillance is conducted by a structure other than the Expanded Programme, if there is a national regulatory authority or if there is a common monitoring scheme for drugs and vaccines[26]. Decisions should be made on what to report, how to report and who is to receive reports. The list of events to be reported should not be complicated. Countries with limited reporting capacity should decide which events should be reported during a campaign[26].

2.5.5. Barriers to reporting

Immunization service providers may not report adverse events after vaccination for a number of reasons,[17,25] such as:

- deciding that the event was not due to vaccination (however, all events after vaccination as per the definition should be reported);
- lack of knowledge about the reporting system and process;
- apathy, procrastination, lack of interest or time; inability to find the reporting form;
- fear that the report will have personal consequences; and
- guilt for having caused harm and being held responsible for the event and diffidence about reporting an event for which the reporter is not confident about the diagnosis.

Unless immunization service providers and units at community level report appropriately, the safety surveillance system will not be adequate[17,24,25]. Staff must be encouraged to report adverse events without fear of penalty. The aim is to improve the system or provide further training and not to blame individuals. Positive feedback to health workers is essential. It should include the outcome of investigations or causality assessments, if conducted, and recommendations for managing the vaccinee, particularly with regard to future vaccination. There must be an adequate supply of reporting forms. Pre-addressed, postage-paid forms may improve reporting in some countries, especially by private physicians[17,24,25].

2.5.6. Vaccine Adverse Events Information Management System (VAEIMS)

The VAEIMS consists of software developed by the International Vaccine Institute in collaboration with WHO[25]. Its purpose is for the transfer of core variables on adverse events after vaccination efficiently and effectively from the periphery of a health care system to a central database for processing and conversion into information to guide actions. The design of VAEIMS takes into account the diverse systems of data collection, transmission, analysis and feedback in different countries[25]. It is tailored to local conditions and provides quick, reliable information to decision-makers in a country at all levels and globally.

VAEIMS allows transfer of data from a national database to the global database (Vigibase), as it is E2B-compatible, for sharing information on adverse events after vaccination[25]. Both a web-based and an offline version of VAEIMS are available free of charge. The web-based version includes real-time data uploading, data sharing and analysis. Later, reporting of adverse events after vaccination from the periphery to national level will be facilitated by the collection of data on mobile telephones.

3. Valid and false contraindications to vaccination

3.1. When to vaccinate safely

National standards for paediatric vaccination include descriptions of valid contraindica¬tions to vaccination and precautions to be taken. The people who administer vaccines should screen patients for contraindications and take precautions before giving each dose of vaccine. Screening is facilitated by consistent use of questionnaires available from certain state vaccination programmes and other sources[18].

A contraindication to vaccination is a rare characteristic of a recipient that increases their risk for a serious adverse reaction. Ignoring contraindications can lead to vaccine reactions. One of the most serious reactions after vaccination is anaphylaxis, which is the only absolute contraindication to subsequent doses of the same vaccine[25]. Most contraindications, such as severe acute illness (e.g. acute respiratory tract infection) or treatment with steroids, are temporary, and the vaccination can be administered later. These are known as “temporary” or “relative” contraindications. In addition, people who are severely immunocompromised generally should not receive live vaccines[25]. Children who experience encephalopathy within 7 days of a dose of diphtheria and tetanus toxoids,

whole-cell pertussis vaccine, DTP, DTaP or Tdap that is not attributable to another identifiable cause should not receive an additional dose of a vaccine that contains pertussis bacteria[25].

There is no evidence that the fetuses of pregnant women vaccinated with inactivated virus, bacterial vaccines or toxoids are at risk[28,29]. Live attenuated vaccines administered to a pregnant woman pose a theoretical risk to the fetus, but the benefits of vaccinating pregnant women usually outweigh the potential risks when the likelihood of exposure to the disease-causing agent is high, when infection would pose a risk to the mother or the fetus and when the vaccine is unlikely to cause harm[29].

The safety and effectiveness of vaccines in immunocompromised persons are determined by the type of immunodeficiency and degree of immunosuppression. Each person is different and should be considered unique with regard to vaccination. Under-immunized people are at risk for serious illness and death, and every effort should be made to ensure adequate protection through vaccination. Nevertheless, inappropriate use of live attenuated vaccine can cause serious adverse events in some immunocompromised people due to uncontrolled replication of the vaccine virus or bacterium[29].

Precautions should be taken when a recipient has a condition that might increase his or her risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity; examples are administration of measles vaccine to a person who is passively immune to measles due to exposure during a blood transfusion, or administration of influenza vaccine to a person with a history of Guillain-Barré syndrome within 6 weeks of a previous influenza vaccination. Such people might experience more severe reactions to the vaccine than would otherwise have been expected; however, the risk is lower than that expected with a contraindication. In general, vaccination should be deferred if precaution is indicated. Vaccination might be indicated, however, if the benefit of protection outweighs the risk for an adverse reaction. For example, a dose of DTaP should be considered for a person in a community with a pertussis outbreak, even if he or she had Guillain-Barré syndrome after a dose. The presence of a moderate or severe acute illness with or without a fever calls for caution in administering any vaccine, and a personal or family history of seizures calls for caution in giving MMR vaccine[29].

3.1.1. Contraindications to commonly used vaccines and precautions to be taken

The main contraindications to commonly used vaccines are listed in Table 8, with precautions to be taken[29].

Table 8. Main contraindications to commonly used vaccines and indications for precautions to be taken

Vaccine	Contraindications	Indications for precautions
DTwP	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g. coma, decreased level of conscious¬ness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of a dose of DTP or DTwP	Progressive neurological disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy: defer DTwP until neurological status known and stabilized Temperature of ≥ 40.5 °C within 48 h of vaccination with a DTP or DTaP Collapse or shock-like state (i.e. hypotonic hyporesponsive episode) within 48 h of a dose of DTP or DTwP Seizure ≤ 3 days of a dose of DTP or DTwP Persistent, inconsolable crying lasting ≥ 3 h within 48 h of a dose of DTP or DTwP GBS < 6 weeks after a dose of tetanus toxoid-containing vaccine History of arthus-type hypersensitivity reaction after a dose of tetanus toxoid-containing vaccine: defer vaccination until at least 10 years since the last tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever
DT, Td	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component	GBS < 6 weeks after a dose of tetanus toxoid-containing vaccine History of arthus-type hypersensitivity reaction after a dose of tetanus toxoid-containing vaccine: defer vaccination until at least 10 years since the last tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever
Tdwp	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g. coma, decreased conscious¬ness or prolonged seizures) not attributable to another identifiable cause within 7 days of a dose of DTP, DTwP or Tdwp	GBS < 6 weeks after a dose of tetanus toxoid-containing vaccine Progressive or unstable neurological disorder, uncontrolled seizures or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of arthus-type hypersensitivity reactions after a dose of tetanus toxoid-containing vaccine: defer vaccination until at least 10 years since the last tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever
MMR[a,b]	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component Pregnancy Known severe immunodeficiency (due e.g. to a haematological or solid tumour, chemotherapy, congenital immunodeficiency or long-term immunosuppressive therapyc or in patients with HIV infection who are severely immunocompromised)b	Recent (≤ 11 months) receipt of antibody-containing blood product (interval depends on product) History of thrombocytopenia or thrombocytopenic purpura Indication for tuberculin skin testing Moderate or severe acute illness with or without fever

Hib	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component Age < 6 weeks	Moderate or severe acute illness with or without fever
Hepatitis B	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component	Infant weight < 2000 g[d] Moderate or severe acute illness with or without fever
OPV	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
Varicella	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (due e.g. to a haematological or solid tumour, chemotherapy, congenital immunodeficiency or long-term immunosuppressive therapy[c] or in patients with HIV infection who are severely immunocompromised)[b] Pregnancy	Recent (≤ 11 months) receipt of antibody-containing blood product (interval depends on product)[e] Moderate or severe acute illness with or without fever
PCV	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a component of PCV7, PCV13 or any diphtheria toxoid-contain¬ing vaccine	Moderate or severe acute illness with or without fever
HPV	Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever

DT, diphtheria and tetanus toxoids; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; GBS, Guillian-Barré syndrome; HBsAg, hepatitis B surface antigen; Hib, *Haemophilus influenzae* type b; HIV, human immunodeficiency virus; HPV, human papillomavirus; OPV, oral poliovirus vaccine; MMR, measles, mumps and rubella; PCV, pneumococcal conjugate vaccine; SCID, severe combined immunodeficiency; Td, tetanus and diphtheria toxoids; Tdwp, tetanus toxoid, reduced diphtheria toxoid and whole-cell pertussis.

Events or conditions listed as indications for precautions should be reviewed carefully, and the benefits and risks of administering a specific vaccine to a person under these circum¬stances should be considered. If the risk of adverse events from the vaccine is considered to outweigh the benefits, the vaccine should not be administered. If the benefit of vaccination is considered to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with a proven or suspected underlying neurological disorder should be decided case by case.

a HIV-infected children may receive varicella and measles vaccine if their CD4+ T-lymphocyte count is > 15%[30]

b MMR and varicella vaccines may be administered on the same day. If not, vaccination with these products should be separated by at least 28 days. Measles vaccine might temporarily suppress tuberculin reactivity. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after MMR vaccination, it should be postponed for ≥ 4 weeks after vaccination. If skin testing is urgently required, it should be done on the understanding that reactivity might be reduced by the vaccine.

c A substantially immunosuppressive steroid dose is considered to be 20 mg or 2 mg/kg body weight per day of prednisone or equivalent for ≥ 2 weeks.

d Hepatitis B vaccination should be deferred for infants weighing < 2000 g if the mother is documented as HBsAg-negative at the time of the infant's birth. Vaccination can commence at a chronological age of 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 h of birth, regardless of their weight.

e Vaccination should be deferred for an appropriate interval if replacement immune globulin products are being administered.

3.1.2. Precautions for administration of rotavirus vaccine

Altered immunocompetence

Children and adults who are immunocompromised due to congenital immunodeficiency or haematopoietic or solid organ transplantation sometimes experience severe or prolonged rotaviral gastroenteritis[31,32]. No data are available, however, on the safety or efficacy of rotavirus vaccine in infants who are immunocompromised or potentially immunocompromised.

In the case of infants who are exposed to or infected with HIV, two considerations support vaccination[31,32]:

- A diagnosis of infection might not be established in infants born to HIV-infected mothers before the age at which they receive the first dose of rotavirus vaccine (for example, only 1.5–3% of HIV-exposed infants in the USA are found to be HIV-infected).
- Vaccine strains of rotavirus are considerably attenuated.

Acute gastroenteritis

Under usual circumstances, rotavirus vaccine should not be administered to infants with acute moderate or severe gastroenteritis until the condition improves; however, infants with mild acute gastroenteritis can be vaccinated, particularly if the delay in vaccination would be substantial, making the infant ineligible for vaccination (e.g. aged > 15 weeks and 0 days before the vaccine series is started)[31,32].

Moderate or severe acute illness

As for all vaccines, the presence of moderate or severe acute illness with or without fever warrants precaution in administering rotavirus vaccine. Infants with moderate or severe acute illness should be vaccinated as soon as they have recovered from the acute phase of the illness. Vaccination should not be delayed because of the presence of mild respiratory tract illness or other mild acute illness with or without fever[31,32].

Pre-existing chronic gastrointestinal disease

Infants with pre-existing gastrointestinal conditions (e.g. congenital malabsorption syndromes, Hirschsprung disease or short-gut syndrome) who are not undergoing immunosuppressive therapy should receive rotavirus vaccine, as the benefits outweigh the theoretical risks[31,32].

History of intussusception

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with a history of intussusception, who are at higher risk for a repeat episode than infants who have never had intussusception[31,32].

Infants with spina bifida or bladder exstrophy

The RV1 oral applicator contains latex rubber, whereas the RV5 dosing tube is latex-free. If RV1 is the only rotavirus vaccine available, it should be administered, because the benefit of vaccination is considered to be greater than the risk for sensitization[31,32].

3.2. Misperceptions about vaccination

Clinicians and other health-care providers might misperceive certain conditions or circumstances as valid contraindications or indications of precaution for vaccination when they actually do not preclude vaccination (Table 9). These misperceptions result in missed opportunities to administer recommended vaccines[33]. Among the most common conditions mistakenly considered to be contraindications are diarrhoea, minor upper respiratory tract illnesses (including otitis media) with or without fever, mild to moderate local reactions to a previous dose of vaccine, current antimicrobial therapy and being in the convalescent phase of an acute illness.

Table 9. Conditions commonly misperceived as contraindications to vaccination[29]

Vaccine	Conditions commonly misperceived as contraindications (i.e. vaccine may be administered under these conditions)
For all vaccines: DTwP, DT, Tdwp, OPV, MMR, Hib, hepatitis B, varicella, rotavirus, PCV, HPV	Mild acute illness with or without fever Mild-to-moderate local reaction (i.e. swelling, redness, soreness); low-grade or moderate fever after previous dose No previous physical examination of a person appearing to be well Current antimicrobial therapy[a] Convalescent phase of illness Preterm birth (except hepatitis B vaccine in certain circumstances)[b] Recent exposure to an infectious disease History of penicillin allergy, other non-vaccine allergies, relatives with allergies or receiving allergen extract immunotherapy
DTwP	Fever of < 40.5 °C, fussiness or mild drowsiness after a previous dose of DTP or DTwP Family history of seizures Family history of sudden infant death syndrome Family history of an adverse event after DTP or DTaP Stable neurological condition (e.g. cerebral palsy, well-controlled seizures or developmental delay)
Tdwp	Fever of ≥ 40.5 °C for < 48 h after vaccination with a previous dose of DTP or DTwP Collapse or shock-like state (i.e. hypotonic hyporesponsive episode) within 48 h of receiving a previous dose of DTP or DTwP Seizure < 3 days after receiving a previous dose of DTP or DTwP Persistent, inconsolable crying lasting > 3 h within 48 h of receiving a previous dose of DTP or DTwP History of extensive limb swelling after DTP, DTwP or Td that is not an arthus-type reaction Stable neurological disorder History of brachial neuritis Latex allergy that is not anaphylactic Breastfeeding Immunosuppression
OPV	Previous receipt of one or more doses of oral poliovirus vaccine

MMR[c,d]	Positive tuberculin skin test
	Simultaneous tuberculin skin testing[e]
	Breastfeeding
	Pregnancy of recipient's mother or other close or household contact
	Female recipient of child-bearing age
	Immunodeficient family member or household contact
	Asymptomatic or mildly symptomatic HIV infection
	Allergy to eggs
Hepatitis B	Pregnancy
	Autoimmune disease (e.g. systemic lupus erythematosis or rheumatoid arthritis)
Varicella	Pregnancy of recipient's mother or other close or household contact
	Immunodeficient family member or household contact[f]
	Asymptomatic or mildly symptomatic HIV infection
	Humoral immunodeficiency (e.g. agammaglobulinaemia)
HPV	Immunosuppression
	Previous equivocal or abnormal Papanicolaou test
	Known HPV infection
	Breastfeeding
	History of genital warts
Rotavirus	Prematurity
	Immunosuppressed household contacts
	Pregnant household contacts

DT, diphtheria and tetanus toxoids; DTP, diphtheria toxoid, tetanus toxoid and pertussis; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; HBsAg, hepatitis B surface antigen; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; OPV, oral poliovirus; MMR, measles, mumps and rubella; PCV, pneumococcal conjugate vaccine; Td, tetanus and diphtheria toxoids; Tdwp, tetanus toxoid, reduced diphtheria toxoid and whole-cell pertussis

a Antibacterial agents have no effect on the response to live, attenuated vaccines, except for live oral typhoid vaccine, and have no effect on inactivated, recombinant subunit or polysaccharide vaccines or toxoids. Typhoid vaccine should not be administered to people receiving antimicrobial agents until 24 h after the last dose. If feasible, to avoid a possible reduction in vaccine effectiveness, antibacterial drugs should not be started or resumed until 1 week after the last dose of oral typhoid vaccine.

b Hepatitis B vaccination should be deferred for infants weighing < 2000 g if the mother is documented as HBsAg-negative at the time of the infant's birth. Vaccination can done at a chronological age of 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 h of birth, regardless of weight.

c MMR and varicella vaccines can be administered on the same day. If not, the two vaccinations should be separated by at least 28 days.

d HIV-infected children should receive immune globulin after exposure to measles. They may receive varicella and measles vaccines if their CD4+ T-lymphocyte count is > 15%.

e Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed on the same day, it should be postponed for at least 4 weeks after vaccination. If a skin test is urgent, it should be understood that reactivity might be reduced by the vaccine.

f If a vaccinee experiences a presumed vaccine-related rash 7–25 days after vaccination, he or she should avoid direct contact with immunocompromised people for the duration of the rash.

A decision to administer or delay vaccination because of a current or recent acute illness depends on the severity of symptoms and the etiology of the condition. Vaccines have been shown to be safe and effective in people who have mild illness. Vaccination **should not be delayed** because of the presence of a mild respiratory tract illness or other acute illness with or without fever but should be deferred in cases of moderate or severe acute illness[29]. This precaution avoids diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination and avoids superimposing adverse effects of the vaccine on the underlying illness. After people with moderate or severe acute illness have been screened for contraindications, they should be vaccinated as soon as their condition has improved. Failure to vaccinate children with minor illnesses can impede vaccination efforts. For people whose compliance with medical care cannot be ensured, every opportunity should be taken to administer appropriate vaccines.

Routine physical examinations and procedures such as measur¬ing temperature are not necessary for vaccinating people who appear to be healthy. The provider should ask the parent or guardian of a child whether he or she is ill. If the child has a moderate or severe illness, vaccination should be postponed.

The conditions commonly misperceived as contraindications to vaccination with injectable vaccines are neurological diseases, neonatal jaundice, low haemoglobin concentration, haemangioma, encephalopathy and low birth weight[29].

4. Facts and myths about vaccination

4.1. Introduction

Vaccination has been shown repeatedly to be one of the most (if not the most) effective interventions for preventing disease worldwide. Readers of *The British Medical Journal* in 2007 voted vaccination as one of the four most important developments in medicine of the previous 150 years, with sanitation, antibiotics and anaesthesia[34].

Modern vaccines provide high levels of protection against an increasing number of diseases and the symptoms, disability and death that may occur. At the same time, serious reactions to vaccines are rare. The fact that vaccines are administered to healthy people to prevent diseases that have become rare, largely thanks to vaccination, contributes to concern about vaccine safety[35]. Because the devastating effects of these diseases are no longer so evident, public attention is focused on the side-effects of vaccination, which influences how people weigh up the risks and benefits of vaccination.

In some instances, concerns about the safety of certain vaccines have led to downturns in vaccination rates and outbreaks of disease[13]. Most of the arguments against vaccination appeal to parents' understandable, deep concern for the health of their children, particularly very young infants. Unfounded allegations of adverse effects of vaccines typically relate to feared diseases

and syndromes or conditions of unknown or uncertain cause, such as autism, sudden infant death syndrome and multiple sclerosis.

Three anti-vaccine profiles have been identified.

- *Uninformed, ignorant, passive objectors*: Such people have no objective reasons or good objective information about vaccines. They are not aware that a decision not to vaccinate is an active decision with consequences. They can be addressed with education and information.
- *Conspiracy freaks*: Such people have hilarious reasons or have built up their own theories of how vaccines are made and the side-effects that can occur, with no supporting rationale. They spread their messages through blogs, web pages and books with no scientific basis and offer alternative explanations for the outstanding benefits of vaccines. This group is difficult to address, and investing time on them is usually not efficient, as they do not listen to reason.
- *Pseudo-intellectuals and alternative life-style parents*: This group is generally made up of parents with a medium or high level of education. They have read or heard information with no scientific basis but have built their own theories about vaccination. They rely on herd protection from vaccinated children around their own children. This group requires education and information to make them change their minds. They usually use homeopathy and "alternative" or "natural" medicine and have a pure, ecological life-style.

4.2. Reasons given for refusing vaccination

Some people believe that vaccine-preventable diseases have been almost entirely eliminated and that the risk for exposure to infectious disease is minimal; therefore, they conclude that no vaccination programme is needed. The public may receive mixed, often confusing messages that leave them feeling ambivalent about vaccination. The majority are supportive of vaccination, and only a minority of parents refuse vaccination of their children. Their rejection may be related to wider scepticism about orthodox medical interventions and support for alternative approaches to health. Others may have had a personal experience in which they, their child or an immediate family member had an adverse event that they consider was attributable to vaccination, or they may be generally concerned about the safety of vaccines for other reasons. Some people become vocal opponents of vaccination, spreading messages against it in the mass and social media and through grassroots lobbying.

4.2.1. Barriers to vaccination

The first step is to identify barriers, which include lack of information, doubts about vaccine efficacy or about the evidence, moral barriers, cost, pressure from the mass media, concern about safety and exposure to anti-vaccine groups. The only means to overcome these barriers is **information**. A number of web sites provide scientific information on vaccination, such as http://onlinenursepractitionerprograms.com/vaccine-immunization/.

Anti-vaccination movements aren't new. Newspaper articles on false concerns about the safety of vaccines can be very harmful, as they tend to appear on the first page! Many publishers are not concerned about whether the information has been countered or confirmed, and the consequences of such statements can reduce vaccine dose distribution rapidly.

What parents want to know about vaccines
Parents need information to answer their questions:

- What are the risks?
- Does it hurt?
- How much does it cost?
- What will it protect my child against?
- Does the disease still exist?
- What's a vaccination programme?
- "I have read that..."

Good examples of vaccination information sheets for parents are available on the WHO web site:

- Seven key reasons for immunization: http://www.euro.who.int/__data/assets/pdf_file/0017/84302/Seven_Key_Reasons.pdf
- New immunization resources launched in 2013: http://www.euro.who.int/en/what-we-do/health-topics/disease-prevention/vaccines-and immunization/european-immunization-week/european-immunization-week-2013/new-immunization-resources-launched-in-eiw-2013

At the same time, general practitioners and paediatricians should be trained. Many web sites offer this kind of training, information and fact sheets, including those of WHO, the Centers for Disease Control and Prevention in the USA, the European Centre for Disease Prevention and Control and local and national authorities.

Not to vaccinate is an active decision
Vaccine-preventable diseases or, worse, deaths are unacceptable. The minimal risks of vaccination are completely overshadowed by the health risks of non-vaccination. The most important misbelief of parents who refuse to vaccinate their children is that vaccination is an active decision while not to vaccinate is not.

A successful vaccination programme requires acceptance, communication, information and education, and collaboration between national public health authorities, health care professionals, patients and parents is crucial.

4.2.2. Objections to vaccines based on religious beliefs

Some religious groups are concerned about the origin or characteristics of some vaccine ingredients, such as gelatin, which is partially hydrolysed collagen, usually of bovine or porcine origin[4,5,36]. Gelatin is added to some vaccines as a stabilizer in adverse conditions, such as temperature extremes, which may affect vaccine quality. Some people of the Islamic and Jewish faiths object to vaccination because vaccines may contain pork products[4,5,36]. Scholars of the Islamic Organization for Medical Sciences, however, have decided that transformation of the original pork product into gelatin alters it sufficiently to make vaccination permissible for observant Muslims[37]. Likewise, leaders of the Jewish faith also permit pork-derived (transformed) additives in medicines.

Concern has been raised about the ethics of receiving a vaccine when the cells in which the vaccine virus was grown were obtained from an aborted fetus. Although, under the right supportive conditions, bacteria can survive and replicate on their own, viruses require cells in order to replicate and can be grown only in the laboratory in cells or "cell lines". A cell line is a specific population of cells that is maintained in culture for an extended period. Cell lines have an unlimited lifespan and represent a renewable, predictable system for growing viruses used in the production of vaccines. The best cell types in which to grow human-specific viruses are often derived originally from a sample of human tissue. It is very hard to grow some viruses that infect humans in any other type of cell. Certain cell lines (human diploid cell lines WI-38 and MRC-5) originated from fetal tissue were obtained from three elective abortions indicated for medical reasons in the 1960s[39]. These cell lines have been growing under laboratory conditions for more than 40 years. No tissue has been obtained from fetuses since that time. Abortions have not been conducted specifically for the purpose of harvesting cell lines. The vaccines that are manufactured in cell lines originally derived from fetal tissue include rubella-containing vaccines (MMR and MMRV), hepatitis A vaccines, varicella vaccines and rabies vaccine[40-46].

Some people with religious objections to abortion have questioned the use of these vaccines. A statement from the Vatican47 includes the comment that "as regards the disease against which there is no alternative … if the latter [population as a whole] are exposed to considerable dangers to their health, vaccines with moral problems pertaining to them may also be used on a temporary basis … this is particularly true in the case of vaccination against German measles [rubella]".

4.3. Responding to concerns

Health professionals are the single most important, powerful influence on a people's decision to vaccinate themselves or their children[48]. Health professionals must be well informed about common concerns associated with vaccination so they can provide authoritative, scientifically valid advice[49]. To obtain consent to vaccinate, the people delivering vaccines must honestly discuss the benefits and risks associated with vaccination and the risks for disease and complications that might result from withholding vaccination. If patients or parents raise arguments against vaccination, the best approach of health professionals is to listen to their concerns, explore their reasoning and then provide information appropriate to the person's circumstances and educational level[49]. A decision about vaccination should be made in partnership between the patient or client and the health professional. Information is best provided in a credible written format and presented in an objective way. Health professionals should avoid downplaying concerns or offering overtly personal opinions, respect differences of opinion and consider the personal, cultural and religious factors that might influence a person's decision about vaccination[49].

