

Supplementary information on vaccine safety

Part 2: Background rates of adverse events following immunization



DEPARTMENT OF VACCINES AND BIOLOGICALS



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Contents

<i>Glossary</i>	v
<i>Acknowledgements</i>	vi
1. Introduction	1
1.1 Background	1
1.2 Common, mild vaccine reaction rates.....	2
1.3 Rare, more sever reaction rates	3
1.4 Programme errors.....	5
Background rates for adverse events for specific vaccines and vitamin A supplementation	
2. Adverse events following BCG vaccine	8
3. Adverse events following cholera vaccine	14
4. Adverse events following diphtheria, tetanus and pertussis vaccines	17
5. Adverse events associated with Haemophilus influenzae type b (Hib) vaccine	26
6. Adverse events following hepatitis A vaccine	31
7. Adverse events associated with the hepatitis B vaccine	34
8. Adverse events following influenza vaccine	40
9. Adverse events following Japanese encephalitis vaccine	45
10. Adverse events following Lyme disease vaccine	48
11. Adverse events following meningococcal polysaccharide vaccine	51
12. Adverse events following measles, mumps and rubella vaccines	55
13. Adverse events following pneumococcal vaccine	69
14. Adverse events following poliomyelitis vaccine	72

15. Adverse events following rabies vaccine	79
16. Adverse events following rotavirus vaccine	84
17. Adverse events following tick-borne encephalitis virus vaccine	87
18. Adverse events following typhoid vaccine	89
19. Adverse events following varicella vaccine	93
20. Adverse events following vitamin A supplementation	97
21. Adverse events following yellow fever vaccine	102

Glossary

ELISA	enzyme-linked immunosorbent assay
GBS	Guillain–Barré syndrome
IDDM	insulin-dependent diabetes mellitus
IOM	Institute of Medicine
IPV	inactivated poliovirus vaccine
LD	lethal dose for mouse
OPV	oral polio vaccine
PFU	plaque forming units
PRP	polyribosylribitol phosphate
RRV-TV	Rhesus rotavirus tetravalent vaccine
RVA	Rabies vaccine adsorbed
SCID	severe combined immunodeficiency
TBE	tick-borne encephalitis
TM	Transverse myelitis
Vi	virulence (antigen)
WC/rBS	whole cell recombinant B subunit

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1. Introduction

1.1 Background

No biological or pharmaceutical product has yet been developed which is 100% safe and 100% effective. The more modified a vaccine becomes for safety reasons, the greater the possibility that it will become less effective. Vaccine manufacturers develop products with the highest safety and effectiveness possible, given current technology. But some very rare vaccine-related adverse events will always occur. Where surveillance is not adequate, these may not come to the notice of immunization staff or the public, but they nonetheless occur.

Programme managers and vaccinators need to know what is “normal” – what reaction rates are to be expected. There is not always a single correct answer to this question as the rates for a given vaccine may be variable, depending on how they are measured. These rates are usually quoted in reference to a given study, but other studies with slightly different designs may produce rather different rates. When there is no clear “best study”, rates in this document have been quoted as a range, e.g. “40–100 per million doses administered”. Without these background rates, it is impossible to know when they are occurring more frequently “than expected”. Indeed rates may appear to be raised in certain situations, such as during mass campaigns (for a detailed explanation, see *Supplementary information on vaccine safety; Part 1: Field issues WHO/V&B/00.24*).

Vaccine reactions may be classified into “common” and “rare”. The majority of vaccine reactions are “common”, mild, settle without treatment, and have no long-term consequences. More serious reactions are very rare – usually of a fairly predictable (albeit extremely low) frequency. A childhood vaccine may also precipitate an event that would probably have occurred anyway (e.g. a first febrile seizure). Most importantly, vaccines are given at a time in an infant or child’s life when many other events are happening: colds and coughs happen whether or not vaccines are given, but because a cough follows vaccination, parents may (not unreasonably) believe the two events are related.

1.2 Common, mild vaccine reaction rates

The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. It is not surprising that vaccination results in certain mild side-effects. Local reaction, fever and systemic symptoms can result as part of the normal immune response. In addition, some of the vaccine's components (e.g. aluminium adjuvant, antibiotics or preservatives) can lead to reactions. A successful vaccine reduces these reactions to a minimum while inducing maximum immunity. Pain, swelling and/or redness at the injection site characterize the local reaction. Symptomatic local reactions can be expected in about 10% of vaccine recipients (except for DTP and TT boosters where it affects about half). Fever occurs in about 10% or less of vaccine recipients (except for DTP where it is again about half).