4.3.1. Vaccine manufacture and testing

Vaaccines must be safe, as they are given to prevent disease; immunization programmes are targeted at all or many members of a population, most of whom are healthy. Concern about the manufacture and testing of vaccines is related mainly to the possibility that vaccines contain toxic or harmful substances or biological agents used in the manufacturing process[4,5,36]. The most common questions and the related facts are summarized below.

- **"Vaccines contain foreign proteins."**

Depending on their purpose and composition, vaccines can contain live viruses, killed viruses, purified viral proteins, inactivated bacterial toxins or bacterial polysaccharides. Vaccines are complex pharmaceutical products that must be able to withstand transport, storage and adverse environmental factors. To ensure that they are stable over time, vaccines may contain additives, such as gelatin or albumin[4,5,36]. Furthermore, some vaccines contain trace residual quantities of substances used during the manufacturing process, such as formaldehyde, antibiotics, egg proteins and yeast proteins[4,5,36].

A question that arises about vaccines that contain foreign material is the presence of egg proteins. Some vaccines are grown in eggs and should be given with caution to people with known egg allergy. The risk for an allergic reaction to these vaccines depends on the amount of egg protein (ovalbumin) in the vaccine and the severity of the allergy[50,51]. Most influenza vaccines currently in use have only trace amounts of ovalbumin (< 1 µg) per dose and can be given safely to most people who are allergic to eggs[51]. Nevertheless, individuals with a severe allergy should seek specialist advice. Yellow fever and one of the rabies vaccines contain larger amounts of ovalbumin and generally should not be given to people with a severe allergy to eggs[52].

The measles and mumps viruses used in vaccines are grown in chick embryo cell lines, not in eggs[50]. It is now recognized that measles- and mumps-containing vaccines (MMR and MMRV) contain negligible amounts of egg protein and can be given to children with an egg allergy, even those who respond with anaphylaxis to egg[50]. If parents ask for reassurance about vaccination of a child with an egg or other allergy, the child can be referred to a specialist immunization clinic, paediatrician or infectious diseases specialist with an interest in immunization. Specialist advice can also be obtained from state or territorial health authorities.

4.3.2. The immune system and the host response

- **"Vaccines weaken or overwhelm the immune system."**

Healthy people can mount a response to any infection they encounter. Vaccines do not weaken their immune system but strengthen it by stimulating the defence mechanisms that provide protection against diseases[53,54]. The body's immune system begins developing before birth. During and soon after birth, when the immune system is still maturing, newborns are protected against many, but not all, serious infections by antibodies from their mothers (maternal antibodies). This protection usually lasts about 4 months[55]. National immunization programmes are planned to balance the capacity of the infant's immune system to respond to a vaccine against their risk for infection. Vaccines contain many fewer antigens than those that children encounter every day in their environment while eating, drinking and playing, and they do not overwhelm or "use up" the immune system[53,54].

If the administration of multiple vaccines overwhelmed the immune system, much weaker immune responses might be expected than when they are given at different times. During the

development of vaccines, however, tests are conducted to confirm that addition of a new vaccine to combinations given at the same time does not change the immune response or the safety profile[54]. In addition, combination vaccines, such as the five- or six-in-one DTPw-containing vaccines and the combination MMRV vaccine, are all rigorously tested during research and development to ensure that the immune response to each vaccine antigen is adequate[54].

- **"Is natural immunity better than vaccine-acquired immunity?"**

Vaccines stimulate the natural immune response, so that exposure to the same pathogen in the future triggers the immune system to "remember" it and mount an effective response to stop the disease from developing or to reduce the severity of disease[53-55].

Some people consider that vaccination is unnatural and that contracting a disease provides optimal protection, as well as benefits to overall health[56]. Tied to this is the belief that vaccination interferes with the body's natural processes[53]. Choosing to remain unvaccinated and have the disease rather than prevent it can, however, have serious consequences. Diseases such as tetanus and meningitis can kill and maim, whereas the vaccines against these diseases are generally well tolerated, with minor side-effects. Vaccines provide the same stimulus to the immune system as an infection and can offer more effective protection against certain pathogens. Most importantly, protection through vaccination avoids the complications associated with the disease. For example, infection with wild measles virus causes encephalitis (inflammation of the brain) in one in 1000 infected individuals, and measles infection kills two of every 1000 infected individuals. In contrast, the combination MMR vaccine causes a severe allergic reaction only once in every 1 000 000 vaccinated individuals, while preventing measles infection[25,26]. The benefits of vaccine-acquired immunity heavily outweigh the serious risks associated with natural infection. The *Haemophilus influenzae* type b (Hib) and tetanus vaccines actually provide more effective immunity than natural infection[53-55]. The benefits of vaccination far outweigh those of infection with a vaccine-preventable disease.

- **"Homeopathic preparations are an alternative to conventional vaccines."**

There is no scientific evidence that any homoeopathic preparation can prevent the diseases targeted by conventional vaccines, whereas the effectiveness of conventional vaccines is well established by large-scale studies[57]. Homoeopathic preparations have been subjected to scientific scrutiny in very few studies[57]. As none included a preparation for use against a disease on the current national immunization schedule, the efficacy of these preparations against those diseases has not been established[57].

Several homoeopathic substances are marketed as "vaccines". Most are manufactured by serial dilutions of a disease-causing organism, tissue or plant extract, to the point where only an infinitesimal amount of the original material is present. This process of "succussion" is said to transfer the protective activity of the original material to the diluting water; however, there is no physically plausible mechanism by which ingestion of such preparations could prevent infection and/or the related diseases. These preparations are unfortunately widely diffused and accepted even by some health care professionals on the basis of their "placebo" effect.

- **"Vaccines cause or worsen asthma and allergies."**

There is no evidence that vaccines cause or worsen allergic diseases such as asthma or eczema[58-62]. Many studies have been conducted to determine whether wheezing occurs more commonly in children after they have received a vaccine, and it is clear that this is not the case[58-62]. It is especially important that children with asthma are given all the recommended vaccines, as a disease like pertussis or influenza can worsen asthma. Influenza vaccination is particularly recommended for children with asthma because of this risk[62].

Vaccines or their components can cause allergic reactions in some people; however, the risk is low[18]. For example, the risk for anaphylaxis after a single vaccine dose has been estimated as less than one in a million[63]. The risk depends, however, on the vaccine type. Components of vaccines that can trigger an allergic reaction include gelatin, yeast and egg protein[50-52]. (Vaccination of people who are allergic to eggs is discussed above.) It is important to determine the presence of an allergy and the exact nature of the allergic response, if present. Children and adults with most food or environmental allergies, such as dust mite or hayfever, can be safely vaccinated[18]. Vaccination is contraindicated for people who have experienced anaphylaxis after a previous dose of a particular vaccine or any vaccine component[18,36].

If a health care provider is unsure about vaccinating a person with a history of an allergic reaction after a vaccine or vaccine component, he or she should contact a specialist immunization clinic, a paediatrician or an infectious diseases specialist with an interest in immunization.

4.3.3. Are vaccines really necessary?

- **"Infectious diseases are not serious."**

Some people argue that infections are a normal, healthy part of growing up; however, the infectious diseases targeted by vaccines can be serious and even fatal[64-67]. These diseases were common in many countries before vaccination, but the number of cases of these diseases has been reduced with the introduction of vaccines and very high vaccination rates in the community[64-67]. Current generations of parents are unlikely to have seen a child paralysed by poliomyelitis, who requires an "iron-lung" to breathe, a child with obstructed breathing due to diphtheria or someone with brain damage due to measles. Other diseases like varicella (chickenpox) are generally considered mild childhood diseases; however, varicella can be severe or fatal, particularly in immunocompromised children and adults[68]. Influenza is sometimes dismissed as not being serious: many people refer to the common cold as "the flu"; however, influenza is not the same as the common cold and can be a serious infection, particularly in elderly people, causing dozens of deaths every year[69-73].

Other vaccine-preventable diseases, such as meningitis due to Hib, meningococcus or pneumococcus, while not seen very commonly in some countries, can also be associated with serious health consequences[74,75].

- **"Improved living standards, not vaccination, have reduced infectious diseases."**

Some people argue that improved health and hygiene were the reasons for the dramatic decrease in infectious diseases during the past century, not vaccines[12]. To support this argument, they use graphs showing decreasing death rates from disease before the introduction of vaccines and no visible impact of vaccination. All these graphs show overall death rates rather than disease incidence, thus hiding the true effect of vaccines.

While overall improvements in living standards, health care and treatment have reduced the numbers of deaths from all diseases, the additional impact of vaccines is illustrated by the near disappearance of deaths from diphtheria, tetanus, pertussis, poliomyelitis and measles[64-67]. Such dramatic decreases after the introduction of vaccines, often over a short period, could not be due to improved living conditions or medical treatment alone.

Examples that demonstrate that vaccines have had a marked impact on the incidence of infectious diseases are listed below.

- Smallpox, which used to kill 5 million people worldwide every year, was eradicated in 1978 and is now all but forgotten[12].
- The WHO Region of the Americas eliminated measles in 2002, only 12 years after a large measles outbreak in 1990, which resulted in more than 250.000 cases and over 10,000 deaths[12,76].
- In the WHO European Region, all Member States agreed upon the target of measles and rubella elimination by 2015. There is still a large burden of measles in the Region, but the number of cases reported has decreased by more than 96%, from 215,767 in 1997 to 7,499 cases in 2010[12,76].
- The WHO European Region was declared free from polio (no endemic polio transmission) in 2002 and reported no cases for 7 years. While the Region has experienced outbreaks of imported wild poliovirus in 2010, it has been interrupted, and the goal of global polio eradication lies within reach. Four countries globally remain endemic for poliovirus (Afghanistan, India, Nigeria and Pakistan). So far, the global fight against polio has saved 5 million people from paralysis[12]

One of the best ways to demonstrate the impact of a vaccination programme on the incidence of a vaccine-preventable disease is to study a community in which the vaccination rate is low but living standards are high. For example:

- Two major epidemics of poliomyelitis occurred in the Netherlands, in 1984 and 1991, in a religious community that refused vaccination. The disease did not spread to the rest of the population, which was well covered with polio vaccine[77].
- The acceptance of pertussis vaccine decreased in the United Kingdom in the mid-1970s. Between 1977 and 1979, there was an epidemic of 102 500 cases of pertussis, during which 27 children died as a direct consequence of pertussis and 17 had permanent neurological damage[13]. Acceptance of pertussis vaccine has now improved to about 93%, and the incidence of pertussis has fallen. Similar large epidemics occurred in Japan and Sweden at about the same time, due to low acceptance of pertussis vaccine[78].

- A resurgence of measles occurred in the United Kingdom after a decrease in measles immunization rates in the wake of now discredited claims of a link between MMR vaccine and autism[79]. Thousands of cases of measles occurred, with some deaths, and the United Kingdom lost its previous measles elimination status.

Some countries with high vaccine coverage and known to have no local measles, having eliminated the disease, are now experiencing measles outbreaks due to imported cases from countries in which measles vaccine coverage rates are low[12]. Higher standards of living and sanitation alone do not ensure protection from infectious diseases. With short travel times over large distances, infectious diseases can be carried from countries with a high disease prevalence. Cases have occurred in unvaccinated people all over the world as a result of travel to and from areas where vaccine-preventable diseases are still common.

- **As the diseases are virtually eliminated, vaccination is not needed."**

Some people believe that vaccine-preventable diseases have been almost entirely eliminated and that the risk for exposure to infectious disease is minimal. Therefore, they conclude that a vaccination programme is unnecessary. Although many people around the world have been immunized, resulting in a marked reduction in the targeted diseases, it is important that the vaccination rates be kept as high as possible, mainly to protect the wider community and vulnerable people with medical problems who cannot be vaccinated[12].

When a significant proportion of individuals in a population is protected against a disease by immunization, those who are still susceptible are indirectly protected, as they are less likely to come into contact with someone with the disease or infection. This effect is known as "herd immunity"[12]. For herd immunity to be effective, however, vaccination rates must be high.

Although many vaccine-preventable diseases are rarely seen in some countries today, they are still common in many other countries. Travellers returning from such countries have been known to bring home diseases such as measles, increasing the potential for an outbreak in communities in which the vaccination rates are low. Reductions in vaccination rates can lead to recurrence of diseases, as seen with regard to polio in many developed countries, diphtheria in eastern Europe and more recently in Spain, and measles in Germany[80-82].

- **"Vaccines cause or spread the diseases they are supposed to prevent."**

The majority of vaccines are inactivated or prepared from only part of the pathogen. The components of the vaccine are therefore not living and therefore cannot cause disease[18]. Exceptions are live attenuated viral vaccines, which contain weakened ("attenuated") forms of the virus against which the vaccine is meant to protect people. The weakened virus replicates in the host to create an immune response but cannot cause disease, except on very rare occasions[18]. Other types of live vaccine contain a naturally occurring organism that does not itself cause the disease in humans but which is closely related to the pathogen that causes the disease and can therefore induce protection against it. Some of the available live vaccines are MMR and MMRV, varicella (chickenpox) and BCG.

After most natural infections and vaccination with most live attenuated vaccines, the infecting organism or antigen does not persist in the body because it is eliminated in the immune response they induce. An exception is the virus that causes chickenpox, which remains dormant in sensory nerves and is sometimes reactivated later in life to cause usually mild herpes zoster (shingles)[12]. This also occurs after natural infection but at a much higher rate. Furthermore, a vesicular skin rash at the injection site of a varicella vaccine (which occurs in five of every 100 people who receive the vaccine) can transmit the vaccine virus to someone else by direct contact with the rash, although this is extremely rare[68]. In the USA, where more than 56 million doses of varicella vaccine have been administered over 10 years, there were only six documented cases of transmission of the vaccine virus from an immunocompetent vaccinated person to others[83]. The MMR vaccine can also cause a transient rash 7–10 days after vaccination, but it is not infectious[68].

- **"People who are vaccinated can still get the disease."**

It has been argued that, as cases of vaccine-preventable disease occur in people who have been vaccinated, vaccines are not effective. This is not completely true, although there is a relation between vaccination rates, vaccine effectiveness and apparent vaccine failures. Thus, where vaccination rates are high and a disease breaks out, the numbers of cases in vaccinated people may appear high in relation to the number of cases among people who were not vaccinated, for two reasons. First, no vaccine is 100% effective. In order to ensure that vaccines are safer than the disease they are designed to prevent, the vaccine bacteria or virus is killed or attenuated. Furthermore, individual genetic make-up means that not all vaccinated people develop immunity. Most routine childhood vaccines are effective in 85–95% of recipients; therefore, 5–15 of every 100 people who receive a vaccine do not develop protective immunity. Secondly, in a country such as Spain, people who have been vaccinated against the common childhood vaccine-preventable diseases vastly outnumber those who have not.

How these two factors bring about a situation in which the majority of cases in an outbreak occur among people who have been vaccinated is illustrated in the following hypothetical scenario. In a school with 1000 pupils, none has had measles. All but five of the pupils have received two doses of measles vaccine and are fully vaccinated. The entire student body is exposed to measles, and every susceptible student becomes infected, including the five unvaccinated pupils. Of the 995 who were vaccinated, several can be expected not to have responded to the vaccine. If the efficacy rate of two doses of measles vaccine is as high as 99%, in this school, 10 pupils will not have responded to the vaccine and will become infected. Therefore, 10 of 15 (67%) of the cases will occur in pupils who were fully vaccinated.

This does not, however, prove that the vaccine did not work. As most of the children in the school had been vaccinated, those who were vaccinated and did not respond outnumbered those who had not been vaccinated. In other words, 100% of the children who had not been vaccinated and only about 1% of those who were vaccinated got measles. Measles vaccine protected most of the pupils. If none of the pupils in the school had been vaccinated, there would probably have been 1000 cases of measles.

4.3.4. Relations between vaccination and neurological disease

Families who refuse vaccination often cite safety as their major concern, particularly the risk for neurological disease, including seizures and epilepsy[84]. Indeed, febrile seizures have been shown to occur at an increased rate after vaccination[85]; however, there is no evidence to suggest that fever caused by a vaccine predisposes the person to seizures, any more than fevers due to other causes[86]. Thus, children who have seizures after vaccination are no more likely to have afebrile seizures or developmental problems than children who have febrile seizures due to other causes[86]. Overall, there is no evidence to suggest that vaccines cause central nervous system injury, epilepsy or infantile spasms[86].

Vaccine-associated encephalopathy has been shown to be caused by a genetic mutation in a sodium channel[87],[88]. These gene mutations arise spontaneously and are only rarely inherited. The cases resemble another disorder, severe myoclonic epilepsy of infancy (Dravet syndrome), and may be wrongly attributed to the vaccine. The mutation explains seizures and developmental regression in these patients, and vaccines are extremely unlikely to be the cause[87],[88]. Mitochondrial disorders are rare, predominantly genetic diseases, which can cause encephalopathy and, rarely, autistic features in affected patients[89]. While these patients may have exacerbated symptoms with febrile illnesses, there is no clear evidence that vaccines trigger these exacerbations[86],[90].

Other general and vaccine-specific misperceptions of causality between vaccination and neurological disease development are discussed below.

- **Lack of association between MMR vaccine and autism and inflammatory bowel disease**

The MMR vaccine does not cause autism or inflammatory bowel disease[91-125]. These associations were proposed by researchers in the United Kingdom in 1998, who suggested that measles virus in the gut caused a new syndrome of inflammatory bowel disease that resulted in decreased absorption of essential vitamins and nutrients through the intestinal tract[126]. They suggested that this, in turn, caused developmental disorders such as autism or worsened symptoms in children with already diagnosed autism, so-called "regressive autism"[126].

Although this report generated much media attention, the few studies on which it was based[127-130] had a number of significant weaknesses that have been highlighted by a plethora of letters to the editor[91-100] and have since been retracted. Ten of the 13 authors of the original study (published in *The Lancet*) published a statement in 2004 retracting the paper's findings, stating that the data were insufficient to establish a causal link between MMR vaccine and autism. *The Lancet* subsequently retracted the original paper[131], and an investigation into the original data showed it to be fraudulent.

Numerous well-conducted studies and expert panel reviews since 1998 have now provided conclusive evidence that there is no link between MMR vaccine and autism or inflammatory bowel disease[132-139] *(4, 5)*, WHO concluded that current scientific data do not show a causal link between the measles virus and autism or inflammatory bowel disease[137]. Extensive reviews published by the Institute of Medicine, an independent expert body in the United States, also concluded that

there is no association between the MMR vaccine and the development of autism. Reviews by the American Academy of Pediatrics, the Chief Medical Officer and the Medical Research Council in the United Kingdom[132] and Canadian[139] experts have also shown no link between autism or inflammatory bowel disease and measles-containing vaccines.

It has been suggested that it would be better to give each component of the MMR vaccine separately rather than giving it as a combination vaccine; however, there is no scientific support for this suggestion[140]. In fact, giving each component separately might be harmful, because vaccination against each disease would be delayed, leaving the child (and, in turn, the population) susceptible to the disease[12]. National and international expert bodies all recommend that MMR vaccine should continue to be used[132-139].

- **Lack of association between mercury in vaccines and autism**

There is no evidence that thiomersal (also known as thimerosal), a mercury-based preservative, in vaccines has caused any health problems, except perhaps minor reactions such as redness at the injection site[4,5,8]. Thiomersal has been used in very small amounts in some vaccines since the 1930s to prevent bacterial and fungal contamination[7]. The form of mercury in thiomersal is organic ethyl mercury, which does not accumulate in the body, unlike the closely related methyl mercury, which accumulates and is neurotoxic. These forms of mercury occur naturally in the environment (in the air, earth and ocean) and in fish.

Mercury is used in industrial processes, dental fillings and thermometers. It is harmful to the body only after it reaches a certain level, and its toxicity depends on the amount consumed, the form of mercury, body weight and the length of exposure. Although methyl mercury has clear neurotoxic effects in humans after absorption, well-designed toxicity studies of the accumulation of ethyl mercury suggest that a relation between ethyl mercury in vaccines and neurological toxicity is biologically implausible[6,7]. Many well-conducted studies and reviews by expert panels have shown that there is no evidence of developmental or neurological abnormalities, such as autism, due to administration of vaccines containing thiomersal[141-148].

Thiomersal has not been used in vaccines since 2000, as they are now produced in single-use sealed vials that do not require addition of a preservative. This reduces the total exposure of young children to any form of mercury in a world where other environmental sources (particularly food such as fish) may be more difficult to eliminate. Some vaccines, such as pneumococcal vaccines, MMR vaccine and other live attenuated viral vaccines, never contained thiomersal[141-148]. Thiomersal may be used as a preservative to prevent the growth of bacteria in vaccines produced in multi-dose vials after the vial has been opened for the first time, for example, as an emergency measure during a pandemic.

- **Pertussis vaccine and brain damage**

The pertussis vaccine does not cause brain damage[149-152]. The pertussis component of DTP vaccine was originally manufactured from inactivated whole pertussis organisms, designated DTPw. DTPw (or whole-cell) vaccines were commonly associated with local reactions such as redness,

swelling and pain at the injection site, fever and mild-to-moderate systemic side-effects such as drowsiness, fretfulness and loss of appetite. In a study of more than 2 million children in the USA, administration of DTPw was not associated with an increased risk for encephalopathy[150]. In a study of all suspected cases of encephalopathy in Canada over 10 years[151], the authors concluded that all the cases were related to a pre-existing medical condition or infection and not to vaccination.

- **Link between vaccines and Guillain-Barré syndrome**

Guillain-Barré syndrome is a rare neurological disorder due to inflammatory demyelination of peripheral nerves. It is estimated that one to two newly diagnosed cases per 100 000 population (0.001–0.002%) occur annually. The most severe cases result in paralysis, requiring respiratory support if the chest wall muscles are affected. Guillain-Barré syndrome can occur spontaneously (with no identified cause) or after events such as infections, including infection with *Campylobacter jejuni*, a bacterium that causes gastroenteritis.

In the USA in 1976, the seasonal influenza vaccine formulation was associated with an increased risk for Guillain-Barré syndrome. Several long-term studies to determine whether influenza vaccines since 1976 were associated with this syndrome found only a very small increase after influenza vaccination, with approximately one case among every one million people vaccinated against influenza additional to the number that would have occurred without vaccination[153-155].

Isolated case reports have suggested a possible association between Guillain-Barré syndrome and several other vaccines, including oral poliovirus, MMR, tetanus toxoid-containing and hepatitis B vaccines[156]. Robust epidemiological studies have not, however, demonstrated a link[157]. In the USA, a possible association with quadrivalent meningococcal conjugate vaccine used in adolescents was reported to the adverse events reporting system, but a subsequent investigation found no increased risk[158].

- **Seizures after vaccination in young children**

Febrile convulsions (sometimes referred to as seizures) are a relatively common response to fever of any cause in young children[159]. In most cases, the seizures are mild and resolve spontaneously. Overall, by the age of 5 years, about three in every 100 children will have experienced a febrile convulsion, irrespective of whether they received a vaccine[159]. As fever is a well-documented adverse event after the administration of many common childhood vaccines, it is not unexpected that febrile convulsions may occur after vaccination, although it is still very rare.

The risk is higher after administration of certain vaccines, such as influenza, MMR and MMRV vaccines[18]. For example, MMR and MMRV vaccines are associated with a higher risk for a febrile convulsion 7–12 days after the first dose of vaccine than at other times[18,160]. It is estimated that one child of every 3000 who receive MMR vaccine will experience a febrile convulsion during this period[18,160]. When MMRV vaccine is given as the first MMR-containing vaccine, the risk for fever and febrile convulsions during this period is approximately two times higher than when MMR and varicella vaccines are given separately[160]. Therefore, MMRV vaccines are not recommended as the

first MMR-containing vaccine in children under 4 years of age, who are more likely to experience convulsions when they have a high fever[160].

- **Autoimmune inflammatory syndrome induced by vaccine adjuvants**

The development and increasing use of new vaccines and global vaccination protocols have stimulated burning debates about the safety of adjuvants and whether they enhance the immunogenicity of vaccines[4,5,8]. An adjuvant is a substance that enhances the antigen-specific immune response, induces the release of inflammatory cytokines and interacts with toll-like receptors and the NALP3 inflammasome[161]. The immunological consequence is stimulation of the innate and adaptive immune responses. Activation of the immune system by adjuvants, a desirable effect, could, however, trigger manifestations of autoimmunity or autoimmune disease[161].

Shoenfeld and Agmon-Levin used the term "autoimmune inflammatory syndrome induced by adjuvants" to describe a complex of variable signs and symptoms that may occur after previous exposure to adjuvants and external environmental triggers and may elicit specific, overt immune-mediated disorders[162]. This entity subsumes five medical conditions: post-vaccination phenomena, Gulf War syndrome, macrophagic myofasciitis syndrome, siliconosis and "sick building" syndrome, but the relevance and extent of the syndrome in children is limited mainly to post-vaccination autoimmune or inflammatory disorders[162].

The main substances associated with autoimmune inflammatory syndrome are squalene (Gulf War syndrome), aluminium hydroxide (post-vaccination phenomena, macrophagic myofasciitis) and silicone (siliconosis)[161,162]. Aluminium hydroxide is the adjuvant used most often in vaccines, but the mechanisms by which it works are complex and little known. Alum adjuvants are good humoral immune potentiators in vaccine formulations, and this property has recently been attributed to NLRP3 inflammasome activation[163]. The inflammasome is an intracellular multiprotein complex that mediates caspase-1 cleavage of the inactive precursor of the pro-inflammatory cytokine interleukin-1β, leading to the release of mature cytokine[161-163]. Inflammasome-mediated cleavage of pro-interleukin-1β in vitro depends on signals that activate both toll-like receptor and nucleotide oligomerization domain-like receptors, such as NLRP3[163.] Activation of these innate immune system receptors is now recognized as a step in effective adaptive immunity in a combination of stimuli for naive T cells. Aluminium salts induce humoral immunity via Th2 responses but have less effect on cell-mediated immunity and are therefore not useful in vaccines against intracellular pathogens[163].

The occurrence of vaccine-triggered phenomena represents a diagnostic challenge for clinicians and a research conundrum for many investigators. In the presence of a favourable genetic background, many autoimmune and inflammatory responses can be triggered by adjuvants and external factors, showing how each person might breach immune tolerance and drive many pathogenetic aspects of human diseases[164].

- **H1N1 vaccine and narcolepsy**

Narcolepsy is a chronic disorder presenting as excessive daytime sleepiness, and its variant with cataplexy, referred to as type 1 narcolepsy, is closely associated with HLA-DQB1*0602, which plays a central role in the immune system by presenting peptides derived from extracellular proteins[165, 166]. Investigations of patients with narcolepsy–cataplexy show that the neuropeptide orexin, which regulates arousal, wakefulness and appetite, is deficient in the cerebrospinal fluid of the majority of these patients[167,168]. More than 1300 cases of narcolepsy had been reported to the European Medicines Agency by January 2015 associated with an AS03-adjuvant influenza vaccine that was distributed to more than 30.5 million people in countries of the European Union and the European Economic Area during the outbreak of A(H1N1)pdm09 influenza[169]. In 2012, studies in Finland and Sweden showed an association between narcolepsy and vaccination with a European A(H1N1)pdm09 vaccine with AS03 adjuvant, an oil-in-water emulsion[170].

With regard to squalene-based adjuvants, no increased risk has been associated with the A(H1N1) pdm09 vaccine in which the adjuvant is MF59, with an estimated 6.5 million doses distributed in Europe and 25 million doses used in Europe and Latin America[170]. A lower risk for narcolepsy was found with an AS03 adjuvant pandemic vaccine, Arepanrix, in Canada than with a similar vaccine, Pandemrix, used in Europe[169]. These observations indicate that vaccine-associated narcolepsy is not due solely to the characteristics of the adjuvant[165-170].

4.3.5. Relation with other diseases

- **Haemangioma**

A haemangioma is a benign, usually self-involuting swelling or growth that most commonly appears as a rubbery, bright-red nodule of extra blood vessels in the skin[171-173]. Sometimes called a "strawberry mark", a haemangioma usually appears in the first weeks of life and grows most rapidly during the first 6 months[171,174-177]. Usually, growth is complete and involution has commenced by 12 months[171, 174-177]. A haemangioma can occur anywhere on the body but is most common on the face, scalp, chest or back[171].

The vast majority of infantile haemangiomas do not require medical or surgical intervention, unless they interfere with vision or breathing[178]. Medical care of clinically significant haemangiomas is limited to a few medications[178], including glucocorticosteroids[179-181] (topical, intralesional and oral), interferon α and, rarely, vincristine and topical imiquimod. Beta-blockers, specifically propranolol, were found serendipitously to induce involution of infantile haemangiomas[182-184].

If treatment with glucocorticosteroids is initiated, especially at a high dose (2 mg/kg body weight per day for more than 14 days), the immune system is weakened, resulting in increased susceptibility to infection. Therefore, it is important to reduce exposure to infections during treatment. No live virus vaccines should be given to people on steroid medication until treatment has been discontinued for at least 1 month18, [179-181]. There are no other contraindications to vaccination. Non-live vaccines may be administered[179-181]. The beta blocker propanolol does not appear to affect the immune system[182-184].

Thus, glucocorticoesteroids are immunosupressants, and treatment with these agents requires a temporary delay in administration of live vaccines; however, haemangiomas are not modified by vaccines, and they do not grow or pose any problem to vaccination[178-184].

- **Sudden infant death syndrome**

Sudden infant death syndrome is the sudden, otherwise unexplained death of an infant. The incidence of the syndrome peaks at 2 months of age, at which most infants receive their first vaccinations. The apparent association between the timing of vaccination and sudden infant death syndrome has been examined to determine whether there is a causal link. Almost all the well-controlled studies in the past 20 years showed that the number of deaths associated in time with DTP vaccination was within the range expected to occur by chance, irrespective of vaccination[185-192]. To date, all the published evidence suggests that vaccination does not increase the risk for sudden infant death syndrome, and some studies suggest that vaccination may lower the risk[187, 190-192].

The well-established risk factors for sudden infant death syndrome include gender (more likely in boys), age (2–3 months), race (in the USA, Black, American Indian and Alaskan Native infants are at higher risk), having siblings or cousins, prematurity, low birth weight, prone face-down sleeping position and parental smoking[185-192]. Major reductions in deaths from this syndrome followed successful campaigns to reduce the risk factors.

- **Diabetes**

Despite research throughout the world, there is no evidence that vaccines cause diabetes[193-202]. The incidence of type 1 diabetes began to increase in developed countries at a similar time to the introduction of widespread childhood vaccination. It was postulated in two studies that vaccination before 2 months of age protected against type 1 diabetes, whereas vaccination after that age increased the risk[203, 204]. The claim implicated hepatitis B and Hib vaccines and later included BCG and more recently MMR and pertussis-containing vaccines[203,204].

Subsequent to those reports, large, well-conducted studies found no link between any of the recommended childhood vaccines and type 1 diabetes, nor could they verify the findings of the earlier studies[193-202]. Changes in the timing of vaccination have not been shown to alter the risk for diabetes[193].

It is recommended that people with diabetes be vaccinated according to the national immunization programme schedule[193]. Furthermore, annual influenza vaccination is currently recommended for people with diabetes[205].

- **Cancer**

Two vaccines, hepatitis B and human papillomavirus (HPV) vaccine directly prevent cancer, as opposed to modifying the risk for cancer by attention to factors such as diet, exposure to tobacco smoke and lifestyle behaviour[206,207]. The hepatitis B vaccine prevents liver cancer (associated

with hepatitis B infection), and the HPV vaccine prevents cervical and other anogenital cancers (associated with HPV infection)[207]. Both these vaccines are inactivated; thus, they do not contain live virus and could not biologically cause cancer.

Some people believe that vaccines can cause cancer, because some batches of injectable polio vaccine produced between 1957 and 1963 were contaminated with a simian virus (SV40) that may be linked to the development of some cancers[208-209]. SV40 is found in some species of monkey and may be involved in causing cancer[208]. Between 1955 and 1963, some of the poliovirus vaccine administered in the USA was unknowingly contaminated with SV40 from the monkey kidney cell lines used to produce the vaccine[208-210]. Because SV40 was not identified until 1960, no one was aware that poliovirus vaccines made in the 1950s could have been contaminated[208-210]. All poliovirus vaccines manufactured since the early 1960s have been screened for SV40.

None of the current poliomyelitis vaccines contains SV40. SV40 is found in certain types of human cancer, such as mesothelioma (rare tumours located in the lungs), brain and bone tumours and some types of non-Hodgkin lymphoma[208-209]. The role of SV40 in human cancers is not, however, fully understood and is the topic of continued research. Most information, including many large studies in Europe and the USA[208], strongly suggests that people given vaccine containing SV40 between 1955 and 1963 were at no higher risk for cancer than people who did not receive poliovirus vaccine at that time.

- **Poliovirus vaccines and HIV/AIDS**

Some people have argued that an oral poliovirus vaccine used in the 1950s was contaminated with simian immunodeficiency virus (SIV), a primate virus that gave rise to HIV-1 that infects humans and causes AIDS[211]. A number of factors counter this argument:

- Testing of the vaccine showed no contamination with either SIV or HIV.
- The vaccine was not given to the people in whom AIDS was first identified.
- The vaccine was given to people in Europe and Africa, but early AIDS cases were seen only in Central Africa.
- The vaccine was produced in cells from Asian monkeys, which do not carry the viruses thought to be responsible for AIDS.

Even if a rumour of unofficial use of cells from chimpanzees in the Belgian Congo were true, recent molecular epidemiological research shows that the form of SIV in these animals did not match the HIV-1 strains that affect humans[212]. The argument that the Koprowski polivrus vaccine contained HIV is therefore thoroughly discredited[212].

- **Hepatitis B vaccine and multiple sclerosis**

There is no evidence that hepatitis B vaccine, or any other vaccine, causes multiple sclerosis, a chronic illness resulting from inflammation of myelin, the protective covering nerves in the brain and spinal cord[213-217]. The cause of multiple sclerosis is unknown, but genetic and environmental factors appear to be important[214].

In the 1990s, concern about hepatitis B vaccination was raised in France after reports of multiple sclerosis or multiple sclerosis-like illness after a large-scale programme of administration of hepatitis B vaccine to adolescents and young adults, in whom multiple sclerosis often first presents[218]. The French Government initially stopped the vaccination programme but resumed it when the rate of multiple sclerosis in vaccinated people was found to be similar to that in the general population.

Numerous other studies around the world and expert panels of WHO and the Institute of Medicine and the Centers for Disease Control and Prevention in the USA agree that there is no evidence to support the theory that vaccination with hepatitis B vaccine, or any other vaccine, is associated with an increased risk for multiple sclerosis[213-217]. There is also evidence that vaccination does not worsen the symptoms or cause relapses of multiple sclerosis[217].

- **HPV vaccines and safety, infertility or problems with pregnancy**

HPV vaccines were developed primarily to prevent cervical cancer; however, they also provide protection against other cancers in both men and women, including anal cancer, penile cancer and head-and neck-cancers[219,220]. HPV vaccines have been evaluated for safety and efficacy in the same way as all other vaccines. The European Medicines Agency, the Food and Drug Administration in the USA and WHO have concluded that HPV vaccines are safe and effective[219-229].

In clinical trials[222-226], the main side-effect of HPV vaccines was a local reaction at the injection site (pain, redness and swelling) in about 80% of those who received the vaccine. Other reported side-effects were fever, headache and fatigue but these were no more common in recipients of vaccine and of placebo[222-226]. Very few serious adverse events were reported after vaccination (in < 0.1%), and they were no more frequent than in those receiving the placebo vaccine[222-226]. Participants in the clinical trials were evaluated for up to 4 years after vaccination to determine whether they had experienced higher rates of new medical conditions, including autoimmune diseases[227]. No trends or patterns of new medical conditions or safety concerns were identified during the follow-up period[221-229]. As with all vaccines, adverse events after vaccination are still being monitored now that the vaccine is in use. Post-licensure surveillance data from various regulatory agencies in different countries confirm these reassuring findings[223, 224, 226].

There is no biologically plausible way in which HPV vaccine could cause infertility in either women or men[219-230]. HPV infection, unlike some other sexually transmitted infections such as chlamydia, is not a cause of infertility. Studies with high doses of HPV vaccine in female and male rats showed no effect on fertility[229,230]. Some Internet sites report a disturbing claim that one ingredient of the vaccine, polysorbate 80, caused infertility in rats. This claim is based on one study of newborn rats (weighing 10–17 g) that were injected in the abdomen with doses of polysorbate 80 that were 20–200 times the amount in Gardasil® HPV vaccine[231]. Several health institutions have reviewed the evidence and concluded that there is no evidence that polysorbate 80 at the level of 50 µg per 0.5-mL dose in Gardasil® poses a hazard to human reproduction or fertility[232]. Polysorbate 80 is found in numerous medications, including other vaccines, and is used as an additive in foods and cosmetics[233].

While it is recommended that vaccination be avoided during pregnancy, there is no evidence that inadvertent administration of HPV vaccine to a pregnant woman will increase her risk for adverse pregnancy outcomes[234,235]. Although participants were requested to avoid pregnancy during phase-3 trials of Gardasil®, 1796 women who received Gardasil® and 1824 who received a placebo became pregnant, and the rate of adverse pregnancy outcomes was similar in the two groups[224].

5. Practical tips for vaccination

5.1. Conservation

Failure to adhere to the recommended specifications for storage and handling of immunobiological material can reduce or destroy their potency, resulting in inadequate or no immune response in the recipient. Recommendations given in product package inserts, including methods for reconstituting the vaccine, should be followed carefully. Maintenance of vaccine quality is the shared responsibility of all handlers of vaccines, from the time a vaccine is manufactured until its administration. All vaccines should be inspected on delivery and monitored during storage to ensure that the recommended temperatures have been maintained. Inadequate vaccine storage can result in the loss of thousands of dollars' worth of vaccine and the cost of inventory replacement.

5.1.1. The cold chain

Maintaining the vaccine cold chain is essential for a successful immunization programme[236]. Vaccine manufacturers clearly state that they do not guarantee the potency of the vaccines if they are not stored at the temperatures recommended on the data sheet, which for most vaccines is 2–8 °C for short-term storage and –20 °C for long-term storage of live vaccines (BCG, OPV, measles and MMR (Table 10)[237]. The "T vaccines" (DPT, DT, TT) should not be frozen, as this may interfere with their efficacy. Some adjuvants (e.g. aluminium) can act as irritants and produce sterile abscesses[238].

Table 10. Recommended vaccine storage and transport temperatures

Vaccine	At state level	At zone level	At district level	At primary and community health centre level	During transport
OPV	–15 to –25 °C up to 6 months	–15 to –25 °C up to 3 months	–15 to –25 °C up to 3 months	+2 to +8 °C up to 1 month	In cold boxes with hard frozen icepacks or dry ice
Measles	+2 to +8 °C up to 6 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 1 month	In cold boxes with icepacks
BCG	+2 to +8 °C up to 6 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 1 month	In cold boxes with icepacks
DPT	+2 to +8 °C up to 6 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 1 month	In cold boxes with conditioned icepacks
Tetanus toxoid	+2 to +8 °C up to 6 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 1 month	In cold boxes with conditioned icepacks
Hepatitis B	+2 to +8 °C up to 6 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 3 months	+2 to +8 °C up to 1 month	In cold boxes with conditioned icepacks

OPV, oral poliovirus vaccine; BCG, bacille Calmette-Guérin; DPT, diphtheria, pertussis and tetanus

5.1.2. Vaccine storage

Refrigerators and freezers used for vaccine storage must maintain the required temperature range around the year, be large enough to hold the year's largest inventory and be dedicated to storage of vaccines[239]. Vaccine storage units must be carefully selected, used properly and consistently monitored to ensure that the recommended temperatures are maintained. Refrigerators without freezers and stand-alone freezers (manually or automatically defrosted) are usually the most effective at maintain¬ing the precise temperatures required for vaccine storage. Single-purpose units sold for home use are less expensive than special medical equipment and are preferable to combination units. A combination refrigerator–freezer unit sold for home use might be adequate for storing limited quan¬tities of vaccine if the refrigerator and freezer compartments have separate external doors. Before a refrigerator is used for vaccine storage, the temperature should be allowed to stabilize and then be measured in various locations within the compartment to ensure that a consistent temperature can be maintained. New units might have to be operated for ≥ 2 days to establish a stable operating temperature, and vaccine should not be stored in the unit until it maintains this temperature[239]. Refrigerator temperatures reflect the actual compartment temperature after the door has remained closed and undisturbed for several hours (e.g. overnight). The refrigerator temperature should be set at the midpoint of the recommended rang[239]. A storage unit should be sufficiently large that vaccines can be placed away from the walls in the part of the unit that best maintains the required temperature. Combination units with separate smaller compartments can be used to store only limited quantities of vaccine. Frequent opening and closing of doors can cause fluctuations in compartment temperature; food, beverages and clinical specimens should not be stored in vaccine storage units[239]. If it becomes necessary to store clinical specimens in the same unit as vaccines, the clinical specimens should be on a shelf below the vaccine to prevent contamination if the specimens leak.

5.1.3. Vaccine vial monitors

A vaccine vial monitor is a thermochromic label placed on vials containing vaccine, which gives a visual indication of whether the vaccine has been kept at the temperature that preserves its potency[239]. The labels were designed to respond to the problem of delivering vaccines to countries where the cold chain was difficult to preserve and where vaccines were formerly rendered inactive and administered ineffectively because they had been denatured by exposure to ambient temperature, especially for OPV, the most thermolabile vaccine[239]. The vial monitor consists of a heat-sensitive square within a circle. When the monitor is exposed to heat, it changes colour over time and at increasing speed in hotter conditions. If the square becomes the same colour as the circle or darker than the circle, the vaccine contained in the vial is damaged and the vial should be discarded (Fig. 8).

Fig. 8. Vaccine vial monitors: usable and unusable stages

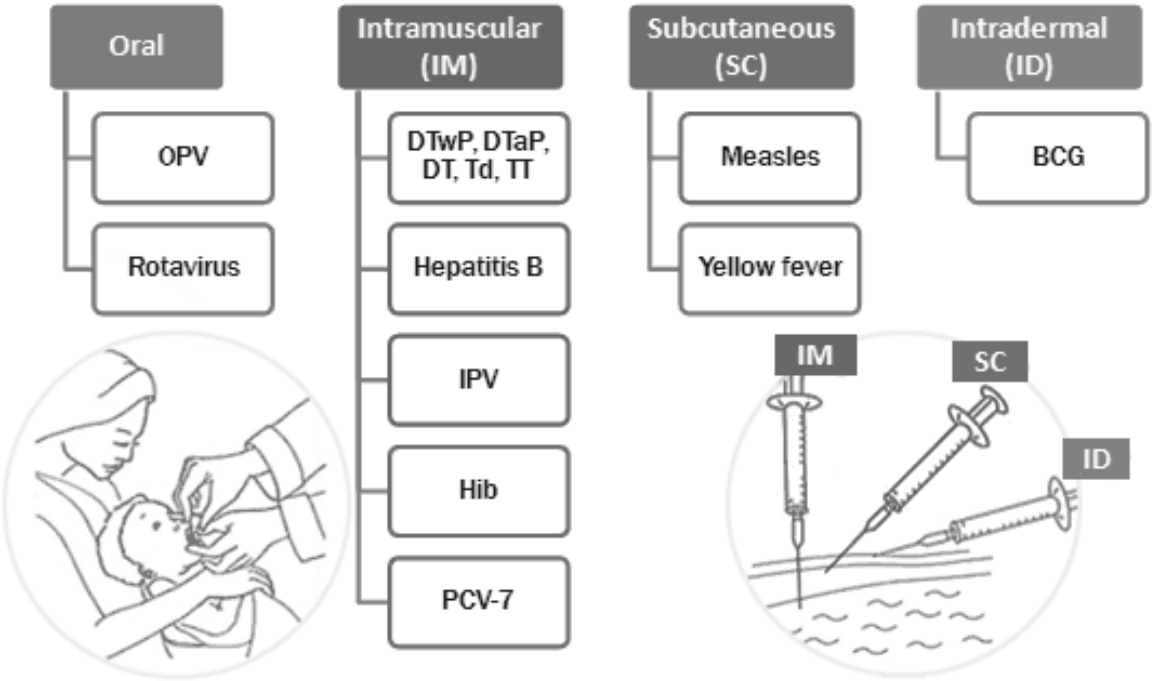
Usable Stages	Unusable Stages
	
Reading the Stages of the VVM The inner square is lighter than the outer circle. If the expiry date has not been passed: USE the vaccine.	Discard Point: The color of the inner square matches that of the outer circle: DO NOT use the vaccine. If the color of the inner square is darker than the outer circle, DO NOT use the vaccine.

VVM, vaccine vial monitor

5.2. Vaccine administration

The route of administration is the path by which a vaccine (or drug) is brought into contact with the body (Fig. 9). This is a critical factor for successful vaccination. A substance must be transported from the site of entry to the part of the body at which is to act. Using the body's transport mechanisms for this purpose is not, however, trivial.

Fig. 9. Routes of administration of vaccines



OPV, oral poliovirus vaccine; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; DTaP, diphtheria and tetanus toxoids and acellular pertussis; DT, diphtheria and tetanus toxoids; Td, tetanus and diphtheria toxoids; TT, tetanus toxoid; IPV, inactivated poliovirus vaccine; Hib, *Haemophilus influenzae* type b; PCV-7, pneumococcal conjugate vaccine; BCG, bacille Calmette-Guérin

OPV, oral poliovirus vaccine; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; DTaP, diphtheria and tetanus toxoids and acellular pertussis; DT, diphtheria and tetanus toxoids; Td, tetanus and diphtheria toxoids; TT, tetanus toxoid; IPV, inactivated poliovirus vaccine; Hib, *Haemophilus influenzae* type b; PCV-7, pneumococcal conjugate vaccine; BCG, bacille Calmette-Guérin

- **Intramuscular** injection is used to administer a vaccine into the muscle mass. Vaccines containing adjuvants should be injected intramuscularly to reduce the risk for local adverse effects[237,239].
- **Subcutaneous** injection is used to administer a vaccine into the subcutaneous layer above the muscle and below the skin.
- **Intradermal** injection is used to administer a vaccine into the topmost layer of the skin. BCG and IDflu are given by this route[237]. Intradermal injection of BCG vaccine reduces the risk for neurovascular injury[237,239]. A short, narrow needle (15 mm, 26-gauge) is required for injecting BCG vaccine, while other vaccines are given with a longer, wider needle (commonly 25 mm, 23 gauge) either subcutaneously or intramuscularly[237,239].
- **Intranasal** administration is performed with the patient in an upright position, and the tip is placed just inside the nostril to ensure that the vaccine is delivered into the nose. The patient should breathe normally.
- **Oral** administration of vaccine eliminated the requirement for a needle and syringe.

5.2.1. Which, when, where and how

Table 12 lists various vaccines, where should they be administered, when and by which route.

Table 12. Main vaccines doses, intervals and routes of administration[237,239]

	Vaccine	Time of vaccination	Dose	Route	Site
Infants	BCG	At or as soon as possible after birth	0.1 mL (0.05 mL until 1 month of age)	Intradermal	Left upper arm
	Hepatitis B	At birth or as soon as possible within 24 h	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
	OPV-0	At birth or as soon as possible within first 15 days	2 drops	Oral	Oral
	OPV 1, 2 and 3	At 6, 10 and 14 weeks	2 drops	Oral	Oral
	DPT 1, 2 and 3	At 6, 10 and 14 weeks	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
	Hepatitis B 1, 2 and 3	At 6, 10 and 14 weeks	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
	Measles	9 completed months, 12 months (give up to 5 years if not received at 9–12 months)	0.5 mL	Subcutaneous	Right upper arm
Children	DPT booster	16–24 months	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
	OPV booster	16–24 months	2 drops	Oral	Oral
	DPT booster	5–6 years	0.5 mL	Intramuscular	Upper arm
	Tetanus toxoid	10 and 16 years	0.5 mL	Intramuscular	Upper arm

BCG, bacille Calmette-Guérin; OPV, oral poliovirus vaccine; DPT, diphtheria, pertussis and tetanus

5.2.2. Simultaneous administration of several vaccines

All vaccines can be administered at the same visit as all other vaccines[237]. The exception is for asplenic children, to whom pneumococcal conjugate and Menactra brand meningococcal conjugate vaccines should not be administered at the same visit but should be separated by at least 4 weeks[237].

For many years, there has been a recommendation that when two live vaccines are required in the same individual, then the vaccines should either be given on the same day, or separated by an interval of at least four weeks[237]. This was based on early studies with measles and smallpox vaccines[240], and supported by the theory that interferon production stimulated by the replication of first vaccine prevented replication of the second agent, thus leading to a poor response to the second vaccine.

Based upon the available evidence and on the different immune mechanisms used by the various vaccines, in February 2014 the JCVI agreed that the guidance to either administer the vaccines on the same day or at four week interval period should not be generalised to all live vaccines[241]. They concluded therefore, that intervals between vaccines should be based only upon specific evidence for any interference of those vaccines (Table 13).

Table 13. Recommendations for giving more than one live attenuated vaccine

Vaccine combinations	Recommendations
Yellow Fever and MMR[242]	A four week minimum interval period should be observed between the administration of these two vaccines. Yellow Fever and MMR should **not** be administered on the same day.
Varicella (and zoster) vaccine and MMR[243]	If these vaccines are not administered on the same day, then a four week minimum interval should be observed between vaccines.
Tuberculin skin testing (Mantoux) and MMR[244]	If a tuberculin skin test has already been initiated, then MMR should be delayed until the skin test has been read unless protection against measles is required urgently. If a child has had a recent MMR, and requires a tuberculin test, then a four week interval should be observed.
All currently used live vaccines (BCG, rotavirus, live attenuated influenza vaccine (LAIV), oral typhoid vaccine, yellow fever, varicella, zoster and MMR) and tuberculin (Mantoux) skin testing.	Apart from those combinations listed above, these live vaccines can be administered at any time before or after each other. This includes tuberculin (mantoux) skin testing

Increasing the interval between doses of a multidose vaccine does not diminish its effectiveness[237]. Decreasing the interval between doses of a multidose vaccine may interfere with antibody response and protection[237]. It is not necessary to restart the series or add doses because of an extended interval between doses[237].

5.3. Vaccination records

5.3.1. Records of health care providers

Documentation of appropriate, timely vaccination helps to ensure not only that the people who should receive the recommended vaccine doses receive them but also that adequately vaccinated patients do not receive excess doses. Curtailing the number of excess doses administered to patients controls the costs incurred by patients, providers, insurers, vaccination programmes and other stakeholders. In addition, excess doses of inactivated vaccines might increase the risk for an adverse reaction[237]. Health care providers who administer vaccines are required to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date a vaccine was administered, the vaccine manufacturer, the vaccine lot number and the name, address and title of the person administering the vaccine[237]. Providers and staff members should systematically update the patient's permanent medical record to reflect any documented adverse events after vaccination and any serological test results related to vaccine-preventable diseases (e.g. those for rubella screening and antibody to HBsAg)[237].