BCG often causes a local reaction that starts two or more weeks after immunization as a papule (lump), which becomes ulcerated, and heals after several months, leaving a scar. Keloid (thickened scar tissue) from the BCG lesion is more common among Asian and African populations.

Table 1: Summary of common minor vaccine reactions and treatment

(Note: the rates due to the vaccine administration will be lower as these symptoms occur independently as part of normal childhood)

Vaccine	Local reaction (pain, swelling, redness)	Fever	Irritability, malaise and non-specific symptoms
BCG	common	-	-
Hib	5–15%	2–10%	-
Hepatitis B	adults up to 30% children up to 5%	1–6%	-
Measles/MMR	up to 10%	up to 5%	up to 5%
Oral polio (OPV)	none	less than 1%	less than 1% ^{a)}
Tetanus/DT	up to 10% ^{b)}	up to 10%	up to 25%
DTP ^{c)}	up to 50%	up to 50%	up to 60%

^{a)} Diarrhoea, headache, and/or muscle pains.

^{b)} Rate of local reactions likely to increase with booster doses, up to 50 to 85%.

^{c)} With whole cell pertussis vaccine. Acellular pertussis vaccine rates are lower.

These common reactions occur within a day or two of immunization, except for fever and systemic symptoms from measles/MMR which occur from 5 to 12 days after immunization. Although fever and/or rash occur in 5–15% of measles/MMR vaccine recipients during this time, only around 3% are attributable to vaccine, the rest being accounted for as normal events in childhood i.e. background events.

1.3 Rare, more severe reaction rates

Most of the rare vaccine reactions (e.g. seizures, thrombocytopaenia, hypotonic hyporesponsive episodes, persistent inconsolable screaming) are self-limiting and do not lead to long-term problems. Table 1 details rare vaccine reactions. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects. Although encephalopathy is included as a rare reaction to measles or DTP vaccine, it is not certain that the vaccines, in fact, cause this.

The information in tables 1 and 2 can be used to:

- Anticipate reactions for a specific immunization programme (type and number).
- Identify events that are unrelated to immunization (e.g. outside the time window).
- Compare reported with expected rates of reactions (the efficiency of reporting).
- Trigger an investigation if the reported rate is greater than the expected rate.

Table 2: Summary of rare, serious vaccine reactions, onset interval and rates

Vaccine	Reaction	Onset interval	Rate per million doses
BCG	Suppurative lymphadenitis	2–6 months	100–1000
	BCG osteitis	1–12 months	1–700
	Disseminated BCG-itis	1–12 months	2
Hib	Nil known		
Hepatitis B	Anaphylaxis	0–1 hour	1–2
	Guillain-Barré Syndrome (plasma-derived)	1–6 weeks	5
Measles/MMR ^{a)}	Febrile seizures	5–12 days	333
	Thrombocytopaenia (low platelets)	15–35 days	33
	Anaphylaxis	0–1 hour	1–50
Oral polio (OPV)	Vaccine-associated paralytic poliomyelitis (VAPP)	4–30 days	1.4–3.4 ^{b)}
Tetanus	Brachial neuritis	2–28 days	5–10
	Anaphylaxis	0–1 hour	1–6
	Sterile abscess	1–6 weeks	6–10
Tetanus–diphtheria	Nil extra to tetanus reactions		
DTP	Persistent (> 3 hours) inconsolable screaming	0–24 hours	1 000–60 000
	Seizures	0–3 days	570 ^{c)}
	Hypotonic, hyporesponsive episode (HHE)	0–24 hours	570
	Anaphylaxis/shock	0–1 hour	20
	Encephalopathy	0–3 days	0–1
Japanese Encephalitis	Serious allergic reaction		10–1 000
	Neurological event		1–2.3
Yellow Fever	Post-vaccination encephalitis	7–21 days	500–4000 in infants less than 6 months ^{d)}
	Allergic reaction/anaphylaxis	0–1 hrs	5–20

^{a)} Reactions (except anaphylaxis) do not occur if already immune (~90% of those receiving a second dose); children over six years unlikely to have febrile seizures.

^{b)} VAPP risk is higher for first dose (1 per 1.4–3.4 million doses) compared to 1 per 5.9 million for subsequent doses and 1 in 6.7 million doses for contacts.

^{c)} Seizures are mostly febrile in origin, and rate depends on past history, family history and age, with much lower risk in infants under the age of 4 months.

^{d)} Isolated cases with no denominator make it difficult to assess the rate in older children and adults, but it is extremely rare (less than 1 case per 8 million doses).

1.4 Programme errors

Most of the reactions listed as “common, mild” and “rare, more serious” are difficult or impossible for the vaccinator to prevent. One type of reaction is, however, very much in the hands of the vaccinator to limit or prevent all together. This is the “programmatic error” caused by an error or errors in the handling or administration of a vaccine. The error is usually the fault of a person rather than the fault of the vaccine or other technology. It can generally be prevented through proper staff training and an adequate supply of safe injection equipment. Every effort must be made to avoid events that can cause untold damage to individual infants, grief to parents and loss of confidence in the programme by the public. In many instances, it may also cause the loss of employment of the vaccinator. There is no short cut to training and supervision for avoiding such events.

A programme error may lead to a cluster of events, especially if one vaccinator fails to observe training. Improper immunization practice may result in abscesses or other blood-borne infections. The worst scenario is the occurrence of toxic shock from improper handling of vaccine vials once reconstituted. A number of infants immunized from the same vial may die within a short time of injection.

Basic rules in avoiding programme errors include:

- Use a sterile needle and sterile syringe for every injection.
- Reconstitute using only the diluent provided with the vaccine.
- Discard reconstituted vaccine (measles, yellow fever and BCG) after six hours and never keep them overnight.
- Follow WHO policy on re-use of multi-dose vials (EPI 199).
- Store drugs and other substances in a different fridge from vaccines.
- Train and supervise workers appropriately to ensure safe injection practices.
- Investigate a programme error so that the same error does not repeat itself.

Table 3: Programme errors and their consequences

Programme error	Adverse event expected
<p><i>Non-sterile injection:</i></p> <ul style="list-style-type: none"> • Reuse of disposable syringe or needle • Improperly sterilized syringe or needle • Contaminated vaccine or diluent • Reuse of reconstituted vaccine at subsequent session 	<ul style="list-style-type: none"> • Infection such as local abscess at injection site, sepsis, toxic shock syndrome, or death. Blood-borne infection transmitted such as hepatitis, HIV.
<p><i>Reconstitution error:</i></p> <ul style="list-style-type: none"> • Reconstitution with incorrect diluent • Drug substituted for vaccine or diluent 	<ul style="list-style-type: none"> • Local abscess from inadequate shaking • Negative effect of drug, e.g. insulin • Death • Vaccine ineffective*
<p><i>Injection at incorrect site:</i></p> <ul style="list-style-type: none"> • BCG given subcutaneously • DTP/DT/TT too superficial • Injection into buttocks 	<ul style="list-style-type: none"> • Local reaction or abscess • Local reaction or abscess • Sciatic nerve damage
<p><i>Vaccine transportation/stored incorrect:</i></p>	<ul style="list-style-type: none"> • Local reaction from frozen vaccine • Vaccine ineffective*
<p><i>Contraindications ignored:</i></p>	<p><i>Avoidable severe reaction</i></p>

* vaccine being ineffective is an “effect”, it is not strictly an adverse event

Contraindications

There are few absolute contraindications to the EPI vaccines (WER, 1988, CDC 1994, CDC 1996). In general, the EPI recommends that health workers should use every opportunity to immunize eligible children; vaccines should be given to all eligible children attending outpatient clinics. Children who are hospitalized should be immunized as soon as their general condition improves and at least before discharge from hospital. In areas of measles transmission, measles vaccine should be given on admission to hospital because of the risk of nosocomial measles transmission (Biellik et al., 1997).

Generally speaking, live vaccines should not be given to individuals who are pregnant, with immune deficiency diseases or to individuals who are immunosuppressed due to malignant disease, therapy with immunosuppressive agents, or irradiation. However, both measles and oral poliomyelitis vaccines should be given to an HIV-infected persons. Children with symptomatic HIV infection should not be immunized with BCG or yellow fever vaccines. A child who is already severely affected by the HIV virus may be considered as for any child who is seriously ill - it may be better to avoid immunization. If the child dies soon after administration of the vaccines, it may incorrectly be assumed that death was caused by the vaccine.