5.3.2. Patient records

Patient records are used in vaccination education programmes to increase the awareness of parents and patients of the need for vaccination. A permanent record card should be established for each newborn infant and maintained by the parent or guardian, who should be informed about the importance of keeping the record up to date and instructed to keep it indefinitely as part of the child's permanent medical record[237]. Cards should be distributed to new mothers before they are discharged from hospital. Vaccination record cards for adolescents and adults are also encouraged[237].

5.3.3. Vaccination information systems

Formerly referred to as "immunization registries", these are confidential, population-based, computerized information systems for collecting and consolidating data on vaccination from multiple health-care providers in a geographical area[245]. They can increase and sustain vaccination coverage by consolidating the records from multiple providers, generating reminder and recall notices for each person and providing official vaccination forms and vaccination coverage assessments[245].

Vaccination providers often change during a vaccination series, and these changes and the vaccination records are often unavailable or not entered into an information system. Missing or inaccurate information on the vaccines received can preclude accurate determination of the vaccines required at the time of a visit, resulting in administration of extra doses[245]. A fully operational information system prevents duplicate vaccination, missed appointments, vaccine waste and staff time required to produce or locate vaccination records or certificates[245]. Most health information systems also allow vaccine management, maintenance of lifetime vaccination histories and interoperability with other systems[245].

5.4. Advice on vaccination

Advice to parents and children determines a successful immunization programme[246]. Various techniques can be used, but what is most important is that all questions or doubts are resolved and the process is as un-traumatic as possible. Examples of information for parents are outlined below.

5.4.1. Before vaccination

Parents should come prepared. They should be advised to take the following steps before vaccination of their child to help make the visit less stressful for both them and their children. They should:

- read all the material about vaccination that they receive from their child's health care professional and write down any questions they may have;
- find their child's vaccination record and bring it to the appointment to ensure that their doctor knows exactly what vaccines their child has already received;
- pack a favourite toy, book or blanket that their child uses regularly for comfort;
- be honest with older children and explain that vaccination may pinch or sting but won't hurt for long;
- engage other family members, especially older siblings, in the support of the child; and
- avoid telling scary stories or making threats about injections.

5.4.2. At the doctor's office

Any question about vaccination should be addressed to the child's doctor or nurse, and the child's doctor should be approached for advice on using non-aspirin pain relievers and other steps that can be takes at home to comfort the child. To make injections easier for a child:

- Distract and comfort the child by cuddling, singing or talking softly.
- Smile and make eye contact with the child; let the child know that everything is under control.
- Comfort the child with a favourite toy or book, such as a blanket that smells familiar.
- Hold the child firmly on the lap whenever possible.

For older children:

- Take deep breaths to help "blow out" the pain.
- Point out interesting things in the room to distract the child.
- Tell or read stories.
- Support the child if he or she cries. Never scold a child for not "being brave."

Remember to schedule your next visit. Familiarization with a child's vaccinations is the best protection against disease. Support is important once a child has received all of the injections, and infants should be held, cuddled, breastfed or offered a bottle. A soothing voice, praise and hugs reassure a child that everything is under control.

5.4.3. After vaccination

Some children experience mild reactions to vaccines, such as pain at the injection site, a rash or a fever. These reactions are normal and will soon resolve. The following tips will help identify and minimize mild side-effects.

- Review any information from your doctor about the injections, especially vaccine information statements and other information on what side-effects to expected.
- Use a cool, wet cloth to reduce redness, soreness and swelling at the place the injection was given.
- Reduce any fever with a cool sponge bath. If your doctor approves, give a non-aspirin pain reliever.
- Give your child lots of liquid. It's normal for some children to eat less during the 24 h after vaccination.
- Pay extra attention to your child for a few days. If you see something that concerns you, call your doctor.

6. Vaccination in special situations

6.1. Altered immunocompetence

The term "altered immunocompetence" is often used synonymously with "immunosuppression" and "immunocompromise". Primary immunodeficiency is generally inherited and includes conditions defined by the absence or quantitative deficiency of cellular or humoral components of immunity (e.g. X-linked agammaglobulinaemia)[247]. Secondary immunodeficiency is generally acquired and is defined by loss or qualitative deficiency in cellular or humoral immune components as a result of a disease process or its treatment (e.g. HIV infection)[247]. The degree to which immunosuppressive drugs cause clinically significant immunodeficiency is usually related to dose and varies by drug[237].

Determination of altered immunocompetence is important for vaccine providers because the incidence or severity of some vaccine-preventable diseases is higher in such people; therefore, certain vaccines (e.g. inactivated influenza vaccine and pneumococcal vaccines) are recommended specifically for persons with these diseases[237]. Vaccines might be less effective during the period of altered immunocompetence. Administration of live vaccines might have to be deferred until immune function has improved, and administration of inactivated vaccines during the period of altered immunocompetence might have to be repeated after immune function has improved[237]. In addition, people with altered immunocompetence might be at increased risk for adverse reactions after administration of live attenuated vaccines because of uninhibited replication[247].

Clinicians and other health care providers must assess the safety and effectiveness of vaccines. Laboratory studies can be useful for assessing the effects of a disease or drug on the immune system. The general principles are:

- Assess whether the patient receive immunosuppressive therapy.
- Review and complete vaccination according to the routine immunization schedule.
- Consider additional vaccines indicated by the underlying disease.
- Order pre-vaccination serology before MMR, hepatitis A, hepatitis B and varicella vaccines.

6.1.1. Immunodeficiency

Before vaccination of a patient who is immunodeficient, consideration must be taken of whether the vaccine is inactivated or live. All inactivated vaccines can be administered safely to people with altered immunocompetence, and the usual doses and schedules are recommended; however, the effectiveness of the vaccine might be suboptimal[237,248]. People with any of most forms of altered immunocompetence should not receive live vaccines, and those with severe cell-mediated immunodeficiency should not receive live attenuated viral or bacterial vaccines[237,248].

6.1.2. Vaccination of contacts

Household and other close contacts of people with altered immunocompetence can receive all the age-appropriate vaccines except smallpox vaccine[237,248]. MMR, varicella and rotavirus vaccines may be administered without restriction, as MMR vaccine viruses are not transmitted to contacts, and transmission of varicella vaccine is rare[248]. No specific precautions are required, unless the varicella vaccine recipient has a rash after vaccination, in which case direct contact with susceptible contacts should be avoided until the rash resolves[248]. All household contacts should wash their hands after changing the diaper of an infant who has received rotavirus vaccine for an undetermined number of weeks after vaccination. Household and other close contacts of people with altered immunocompetence should be vaccinated against influenza annually[237,248]. Live attenuated influenza vaccines may be administered to healthy household and other close contacts of people with altered immunocompetence[237,248].

6.2. Conditions that might cause immunodeficiency

6.2.1. HIV infection

Children infected with HIV are vulnerable to severe, recurrent or unusual infections with the pathogens that cause vaccine-preventable diseases[249]. The efficacy and safety of vaccines depends on the extent of their immunodeficiency[249]. In general, most vaccines are safe and efficacious in early life, as the immune system is relatively well preserved, although the duration of protection may be compromised, as the memory response is impaired with immune attrition[249]. Vaccines are significantly less effective and safe in children with advanced disease, and consideration should be given to re-administering childhood vaccines to such children when their immune status has improved after antiretroviral therapy[249]. An infant born to an HIV-positive mother but with an indeterminate HIV status should be vaccinated according to the normal schedule[249]. Table 14 summarizes recommendations for vaccination of HIV-infected children[237,249].

Table 14. Recommendations for vaccination of HIV-infected children

Vaccine	Asymptomatic child	Symptomatic child
BCG	Yes (at birth)	No
DTwP/TT/Td/Tdwp	Yes, as per routine schedule	
Hib	Yes, as per routine schedule	
Polio vaccines	IPV; OPV if IPV not affordable	
Measles vaccine	Yes	Yes, if CD4 count > 200 (> 15%)
Inactivated influenza vaccine	Yes, recommended if not part of routine schedule	
Rotavirus	Insufficient data	
Hepatitis B	Yes	Yes, four doses, double dose, check seroconversion, boosters
Hepatitis A	Yes	Yes, check seroconversion, boosters
Varicella	Yes	Yes, if CD4 count > 200 (> 15%)
Vi typhoid	Yes	Yes, if CD4 count > 200 (> 15%)
HPV	Yes, as per routine schedule	
Pneumococcal	Yes, 3+1 schedule (boosters may be needed)	
Men ABCWY	Yes, recommended if not in routine schedule	

BCG, bacille Calmette-Guérin; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; TT, tetanus toxoid; Td, tetanus and diphtheria toxoids; Tdwp, tetanus toxoid, reduced diphtheria toxoid and whole-cell pertussis; Hib, *Haemophilus influenzae* type b; Vi typhoid, capsular polysaccharide typhoid vaccine; Men, meningococcal

6.2.2. Congenital immunodeficiency in children

Live vaccines, including OPV, BCG, oral typhoid and live attenuated influenza, are contraindicated in patients with severe B-cell immunodeficiency (X-linked agammaglobulinaemia)[237,249]. Measles and varicella vaccines may be given, but they may be ineffective due to concomitant immunoglobulin therapy[237,249]. Inactivated vaccines may be given but are ineffective[237,249]. In less severe B-cell deficiency, such as IgA and IgG subclass deficiency, only OPV is contraindicated[237,249]. In patients with severe T-cell immunodeficiency (e.g. SCID), all live vaccines are contraindicated, and all vaccines are ineffective[237,249]. Patients who have received live vaccine, especially BCG, before diagnosis are at increased risk for complications, including disseminated BCG disease[249]. For patients with combined immunodeficiency, such as Di George syndrome, Wiskott-Aldrich syndrome and ataxia telangiectasia, inactivated vaccines may be given, but live vaccines are contraindicated[249]. All vaccines may be safely given to children with complement deficiency, and pneumococcal, Hib and meningococcal vaccines are particularly indicated[249]. In patients with phagocyte defects such as chronic granulomatous disease, only live bacterial vaccines are contraindicated; other vaccines may be given safely and effectively[249]. See Table 15 for more details.

Table 15. Recommendations for vaccination in cases of the main types of immunodeficiency

Type of immunodeficiency	Vaccines contraindicated	Vaccines indicated	Comments
Major antibody deficiency (agammaglobulinaemia, hypogammaglobulinaemia)	All live vaccines	Influenza Other inactivated vaccines on immunization calendar	Vaccination with Men C or Men ACWY (preferred) recommended
Minor antibody deficiency (IgA deficiency of polysaccharide antibody deficiency)	OPV	All vaccines on immunization calendar, including live vaccines Influenza	Vaccination with Men C or Men ACWY (preferred) recommended Pneumococcal vaccination in combined schedule (PCV13 + PS23) recommended
Complement deficiency (classical or alternative pathway)	No contraindications	All vaccines on immunization calendar Pneumococcal, Hib and meningococcal are **mandatory**	Vaccination with Men C or Men ACWY (preferred) New Men B vaccine recommended
Phagocytic system deficiencies (chronic granulomatous disease), adhesion molecule defect, Chédiak–Higashi syndrome, congenital neutropenia	Live bacterial vaccines (BCG, oral typhoid vaccines) in chronic granulomatous disease All live vaccines in adhesion molecule defect and Chédiak–Higashi syndrome	All vaccines on immunization calendar, except all live vaccines in adhesion molecule defect and Chédiak–Higashi syndrome	Pneumococcal vaccination in combined schedule (PCV13 + PS23) recommended
Innate immune defects (IL-12, interferon-γ	All live vaccines (BCG, oral typhoid, MMR, varicella)	All vaccines on immunization calendar, except live vaccines Influenza	Pneumococcal vaccination in combined schedule (PCV13 + PS23) recommended
Mixed or combined T-cell deficiency (complete DiGeorge syndrome, ataxia telangiectasia, Wiskott-Aldrich syndrome, hyper-IgE syndrome)	All live vaccines (BCG, oral typhoid, MMR, varicella)	Some guidance does not recommend inactivated vaccines if the patient is receiving intravenous immunoglobulin Influenza	Patients with incomplete DiGeorge syndrome may receive MMR and varicella vaccines if their CD3 count is > 500/m^3, their CD8 count ≥ 200/m^3 and a normal mitogen response

Men, meningococcus; Ig, immunoglobulin; OPV, oral poliovirus vaccine; PCV, pneumococcal conjugate vaccine; PS23, 23-valent pneumococcal polysaccharide vaccine; IL, interleukin; MMR, measles, mumps and rubella

6.2.3. Recipients of haematopoietic cell transplants

Recipients of haematopoietic stem cell transplants are no longer immunized, as they lose all memory responses in marrow ablation[250]. Influenza vaccine should be given before the transplant, 6 months after the transplant and for life[237,250]. MMR and varicella vaccines may be given 24 months after transplant if the recipient is judged to be immunocompetent[237,250]. Inactivated vaccines may be given 6–12 months after transplant[237,250].

All susceptible contacts of haematopoietic stem cell transplant recipients, including household and health care worker contacts should be vaccinated against varicella and influenza 6 weeks before the transplantation[237,250].

6.2.4. Recipients of solid organ transplants

Recipients of solid organ transplants should complete all vaccinations before the transplant, in accelerated schedules if necessary[237,251]. Vaccination with live vaccines should be completed at least 4 weeks before the transplant and seroconversion should be documented[237,251]. After transplantation, all live vaccines are contraindicated[251]. In patients who have not completed vaccination before the transplant, inactivated vaccines can be given 6 months afterwards when immunosuppression has been lowered[237,251]. Boosters for inactivated vaccines should be given 6 months after the transplant as per the schedule when antibody levels wane (hepatitis A and B)[237,251]. Annual vaccination against influenza is recommended[237,251]. All household and health care worker contacts should be vaccinated against influenza and varicella[237].

6.2.5. Anatomical or functional asplenia

People with anatomical asplenia (e.g. after surgical removal or congenital absence of the spleen) or functional asplenia (as in sickle-cell disease) are at increased risk for infection by encapsulated bacteria, especially *Streptococcus pneumoniae, Neisseria meningitidis* and Hib[252]. Children aged < 5 years with anatomical or functional asplenia should receive the age-appropriate series of PCV, and those aged ≥ 2 years should receive two doses of pneumococcal polysaccharide vaccine separated by 5 years[237,253].

Quadrivalent meningococcal polysaccharide vaccine also should be administered to asplenic children greater than or equal to 2 years of age[237,253]. Immunization with Hib vaccine should be initiated in infancy at the same dosage and schedule as recommended for otherwise healthy children[237,253].

Pneumococcal, meningococcal and Hib vaccines should be administered at least 14 days before elective splenectomy, if possible[237,253]. If they are not administered before surgery, they should be administered 2 weeks after the procedure, as soon as the patient's condition is stable[237].

6.2.6. Bleeding disorders

Because of the risk for haematoma formation after intramuscular injection, people with bleeding disorders are often given vaccines that are usually administered by this route subcutaneously or intradermally[237,254]. In one study, hepatitis B vaccine was administered intramuscularly to 153 people with haemophilia with a 23-gauge or smaller calibre needle, followed by application of steady pressure to the site for 1–2 min[255]. The bruising rate was low (4%), and no patients required factor supplements[255]. It is not known whether intramuscular administration of antigens that produce more local reactions (e.g. pertussis) would result in an equally low rate of bruising.

When hepatitis B or another intramuscularly administered vaccine is indicated for a patient with a bleeding disorder, it should be administered only if a physician familiar with the patient's risk for bleeding determines that the administration would be reasonably safe[237]. If the patient receives

antihaemophilia or similar therapy, intramuscularly administered vaccines can be scheduled shortly after such therapy is administered[237,254]. A fine-gauge needle (23-gauge or smaller calibre) should be used, followed by firm pressure on the site, without rubbing, for at least 2 min[237,254]. The patient or family should be informed about the risk for haematoma from the injection.

Patients receiving anticoagulation therapy presumably have the same bleeding risk as patients with clotting factor disorders, and the same guidelines for intramuscular administration should be followed[237,254].

6.2.7. Chronic illnesses in children

Children with chronic neurological, endocrinological (diabetes), hepatic, renal, haematological, cardiac, pulmonary or gastrointestinal disease are at increased risk for infection and for serious infections[256]. Live vaccines may be given safely to these children (except those with immunosupression)[237,257,258]. They should be offered pneumococcal, hepatitis A and B, meningococcal, varicella and influenza vaccines[257,258]. It is important to stress the role of hepatitis A vaccine in patients with liver disease, pertussis boosting in those with stable neurological disease and influenza in those with cardiac or pulmonary disease[257,258]. The main recommendations for vaccination of children with chronic illnesses are summarized in Table 16.

Table 16. Recommendations for administration of vaccines to patients with chronic illnesses

Vaccine	Asplenia or hyposplenia	Renal disease or dialysis	Neurological disorders	Lung disease	Liver disease	Endocrine and metabolic diseases	Heart disease	Chronic inflammatory diseases	Non-malignant haematological disorders
Inactivated									
DTaP	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use
Hib	Recommended (all ages)	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use
Hepatitis A	Recommended before transfusions (sickle-cell disease)	Recommended if not routine	Recommended if not routine	Recommended if not routine	Recommended	If indicated	Recommended if not routine	Recommended if not routine	Recommended in haemophilia and repeated infusions
Hepatitis B	Routine use, recommended before transfusions	Recommended	Routine use	Routine use	Recommended	Routine use	Routine use	Routine use	Recommended in haemophilia and repeated infusions
Influenza (TIV)	Recommended annually	Recommended annually	Recommended annually	Recommended annually	Recommended annually	Recommended annually	Recommended annually	Recommended annually if immune-suppressed	Recommended annually in anaemia or haemoglobinopathy
Meningococcal	Recommended (all ages) Men ACYW indicated	Recommended if not routine	Recommended if not routine	Recommended if not routine	Recommended if not routine	Recommended if not routine	Recommended if not routine	Recommended if not routine	Recommended if not routine
Pneumonia 13-V	Recommended (all ages)	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended if immune-suppressed	Recommended in haemoglobinopathy
Pneumonia 23-V	Recommended (> 2 years)	Recommended (> 2 years)	Recommended (> 2 years)	Recommended (> 2 years)	Recommended (> 2 years)	Recommended in diabetes	Recommended (> 2 years)	Recommended if immune-suppressed	Recommended in haemoglobinopathy
Live									
BCG	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use
MMR	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use if not immune-suppressed	Routine use
OPV	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use if not immune-suppressed	Routine use
Rotavirus	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use if not immune-suppressed	Routine use
Varicella	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use	Routine use if not immune-suppressed	Routine use

DTaP, diphtheria and tetanus toxoids and acellular pertussis; Hib, *Haemophilus influenzae* type b; TIV, trivalent inactivated vaccine; V, valent; BCG, bacille Calmette-Guérin; MMR, measles, mumps and rubella; OPV, oral poliovirus vaccine

6.3. Drugs that might cause immunodeficiency

6.3.1. Corticosteroids

Corticosteroid therapy is not usually a contraindication to administering live-virus vaccine when it is given[237,259]:

- for < 14 days;
- at a low-to-moderate dose (< 20 mg of prednisone or equivalent per day);
- as long-term, alternate-day treatment with a short-acting preparation;
- as a physiological maintenance dose (replacement therapy) or
- topically (skin or eyes), inhaled or by intraarticular, bursal or tendon injection.

No severe reactions have been reported to live, attenuated viral vaccines in people receiving corticosteroid therapy by aerosol, and this therapy should not delay vaccination[237,259].

Although the immunosuppressive effects of steroid treatment vary, most clinicians consider that a dose equivalent to ≥ 2 mg/kg body weight per day or ≥ 20 mg/day of prednisone or equivalent to people who weigh > 10 kg administered for ≥ 14 days at ≥ 2 mg/kg body weight per day (or ≥ 28 days at ≥ 1 mg/kg body weight per day) is sufficiently immunosuppressive to raise concern about the safety of vaccination with live-virus vaccines[237,259]. Corticosteroids given at greater than physiological doses can reduce the immune response to vaccines. Vaccination providers should defer live-virus vaccination for at least 1 month after discontinuation of high-dose, systemically absorbed corticosteroid therapy administered for > 14 days[237,259].

6.3.2. Other immunosuppressive drugs

When feasible, clinicians should administer all the indicated vaccines to all patients before initiating chemotherapy, before treatment with other immunosuppressive drugs and before radiation or splenectomy[237,260].

Chemo- and radiotherapy

Patients receiving chemotherapy or radiation for leukaemia and other haematopoietic malignancies, for solid tumours or after solid organ transplant should be assumed to have altered immunocompetence[260]. Live, attenuated vaccines should not be administered for at least 3 months after such therapy[261]. Inactivated vaccines that are administered during chemotherapy should be re-administered after immune competence is regained[237,261]. Children receiving chemotherapy for leukaemia, lymphoma and other malignancies or radiation are generally considered to retain immune memory after treatment, although revaccination with the common childhood vaccines after chemotherapy for acute lymphoblastic leukaemia might be indicated[237,260,261]. In general, revaccination of a person after chemotherapy or radiation therapy is considered unnecessary if the previous vaccination was done before and not during therapy, with the exception of recipients of haematopoietic cell transplantation, who should be revaccinated as recommended previously[237].

Other immunosuppressive drugs

Several immunosuppressive drugs can be used in chronic autoinmune diseases. Methotrexate

at < 0.4 mg/kg body weight per week, 6-mercaptopurine at < 1.5 mg/kg body weight per day and azathioprine at < 3 mg/kg body weight per day confer little immunosupression, whereas anti-TNF (such as etanercept, infliximab and adalidumab), rituximab, anti-IL-1 (anakinra, canakinumab), anti-IL-6 (tocilizumab), anti-IL-12 and anti-IL-23 (ustekinumab) confer high immunosuppression[137,262-266].

Inactivated vaccines may be administered during low-dose intermittent or maintenance therapy with immunosuppressive drugs; however, the safety and efficacy of live, attenuated vaccines during such therapy is unknown[137,262-266]. Physicians should carefully weigh the risks and benefits of giving injectable live vaccines to adults receiving immunosuppressive therapy for chronic autoimmune disease[137,262-266]. In general, vaccination is considered safe when done 1 month after discontinuation of immunosuppressive therapy with corticosteroids, 3 months after discontinuation if they cause low immunosuppression and 6 months after discontinuation if they cause high immunosupression[137]. Varicella vaccine can be given safely 4 weeks before starting immunosuppressive drugs and MMR vaccine 6 weeks before treatment[137].

Further recommendations include administration of hepatitis A vaccine to patients receiving hepatotoxic drugs (methotrexate or tocilizumab), HPV vaccine to males and females receiving immunosuppressive drugs and meningoccocal ABCWY, Hib and pneumococcal vaccine to patients receiving eculizumab[137,266].

6.3.3. Antibody-containing products

Inactivated vaccines can be safely administered simultaneously but at different sites or at any time with antibody-containing products (whole blood, packed red cells, plasma, immunoglobulin) with no loss of immunogenicity or efficacy[137,267-269]. The exception is administration of rabies immunoglobulin 7 days after rabies vaccine[137,267-269]. Live vaccines, including MMR and varicella, should be avoided for at least 3 months (Table 17) after reception of antibody-containing products, and these products should be avoided for 2 weeks after receipt of these vaccines[137,267-269]. If vaccination outside this prescribed period has been conducted, the serological response should be checked and vaccination repeated if indicated[137,267-269]. Oral typhoid vaccine, live attentuated influenza vaccine, OPV and yellow fever vaccine may be given at any time in relation to antibody-containing products[137,267-269]. Rotavirus vaccine should be avoided for 6 weeks after such products are given, although the vaccine may be given if deferral results in postponement of the first dose of rotavirus vaccine beyond 15 weeks[137,267-269].

Table 17. Recommended intervals for administration of MMR vaccine after immunoglobulin or blood product transfusión

Product	Timing of administration of MMR vaccine (months)
Non-specific immunoglobulins	3
Polyvalent Ig at 0.02–0.06 mL/kg body weight	5
Polyvalent Ig at 0.25 mL/kg body weight	6
Polyvalent Ig at 0.50 mL/kg body weight	8
Polyvalent Ig immunodeficiency therapy at 300–400 mg/kg body weight	8–10
Polyvalent Ig immunodeficiency therapy at 400–1000 mg/kg body weight	8
Prophylaxis after exposure to varicella at 400 mg/kg body weight	11
Therapy for Kawasaki disease at 2 g/kg body weight	3
Anti-hepatitis B immunoglobulin	4
Anti-rabies immunoglobulin	3
Anti-tetanus immunoglobulin	5
Anti-varicella zoster immunoglobulin	
Blood and blood products	
Blood	6
Red cells	6
Plasma or platelets	7

6.3.4. Concurrent administration of antimicrobial agents and vaccines

With a few exceptions, administration of antimicrobial agents is not a contraindication to vaccination[137]. Antibacterial agents have no effect on the response to live, attenuated vaccines, except for live oral typhoid vaccine, and have no effect on inactivated, recombinant subunit or polysaccharide vaccines or toxoids[137,270]. Typhoid vaccine should not be administered to people receiving antimicrobial agents until 24 h after the last dose[270]. If feasible, to avoid a possible reduction in vaccine effectiveness, antibacterial drugs should not be started or resumed until 1 week after the last dose of oral typhoid vaccine[270].