A severe adverse event following a dose of vaccine (anaphylaxis, collapse or shock, encephalitis/encephalopathy, or non-febrile convulsions) is a true contraindication to immunization (Galazka et al., 1984). Such events can be recognized easily by the mother and the health worker. A second or third DTP injection should not be given to a child who has suffered such a severe adverse reaction to the previous dose.

The pertussis component should be omitted and diphtheria and tetanus immunization completed with DT vaccine. Vaccines containing the whole cell pertussis component should not be given to children with an evolving neurological disease (e.g. uncontrolled epilepsy or progressive encephalopathy).

Persons with a history of anaphylactic reactions (generalized urticaria, difficulty in breathing, swelling of the mouth and throat, hypertension, or shock) following egg ingestion should not receive vaccines prepared on hen's egg tissues (e.g. yellow fever vaccine and influenza vaccine). Vaccine viruses propagated in chicken fibroblast cells (measles or combined measles-mumps-rubella vaccines) can usually be given to such individuals without problems.

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2. Adverse events following BCG vaccine

Vaccine preparation

The original BCG vaccine is a live *Mycobacterium bovis* strain attenuated by passage on culture-medium that contained glycerol, potato slices and beef bile. The original strain was distributed to several laboratories in the world from which each laboratory produced its own BCG and maintained it by serial passage. A stabilizer – monosodium glutamate or albumin – is added to the preparation, but no adjuvant or preservative is added. The diluent is either saline solution or distilled water (Milstien & Gibson, 1990).

Four main strains account for more than 90% of the vaccines currently in use worldwide: the French Pasteur strain 1173 P2, used in 14 countries for their own production, the Danish strain 1331, the Glaxo strain 1077 derived from the Danish one and the Tokyo strain 172. Despite WHO's attempts to standardize production and vaccine characteristics, by stabilization and lyophilization, the concentration ranges from 50 000 to 3 million live particles per dose, according to the strains. According to immunogenicity in animal models, some vaccines (Pasteur 1173 P2 and Danish 1331) are called "strong" strains, whereas Glaxo strain 1077 and Tokyo 172 are called "weak" (Smith et al., 1979). It is difficult to demonstrate that one strain is clearly superior to another in the protection of human beings. The incidence of side-effects with BCG vaccination differs between "strong" and "weak" strains.

Adverse events are predominantly related to infection by the live attenuated bacterium, and errors in achieving intradermal inoculation – a difficult field technique.

Mild adverse events

Side-effects of BCG vaccination have been reported for a long time in most countries of the world. A review was published by Lotte et al. in 1984, gathering more than 1000 publications. Since then, the only new condition is related to HIV infection.

In 90–95% of vaccine recipients, BCG causes a specific lesion that starts as a papule two or more weeks after vaccination. This then becomes ulcerated and heals after several months leaving a scar. The duration of suppuration may alter the willingness of mothers to allow their children to receive other antigens (Loevinsohn & Garealla, 1990). More serious local reactions have also been described (Lotte et al., 1984): limited lupoid reaction, lasting a few months, keloids, and real tuberculous lupus (1/200 000 inoculations) have been reported (Misery & Combemale, 1993; Marrak et al., 1991).

Mild reactions are mostly local with or without regional manifestations. Local reactogenicity differs between vaccines, varying with both strain and number of viable bacilli. Thus the Pasteur and Copenhagen strains have generally been found to be more reactogenic than the Tokyo, Glaxo or Brazilian (Moreau) strains (Milstien, 1990). There were several reports in the late 1980s of “outbreaks” of BCG reactions, manifested as large ulcers and local lymphadenopathy or suppurative lymphadenitis. At this time, changes in vaccine availability led many programmes to switch from the less reactogenic Glaxo1077 to the more reactogenic Pasteur 1173P2 strain without staff being notified of the necessary change in dosage it implied (in Austria: Hengster et al., 1992; in India: Kabra et al., 1993; in Jamaica: Noah et al., 1990; in Mozambique: WER, 1988; in Zimbabwe: WER, 1989).

Axillary or cervical lymphadenitis usually heals spontaneously and it is best not to treat the lesion if it remains non-adherent to the skin. An adherent or fistulated lymph gland, however, may be drained and an anti-TB drug may be instilled locally. Some authors recommend systemic treatment of severe persistent lesions with erythromycin (Bandhari et al., 1980), while others have tried systemic treatment with isoniazid (Hanley et al., 1985) and local streptomycin with aspiration (Kuyucu et al., 1998). However, lesions have persisted for one month after therapy with either drug, and placebo-controlled trials of treatment are still needed (Hanley et al., 1985).

Local and regional *suppurative lymphadenitis* is now becoming rare, especially when BCG inoculations are performed by well-trained staff, with a standardized freeze-dried vaccine and a clearly stated individual dose depending on the age of the vaccinated subjects.

Severe adverse events

Osteitis may occur as a BCG complication. BCG osteitis/osteomyelitis is another of the rare and severe consequences of BCG vaccination, and has been reported, in particular in Scandinavia and Eastern Europe, typically associated with changes in BCG vaccine strain. Thus there was a report of an increase in osteitis to 35 per million in Czechoslovakia after a shift from the Prague to Russian strain BCG (Lotte, 1988). Both Finland and Sweden reported increases in osteitis after 1971, when they shifted to a Gothenburg strain produced in Denmark. Sweden reported rates as high as 1 in 3000 vaccine recipients, which declined rapidly when the national programme shifted to a Danish (Copenhagen 1331) vaccine strain (Lotte, 1988).

Those have been described mostly in Scandinavian countries and seem to be linked to the Göteborg strain. According to Kröger et al. (1994), the incidence rate of such complications ranged from 15 to 73 per 100 000 vaccinated between 1971 and 1978. Dittmann (1992) quotes a frequency between < 0.1 and 30 per 100 000 vaccine recipients. These accidents were also described rarely after injection of the Pasteur or Japanese strains.

Tuberculous meningitis

The complication due to BCG has been described (Tardieu et al., 1988) but this is also exceptional.

Generalized infection due to BCG vaccination has also been reported, sometimes being fatal. Systemic BCG-itis is a recognized but rare consequence of BCG vaccination, and traditionally has been seen in children with severe immune deficiencies. A recent multicentre study has identified the syndrome in children with severe combined immunodeficiency (SCID), chronic granulomatous disease, Di George syndrome and homozygous complete or partial interferon gamma receptor deficiency (Jouanguy, 1996; Jouanguy 1997; Casanova, 1995). Its frequency is reported as less than 5 per million vaccine recipients, reflecting the rarity of the underlying conditions (Lotte, 1988). If not properly managed, these cases may be fatal.

According to Mande, 1980, the first case was reported in 1953, 30 years after BCG had first been applied to man. Between 1954 and 1980, 34 cases were published in the global literature, and the Lotte et al. study estimates the incidence as 2.19 per one million vaccine recipients. Nevertheless, three recent Canadian cases were reported in 1998. Severe and generalized BCG infection that may occur in immunocompromised individuals should be treated with anti-tuberculous drugs including isoniazid and rifampicin (Romanus et al., 1993).

BCG in HIV-infected infant

There has been particular concern over the implications of HIV for the safety of BCG vaccination, after early case reports of systemic BCG-itis in individuals with AIDS (Anon, 1985). A series of studies was initiated in Africa to compare reactogenicity in infants born to HIV-positive and HIV-negative women. Only one study found a significant excess of reactions among the HIV “exposed” and positive infants. This occurred following the mistaken administration of more than twice the recommended dose of BCG Pasteur vaccine. Four out of 13 HIV-infected infants had “mild” reactions (e.g. lymphadenitis, three infants) or “moderate” reactions (abscess or fistula, one infant) in comparison to 16 of 166 infants born to HIV-uninfected mothers ($p = 0.04$) (O’Brien, 1995). In general the data available to date have supported the WHO policy of exempting only individuals with symptomatic HIV infection (AIDS) from routine BCG vaccination at birth (WHO, 1987).

The main concern is currently linked with the HIV infection. A recent study conducted by O’Brien et al. (1995) has confirmed the absence of severe adverse events in asymptomatic children infected with HIV and immunized at birth. Symptoms of immunodeficiency rarely appear before several months of age in neonates infected at birth. Nevertheless, Talbot et al. (1997), reviewed the literature published between 1980 and 1996, and gathered 28 cases of generalized infection by BCG; 24 of them occurred in immunocompromised children, and 9 of them were AIDS cases. The mortality was 78%, but it has not been possible to estimate the part attributable to AIDS in these deaths. Moreover, Talbot et al. have shown that these systemic infections could also occur after revaccination, and that they were not responsive to standard treatment.