Antiviral drugs used for treatment or prophylaxis of influenza virus infections have no effect on the response to inactivated influenza vaccine; however, live, attenuated influenza vaccine should not be administered until 48 h after cessation of therapy[137,271]. If feasible, to avoid possible reduction in vaccine effectiveness, antiviral medication should not be administered for 14 days after live attenuated influenza vaccine[271]. Antiviral drugs that are active against herpesviruses (e.g. acyclovir and valacyclovir) might reduce the efficacy of live, attenuated varicella and zoster vaccines, and these drugs should be discontinued at least 24 h before administration of vaccines containing varicella zoster virus, including zoster vaccine, if possible[137,272,273]. Use or resumption of antiviral therapy should be delayed for 14 days after vaccination[137,272,273]. There is no evidence that commonly used antiviral drugs affect the efficacy or safety of rotavirus or MMR vaccine[137].

6.4. Vaccination of preterm infants

In most cases, preterm infants (born before 37 weeks' gestation), regardless of birth weight, should be vaccinated at the same chronological age and according to the same schedule and with the same precautions as for full-term infants and children (Table 18)[137,274-279]. Birth weight and size do not determine whether a clinically stable preterm infant should be given the full recommended dose of each vaccine; divided or reduced doses are not recommended[274-279].

Table 18. Administration of vaccines to preterm infants

Vaccine	Considerations for administrations to preterm infants
Tuberculosis (BCG)	Eligible infants born ≥ 34 weeks' gestation can receive BCG vaccine soon after birth. Eligible infants born before 34 weeks' gestation should not receive BCG vaccine until 34 weeks' gestational age.
DPT, polio and Hib	Three doses beginning at 6 weeks of age
Invasive pneumococcal disease (PCV)	Preterm infants born < 32 weeks' gestational age or with chronic lung disease are eligible for: • 13-valent pneumococcal conjugated vaccine (Prevenar13®): 3+1 vaccination schedules, otherwise as per immunization calendar, followed by • two 23-valent pneumococcal polysaccharide vaccine doses (Pneumovax® 23), the first at ≥ 2 years of age and the second 5 years after the first
Rotavirus	Medically stable preterm infants should be vaccinated according to the same schedule as full-term infants. There is a theoretical risk of disease resulting from horizontal transfer of the vaccine virus. The first dose to infants who are still hospitalized at 6 weeks of age: • should be deferred until the day they are discharged if this is to occur before the infant is 15 weeks of age or • should be administered while the infant is still in hospital if discharge is not anticipated before the infant is 15 weeks of age.

The main considerations in vaccinating preterm infants are as follows[274-279].

- The preferred site for intramuscular injection is the vastus lateralis.
- A 23–25-gauge, 16-mm needle inserted at a 90° angle to the skin is usually adequate.
- Preterm infants may have a poor immune response to some vaccines, although evidence suggests that the response is still protective[274-283].
- Vaccination of these infants is safe and effective, although post-vaccination apnoea with or without associated bradycardia up to 48 h after vaccination may occur more frequently in some groups[284].

If a child aged at least 6 weeks has been in hospital since birth, deferral of rotavirus vaccination is recommended until the time of discharge[285]. The rotavirus vaccine series should not be initiated for infants aged ≥ 15 weeks[285].

Preterm infants weighing < 2000 g at birth may have decreased seroconversion rates after administration of hepatitis B vaccine at birth. By a chronological age of 1 month, however, all

preterm infants, regardless of their birth weight, are likely to respond as adequately as larger infants[280-282]. Preterm infants born to HBsAg-positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine within 12 h of birth[286]. The initial vaccine dose should not be counted in completion of the series, and three additional doses of hepatitis B vaccine should be administered, starting when the infant is 1 month of age.

6.5. Vaccination during breastfeeding

Neither inactivated nor live-virus vaccines administered to a lactating woman affects the safety of women or their breastfeeding infants[137]. Although live viruses in vaccines can replicate in vaccine recipients (i.e. the mother), most live viruses in vaccines, including varicella vaccine virus, are not excreted in human milk[288]. Although rubella vaccine virus might be excreted, it usually does not infect the infant. If infection does occur, it is well tolerated because the virus is attenuated[289].

Inactivated, recombinant, subunit, polysaccharide and conjugate vaccines, as well as toxoids, pose no risk for mothers who are breastfeeding or for their infants. Breastfeeding is a contraindication for smallpox vaccination of the mother because of the theoretical risk for contact transmission from mother to infant. Yellow fever vaccine should be not be given to breastfeeding women[290]; however, if a nursing mother cannot avoid or postpone travel to areas endemic for yellow fever in which risk for acquisition is high, she should be vaccinated.

Limited data indicate that breastfeeding enhances the response to certain vaccine antigens[292]. There is no evidence that passive transfer of antibodies to human milk affects the efficacy of live-virus vaccines. Breastfed infants should be vaccinated according to the recommended schedule[292-294].

6.6. Vaccination during pregnancy

Developing fetuses are theoretically at risk from vaccination of the mother during pregnancy. There is no evidence of risk to the fetus from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids[295,296]. As live vaccines administered to a pregnant woman pose a theoretical risk to the fetus, live, attenuated virus and live bacterial vaccines are generally contraindicated[137]. The benefits of vaccinating pregnant women usually outweigh the potential risks when the likelihood of exposure to the disease is high, when infection would pose a risk to the mother or fetus and when the vaccine is unlikely to cause harm[137].

Pregnant women who received the last dose of tetanus toxoid-containing vaccine > 10 years previously should generally receive tetanus and diphtheria toxoids while they are pregnant[297]. A dose during pregnancy ensures adequate immunity to tetanus in the mother and prevents disease in both the mother and infant. The dose of Td can be withheld if the provider is confident that the pregnant woman is immune to tetanus[298]. Pregnant women who have not been vaccinated or are only partly vaccinated against tetanus should complete the primary series[297]. Women for whom Td is indicated but who did not complete the recommended three-dose series during pregnancy should receive follow-up after delivery to ensure that the series is completed.

Women in the second and third trimesters of pregnancy are at increased risk for hospitalization for influenza[299,300]. As vaccination against influenza before the season begins is critical and predicting

exactly when the season will begin is impossible, routine influenza vaccination is recommended for all women who are or will be pregnant (in any trimester) during the influenza season[299].

IPV can be administered to pregnant women who are at risk for exposure to wild-type poliovirus infection. Hepatitis A, pneumococcal polysaccharide, meningococcal conjugate and meningococcal polysaccharide vaccines should be considered for women at increased risk for those infections[301-303]. Pregnant women who must travel to areas where the risk for yellow fever is high should receive yellow fever vaccine because the limited theoretical risk from vaccination is outweighed substantially by the risk for infection[304]. Hepatitis B vaccine is not contraindicated in pregnancy and should be given to any pregnant woman for whom it is indicated[305].

Pregnancy is a contraindication for smallpox vaccine and measles-, mumps-, rubella- and varicella-containing vaccines[137]. Smallpox vaccine is the only vaccine known to harm the fetus when administered to a pregnant woman[137]. In addition, smallpox vaccine should not be administered to a household contact of a pregnant woman[306].

Studies of children born to mothers vaccinated with rubella vaccine during pregnancy indicate the presence of rubella antibodies in unvaccinated infants, which may represent passive transfer of maternal antibody or a fetal antibody response to vaccine virus infection[307-309]. No cases of congenital rubella, varicella syndrome or abnormalities attributable to fetal infection have been observed in infants born to susceptible women who received rubella or varicella vaccines during pregnancy[307-309]. Because of the importance of protecting women of childbearing age against rubella and varicella, reasonable practices in any vaccination programme include asking women whether they are pregnant or might become pregnant in the coming 4 weeks; not vaccinating women who state that they are or plan to become pregnant; explaining the theoretical risk of the fetus if MMR, varicella or MMRV vaccine is administered to the pregnant mother and counselling women who are vaccinated not to become pregnant for 4 weeks after MMR, varicella or MMRV vaccination[137]. Vaccination with MMRV is an unlikely option for a pregnant woman because the vaccine is licensed only for children < 12 years of age. Routine pregnancy testing of women of childbearing age before administration of a live-virus vaccine is not recommended[137]. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks of MMR or varicella vaccination, she should be counselled about the theoretical basis of concern for the fetus; however, MMR or varicella vaccination during pregnancy should not be considered a reason to terminate pregnancy[310-311].

People who receive MMR vaccine do not transmit the vaccine viruses to contacts[310], and transmission of varicella vaccine virus to contacts is rare[137]. MMR and varicella vaccines should be administered when indicated to children and other household contacts of pregnant women. Infants living in households with pregnant women should be vaccinated with rotavirus vaccine according to the same schedule as infants in households without pregnant women[137,310].

Pertussis is a highly contagious, potentially fatal vaccine-preventable disease that continues to emerge as outbreaks worldwide, despite high childhood vaccination rates[312]. The highest incidence of pertussis, its associated complications and the majority of pertussis-related deaths

occur in infants who were too young to be vaccinated (aged < 2 months) or were incompletely immunized (aged < 6 months)[312,313]. Infants too young to receive the primary DTP series as recommended depend on passive maternal antibodies for protection against pertussis; however, pregnant women have very low concentrations of pertussis antibodies[315,316]. To protect young infants, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine has been recommended initially for postpartum women and close contacts of infants, for pregnant women who have not previously received Tdap and then for all pregnant women during every pregnancy, regardless of their history of Tdap vaccination[315,316].

Vaccination of pregnant women with Tdap in the second and third trimester is well tolerated and elicits immune responses similar to those in vaccinated nonpregnant women[313]. Preliminary evaluation indicated no increased risk for adverse events among women who received Tdap vaccine during gestation or in their infants[313]. Secondary assessments showed that maternal vaccination with Tdap resulted in significantly higher concentrations of antibodies to all vaccine antigens in their infants from birth until initiation of vaccination at 2 months of age and did not substantially alter the infants' response to DTaP[313]. As the kinetics of maternal antibodies might differ by region according to the country's epidemiology, vaccine strategy, vaccine brand used and population targeted, larger studies should be conducted, with longer follow-up, to understand the immunological responses of pregnant women, the required frequency of booster Tdap administration and the consequences on neonatal immunity.

6.7. Vaccination of patients with tuberculosis

6.7.1. Tuberculosis skin test reactivity

Measles, severe acute or chronic infections, HIV infection and malnutrition can create a relatively anergic state, during which the tuberculin skin test (TST) might show a false-negative reaction[317-319]. Although any live, attenuated measles vaccine can theoretically suppress TST reactivity, the degree of suppression will probably be less than that after acute infection with wild measles virus[317]. Although routine TST screening of all children is no longer recommended, TST screening is sometimes required (e.g. for child care, school entrance or employee health check-ups) at the time of administration of a measles-containing vaccine. The TST and measles-containing vaccine can be administered at the same visit (preferred option); simultaneous administration does not interfere with reading the TST result at 48–72 h and ensures that the person has received measles vaccine[137,317]. Otherwise, TST screening can be delayed for at least 4 weeks after vaccination to remove concern about any theoretical but transient suppression of TST reactivity from the vaccine[317]. The TST can also be performed and read before administration of measles-containing vaccine[317]. This option is the least favoured because it delays receipt of the vaccine. If a person has suspected TB, MMR vaccine should be withheld not only before the TST but until after initiation of treatment, because a person with active TB who is moderately or severely ill should not receive MMR vaccine[137]. In general, if TB is not suspected, a TST may be done simultaneously with administration of live vaccine or deferred for 28 days after vaccination[317].

No information is available about the extent of TST suppression that might be associated with other live, attenuated virus vaccines (e.g. varicella or yellow fever). In the absence of information,

it is prudent to follow guidelines for measles-containing vaccine when scheduling TST screening and administering other live, attenuated virus vaccines[317]. Vaccination should not be delayed only because of these theoretical considerations[137]. Because of similar concerns about smallpox vaccine and TST suppression, a TST should not be performed until 4 weeks after smallpox vaccination[317,320].

A more specific test for diagnosis of TB or latent TB infection was licensed in 2005. The interferon-γ release assay requires only one visit and is less sensitive to the effects of previous BCG vaccination. The same timing guidelines that apply to the interval between a live vaccine and TST apply to this assay (28 days if they are not done on the same day), because the interferon-γ release assay (like TST) might be suppressed by immunological mechanisms[321].

The potential that TST can boost results should be considered in patients who might have latent TB and have a negative initial TST, and the two-step tuberculin test is recommended in certain situations[321]. As this test consists of two TSTs (or a TST followed by interferon-γ release assay) separated by an interval of 1–3 weeks, there is a longer time during which live vaccine replication could suppress reactivity[321]. If a live vaccine is administered, the first dose of a two-step TST should be delayed for 4 weeks, and, if additional doses of live vaccines are indicated thereafter, they should be delayed until the second TST (or the interferon-γ release assay after an initial TST)[321].

Reactivity to either assay in the absence of TB disease is not a contraindication to administration of any vaccine, including live, attenuated virus vaccines[137,317]. TB is not a contraindication to vaccination, unless the person is moderately or severely ill[137]. Although the effects of MMR vaccine on people with untreated TB have not been studied, measles vaccine might theoretically exacerbate it. Therefore, anti-TB therapy should be initiated before administration of MMR to people with untreated active TB[137]. It is also prudent to consider whether concurrent immunosuppression (e.g. due to HIV infection) is a concern before administering live, attenuated vaccines[137].

6.7.2. Screening of people vaccinated with bacille Calmette-Guérin (BCG)

The sensitivity of people vaccinated with BCG to tuberculin is highly variable, depending on the strain of BCG used and the group vaccinated[322]. The presence or size of a post-vaccination TST reaction does not predict whether BCG provides protection against TB[323]. Furthermore, the size of a TST reaction in a BCG-vaccinated person does not determine whether the reaction is due to infection with *Mycobacterium tuberculosis* or the BCG vaccination[323].

TST is not contraindicated for people who have been vaccinated with BCG, and the results are used to diagnose *M. tuberculosis* infection[324]. A diagnosis of infection and treatment of latent TB infection should be considered for any BCG-vaccinated person who has a TST reaction of > 15 mm of induration, especially if the person[137,322-324]:

- is a contact of another person who has infectious TB, particularly if the infectious person has transmitted *M. tuberculosis* to others;
- was born or has resided in a country in which the prevalence of TB is high; or
- is exposed continually to populations in which the prevalence of TB is high, such as health care workers, employees and volunteers at homeless shelters and workers at drug-treatment centres.

Treatment of latent TB infection should be considered for BCG-vaccinated people with a TST reaction of > 5 mm induration if they are infected with HIV and at risk for *M. tuberculosis* infection[323]. BCG-vaccinated people who have a positive reaction in a TST but who do not have TB should be evaluated for treatment of latent TB infection[323]. The possibility of TB should be considered for BCG-vaccinated persons who have symptoms suggestive of TB[323].

6.7.3. Efficacy of BCG

The effectiveness of BCG vaccination and its policy implications differ for countries with a high and a low incidence of TB, especially in terms of cost–effectiveness[324]. Countries with a policy of vaccination at birth tend to be those with a high incidence of TB (> 20/100 000 according to the European Centre for Disease Prevention)[324]. Given the incomplete control of TB, especially in high-burden countries, use of BCG should be optimized. The study[324] indicates that children should be vaccinated as soon as possible after birth to prevent infection and disease. The results provide evidence that BCG protects against severe and disseminated TB infection in infants in epidemiologically different settings, independently of the type of interferon-γ release assay used to detect infection[324]. Future trials of candidate vaccines should address their efficacy against infection and early and late progression to active disease.

6.7.4. Revaccination with BCG

A systematic review[324] of nine studies showed no significant difference in the incidence rate ratio (range, 0.57–1.74), relative risk (range, 0.39–0.59) or hazard ratio (1.20; 0.77–1.89) for TB. In addition, there was no significant difference in the relative risk for an adverse reaction (2.3; 0.67–7.80) or in vaccine efficacy (8; –77–52), but a significant increase in immune response was found in the revaccinated group[324]. In general, the review concluded that BCG revaccination does not provide a significant additional protective effect against TB, mortality from TB or adverse reactions[324]. The findings support the 1995 WHO recommendation against BCG revaccination[325].

Athough revaccination does not confer additional protection against TB, BCG provides protection against the severe form of TB and TB in childhood[326]. Meta-analyses of studies on the protective effect of a single dose of BCG showed an effect of 73–86%[324]. A study in Brazil of adolescents aged 15–20 years who received BCG vaccination at birth found a prolonged protective effect of the first dose, of 9–58%[327].

6.7.5. Screening for severe combined immunodeficiency disease in countries with universal BCG vaccination

SCID comprises a heterogeneous group of genetic conditions characterized by profound deficiencies in the numbers and function of T and, in some types, B and/or NK cells[328]. If untreated, infants with typical SCID succumb early in life to severe and recurrent infections[328]. BCG, like other live-attenuated vaccines, is contraindicated for SCID patients[329]. However, because BCG is usually administered at birth, SCID patients are often vaccinated before their immune deficiency is diagnosed. The prevalence of complications following vaccination with BCG has been estimated to be higher in patients with SCID than in the general population[329-331], although an effect has not been established definitively. The cumulative experience of 28 centres in 17 countries in Africa, the Americas, Asia and Europe confirms that (as expected) complications are more prevalent in

SCID patients than in the general population[332]. Recent studies have found that the total number of T cells at the time of SCID diagnosis and the patient's age at BCG vaccination are significantly correlated with the increased prevalence of complications[333].

The worldwide coverage of BCG vaccination is 88%[334], and it is usually administered at birth[335] Until safer, more efficient anti-TB vaccines become available, delaying BCG vaccination beyond 1 month of age is likely to be favourable for this highly vulnerable population and in neonates who are susceptible due to e.g. HIV infection. Moreover, delaying BCG vaccination enhances the clinical impact of neonatal SCID screening, obviating administration of a contraindicated vaccine before the diagnosis is established. Two major drawbacks to delaying BCG vaccination can, however, be foreseen: the "missed opportunity" of vaccinating infants after birth might lead to decreased coverage, and there is a very low potential of increased risk for BCG-preventable diseases during the "unprotected" interval. WHO data demonstrate BCG coverage of 89.2% in countries that encourage vaccination at birth, similar to the 89% coverage with the third dose of DPT in the same countries, which is typically given at 6 months of age[336]. This suggests little or no decrease in coverage due to delaying BCG vaccination. In addition, BCG-preventable mycobacterial diseases within the first 6 months of age are extremely uncommon. Studies on paediatric tuberculous meningitis, a BCG-preventable disease, show that the mean age at which this life-threatening disease occurs is 23–49 months, although a few cases have been described during the first 6 months of life, and the median is 12–24 months[337-341]. Modification of BCG vaccination policy requires extensive discussion, balancing the needs of the immunocompetent general population and highly vulnerable immunodeficient patients.

6.8. Vaccination of people with lapsed or unknown immunity

A vaccine series need not be re-started, regardless of the time elapsed between doses, because of immune memory[137]. The next dose should be given as if the usual interval had elapsed, and the immunization schedule should be completed at the next opportunity[137]. Doses should not be given ≤ 4 days before the minimum interval[137]. If a dose is inadvertently given ≥ 5 days after the minimum interval, it should not be counted[137]. Children of unknown immunization status should be considered unimmunized and vaccinated accordingly[137]. Self-reports should not be accepted in the absence of documentation, except for influenza vaccine and PPV[137]. Serological testing may be conducted in patients with uncertain status but is usually not cost–effective, may reduce compliance and may result in missed opportunities for vaccination[137].

6.8.1. Interchangeability of brands

There is sufficient evidence that different brands of Hib, hepatitis B and hepatitis A vaccines can be safely interchanged without compromising immunogenicity or efficacy[343,344]. Robust data on the immunogenicity of vaccination with different brands of DTwP is lacking, however, and vaccination with DTwP should be completed with the same brand unless the previous brand is unknown or no longer available[344]. Vaccination should not be delayed or cancelled.

6.8.2. Catch-up vaccination

Catch-up vaccination regimens should preferably be individualized. Any number of live or inactivated vaccines may be given on the same day, either singly or as combination, maintaining

a distance of 5 cm between injection sites. The exception is administration of BCG, measles and MMR vaccines, which should not be given on the same day[137,237,241]. Inactivated vaccines can be given at any interval with other live or inactivated vaccines[137,237,241]. If two live injectable vaccines, especially MMR and varicella and also yellow fever and live attenuated influenza vaccines, are not given on the same day, an interval of 4 weeks should be maintained[137,237,241]. OPV, rotavirus and oral typhoid vaccines may be given at any interval with any live or inactivated vaccine[137,237,241]. In catch-up vaccination, doses should preferably be given at the shortest interval to ensure early protection.

Catch-up schedule tables are useful for planning the number of doses and the best way to organize visits and coadministration for unimmunized children or children who have interrupted the primary series[137,237,241]. Table 19 gives examples.

Table 19. Examples of catch-up schedules

Antigen		Age of 1st Dose	Doses in Primary Series (min interval between doses)**	Interrupted primary series***	Doses for those who start vaccination late		Booster Dose
					If ≤ 12 months of age	If > 12 months of age	
Recommendations for certain regions							
Japanese Encephalitis [11]	Inactivated Vero cell-derived vaccine	6 months	2 (4 weeks) generally	Resume without repeating previous dose	2 doses (generally)	2 doses (generally)	Not recommended
	Live attenuated	8 months	1	NA	1 dose	1 dose	
	Live recombinant vaccine	9 months	1	NA	1 dose	1 dose	
Yellow Fever [12]		9-12 months	1 dose with measles containing vaccine	NA	1 dose	1 dose	Not recommended
Tick-Borne Encephalitis [13]	FSME-Immun & Encepur	≥ 1 yr	3 doses (1st to 2nd 1-3 mos; 2nd to 3rd 12 mos)	Resume without repeating previous dose	3 doses	3 doses	At least 1 booster
	TBE_Moscow & EnceVir	≥ 3 yr	3 doses (1st to 2nd 1-7 mos; 2nd to 3rd 12 mos)	Resume without repeating previous dose	3 doses	3 doses	Every 3 years
Recommendations for some high-risk populations							
Typhoid [14]	Vi PS	2 years (min)	1 dose	NA	Not recommended	1 dose	Every 3 years
	Ty21a	Capsules 5 years (min) (see footnote)	3-4 doses (1 day) (see footnote)	If interruption between doses is < 21 days resume without repeating previous dose; If > 21 days restart primary series	Not recommended	> 5 yrs: 3-4 doses	Every 3-7 years
Cholera [15]	Dukoral (WC-rBS)	2 years (min)	2-5 yrs: 3 doses ≥ 6 yrs: 2 doses (≥ 7 days)	If interval since last dose ≥ 6 weeks restart primary series	Not recommended	2-5 yrs: 3 doses > 6 yrs: 2 doses	2-5 yrs: every 6 months. If booster is delayed > 6 months the primary series must be repeated. >6 yrs: every 2 years. If booster is delayed > 2 yrs the primary series must be repeated.
	Shanchol and mORCVAX	1 year (min)	2 doses (2 weeks)	Resume without repeating previous dose	Not recommended	2 doses	After 2 years
Meningococcal [16]	MenA conjugate (5µg)	9-18 months	1	NA	2 doses if < 9 months with 8 week interval	1 dose of 5µg up to 24 months	Not recommended
	MenC conjugate	2-11 months	2 (8 weeks min)	Resume without repeating previous dose	2 doses	1 dose	2-11 months of age after 1 year
		>12 months	1	NA			
	Quadrivalent conjugate	9-23 months	2 (12 weeks min)	Resume without repeating previous dose	2 doses	1 dose	
		≥ 2 years	1	NA			
Hepatitis A [17]		1 year (min)	At least 1 dose		Not recommended	At least 1 dose	Not recommended
Rabies [18]		As required	3 doses (1st to 2nd 7 days; 2nd to 3rd 14-21 days)	Resume without repeating previous dose; Interval between last two doses should be 14 days minimum	3 doses	3 doses	Only if occupation puts a frequent or continual risk of exposure
Dengue (CYD-TDV) [19]		9 years (min)	3 doses (6 months)	Resume without repeating dose	Not recommended	3 doses ≥ 9 years	Not recommended
Recommendations for immunization programmes with certain characteristics							
Mumps [20]		12-18 months	2 doses with measles containing vaccine (4 weeks)	Resume without repeating previous dose	Not recommended	2 doses	Not recommended
Seasonal influenza (inactivated tri- and qudri-valent) [21]		6 months (min)	< 9 yrs: 2 doses (4 weeks) ≥ 9 yrs: 1 dose	Resume without repeating previous dose	2 doses	< 9 yrs: 2 doses ≥ 9 yrs: 1 dose	Revaccinate annually 1 dose only
Varicella [22]		12-18 months	1-2 (4 weeks – 3 months, depending on manufacturer)	Resume without repeating previous dose	Not recommended	1-2 doses	

BCG, bacille Calmette-Guérin; NA, not applicable; DTP, diphtheria and tetanus toxoids and pertussis; OPV, oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; HPV, human papillomavirus

Table 20 shows a suggested catch-up schedule. Other vaccines may be given after discussion with parents.