To prevent any risk of generalized infection with BCG in these patients, WHO recommends giving BCG to neonates as soon as possible after birth in countries where tuberculosis is an important public health problem, *except* in the case of children with clinical symptoms of AIDS (SPA and EPI, 1987). These recommendations are supported by the findings of several studies, among others in Rwanda (WER, 1992).

There are several observations of adverse events following BCG administration as a therapy for bladder cancer. The vaccine is administered intravesically and the doses used in this indication are much higher than those used for infant immunization. The most frequent complications are pulmonary, hepatic, bone marrow, and joint infections, but a laryngeal tumour has also been reported. General signs such as fever and inflammatory signs are common (Sicard et al., 1992)

Around 1.5 billion subjects had already been vaccinated before EPI was launched in 1974. Around 100 000 000 neonates have been vaccinated each year with BCG since then. Very few adverse events have been reported, considering these figures.

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3. Adverse events following cholera vaccine

The vaccines

The four types of cholera vaccines currently available are:

1. The original killed cholera vaccine given parenterally, consisting of a heat-killed, phenol-preserved mixed suspension of Inaba and Ogawa subtypes of *Vibrio cholerae*, Serovar 01 (Dittman, 1992). This vaccine is no longer recommended for use, and WHO requirements have been discontinued.
2. Two new cholera vaccines given orally (Sack et al., 1999).
 - Killed whole *V. cholerae* 01 in combination with purified recombinant B subunit of cholera toxin (WC/rBS). The vaccine is prepared from four strains of killed *V. cholerae*, including a heat-killed classic Inaba, a heat-killed classic Ogawa, a formalin-killed El Tor Inaba and a formalin-killed classic Ogawa. This vaccine is licensed in Argentina, Guatemala, Honduras, Nicaragua, Norway, Peru, Salvador and Sweden.
 - An attenuated live oral cholera vaccine, containing the genetically manipulated *V. cholerae* 01 strain 103-HgR. This vaccine is licensed in Argentina, Canada, Peru, Philippines and Switzerland. It contains aspartame (a phenylalanine derivative, which is added as a sweetener). The buffer contains sodium bicarbonate, ascorbic acid, which serves to neutralize gastric acid.
3. As a result of technology transfer, a variant of the whole-cell vaccine but without the B subunit has been produced and tested in Viet Nam (Trach et al., 1997) and looks promising for mass campaigns in the future.

Mild adverse events

Side-effects from *parenteral whole-cell cholera vaccine* are similar to those from whole-cell typhoid vaccine, although somewhat less severe (Benenson et al., 1968). Approximately 50% of vaccine recipients develop a soreness and inflammation at the site, and 10 to 30% develop generalized symptoms of fever and malaise. Symptoms usually last one to three days, although some individuals experience a delayed reaction and develop a sore arm between days four and seven (Sack et al., 1999).

Mild post-vaccination gastrointestinal symptoms were reported with equal frequency for both vaccine and placebo recipients in randomized, placebo-controlled, double-blind trials of the reactogenicity of oral BS/WCV that is currently licensed using the recommended immunization schedule of two doses two weeks apart (Begue et al., 1995).

Following administration of the currently-licensed CVD 103-HgR strain, gastrointestinal symptoms were reported with equal frequency for vaccine recipients and placebo recipients in randomized, placebo-controlled, double-blind trials conducted in North American and European populations using 5×10^8 CFU dose (Cryz et al., 1990; Kotloff et al., 1992). In developing countries, side-effects were also identical in vaccine recipients and placebo group, using 5×10^9 CFU dose (Arehawaratana et al., 1992; Simanjutak et al., 1992; Lagos et al., 1998).

Live oral cholera vaccine 103-HgR was safe in HIV-positive subjects (Perry, 1998) and was well-tolerated even in infants as young as 3 months of age (Lagos et al., 1998; 1999).

Severe adverse events

The *original parenteral killed cholera vaccine* is no longer recommended. When in use, life-threatening reactions used to be extremely rare, but allergic anaphylactic reactions were possible following its administration. Dittmann (1992), cited occasional reports of neurological and psychiatric reactions. He also reported one case of Guillain-Barré syndrome; two cases of myocarditis and two cases of myocardial infarction as well as fatal anaphylactic reaction, acute renal failure and pancreatitis.

There are no specific contraindications for *killed oral vaccines*. The safety of the vaccines in pregnant women or immunosuppressed people has not been studied. Because this is a killed oral vaccine, the risk seems minimal (Sack et al., 1999).

No severe adverse events related to the administration of *live oral vaccines* have been reported.

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4. Adverse events following diphtheria, tetanus and pertussis vaccines

Vaccines

Available vaccines against diphtheria, pertussis and tetanus for use in infants and young children contain the following active ingredients (Mortimer Jr et al., 1999; Wassilak et al., 1999; Edwards et al., 1999):

- Diphtheria and tetanus toxoids.
- Vaccine against pertussis of one of the two types:
 - whole-cell vaccine, inactivated bacterium *Bordetella pertussis*;
 - acellular vaccine, consisting of between one and five purified proteins of the bacterium.
- Preserving agents (e.g. thiomersal or phenoxyethanol), stabilizing agents (e.g. gelatin or polysorbate 80) and adjuvants such as aluminium hydroxide or aluminium phosphate.

Vaccines against diphtheria, pertussis and tetanus (DPT) are combined so that they can be administered to the child in a single injection. For adults, the vaccines used are generally a combination of only diphtheria and tetanus, with lower concentrations of the diphtheria toxoid (Td) or tetanus toxoid (TT) only for pregnant women in order to control neonatal tetanus.

a) DIPHTHERIA TOXOID

Diphtheria toxoid is a preparation of inactivated diphtheria toxin. Usually it is available as a preparation adsorbed with aluminium hydroxide or phosphate and combined with other toxoids or vaccines. The amount of toxoid present is measured in flocculating units (Lf), and the immunizing potency in International Units (IU) per dose (these values are measured in different ways and do not convert directly). WHO recommendations stipulate a potency of not less than 40 IU per dose up to the age of seven years.

Mild adverse events

Fifty years ago, efforts to maintain protection against diphtheria in children and adults met with unacceptable local and systemic reactions. In general, these were type IV delayed hypersensitivity reactions to the diphtheria proteins. Purifying the toxoid, adsorbing it on an aluminium hydroxide and reducing its concentration (Mortimer Jr et al., 1990) considerably reduced the frequency of such reactions.

Reactions to adsorbed diphtheria toxoid are more frequent among people who have already received several boosters (Edsall et al., 1954). Their frequency varies with the toxoid concentration and the level of diphtheria toxin antibodies present in the blood prior to vaccination.

Mild reactions include:

- Local reactions, light to moderate: redness, pain and hardening at the injection point (11% to 38%).
- Systemic reactions: transient fever (1%), malaise, aches, flushing.

Severe adverse events

Generalized urticaria or pruritus have been reported and, rarely, anaphylactic reactions. Recent data on adverse reaction to diphtheria toxoid alone are scarce, since it is usually combined with tetanus toxoid for adults and with pertussis vaccine for children under seven years of age.

b) TETANUS TOXOID

Tetanus toxoid is a preparation of inactivated toxin. The toxoid is available in a plain (unadsorbed) form or adsorbed with aluminium phosphate or hydroxide, alone or in combination with other toxoids or vaccines. The potency of tetanus toxoid, expressed in International Units varies widely according to the preparation and the manufacturer, but WHO stipulates not less than 60 IU per dose. The frequency and gravity of local reaction to tetanus vaccination increases with the number of doses administered and with age (Myers et al., 1982). The risk of local reaction and sterile abscess increases when an injection of adsorbed vaccine puts the adjuvant in contact with the subcutaneous tissue (EPI, 1982; Mark, 1999). This is of particular importance in the programme of prevention of neonatal tetanus through immunization of pregnant women in developing countries.

Mild adverse events

Minor local reactions such as pain and erythema are the most frequent and are found in 25% to 85% of cases (Mortimer Jr et al., 1999). In some cases, a nodule can form at the point of injection and remain for several weeks. A sterile abscess appears in 6 to 10 cases per million doses administered.

Systemic reactions occur with booster injections in 0.5% to 10% of cases; such reactions entail fever, malaise, shivering, general aches and headaches.

Severe adverse events

Allergic reactions

Reactions such as generalized urticaria and anaphylaxis, are rare (1 to 6 cases per million doses administered). An Arthus-type hypersensitivity reaction (hypersensitivity to immune complexes) and serious local reactions can occur in hyper-immunized persons, i.e. persons who have high titres of anti-tetanus antibody before the vaccination.