Table 20. Suggested vaccination schedule for an unimmunized child

Visit	Suggested vaccines
First	Measles (MMR if > 12 months) DTwP 1/DTaP 1 (Tdap if ≥ 7 years) OPV 1/IPV 1 (only if < 5 years) Hib 1 (only if < 5 years) Hepatitis B 1
Second (1 month after first visit)	BCG (only if < 5 years) DTwP 2/DTaP 2 (Td if ≥ 7 years) OPV 2 (if OPV given earlier) Hepatitis B 2 Hib 2 (if< 15 months)
Third (1 month after second visit)	OPV 3/IPV 2 MMR (if > 12 months) Typhoid (if > 2 years)
Fourth visit (6 months after first visit)	DTwP 3/DTaP 3 (Td if ≥ 7 years) OPV 4/IPV 1 Hepatitis B 3

MMR, measles, mumps and rubella; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; DTaP, diphtheria and tetanus toxoids and acellular pertussis; Tdap, tetanus toxoid and acellular pertussis; OPV, oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; Hib, *Haemophilus influenzae* type b; Td, tetanus and diphtheria toxoids; IPV B1,

6.10 Vaccination for travellers

The vaccine recommendations for travellers depend on the epidemiology of endemic illnesses in the countries they will visit, the duration of the trip and the nature and conditions of travel[137]. Physicians should update routine vaccinations and provide vaccines specific for the destination. For instance, vaccines commonly recommended for travellers from India include yellow fever vaccine for those going to destinations in South America and sub-Saharan Africa, polio and meningococcal vaccines for those on a hajj pilgrimage to Saudi Arabia and quadrivalent meningococcal vaccine for those visiting countries in the African meningitis belt[345-348]. Visitors to India are usually advised to be vaccinated against typhoid, hepatitis A, hepatitis B, rabies and Japanese encephalitis (if they visit rural areas endemic for Japanese encephalitis in the relevant season)[347].

Examples of the most frequent vaccine-preventable diseases and the dose schedules are shown In Table 21.

Table 21. Most frequent vaccine-preventable diseases and dose schedules

Vaccine	Travel destination	Dose
Meningococcus	United Kingdom, USA, endemic areas Africa and Saudi Arabia	Two doses 4–8 weeks apart
Yellow fever	Endemic zones	10 days before travel
Cholera	Endemic area or an outbreak	Two doses of oral vaccine 1 week apart
Japanese B encephalitis	Endemic areas	Single dose (≤ 15 years)
Rabies (prophylaxis)	Trekking	0, 7 and 28 days

7. Conclusion

Non-vaccination is an ACTIVE decision

Minimal risks of vaccination are completely overshadowed by the health risks of non-vaccination

8. Clinical cases

8.1. Case 1

A 2-month-old infant born prematurely at 32 weeks of gestational age with cerebral palsy as a sequel of ventricular leukomalacia visits a clinic for routine vaccination. The mother reports that the infant has had diarrhoea for the past 2 days and has been taking antibiotic therapy for pharyngoamigdalitis for 10 days. The physical examination shows increased bowel sounds but no other acute major finding. Please choose among the following answers for this patient:

Q1. Can this patient be vaccinated with DTwp, Hib and hepatitis B vaccines at this visit?

1. No, the patient has several absolute contraindications for vaccination (prematurity, cerebral palsy).
2. No, vaccination should be re-scheduled once the acute episode of diarrhoea has resolved.
3. Yes, I would not lose the opportunity to vaccinate the patient.
4. No, because the antibiotic therapy might interfere the immune response.

Answer to Q1:

There is no evidence that acute illness reduces the efficacy of vaccines or increases the incidence of adverse events after vaccination. As a precaution, however, in cases of moderate or severe acute illness, all vaccines should be delayed until the illness has resolved. Mild

illnesses such as otitis media, upper respiratory infection and diarrhoea are not contraindications to vaccination. Children with mild acute illnesses such as low-grade fever, upper respiratory infection, colds, otitis media and mild diarrhoea should be vaccinated on schedule. Several large studies[137,349] have shown that young children with these conditions respond as well to measles vaccine as those without them. There is no evidence that mild diarrhoea reduces the immune response of infants. The temperature of infants and children need not be measured before vaccination if they do not appear to be ill and the parent does not report that the child is currently ill. The decision to vaccinate should be based on an overall evaluation of the person rather than on arbitrary body temperature.

Vaccination should not be withheld for a person taking antibiotics. Antibiotics do not affect the immune response to most vaccines. The only commonly used antimicrobial drug that will inactivate a live-virus vaccine is a sulfonamide, which will inactivate the oral typhoid vaccine, which should therefore be administered at least 72 h after a dose of sulfonamide. Antiviral drugs may affect vaccine replication in some circumstances, and live attenuated influenza vaccine should not be administered until 48 h after cessation of therapy with drugs against influenza (amantadine, rimantadine, zanamivir, oseltamivir). Antiviral drugs against herpesviruses (acyclovir, famciclovir) should be discontinued 24 h before administration of a varicella-containing vaccine, if possible.

Q2. Does prematurity pose any limitation or contraindication for vaccination?

1. Yes, a premature patient cannot receive rotavirus vaccine because of gastrointestinal immaturity.
2. Yes, a premature patient should not receive the first dose of hepatitis B vaccine until his or her weight is > 2500 g.
3. Yes, a premature patient should not receive pertussis-containing vaccines because of immune immaturity.
4. All the previous answers are false.

Answer to Q2:

Prematurity is not a contraindication for vaccination. On the contrary, premature patients are at increased risk for infectious diseases and for more severe disease than healthy children. Timely vaccination of premature infants is therefore essential.

Q3. Can this premature patient receive rotavirus vaccine?

1. This patient is already experiencing an acute episode of gastroenteritis, and thus rotavirus vaccination is no longer indicated.
2. As soon as the patient recovers, he or she should receive the first dose of rotavirus vaccine, ideally before 15 weeks of age
3. The first dose of rotavirus vaccine should be administered only after 3 months of age.
4. The patient could be vaccinated, as the acute illness is mild,

Answer to Q3:

There are very few contraindications to rotavirus vaccines. These are:

- a history of a severe allergic reaction (e.g. anaphylaxis) after a previous dose of either rotavirus vaccine or any component of the vaccine being given;
- severe combined immunodeficiency; the risk–benefit ratio for children with known or suspected altered immunocompetence should be assessed individually. Children and adults with congenital immunodeficiency, haematopoietic transplantation or solid organ transplantation sometimes experience severe or prolonged rotavirus gastroenteritis.
- a history of intussusception, which places children at greater risk than children who have never had it.

Moderate or severe acute illness with or without a fever indicates precaution in administering all vaccines, including rotavirus vaccine. Vaccination should not, however, be delayed due to mild respiratory tract or other acute illness with or without fever. In the case described above, the patient had diarrhoea, probably related to antibiotics, and rotavirus vaccine could be administered safely, although some authors[350] consider diarrhoea in acute gastroenteritis a reason for postponing rotavirus vaccination. Usually, rotavirus vaccine should not be administered to infants with acute moderate or severe gastroenteritis until the condition improves.

Infants with mild acute gastroenteritis can be vaccinated, particularly if the delay in vaccination might be substantial and might make the infant ineligible to receive vaccine (e.g. age > 15 weeks before the vaccine series is started). Even a documented episode of naturally occurring rotavirus acute gastroenteritis after an episode of acute gastroenteritis does not contraindicate rotavirus vaccination.

In some low- and middle-income countries, the window for rotavirus vaccination is wider (up to 3 years of age), as the additional lives saved by removing age restrictions on rotavirus vaccination by far outnumber the excess vaccine-associated deaths due to intussusception. In other cases, a restricted schedule (initiate by 15 weeks and complete by 32 weeks) should be followed strictly.

Q4. This patient has cerebral palsy as a sequel of prematurity. Which of the following statements is true?

1. Cerebral palsy is an absolute contraindication for vaccination.
2. The vaccine is not contraindicated, but the schedule of vaccination is different.
3. The patient can be vaccinated normally.
4. The patient can be vaccinated normally except with any vaccine containing pertussis antigen.

Answer to Q4:

Chronic diseases may increase a person's risk for infection or for more severe disease if infection occurs, so that prevention by vaccination is essential. The patient is also at increased risk for nosocomial infection with vaccine-preventable diseases because of the increased likelihood of prolonged hospitalization and frequent outpatient visits. Therefore, it is particularly important that **people with chronic diseases who are immunocompetent be immunized in a timely manner with both live and inactivated vaccines according to the routine immunization schedule.** Vaccines may be less immunogenic in this population. Ideally, **vaccination should be completed early in the disease course** when the response is likely to be

similar to that of other people of a similar age with no chronic medical condition.

The vaccine requirements and recommendations may change for people with immunosuppression or receiving immunosuppressive therapy, and the vaccination scheduled should be carefully reviewed, particularly for live vaccines.

As our patient has a stable, chronic neurological disease, he or she should be vaccinated normally.

Q5. The mother is breastfeeding the preterm baby. Which of the following statements is true?

1. Vaccination might interfere with the immune response of the infant but with no clinical consequences.
2. Vaccination should be postponed until breastfeeding is finished.
3. Vaccination interferes only with rotavirus vaccine.
4. Breastfed infants should be vaccinated according to the recommended schedule.

Answer to Q5:

Breastfeeding does not decrease the responses to routine childhood vaccines and is not a contraindication for any vaccine except smallpox. Yellow fever vaccine should be avoided; however, if a nursing mother cannot avoid or postpone travel to areas endemic for yellow fever in which risk for acquisition is high, they should be vaccinated. Breastfeeding does not extend or improve the passive immunity to vaccine-preventable disease provided by maternal antibodies, except possibly for Hib. Breastfed infants should be vaccinated according to the recommended schedule. Although rubella vaccine virus might be shed in human milk, infection of infants is rare. Breastfeeding and prematurity (< 37 weeks' gestation) do not impair the immune response to rotavirus vaccine, as proven in recent studies in Africa and Asia[351-353].

8.2. Case 2

An 18-month-old boy is taken to a clinic because of a tonic–clonic seizure that lasted 2 min and ceased spontaneously. He has fever of 38.5 °C. He had received DTwp-Hib-hepatitis B vaccine the day before. After careful history-taking and a physical examination, no other findings are detected. Please answer the following questions regarding this patient:

Q1. What is your interpretation of this case?

1. The child had a febrile seizure secondary to central nervous stimulation by vaccination.
2. The child had a febrile seizure due to fever, which was probably related to vaccination.
3. The child has epilepsy, and antiepileptic drugs should be started; further vaccines are contraindicated.
4. The child has epilepsy secondary to vaccination.

Answers to Q1:

Febrile seizures can occur with any condition that causes fever. During a febrile seizure, a child often has spasms or jerking movements and may lose consciousness. Febrile seizures usually last 1–2 min, and they do not cause any permanent neurological damage. They are most

common with fevers of ≥ 38.9 °C but can also occur at lower body temperatures or when a fever is going down. One in three children who have one febrile seizure will have at least one more during childhood; some are linked to the family health history.

The causes include common childhood illnesses like colds, influenza, an ear infection or roseola.

Vaccines sometimes cause fevers but rarely febrile seizures. Infants and young children are at highest risk for febrile seizures: ≤ 5% of young children will have at least one febrile seizure, usually associated with illness. Most febrile seizures occur in children aged 6 months to 5 years, although the commonest age range is 14–18 months.

Vaccines prevent many febrile seizures. Vaccination of a child as recommended prevents febrile seizures by protecting tham against measles, mumps, rubella, chickenpox, influenza, pneumococcal infections and other diseases that can cause fever and febrile seizures. The risk–benefit relation of vaccination and the onset of febrile seizures always favours vaccination.

Q2. How would you interpret the event with regards to the vaccine?

1. The seizure was caused by the vaccine.
2. The seizure was temporarily related to vaccination.
3. The seizure was totally unrelated to vaccination.
4. The vaccination caused epilepsy in the child.

Answer to Q2:

Vaccines, like any medication, can have side-effects; however, most are minor (for example, a sore arm or low-grade fever) and resolve within a few days. **Usually, there is only a temporary link between vaccination and the event, which does not indicate a causal relation.** Caution should be exercised before a judgement is made or communicating it to the parent, as it may affect future vaccination.

Studies have indicated that there is no increased risk for febrile seizures after administration of acellular pertussis vaccine, DTaP, Hib, hepatitis B or varicella vaccine[159,160,354]. DTwP has been reported to be associated with a small increase in risk for febrile seizures the day after administration[355]. This small or absent risk is, however, negligible in comparison with the benefits that the vaccine may provide. Furthermore, the risk does not appear to be associated with any long-term adverse consequences[356].

Q3. How would you manage the patient with regard to future vaccination?

1. The patient shouldnot receive this or any other vaccine in the future.
2. The patient should not receive this vaccine but could receive other vaccines.
3. The patient can receive this vaccine only under surveillance in a special unit for vaccine allergy.
4. The patient can be vaccinated normally with this or any other vaccine.

Answer to Q3:

The parents should be informed that vaccines are prepared in accordance with the highest standards

of safety. Years of testing are required by law before a vaccine is licensed and distributed. Once in use, vaccines are continually monitored for safety and efficacy. Like any medical procedure, vaccination is associated with some risks as well as substantial, proven benefits. Individuals react differently to vaccines, and the reaction of an individual to a particular vaccine cannot be predicted precisely. Anyone who is vaccinated should be fully informed about both the benefits and the risks, and any questions or concerns should be discussed with a physician or other health care provider.

Febrile seizures can be frightening, but nearly all children who have a febrile seizure recover quickly and are healthy afterwards. Even in the rare cases that an episode of febrile seizure can be related to administration of DTwp-Hib-hepatitis B, future doses of this and other vaccines can be administered safely.

Q4. If it is suspected that this case and any other unusual reaction or clinical event is related to vaccination, what should be the procedure?

1. Don't tell anyone, as this is bad publicity for vaccines.
2. Vaccines have no adverse effects.
3. The event should be reported to the local authorities, even if it is only suspected.
4. The event should be reported to the local authorities according to the procedure only if the relation is proven.

Answer to Q4:

Anyone who administers vaccines is encouraged to report any significant health problem or unexpected event, even if they are uncertain that the vaccine caused the event. Adverse events listed on the manufacturer's package insert and any other clinically significant or unexpected event after vaccination should be reported. A report of an adverse event does not necessarily mean that the vaccine caused the event. The report should include

- the type of vaccine received,
- the timing of vaccination,
- the onset of the adverse event,
- current illnesses or medication,
- history of adverse events after vaccination and
- demographic information about the recipient.

Q5. If in the same week that the child was vaccinated, two other children who received the same type of vaccine in the same facilities present with the same symptoms, how would you interpret the episode?

1. I would clearly associate the vaccine with seizures and never vaccinate other children with DTwp-Hib-hepatitis B vaccine.
2. I would report the event for further investigations of the vaccine lot, transport and storage.
3. I would inform the parents that an increased rate of seizures due to DTwp-Hib-hepatitis B vaccine has been confirmed.
4. I would assume that the event was coincidental and take no further measures.

Answer to Q5:

It may be difficult to identify the causes of adverse events after vaccination. Once the adverse event has been reported, caution should be exercised in making associations. Vaccination should be continued; however, if further cases of the same adverse event occur with the same vaccine, errors in its manufacture, transport and storage must be ruled out. Meanwhile, health care professionals should remain alert for new cases but provide the same information to parents. No alarm should be given until an official report of causality is available, as it is essential to build trust in immunization programmes.

References

1. Milstien, JB. "Regulation of vaccines: strengthening the science base," Journal Public Health Policy, 2004: 25(2):173–189.
2. Baylor NW, Midthun K. "Regulation and testing of vaccines," In: Plotkin S, Orenstein W, Offit PA. Vaccines, 5th edition, Philadelphia: Saunders, 2008.
3. World Health Organization. Immunization standards. National regulatory authorities. http://www.who.int/immunization_standards/national_regulatory_authorities/role/en/ (Last accessed September 2016)
4. Eldred BE, Dean AJ, McGuire TM, Nash AL. Vaccine components and constituents: responding to consumer concerns. Medical Journal of Australia 2006;184:170-5.
5. Finn TM, Egan W. Vaccine additives and manufacturing residuals in the United States: licensed vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6th ed. Philadelphia: Elsevier Saunders; 2013.
6. Hurley AM, Tadrous M, Miller ES. Thimerosal-containing vaccines and autism: a review of recent epidemiologic studies. Journal of Pediatric Pharmacology and Therapeutics 2010;15:173-81.
7. Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. The Lancet Infectious Diseases 2004;4:84-90.
8. Offit PA, Jew RK. Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? Pediatrics 2003;112:1394-401.
9. Orenstein WA, Paulson JA, Brady MT, Cooper LZ, Seib K. Global vaccination recommendations and thimerosal. Pediatrics 2013;131:149-51.
10. Chen RT, Shimabukuro TT, Martin DB, Zuber PLF, Weibel DM, Sturkenboom M. Enhancing vaccine safety capacity globally: a lifecycle perspective. Vaccine. 2015;33(0 4):D46-D54
11. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine. 1994 May;12(6):542-50
12. World Health Organization. Seven Key Reasons. Why immunization must remain a priority in the WHO European Region. Available at: http://www.euro.who.int/__data/assets/pdf_file/0017/84302/Seven_Key_Reasons.pdf (accessed September 2016)
13. Immunisation against infectious disease 1996, Eds. Salisbury DM and Begg NT. En: Edward Jenner, Bicentenary Edition
14. Duclos P, Delo A, Aguado T, Bilous J, Birmingham M, Kieny MP, Milstien J, Wood D, Tarantola D (2003) Immunization safety priority project at the World Health Organization. Semin Pediatr Infect Dis 14: 233–239
15. World Health Organization (WHO), United Nations Children's Fund (UNICEF), World Bank. State of the world's vaccines and immunization, 3rd ed, Geneva: WHO, 2009.
16. Definition and application of terms for vaccine pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences, World Health Organization, 2012. Available at: www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf (accessed May 2016).
17. World Health Organization. Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. Available at: http://www.who.int/vaccine_safety/publications/aevi_manual.pdf (accessed Nov 2015)

18. World Health Organization. Vaccine safety basics: e-learning course. Module 3: adverse events following immunization. Available at: http://vaccine-safety-training.org/vaccine-reactions.html (accessed Feb 2016)
19. Infant mortality and births from 2008 Immunization summary, WHO/UNICEF (The 2010 edition).
20. World Health Organization (WHO). "BCG vaccine: WHO position paper", Weekly Epidemiological Record, Geneva: 2004:79(4):25–40.
21. World Health Organization (WHO). "Introduction of inactivated poliovirus vaccine into oral poliovirus vaccine-using countries", Weekly Epidemiological Record, Geneva: 2003:78(28):241–252.
22. World Health Organization (WHO). "Pertussis vaccine: WHO position paper", Weekly Epidemiological Record, Geneva: 2005:80(4):29–40.
23. World Health Organization (WHO). "Measles vaccines: WHO position paper", Weekly Epidemiological Record, Geneva: 2009:84(35):349–360.
24. World Health Organization (WHO). Immunization safety surveillance: guidelines for immunization programme managers on surveillance of adverse events following immunization (Third Edition). Available at: http://iris.wpro.who.int/bitstream/handle/10665.1/12620/9789290617457_eng.pdf (accessed Sep 2016)
25. World Health Organization (WHO). Global manual on surveillance of adverse events following immunization. Available at: http://www.who.int/vaccine_safety/publications/Global_Manual_revised_12102015.pdf (accessed Jul 2016)
26. World Health Organization (WHO). Mass measles immunization campaigns: reporting and investigating adverse events following immunization (Revision May 2002). Available at: http://www.who.int/vaccine_safety/en/AEFI_measles_campaigns.pdf (accessed Sep 2016)
27. Brighton collaboration. Case definitions. Available at: https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions/available-definitions.html (accessed Sep 2016)
28. World Health Organization (WHO). Report on Safety of Immunization during Pregnancy. Global Advisory Committee on Vaccine Safety 18 October 2013. Available at: http://www.who.int/immunization/sage/meetings/2013/november/2_GACVS_pregnancy_report.pdf (accessed Sep 2016)
29. Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011; 60 (No. 2): 26.
30. American Academy of Pediatrics. Passive immunization. In: Pickering LK, editor. Red book: 2009 report of the Committee on Infectious Diseases. 28th edition. Elk Grove Village, IL; 2009
31. Rotavirus vaccines WHO position paper: January 2013 - Recommendations. Vaccine. 2013 Dec 16;31(52):6170-1.
32. Committee on Infectious Diseases; American Academy of Pediatrics. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. Pediatrics. 2009 May;123(5):1412-20
33. Szilagyi PG, Rodewald LE. Missed opportunities for immunizations: a review of the evidence. J Public Health Manag Pract 1996;2:18-25
34. Ferriman A. BMJ readers choose the "sanitary revolution" as greatest medical advance since 1840. BMJ : British Medical Journal. 2007;334(7585):111

35. World Health Organization. Global Vaccine Safety Initiative. Six common misconceptions about immunization. Geneva; www.who.int/vaccine_safety/initiative/detection/immunization_misconceptions/en/index.html
36. Offit PA, Jew RK. Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? Pediatrics 2003;112:1394–401.
37. WHO Letter Reports On Islamic Legal Scholars' Verdict on the Medicinal Use Of Gelatin Derived From Pork Products. Available at: http://www.immunize.org/concerns/porcine.pdf (accessed Sep 2016)
38. National Network for Immunization Information (NNii). Vaccine components. Human fetal links with some vaccines. 2008. www.immunizationinfo.org/vaccine_components_detail.cfv?id=32 (accessed Jul 2016).
39. Plotkin SA. The History of Rubella and Rubella Vaccination Leading to Elimination. Clin Infect Dis. 2006 43 (Supplement 3): S164-S168.
40. Barr Labs. Package Insert - Adenovirus Type 4 and Type 7 Vaccine, Live, Oral. 2011. Available:http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM247515.pdf (accessed Dec 2015)
41. GlaxoSmithKline. Package Insert – Havrix. 2011. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM224555.pdf (accessed Dec 2015).
42. GlaxoSmithKline. Package Insert – Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine. 2011. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110049.pdf (accessed Dec 2016)
43. Merck & Co, Inc. Package Insert – Measles, Mumps, and Rubella Virus Vaccine Live. 2009. Available:http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123789.pdf. (accessed Dec 2016)
44. Merck & Co, Inc. Package Insert – MERUVAX II. 2006. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142553.pdf (accessed Dec 2016)
45. Merck & Co, Inc. Package Insert – VAQTA – Hepatitis A Vaccine, Inactivated. 2011. Available:http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110049.pdf. (accessed Dec 2016)
46. Merck & Co, Inc. Package Insert – Varivax (Frozen). 2010. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142813.pdf. (accessed Dec 2016)
47. Pontificia Academia Pro Vita. Vatican statement: moral reflections on vaccines prepared from cells derived from aborted human foetuses. Vatican; 2005. www.cogforlife.org/vaticanresponse.htm
48. Rosenthal D, Dyson S, Pitts M, Garland S. Challenges to accepting a human papilloma virus (HPV) vaccine: a qualitative study of Australian women. Women Health. 2007;45(2):59-73.
49. Betsch C. Overcoming healthcare workers' vaccine refusal – competition between egoism and altruism. Euro Surveill. 2014;19(48):pii=20979.
50. Khakoo GA, Lack G. Recommendations for using MMR vaccine in children allergic to eggs. BMJ 2000;320:929-32.
51. Mullins RJ, Kemp A, Gold M. Influenza vaccination of the egg-allergic individual. Medical Journal of Australia 2010;193:254-5.

52. Franceschini F, Bottau P, Caimmi S, et al. Vaccination in children with allergy to non active vaccine components. Clinical and Translational Medicine. 2015;4:3.
53. Offit PA, Quarles J, Gerber MA, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? Pediatrics 2002;109:124-9.
54. World Health Organization (WHO), Global Advisory Committee on Vaccine Safety. Immune overload. 2006. www.who.int/vaccine_safety/committee/topics/immune_overload (accessed Jul 2016).
55. Adkins B, Leclerc C, Marshall-Clarke S. Neonatal adaptive immunity comes of age. Nature Reviews Immunology 2004;4:553-64.
56. Bedford H, Elliman D. Concerns about immunisation. BMJ 2000;320:240-3.
57. Rieder MJ, Robinson JL. 'Nosodes' are no substitute for vaccines. Paediatr Child Health. 2015 May;20(4):219-22.
58. Bremner SA, Carey IM, DeWilde S, et al. Timing of routine immunisations and subsequent hay fever risk. Archives of Disease in Childhood 2005;90:567-73.
59. Bueving HJ, Bernsen RM, de Jongste JC, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. American Journal of Respiratory and Critical Care Medicine 2004;169:488-93.
60. DeStefano F, Gu D, Kramarz P, et al. Childhood vaccinations and risk of asthma. Pediatric Infectious Disease Journal 2002;21:498-504.
61. Koppen S, de Groot R, Neijens HJ, et al. No epidemiological evidence for infant vaccinations to cause allergic disease. Vaccine 2004;22:3375-85.
62. Vasileiou E, Sheikh A, Butler C, von Wissmann B, McMenamin J, Ritchie L, et al. Effectiveness of influenza vaccination for preventing influenza-related complications in people with asthma: a systematic review protocol. BMJ Open. 2016 Mar 29;6(3):e010133.
63. Erlewyn- Lajeunesse M, Bonhoeffer J, Ruggeberg JU, Heath PT. Anaphylaxis as an adverse event following immunisation. *Journal of Clinical Pathology*. 2007;60(7):737-739. doi:10.1136/jcp.2006.037457
64. Ehreth J. The global value of vaccination. Vaccine. 2003 Jan 30;21(7-8):596-600.
65. Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ, et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. Bull World Health Organ. 2008 Feb;86(2):140-6. Review.
66. Bloom DE, et al. The value of immunization. World Economics. 2005 July-Sept; 6(3):15-39.
67. World Health Organization. The Expanded Programme on Immunization. Benefits of immunization. Last updated 1 December 2013. Available at: http://www.who.int/immunization/programmes_systems/supply_chain/benefits_of_immunization/en/ (Accessed July 2016).
68. Gershon AA, Gershon MD. Pathogenesis and Current Approaches to Control of Varicella-Zoster Virus Infections. *Clinical Microbiology Reviews*. 2013;26(4):728-743
69. WHO, World Health Organization. Influenza (seasonal). Fact sheet nº211. March 2014. Available at: http://www.who.int/entity/mediacentre/factsheets/fs211/en/index.html. (Accessed July 2016).
70. Jevsnik M, Ursic T, Zigon N, Lusa L, Krivec U, Petrovec M. Coronavirus infections in hospitalized pediatric patients with acute respiratory tract disease. *BMC infectious diseases* 2012;12:365
71. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;349:1436-1442.

72. Mizgerd JP. Lung infection--a public health priority. *PLoS medicine* 2006;3:e76
73. Nair H, Simões EAF, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *The Lancet* 2013;381:1380-1390
74. Bärnighausen T, Bloom DE, Canning D, Friedman A, Levine OS, O'Brien J, Privor-Dumm L, Walker D. Rethinking the benefits and costs of childhood vaccination: the example of the Haemophilus influenzae type b vaccine. Vaccine. 2011 Mar 16;29(13):2371-80.
75. World Health Organization (WHO). Meningococcal meningitis. Available at: http://www.who.int/immunization/diseases/meningitis/en/ (Accessed Sep 2016)
76. World Health Organization (WHO). Annual Report 2013. Available at: http://www.who.int/immunization/diseases/rubella/mri_annual-report_2013.pdf (Accessed Sep 2016)
77. Rümke HC, Oostvogel PM, Van Steenis G, Van Loon AM. Poliomyelitis in The Netherlands: a review of population immunity and exposure between the epidemics in 1978 and 1992. Epidemiol Infect. 1995 Oct;115(2):289-98
78. Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. Pediatr Infect Dis J. 1987 Apr;6(4):364-71
79. Hurley AM, Tadrous M, Miller ES. Thimerosal-containing vaccines and autism: a review of recent epidemiologic studies. J Pediatric Pharmacol Ther 2010;15:173–81.
80. World Health Organization (WHO). Poliomyelitis (polio) transmission in Ukraine interrupted, but efforts must continue to protect children. Available at: http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/news/news/2016/05/poliomyelitis-polio-transmission-in-ukraine-interrupted,-but-efforts-must-continue-to-protect-children (Accessed Sep 2016)
81. World Health Organization (WHO). Diphtheria detected in Spain. Available at: http://www.euro.who.int/en/countries/spain/news/news/2015/06/diphtheria-detected-in-spain (Accessed Sep 2016)
82. World Health Organization (WHO). Germany adopts innovative approach to help eliminate measles and rubella. Available at: http://www.euro.who.int/en/countries/germany/news/news/2015/01/germany-adopts-innovative-approach-to-help-eliminate-measles-and-rubella (Accessed Sep 2016)
83. Dennehy PH. Active Immunization in the United States: Developments over the Past Decade. *Clinical Microbiology Reviews*. 2001;14(4):872-908. doi:10.1128/CMR.14.4.872-908.2001.
84. Bardenheider B, Yusuf H, Schwartz B, Gust D, Barker L, Rodewald L. Are parental vaccine safety concerns associated with receipt of measles-mumps-rubella, diphtheria and tetanus toxoids with acellular pertussis, or hepatitis B vaccines by children? Arch Pediatr Adolesc Med. 2004;158:569–75
85. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001;345:656–61.
86. Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage' Curr Opin Neurol. 2007;20:181–7
87. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene *SCN1A* cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 2001;68:1327–32.
88. Berkovic SF, Harkin L, McMahon JM, et al. De-novo mutations of the sodium channel

gene *SCN1A* in alleged vaccine encephalopathy: A retrospective study. Lancet Neurol. 2006;5:488–92

89. Poling JS, Frye RE, Shoffner J, Zimmerman AW. Developmental regression and mitochondrial dysfunction in a child with autism. J Child Neurol. 2006;21:170–2
90. Doja A. Genetics and the myth of vaccine encephalopathy. *Paediatrics & Child Health*. 2008;13(7):597-599.
91. Sinclair L. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:1355.
92. Lee JW, Melgaard B, Clements CJ, Kane M, Mulholland EK, Olive J-M. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:905.
93. Walker DR. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:1355.
94. Richmond P, Goldbatt first initial. Autism,inflammatory bowel disease and MMR vaccine. Lancet 1998;351:905. Rouse A. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:905.
95. Bleck D, Prempeh H, Baxter T. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:905-6.
96. Beale AJ. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:906.
97. O.Brien SJ, Jones IG, Christie P. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:906-7.
98. Payne C. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:907.
99. Bedford H, Booy R, Dunn D, DiGuiseppi C, Gibb D, Gilbert R, et al. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:907.
100. Lindley KJ. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998;351:907-
101. DeStefano F. *Age at First Measles-Mumps-Rubella Vaccination in Children with Autism and School-Matched Control Subjects:* A Population-Based Study in Metropolitan Atlanta. Pediatrics 2004; 113(2): 259- 66
102. Lingam R et al. *Prevalence of Autism and Parentally Reported Triggers in a North East London Population*. Arch Dis Child 2003; 88(8):666-70
103. Makela A et al. *Neurologic Disorders after Measles-Mumps-Rubella Vaccination*. Pediatrics 2002; 110:957-63
104. Madsen KM et al. *A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism*. N Engl J Med 2002; 347(19):1477-82
105. Black C et al. *Relation of Childhood Gastrointestinal Disorders to Autism: Nested Case Control Study Using Data from the UK General Practice Research Database*. BMJ 2002; 325:419-21
106. Taylor B et al. *Measles, Mumps, and Rubella Vaccination and Bowel Problems or Developmental Regression in Children with Autism: Population Study*. BMJ 2002; 324(7334):393-6
107. Fombonne E et al. *No Evidence for a New Variant of Measles-Mumps-Rubella-Induced Autism*. Pediatrics 2001;108(4):E58
108. Davis RL et al. *Measles-Mumps-Rubella and Other Measles-Containing Vaccines Do Not Increase the Risk for Inflammatory Bowel Disease: A Case-Control Study from the Vaccine Safety Datalink Project*. Arch Pediatr Adolesc Med 2001;155(3):354-9
109. Dales L et al. *Time Trends in Autism and in MMR Immunization Coverage in California*. JAMA 2001; 285(9):1183-5
110. Kaye JA et al. *Mumps, Measles, and Rubella Vaccine and the Incidence of Autism Recorded by General Practitioners: A Time Trend Analysis*. BMJ 2001; 322:460-63

111. Afzal MA, et al.*Further Evidence of the Absence of Measles Virus Genome Sequence in Full Thickness Intestinal Specimens from Patients with Crohn's Disease*. J Med Virol 2000; 62(3):377-82
112. Taylor B et al. *Autism and Measles, Mumps, and Rubella Vaccine: No Epidemiological Evidence for a Causal Association*. Lancet 1999;353 (9169):2026-9
113. Afzal MA et al. *Absence of Detectable Measles Virus Genome Sequence in Inflammatory Bowel Disease Tissues and Peripheral Blood Lymphocytes*. J Med Virol 1998; 55(3):243-9
114. Peltola H et al. *No Evidence for Measles, Mumps, and Rubella Vaccine-Associated Inflammatory Bowel Disease or Autism in a 14-year Prospective Study*. Lancet 1998; 351:1327-8
115. Nielsen LL et al. *Exposure to Measles in Utero and Crohn's Disease: Danish Register Study*. BMJ 1998; 316(7126):196-7
116. Liu Y et al. *Immunocytochemical Evidence of Listeria, Escherichia coli, and Strep- tococcus Antigens in Crohn's Disease*. Gastroenterology 1995; 108(5):1396-1404
117. Hornig M et al. P *Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study*LoS ONE 2008; 3(9): e3140
118. Baird G et al. *Measles Vaccination and Antibody Response in Autism Spectrum Dis- orders*. Arch Dis Child 2008; 93(10):832-7.
119. Uchiyama T et al. *MMR-Vaccine and Regression in Autism Spectrum Disorders: Negative Results Presented from Japan*. J Autism Dev Disord 2007; 37(2):210-7
120. D'Souza Y et al. *No Evidence of Persisting Measles Virus in Peripheral Blood Mononuclear Cells from Children with Autism Spectrum Disorder*. Pediatrics 2006; 118(4):1664-75
121. Doja A, Roberts W. *Immunizations and Autism: A Review of the Literature*. Can J Neurol Sci. 2006; 33(4):341-
122. Fombonne E et al. *Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links with Immunizations*. Pediatrics. 2006;118(1):e139-50
123. Klein KC, Diehl EB. *Relationship between MMR Vaccine and Autism*. Ann Pharmacother. 2004; 38(7-8):1297-300
124. Institute of Medicine. *Immunization Safety Review: Vaccines and Autism*. The National Academies Press: 2004 (www.nap.edu/books/030909237X/ html)
125. Smeeth L et al. *MMR Vaccination and Pervasive Developmental Disorders: A Case- Control Study*. Lancet 2004; 364(9438):963-9
126. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998;351: 637-41.
127. Thompson NP, Montgomery SM, Pounder RE, Wakefield AJ. Is measles vaccination a risk factor for inflammatory bowel disease? Lancet 1995;345:1071-4.
128. Daszak P, Purcell M, Lewin J, Dhillon AP, Pounder RE, Wakefield AJ. Detection and comparative analysis of persistent measles virus infection in Crohnís disease by immunogold electron microscopy. J Clin Pathol. 1997;50:299-304
129. Lewin J, Dhillon AP, Sim R, Mazure G, Pounder RE, Wakefield AJ. Persistent measles virus infection of the intestine: con- firmation by immunogold electron micros- copy. Gut 1995;36:564-9.
130. Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A. Detection and sequencing of measles virus from peripheral mononuclear cells from patients with

inflammatory bowel disease and autism. Dig Dis Sci 2000;45:723-9.
131. The editors of the Lancet. Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*2010;375:445
132. Medical Research Council. Review of Autism Research: epidemiology and causes. December 2001. Available at: http:// www.mrc.ac.uk/pdf-autism-report.pdf. Accessed July 2016.
133. Halsey NA, Hyman SL and the Conference Writing Panel. Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12-13, 2000. Pediatrics 2001;107:E84 (1-23).
134. American Medical Association. Current scientific data do not support a causal association between autism and the MMR vaccine. Available at: http://www.ama-assn.org/ ama/pub/ article/1824-6108.html. Accessed July 2016.
135. IOM. Immunization Safety Review Committee Meeting: MMR Vaccine and Autism. Available at: http://www.iom.edu/ event.asp?id=6693. Accessed July 2016.
136. IOM. Public Access Files: Immunization Safety Review: Meeting Two. Available http://www.iom.edu/file.asp?id=8168. Accessed July 2016.
137. World Health Organization. Adverse events following measles, mumps and rubella vaccines. Available at: http://www.who.int/ vaccines-diseases/safety/infobank/ mmr.shtml. Accessed July 2016
138. Access Files: Immunization Safety Review: Meeting Two. http://www.iom.edu/ subpage.asp?id=7553ósite for speakers and audio Accessed July 2016
139. Strauss B, Bingham M. Does measles- mumps-rubella (MMR) vaccination cause inflammatory bowel disease and autism? Can Commun Dis Rep 2001;27:65-72.
140. Insel R. Potential alterations in immunogenicity by combining or simultaneously administering vaccine components. Ann N Y Acad Sci 1995;754:35 – 47
141. Heron J, Golding J; ALSPAC Study Team. Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United kingdom does not support a causal association. Pediatrics. 114(3): 577-583, 2004
142. Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association. Pediatrics. 114(3): 584-591, 2004
143. Immunization Safety Review Committee, Institute of Medicine. Immunization Safety Review: Vaccines and Autism. National Academy Press Washington DC 2004.
144. Immunization Safety Review Committee, Institute of Medicine. Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders. Stratton K, Gable Am McCormick MC eds. National Academy Press Washington DC 2001.
145. Pichichero ME. Cernichiari E. Lopreiato J. Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. Lancet. 360(9347):1737-1741, 2002.
146. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA. 290(13):1763-1766, 2003.
147. Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics. 112(3 Pt 1):604-606, 2003.
148. Verstraeten T, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, Shinefield H, Chen

RT; Vaccine Safety Datalink Team. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. Pediatrics. 112(5):1039-1048, 2003.
149. Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. Vaccine 2003;21:2003-14.
150. Ray P, Hayward J, Michelson D, et al. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case–control study. Pediatric Infectious Disease Journal 2006;25:768-73.
151. Moore DL, Le Saux N, Scheifele D, Halperin SA, Members of the Canadian Paediatric Society/ Health. Canada Immunization Monitoring Program, Active (IMPACT). Lack of evidence of encephalopathy related to pertussis vaccine: active surveillance by IMPACT, Canada, 1993–2002. Pediatric Infectious Disease Journal 2004;23:568-71.
152. Zhang L, Prietsch SO, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. Cochrane Database of Systematic Reviews 2012;(3):CD001478.
153. Nelson KE. Invited commentary: Influenza vaccine and Guillain-Barré syndrome – is there a risk? American Journal of Epidemiology 2012;175:1129-32.
154. Souayah N, Yacoub HA, Khan HM, et al. Guillain-Barré syndrome after influenza vaccination in the United States, a report from the CDC/FDA Vaccine Adverse Event Reporting System (1990–2009). Journal of Clinical Neuromuscular Disease 2012;14:66-71.
155. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. American Journal of Epidemiology 2009;169:382-8.
156. Zhou W, Pool V, Iskander JK, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS) —United States, 1991–2001. MMWR Morb Mortal Wkly Rep 2003; 52(SS-1): 1–24
157. Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Safety 2009;32:309-23.
158. Velentgas P, Amato AA, Bohn RL, et al. Risk of Guillain-Barré syndrome after meningococcal conjugate vaccination. Pharmacoepidemiology and Drug Safety 2012;21:1350-8.
159. Kohl KS, Marcy SM, Blum M, et al. Fever after immunization: current concepts and improved future scientific understanding. Clinical Infectious Diseases 2004;39:389-94.
160. Marin M, Broder KR, Temte JL, Snider DE, Seward JF; Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010 May 7;59(RR-3):1-12.
161. Vera-Lastra O, Medina G, Cruz-Dominguez Mdel P, Jara LJ, Shoenfeld Y. Autoimmune/ inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum. Expert Rev Clin Immunol. 2013 Apr;9(4):361-73.
162. Shoenfeld Y, Agmon-Levin N. 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011 Feb;36(1):4-8.
163. Demento SL, Eisenbarth SC, Foellmer HG, et al. Inflammasome-activating nanoparticles as modular systems for optimizing vaccine efficacy. *Vaccine*. 2009;27(23):3013-3021.
164. Esposito S, Prada E, Mastrolia MV, Tarantino G, Codecà C, Rigante D. Autoimmune/ inflammatory syndrome induced by adjuvants (ASIA): clues and pitfalls in the pediatric

background. Immunol Res. 2014 Dec;60(2-3):366-75.
165. Nishino S. Clinical and Neurobiological Aspects of Narcolepsy. *Sleep medicine*. 2007;8(4):373-399
166. Kumar S, Sagili H. Etiopathogenesis and Neurobiology of Narcolepsy: A Review. *Journal of Clinical and Diagnostic Research : JCDR*. 2014;8(2):190-195.
167. Overeem S, Scammell TE, Lammers GJ. Hypocretin/orexin and sleep: implications for the pathophysiology and diagnosis of narcolepsy. Curr Opin Neurol. 2002 Dec;15(6):739-45
168. Tsujino N, Sakurai T. Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. Pharmacol Rev. 2009 Jun;61(2):162-76
169. Harris T, Wong K, Stanford L, Fediurek J, Crowcroft N, Deeks S. Did narcolepsy occur following administration of AS03-adjuvanted A(H1N1) pandemic vaccine in Ontario, Canada? A review of post-marketing safety surveillance data. Euro Surveill. 2014 Sep 11;19(36)
170. Ahmed SS, Montomoli E, Pasini FL, Steinman L. The Safety of Adjuvanted Vaccines Revisited: Vaccine-Induced Narcolepsy. Isr Med Assoc J. 2016 Mar-Apr;18(3-4):216-20.
171. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in Children. New England Journal of Medicine. 1999;341(3):173-181.
172. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25(2):168-173.
173. Kanada KN, Merin MR, Munden A, Friedlander SF. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. J Pediatr. 2012;161:240-245.
174. Bivings L. Spontaneous regression of angiomas in children: twenty-two years' observation covering 236 cases. J Pediatr. 1954;45(6):643-647.
175. Bowers RE, Graham EA, Tominson KM. The natural history of the strawberry nevus. Arch Dermatol. 1960;82(5):667-670.
176. Jacobs AH. Strawberry hemangiomas: the natural history of the untreated lesion. Calif Med. 1957;86(1):8-10.
177. Tollefson MM, Frieden IJ. Early growth of infantile hemangiomas: what parents' photographs tell us. Pediatrics. 2012;130(2):e314-e320.
178. Darrow DH, Greene AK, Mancini AJ, et al. Diagnosis and management of infantile hemangioma. Pediatrics 2015;136(4):e1060-1104.
179. Bennett ML, Fleischer AB, Chamlin SL, et al. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. Arch Dermatol 2001;137(9):1208-13.
180. Sadan N, Wolach B. Treatment of hemangiomas of infants with high doses of prednisone. J Pediatr 1996;128(1):141-6
181. Greene AK, Couto RA. Oral prednisolone for infantile hemangioma: efficacy and safety using a standardized treatment protocol. Plast Reconstr Surg 2011;128(3):743-52.
182. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358(24):2649-51.
183. Hogeling M et al. (August 2011). "A randomized controlled trial of propranolol for infantile hemangiomas". Pediatrics 128 (2): e259–e266.
184. Leaute-Labreze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015;372(8):735-46.
185. Brotherton JM, Hull BP, Hayen A, Gidding HF, Burgess MA. Probability of coincident vaccination

in the 24 or 48 hours preceding sudden infant death syndrome death in Australia. Pediatrics 2005;115:e643–6.
186. Kuhnert R, Schlaud M, Poethko-Müller C, et al. Reanalyses of case–control studies examining the temporal association between sudden infant death syndrome and vaccination. Vaccine 2012;30:2349–56.
187. Vennemann MM, Butterfaß-Bahloul T, Jorch G, et al. Sudden infant death syndrome: no increased risk after immunisation. Vaccine 2007;25:336–40.
188. Müller-Nordhorn J, Hettler-Chen C-M, Keil T, Muckelbauer R. Association between sudden infant death syndrome and diphtheria-tetanus-pertussis immunisation: an ecological study. *BMC Pediatrics*. 2015;15(1):1. doi:10.1186/s12887-015-0318-7.
189. Hunt CE, Hauck FR. Sudden infant death syndrome. *CMAJ : Canadian Medical Association Journal*. 2006;174(13):1861-1869.
190. Jorch G, Tapiainen T, Bonhoeffer J, Fischer TK, Heininger U, Hoet B, et al; Brighton Collaboration Unexplained Sudden Death Working Group. Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5707-16.
191. Silvers LE, Ellenberg SS, Wise RP, Varricchio FE, Mootrey GT, Salive ME. The epidemiology of fatalities reported to the vaccine adverse event reporting system 1990-1997. Pharmacoepidemiol Drug Saf. 2001 Jun-Jul;10(4):279-85.
192. Institute of Medicine (US) Immunization Safety Review Committee; Stratton K, Almario DA, Wiemann TM, McCormick MC, editors. Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy. Washington (DC): National Academies Press (US); 2003.
193. DeStefano F, Mullooly JP, Okoro CA, et al. Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. Pediatrics 2001;108:e112.
194. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Childhood vaccination and type 1 diabetes. N Engl J Med 2004;350:1398–404.
195. Jefferson T, Demicheli V. No evidence that vaccines cause insulin dependent diabetes mellitus. J Epidemiol Community Health. 1998 Oct;52(10):674-5.
196. lom L, Nystrom L, Dahlquist G. The Swedish childhood diabetes study: vaccinations and infections as risk determinants for diabetes in childhood. *Diabetologia*.1991 ;34:176–181
197. Hyoty H, Hiltunen M, Reunanen A, et al. Decline of mumps antibodies in type 1 (insulin-dependent) diabetic children and a plateau in the rising incidence of type 1 diabetes after introduction of the mumps-measles-rubella vaccine in Finland. *Diabetologia*.1993 ;36:1303–1308
198. Dahlquist G, Gothefors L. The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG-vaccination. *Diabetologia*.1995 ;38:873–874
199. Parent M, Fritschi L, Siemiatycki J, Colle E, Menzies R. Bacille Calmette-Guérin vaccination and incidence of IDDM in Montreal, Canada. *Diabetes Care*.1997 ;20:767–772
200. Heijbel H, Chen RT, Dahlquist G. Cumulative incidence of childhood-onset IDDM is unaffected by pertussis immunization. *Diabetes Care*.1997 ;20:173–175
201. Institute for Vaccine Safety Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety Workshop. *Pediatr Infect Dis J*.1999 ;18:217–222
202. Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and *Haemophilus*

influenzae type b vaccination: birth cohort study. *BMJ*.1999 ;318:1169–1172
203. Classen DC, Classen JB. The timing of pediatric immunization and the risk of insulin-Classen JB. The timing of immunization affects the development of diabetes in rodents. *Autoimmunity*.1996 ;24:137–145
204. dependent diabetes mellitus. *Infect Dis Clin Pract*.1997 ;6:449–454
205. Vamos EP, Pape UJ, Curcin V, Harris MJ, Valabhji J, Majeed A, Millett C. Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes. CMAJ. 2016 Jul 25.
206. Institute of Medicine (US) Committee on Cancer Control in Low- and Middle-Income Countries; Sloan FA, Gelband H, editors. Cancer Control Opportunities in Low- and Middle-Income Countries. Washington (DC): National Academies Press (US); 2007. 2, Cancer Causes and Risk Factors and the Elements of Cancer Control. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54025/
207. White MC, Peipins LA, Watson M, Trivers KF, Holman DM, Rodriguez JL. Cancer Prevention for the Next Generation. The Journal of adolescent health : official publication of the Society for *Adolescent Medicine*. 2013;52(5 0):S1-S7. doi:10.1016/j.jadohealth.2013.02.016.
208. Cossart Y. Review of the health consequences of SV40 contamination of poliomyelitis vaccines, and in particular a possible association with cancers. Canberra: Australian Government Department of Health and Ageing, Therapeutic Goods Administration; 2004. www.tga.gov.au/pdf/alerts-medicine-poliovaccine-041214.pdf
209. Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention, Institute of Medicine of the National Academies. Stratton K, Almario DA, McCormick MC, eds. Immunization safety review. SV40 contamination of polio vaccine and cancer. Washington, D.C.: The National Academies Press; 2003.
210. Cutrone R, Lednicky J, Dunn G, Rizzo P, Bocchetta M, Chumakov K, Minor P,Carbone M. Some oral poliovirus vaccines were contaminated with infectious SV40 after 1961. Cancer Res. 2005 Nov 15;65(22):10273-9.
211. Koprowski H. First decade (1950–1960) of studies and trials with the polio vaccine. Biologicals 2006;34:81–6.
212. Worobey M, Santiago ML, Keele BF, et al. Origin of AIDS: contaminated polio vaccine theory refuted. Nature 2004;428:820.
213. Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention, Institute of Medicine of the National Academies. Stratton K, Almario DA, McCormick MC, eds. Immunization safety review. Hepatitis B vaccine and demyelinating neurological disorders. Washington DC: The National Academies Press; 2002.
214. Langer-Gould A, Qian L, Tartof SY, Brara SM, Jacobsen SJ, Beaber BE, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. JAMA Neurol. 2014 Dec;71(12):1506-13
215. Wood H. Demyelinating disease: new study refutes link between vaccines and demyelination. Nat Rev Neurol. 2014 Dec;10(12):673.
216. Krone B, Grange JM. Vaccination, infection, and the risk for multiple sclerosis. JAMA Neurol. 2015 Apr;72(4):480.
217. Ristori G, Mechelli R, Salvetti M. Association between vaccines and neuroinflammation: time, risks, and benefits. JAMA Neurol. 2015 May;72(5):605.

218. Fourrier A, Touze E, Alperovitch A, Begaud B. Association between hepatitis B vaccine and multiple sclerosis: a case-control study. Pharmacoepidemiol Drug Saf 1999;8:Suppl:S140-S141 abstract
219. Palefsky JM. Human Papillomavirus-Related Disease in Men: Not Just a Women's Issue. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 2010;46(4 Suppl):S12-S19.
220. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. *Preventive Medicine*. 2011;53(Suppl 1):S5-S11.
221. World Health Organization (WHO). Global Advisory Committee on Vaccine Safety, 2–3 December 2015. *Weekly Epidemiological Record* 2016;91:21-31. Available from: www.who.int/wer/2016/wer9103.pdf?ua=1 (Accessed March 2016)
222. Macartney K, Chiu C, Georgousakis M, Brotherton JM. Safety of human papillomavirus vaccines: a review. *Drug Safety* 2013;36:393-412.
223. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009;302:750-7.
224. Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine. *Pediatric Infectious Disease Journal* 2010;29:95-101.
225. Ferris D, Samakoses R, Block SL, et al. Long-term study of a quadrivalent human papillomavirus vaccine. *Pediatrics* 2014;134:e657-65.
226. Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine* 2011;29:8279- 84.
227. Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *Journal of Internal Medicine* 2012;271:193-203.
228. Centers for Disease Control and Prevention (CDC). Resurgence of wild poliovirus type 1 transmission and consequences of importation – 21 countries, 2002–2005. *MMWR Morbidity and Mortality Weekly Report* 2006;55:145-50.
229. Wise LD, Wolf JJ, Kaplanski CV, et al. Lack of effects on fertility and developmental toxicity of a quadrivalent HPV vaccine in Sprague-Dawley rats. *Birth Defects Research Part B: Developmental and Reproductive Toxicology* 2008;83:561-72.
230. Wise LD, Pauley CJ, Michael B, Wolf JJ. Lack of effects on male fertility from a quadrivalent HPV vaccine in Sprague-Dawley rats. *Birth Defects Research Part B: Developmental and Reproductive Toxicology* 2010;89:376-81.
231. Gajdová M, Jakubovsky J, Války J. Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats. Food Chem Toxicol. 1993 Mar;31(3):183-90.
232. Harper DM, Vierthaler SL, Santee JA. Review of Gardasil. *Journal of vaccines & vaccination*. 2010;1(107):1000107.
233. Grabenstein JD. *ImmunoFacts: Vaccines and Immunologic Drugs* – 2013 (38th revision). St Louis, MO: Wolters Kluwer Health, 2012.
234. Dana A, Buchanan KM, Goss MA, et al. Pregnancy outcomes from the pregnancy registry of a human papillomavirus type 6/11/16/18 vaccine. *Obstetrics and Gynecology* 2009;114:1170-8.
235. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized

controlled trials. *Obstetrics and Gynecology* 2009;114:1179-88.
236. Cheriyan E. Monitoring the vaccine cold chain. *Archives of Disease in Childhood*. 1993;69(5):600-601
237. Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(no. RR-2): 23-27, http://www.cdc.gov/vaccines/pubs/ ACIP-list.htm
238. Klein NP, Edwards KM, Sparks RC, Dekker CL; Clinical Immunization Safety Assessment (CISA) Network. Recurrent sterile abscesses following aluminium adjuvant-containing vaccines. BMJ Case Rep. 2009;2009.
239. Centers for Disease Control and Prevention (CDC). Epidemiology and Prevention of Vaccine-Preventable Diseases. Vaccine Storage and Handling. Available at: http://www.cdc.gov/vaccines/pubs/pinkbook/vac-storage.html (Accessed Jan 2016)
240. Petralli JK, Merigan TC, Wilbur JR. Action of endogenous interferon against vaccinia infection in children. Lancet 1965;286(7409):401-405.
241. Joint Committee on Vaccination and Immunisation (JCVI) 2014. Minutes of the February 2014 meeting. Available at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation
242. Nascimento, Silva JR et al (2011). Mutual interference on the immune response to Yellow Fever vaccine and combined vaccines against measles, mumps and rubella. Vaccine, 2011 29 (3). 6327- 6334.
243. Mullooly, J. Black, S. (2001). Simultaneous administration of varicella vaccine and other recommended childhood vaccines. United States. Nov 30; 2001. 50 (47). Pp. 1058-
244. Statens Serum Institute (2011). Description of Tuberculin PPD RT 23. Available at: http://www.ssi.dk/English/Vaccines/Tuberculin%20PPD%20RT%2023%20SSI/Description%20of%20Tuberculin%20PPD%20RT%2023.aspx
245. Groom H, Hopkins DP, Pabst LJ, Murphy Morgan J, Patel M, Calonge N, et al; Community Preventive Services Task Force. Immunization information systems to increase vaccination rates: a community guide systematic review. J Public Health Manag Pract. 2015 May-Jun;21(3):227-48.
246. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger JA. Vaccine hesitancy: An overview. *Human Vaccines & Immunotherapeutics*. 2013;9(8):1763-1773.
247. Lim MS, Elenitoba-Johnson KSJ. The Molecular Pathology of Primary Immunodeficiencies. *The Journal of molecular diagnostics : JMD*. 2004;6(2):59-83
248. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014 Feb;58(3):309-18.
249. Obaro SK, Pugatch D, Luzuriaga K. Immunogenicity and efficacy of childhood vaccines in HIV-1-infected children. Lancet Infect Dis. 2004 Aug;4(8):510-8.
250. Small TN, Robinson WH, Miklos DB. B cells and Transplantation: An educational resource for the 2009 ASBMT Meeting. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2009;15(1 Suppl):104-113.
251. Burroughs M, Moscona A. Immunization of pediatric solid organ transplant candidates and recipients. Clin Infect Dis. 2000 Jun;30(6):857-69.
252. Leone G, Pizzigallo E. Bacterial Infections Following Splenectomy for Malignant and

Nonmalignant Hematologic Diseases. *Mediterranean Journal of Hematology and Infectious Diseases*. 2015;7(1):e2015057.
253. Prevention and therapy of bacterial infections for children with asplenia or hyposplenia. *Paediatrics & Child Health*. 1999;4(6):417-421.
254. Makris M, Conlon CP, Watson HG. Immunization of patients with bleeding disorders. Haemophilia. 2003 Sep;9(5):541-6.
255. Evans DIK, Shaw, A. Safety of intramuscular injection of hepatitis B vaccine in haemophiliacs, BMJ 1990;300:1694-5.
256. O'Connor SM, Taylor CE, Hughes JM. Emerging infectious determinants of chronic diseases. Emerg Infect Dis. 2006 Jul;12(7):1051-7.
257. American Academy of Pediatrics. Immunization in Special Clinical Circumstances. En: Pickering LK, Baker CJ, Kimberlin DW, Long SS (eds.). Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012. p. 111-214.
258. Crawford NW, Bines JE, Royle J, Buttery JP. Optimizing immunization in pediatric special risk groups. Expert Rev Vaccines. 2011;10:175-86.
259. American Academy of Pediatrics. Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS. eds. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009
260. Brodtman DH, Rosenthal DW, Redner A, Lanzkowsky P, Bonagura VR. Immunodeficiency in children with acute lymphoblastic leukemia after completion of modern aggressive chemotherapeutic regimens. J Pediatr 2005;146:654–61.
261. Esposito S, Cecinati V, Brescia L, Principi N. Vaccinations in children with cancer. Vaccine. 2010;28:3278-84.
262. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66:1016-26.
263. Kobayashi I, Mori M, Yamaguchi K, Ito S, Iwata N, Masunaga K, *et al*. Pediatric Rheumatology Association of Japan recommendation for vaccination in pediatric rheumatic diseases. Mod Rheumatol. 2015;25:335-43.
264. Ljungman P. Vaccination of immunocompromised patients. Clin Microbiol Infect. 2012;18:93-9.
265. Lodhia N. The appropriate use of vaccines in patients with inflammatory bowel disease. J Clin Gastroenterol. 2014;48:395-401.
266. Mellado Peña MJ, Moreno-Pérez D, Ruiz Contreras J, Hernández-Sampelayo Matos T, Navarro Gómez ML, grupo de colaboradores del Documento de Consenso SEIP-CAV de la AEP. Documento de consenso de la Sociedad Española de Infectología Pediátrica y el Comité Asesor de Vacunas de la Asociación Española de Pediatría para la vacunación en inmunodeprimidos. AnPediatr (Barc). 2011;75:413.e1-22.
267. Siber GR, Snydman DR. Use of immune globulin in the prevention and treatment of infections. In: Remington J, Swartz M, eds. Current clinical topics in infectious diseases, vol. 12. Oxford: Blackwell Scientific; 1992.
268. Public Health Agency of Canada. Canadian Immunization Guide. Part 5. Passive immunizing agents. April 2014. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p05-01-eng.

php
269. Public Health Agency of Canada. Canadian Immunization Guide, 2013. Blood products, human immune globulin and timing of immunization. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-10-eng.php
270. CDC. Typhoid immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1994;43 (No. RR-14).
271. CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR 2010;59(No. RR-8).
272. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56(No. RR-4).
273. CDC. Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices. MMWR 2008;57(No. RR-5).
274. Saari TN; American Academy of Pediatrics Committee on Infectious Diseases.Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics. 2003 Jul;112(1 Pt1):193-8.
275. Bernbaum JC, Daft A, Anolik R, et al. Response of preterm infants to diphtheria-tetanus-pertussis immunizations. J Pediatr 1985;107: 184–8.
276. Koblin BA, Townsend TR, Munoz A, Onorato I, Wilson M, Polk BF. Response of preterm infants to diphtheria-tetanus-pertussis vaccine. Pediatr Infect Dis J 1988;7:704–11.
277. Smolen P, Bland R, Heiligenstein E, et al. Antibody response to oral polio vaccine in premature infants. J Pediatr 1983;103:917–9.
278. Omenaca F, Garcia-Sicilia J, Garcia-Corbeira P, et al. Response of preterm newborns to immunization with a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio and Haemophilus influenzae type b vaccine: first experiences and solutions to a serious and sensitive issue. Pediatrics 2005;116:1292–8.
279. Shinefield H, Black S, Ray P, Fireman B, Schwalee M, Lewis E. Efficacy, immunogenicity and safety of heptavalent pneumococcal conjugate vaccine in low birthweight preterm infants. Ped Inf Dis J 2002;21: 182–6.
280. Lau YL, Tam AY, Ng KW, et al. Response of preterm infants to hepatitis B vaccine. J Pediatr 1992;121:962–5.
281. Patel DM, Butler J, Feldman S, Graves GR, Rhodes PG. Immunogenicity of hepatitis B vaccine in healthy very low birth weight infants. J Pediatr 1997;131:641–3.
282. Kim SC, Chung EK, Hodinka RL, et al. Immunogenicity of hepatitis B vaccine in preterm infants. Pediatrics 1997;99:534–6.
283. Losonsky GA, Wasserman SS, Stephens I, et al. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Pediatrics 1999;103:14.
284. Sen S, Cloete Y, Hassan K, Buss P. Adverse events following vaccination in premature infants. Acta Paediatr. 2001 Aug;90(8):916-20.
285. CDC. Prevention of rotavirus gastroenteritis among infants and chil¬dren: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(No. RR-2).
286. CDC. A comprehensive immunization strategy to eliminate transmis¬sion of hepatitis B virus infection in the United States: recommenda¬tions of the Advisory Committee on Immunization Practices (ACIP); part 1: immunization of infants, children, and adolescents.

MMWR 2005;54(No. RR-16).
287. Bohlke K, Galil K, Jackson LA, et al. Postpartum varicella vaccination: is the vaccine virus excreted in breast milk? Obstet Gynecol 2003;102: 970–7.
288. Krogh V, Duffy LC, Wong D, Rosenband M, Riddlesberger KR, Ogra PL. Postpartum immunization with rubella virus vaccine and antibody response in breast-feeding infants. J Lab Clin Med 1989;113:695–9.
289. Krogh V, Duffy LC, Wong D, Rosenband M, Riddlesberger KR, Ogra PL. Postpartum immunization with rubella virus vaccine and antibody response in breast-feeding infants. J Lab Clin Med 1989;113:695–9.
290. CDC. Yellow fever vaccine: recommendations of the Immunization Practices Advisory Committee (ACIP), 2010. MMWR 2010:59 (No. RR-7).
291. Pickering LK, Granoff DM, Erickson JR, et al. Modulation of the immune system by human milk and infant formula containing nucleotides. Pediatrics 1998;101:242–9.
292. Kim-Farley R, Brink E, Orenstein W, Bart K. Vaccination and breast feeding [Letter]. JAMA 1982;248:2451–2.
293. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral polio vaccine in developing countries: review. Rev Infect Dis 1991;13:926–39.
294. Hahn-Zoric M, Fulconis F, Minoli I, et al. Antibody responses to parenteral and oral vaccines are impaired by conventional and low-protein formulas as compared to breast feeding. Acta Paediatr Scand 1990;79:1137–42.
295. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338: 1128–37.
296. Grabenstein JD. Vaccines and antibodies in relation to pregnancy and lactation. Hospital Pharmacy 1999;34:949–60.
297. CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. MMWR 2006;55(No. RR-17).
298. CDC. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008;57(No. RR-4).
299. CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR 2010;59(No. RR-8).
300. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094–102.
301. CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997;46 (No. RR-8).
302. CDC. Prevention and control of meningococcal disease: recommenda¬tions of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005;54 (RR-7).
303. CDC. Prevention of hepatitis A through active or passive immuniza¬tion: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-7).
304. Tsai TF, Paul R, Lynberg MC, Letson GW. Congenital yellow fever virus infection after immunization in pregnancy. J Infect Dis 1993;168: 1520–3.
305. CDC. A comprehensive immunization strategy to eliminate transmis¬sion of hepatitis B virus infection in the United States: recommenda¬tions of the Advisory Committee on Immunization Practices (ACIP); part 1: immunization of infants, children, and adolescents. MMWR 2005;54(No. RR-16).

306. CDC. Recommendations for using smallpox vaccine in a pre-event vaccination program: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR 2003;52(No. RR-7).
307. Wilson E, Goss MA, Marin M, et al. Varicella vaccine exposure during pregnancy: data from 10 years of the pregnancy registry. J Infect Dis 2008;197 (Suppl 2):S178–84.
308. CDC. Revised ACIP recommendation for avoiding pregnancy after receiving a rubella-containing vaccine. MMWR 2001;50:1117.
309. CDC. Rubella vaccination during pregnancy—United States, 1971–1988. MMWR 1989;38:289–93
310. CDC. Measles, mumps, and rubella—vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1998;47(No. RR-8).
311. Black NA, Parsons A, Kurtz JB, McWhinney N, Lacey A, Mayon-White RT. Post-partum rubella immunization: a controlled trial of two vaccines. Lancet 1983;2:990–2.
312. Bart MJ, Harris SR, Advani A, et al. Global Population Structure and Evolution of Bordetella pertussis and Their Relationship with Vaccination. mBio. 2014;5(2):e01074-14.
313. Munoz FM, Bond NH, Maccato M, et al. Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants: A Randomized Clinical Trial. *JAMA*. 2014;311(17):1760-1769.
314. Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis 2004;190(2):335–340.
315. Gonik B, Puder KS, Gonik N, Kruger M. Seroprevalence of Bordetella pertussis antibodies in mothers and their newborn infants. Infect Dis Obstet Gynecol 2005;13(2):59–61.
316. Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine. J Infect Dis 1990;161(3):487–492.
317. Starr S, Berkovich S. Effects of measles, gamma-globulin-modified measles and vaccine measles on the tuberculin test. N Engl J Med 1964;270:386–91.
318. Brickman HF, Beaudry PH, Marks MI. Timing of tuberculin tests in relation to immunization with live viral vaccines. Pediatrics 1975;55: 392–6.
319. Berkovich S, Starr S. Effects of live type 1 poliovirus vaccine and other viruses on the tuberculin test. N Engl J Med 1966;274:67–72.
320. CDC. Recommendations for using smallpox vaccine in a pre-event vaccination program: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR 2003;52(No. RR-7).
321. CDC. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. MMWR 2010;59(No. RR-5).
322. Romanus V, Fasth A, Tordai P, Wiholm BE. Adverse reactions in healthy and immunocompromised children under six years of age vaccinated with the Danish BCG vaccine, strain Copenhagen 1331: implications for the vaccination policy in Sweden. Acta Paediatrics 1993 82(12):1043–1052.
323. CDC. BCG vaccine. Fact sheets. Available at: http://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm Accessed Sep 2016)

324. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ. 2014 Aug 5;349:g4643.
325. World Health Organization (WHO). Guidance on how to prioritize globally constrained BCG vaccine supply to countries produced by WHO Dept. of Immunizations, Vaccines and Biologicals, the WHO Global Tuberculosis Programme and UNICEF Supply and Programme Divisions 22 July 2015. Available at: http://www.who.int/immunization/diseases/tuberculosis/BCG-country-prioritization.pdf (Accessed Sep 2016)
326. Buddle BM, Wedlock DN, Parlane NA, Corner LA, De Lisle GW, Skinner MA. Revaccination of neonatal calves with Mycobacterium bovis BCG reduces the level of protection against bovine tuberculosis induced by a single vaccination. Infect Immun. 2003 Nov;71(11):6411-9.
327. Pereira SM, Dantas OM, Ximenes R, Barreto ML. [BCG vaccine against tuberculosis: its protective effect and vaccination policies]. Rev Saude Publica. 2007 Sep;41 Suppl 1:59-66.
328. Tasher D, Dalal I. The genetic basis of severe combined immunodeficiency and its variants. *The Application of Clinical Genetics*. 2012;5:67-80.
329. Global Tuberculosis Report, 2012, World Health Organization, http://www.who.int/tb/publications/global_report/gtbr12_main.pdf
330. Gonzalez B, Moreno S, Burdach R. Clinical presentation of Bacillus Calmette-Guerin infections in patients with immunodeficiency syndromes. Pediatr Infect Dis J 1989;8:201–6.
331. Yao CM, Han XH, Zhang YD, et al. Clinical characteristics and genetic profiles of 44 patients with severe combined immunodeficiency (SCID): report from Shanghai, China (2004–2011). J Clin Immunol 2013 33(3):526–539.
332. Marciano BE, Huang CY, Joshi G, Rezaei N, Costa-Carvalho B, Allwood Z, et al. J Allergy Clin Immunol 2014; 133(4): 1134–1141.
333. van Well GT, Paes BF, Terwee CB, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. Pediatrics 2009; 123(1):e1–8.
334. World Health Organization. Baccille Calmette Guérin vaccine. Reported estimates of BCG coverage. Available at: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragebcg.html (Accessed sep 2016)
335. The BCG World Atlas. Zwerling A, Behr M, Verma A, Brewer T, Menzies D & Pai M Affiliations: McGill University & McGill University Health Center Montreal Quebec, Canada Supported in part by the Public Health Agency of Canada. Available at: http://www.bcgatlas.org (Accessed sep 2016)
336. World Health Organization. Third dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine. Available at: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragedtp3.html (Accessed sep 2016)
337. Lee LV. Neurotuberculosis among Filipino children: an 11 years experience at the Philippine Children's Medical Center. Brain Dev 2000;22(8):469–474.
338. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. J Infect 2000 41(1):61–68.
339. Yaramis A, Gurkan F, Elevli M, et al. Central nervous system tuberculosis in children: a review of 214 cases. Pediatrics 1998 102(5):E49.
340. Doerr CA, Starke JR, Ong LT. Clinical and public health aspects of tuberculous meningitis in children. J Pediatr 1995 127(1):27–33.

341. Greenberg DP, Pickering LK, Senders SD et al. Interchangeability of 2 diphtheria-tetanus-acellular pertussis vaccines in infancy. Pediatrics 2002;109:666-72.
342. Paganini H, Gonzalez F, Santander C, Casimir L, Berberian G, Rosanova MT. Tuberculous meningitis in children: clinical features and outcome in 40 cases. Scand J Infect Dis 2000; 32(1):41–45.
343. Feldman S. Interchangeability of vaccines. Pediatr Infect Dis J 2001;20 (Suppl 1):S23-29.
344. Rymer W, Zalewska M, Szymczak A, Zubkiewicz-Zarębska A, Knysz B. Interchangeability of 3 recombinant anti-HBV vaccines in primary schedule irrespective of dose and HBsAg subtype: the first prospective, open-label, randomized study in healthy adult population. Pol Arch Med Wewn.2015;125(9):695-7. Epub 2015 Sep 3.
345. Patel RR, Liang SY, Koolwal P, Kuhlmann FM. Travel advice for the immunocompromised traveler: prophylaxis, vaccination, and other preventive measures. Therapeutics and Clinical Risk Management. 2015;11:217-228.
346. Steffen, R. (2010), The Risk of Meningococcal Disease in Travelers and Current Recommendations for Prevention. Journal of Travel Medicine, 17: 9–17.
347. Verma R, Khanna P, Chawla S. Recommended vaccines for international travelers to India. Human Vaccines & Immunotherapeutics. 2015;11(10):2455-2457
348. Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al; Infectious Diseases Society of America. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006 Dec 15;43(12):1499-539.
349. Lapphra K, Scheifele D. Can children with minor illnesses be safely immunized? Paediatrics & Child Health. 2011;16(8):463.
350. Cardemil CV, Estivariz C, Shrestha L, Sherchand JB, Sharma A, Gary HE Jr, et al. The effect of diarrheal disease on bivalent oral polio vaccine (bOPV) immune response in infants in Nepal. Vaccine. 2016 May 11;34(22):2519-26.
351. Flanagan KL, Burl S, Lohman-Payne BL, Plebanski M. The challenge of assessing infant vaccine responses in resource-poor settings. Expert review of vaccines. 2010;9(6):665-674.
352. Sengupta P. Rotavirus: The Challenges Ahead. Indian Journal of Community Medicine : Official Publication of Indian Association of Preventive & Social Medicine. 2009;34(4):279-282
353. Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomized, double- blind controlled study. *Lancet* 2007;370:1757-63.
354. Ma SJ, Xiong YQ, Jiang LN, Chen Q. Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis. Vaccine. 2015 Jul 17;33(31):3636-49.
355. Berg AT. Seizure Risk with Vaccination. Epilepsy Currents. 2002;2(1):15-16.
356. Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al; Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001 Aug 30;345(9):656-61.

Annex. Frequency of adverse reactions to commonly used vaccines

BCG Vaccine Summary

Vaccine Adverse Reactions	Frequency category
Injection site reaction (Papule, mild ulceration orscar)	Very common
Suppurative lymphadenitis	Uncommon to Rare
BCG osteitis	Uncommon to Very rare
Disseminated BCG disease or systemic BCG-itis	Very Rare
Immunine Reconstitution Inflammatory Syndrome (IRIS)	Very Rare

DTP Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Whole cell Pertussis vaccines	
Fever 100.1°F - 102°F	Very common
Injection site Redness	Very common
Swelling	Very common
Pain (Severe-Moderate)	Very common
Fussiness (Severe-Moderate)	Very common
Drowsiness	Very common
Anorexia	Very common
Vomiting	Common
Persistent screaming	Uncommon to Rare
HHE	Very rare
Seizures	Very rare
Encephalopathy	Very rare
Anaphylaxis	
A cellular Pertussis vaccines	
Fever 100.1°F - 101°F	Very common
Fever 100.1°F - 102°F	Common
Injection site Redness	Common to Very common
Injectionsite swelling	Common to Very common
Pain (Severe-Moderate)	Uncommon to Common
Fussiness (Severe-Moderate)	Common to Very common
Drowsiness	Very Common
Anorexia	Very Common
Vomiting	Very Common
Persistent screaming	Uncommon
HHE	Rare
Seizures	Very rare

Tetanus vaccines Summary

Vaccine Adverse Reactions	Frequency category
Brachial neuritis	Very rare
Anaphylaxis	Very rare

Hepatitis B Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Fever	Common
Headache	Common
Injection site pain	Common to Very common
Injection site redness	Common
Injection site swelling	Common
Anaphylaxis	Very rare

Human Papiloma Vaccines (HPV) Summary

Vaccine Adverse Reactions	Frequency category
Bivalent HPV Vaccine	
Fever	Common
Headache	Very common
Injection site pain	Very common
Redness	Very common
Swelling	Very common
Rash	Uncommon
Arthralgia	Very common
Myalgia	Very common
Fatigue	Very common
Gastrointestinal disorders	Very common
Quadrivalent HPV Vaccine	
Fever 100.1°F - 101°F	Very common
Fever 100.1°F - 102°F	Very Common
Injection site Redness	Common
Injectionsite swelling	Common
Pain (Severe-Moderate)	Common
Fussiness (Severe-Moderate)	Common
Drowsiness	Common
Anorexia	Common
Vomiting	Common
Persistent screaming	Common
HHE	Very common
Seizures	Very rare

Hib Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Fever	Common
Injection site reaction	Very common

Polio Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Whole cell Pertussis vaccines	
■ VAPP	
– Recipient VAPP	Very Rare
– Total VAPP	Very Rare
Inactivated Polio Vaccine (IPV)	
■ Injection site erythema	Un common to Common
■ Injection site induration	Common to Very common
■ Injection site tenderness	Very Common

Measles Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Fever	Common to Very common
■ Rash	Common
■ Injection site reaction	Very common
■ Febrile seizures	Rare
■ Encephalomyelitis	Very rare
■ Thrombocytopenia	Very rare
■ Anaphylaxis	Very rare

Pneumococcal vaccines Summary

Vaccine Adverse Reactions	Frequency category
Unconjugated vaccine (PPSV)	
■ Fever > 39°C	Uncommon
■ Injection site reaction	Very common
Conjugated vaccine (PCV)	
■ Fever > 39°C	Uncommon
■ Injection site reaction	Very common

Rubella Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Fever	Common
■ Injection site reaction	Very common
■ Acute Arthralgia (adults)	Very common
■ Acute Arthritis (adults)	Very common

Varicella Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Febrile seizures	Rare
■ Fever > 39°C	Very Common
■ Injection site reaction	Common to Very Common
■ Site rash (local/generalized)	Common

Mumps Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Injection site reaction	Very common
■ Parotid swelling	Common
■ Aseptic meningitis	Very common

Rotavirus Vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Intussusception	Very rare

Yellow Fever vaccines Summary

Vaccine Adverse Reactions	Frequency category
■ Vaccine-associated viscerotropic disease	Very rare

Source: WHO Fact sheets www/who.int/vaccines safety/initiative/tools/vaccinfosheets

Key

Very common	> 1/10	> 10%
Common	> 1/100 and < 1/10	> 1% and < 10%
Uncommon	> 1/1,000 and < 1/100	> 0.1% and < 1 %
Rare	> 1/10,000 and < 1/1,000	> 0.01% and < 0.1%
Very rare	< 1/10,000	< 0.01%

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The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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