Brachial neuriti

This defined as dysfunction limited to the upper extremity nerve plexus, without involvement of other peripheral or central nervous system structure (AAP, 1997) has been reported after administration of tetanus toxoid (relative risk of 5 to 10; 0.5 to 1 cases per 100 000 doses administered) (Vaccine Safety Committee, 1994). It is usually associated with the administering of multiple doses (Rutledge & Carter, 1986).

Guillain-Barré syndrome

This appears within six weeks of vaccination, and has been associated with the tetanus component. An American study reviewed 306 cases of the syndrome in adults and children, and concluded that, if such an association exists, it is very rare (Tuttle et al., 1997)

c) COMBINED DIPHTHERIA AND TETANUS TOXOIDS

Combined diphtheria and tetanus vaccine with reduced diphtheria content is given to subjects aged seven years and over. The intensity and frequency of local and systemic reactions increase with age, with the number of doses administered and with the concentration of toxoid (Myers et al., 1982; CDC, 1996; NCCI, 1998). Thus, reducing diphtheria content, the number and severity of reactions are reduced. The available data suggest that both diphtheria and tetanus toxoids contribute to the adverse reactions.

Mild adverse events

The Td vaccine causes local reactions, pain, induration and erythema in 10% to 75% of cases. In some cases, a nodule can develop at the point of injection and remain there for several weeks. A sterile abscess appears in 6 to 10 cases per million doses administered. Fever and other systemic reactions (muscular aches and headaches) occur in 10% of cases.

Severe adverse events

The remarks on allergic reactions, brachial neuritis and Guillain-Barré syndrome in the above section on tetanus apply also to the Td vaccine.

d) PERTUSSIS VACCINES

Two classes of pertussis vaccine are currently available: whole-cell vaccines and acellular vaccines.

- The whole-cell vaccines are suspensions of killed *B. pertussis* organisms at a concentration of more than 4 IU.
- The acellular vaccines are made from purified antigens of *B. pertussis*. All the current vaccines contain pertussis toxoid (3.2 to 40µg per dose) and most contain filamentous agglutinin (2.5 - 34.4 µg per dose). Other antigens in the vaccines may include pertactin (1.6 - 23.4 µg per dose), fimbriae 2 (0.8 to 5 µg per dose) and fimbriae 3 (5 µg per dose), (CDC, 1997).

The adverse reactions following injection of pertussis vaccines, in combination with diphtheria and tetanus toxoids, are listed in the two sections below.

e) **COMBINED DTP VACCINES CONTAINING WHOLE-CELL PERTUSSIS VACCINE**

Mild adverse events

The whole-cell component of pertussis is largely but not solely responsible for reactions occurring after administration of combined DTP vaccine (Cody, 1981; Scheifele, 1994; Gupta, 1991; Cherry, 1996). A study comparing DT and DTP vaccination of under-six year olds showed significantly lower rates for DT with respect to sensitivity, redness, oedema, fever, drowsiness, irritation, vomiting, loss of appetite and persistent weeping, except screaming (Cody, 1981).

In another study comparing a placebo arm was included in six month old children who had received two doses of DTP previously (Long, 1990). DTP caused significantly more reactions of all types, except oedema of more than 5 cm, a temperature in excess of 39.4°C and screaming.

Minor local reactions such as pain, oedema and erythema occur in 40% to 80% of cases when DTP vaccine is administered. In rare cases, a nodule can form at the point of injection and remain there several weeks. A sterile abscess appears in 6 to 10 cases per million doses administered.

Mild systemic reactions consist of temperature over 38°C and irritation (40% to 75%), drowsiness (33% to 62%), loss of appetite (20% to 35%), and vomiting (6% to 13%).

The frequency of local reactions tends to increase with the number of doses administered, while systemic reactions (Cody, 1981; Communicable diseases in Canada, 1992; 1994) with the exception of fever (Cherry, 1996), diminish with subsequent doses. Local reactions are more intense when the intramuscular injection of adsorbed vaccines introduces aluminium salt into subcutaneous tissue (Ipp, 1989).

Severe adverse events

Specific severe adverse events are described:

- Persistent, inconsolable crying for more than three hours (mostly from pain, 1%).
- Temperature in excess of 40.5°C (0.3%).
- Unusual screams (0.1%).
- Convulsions (usually related to fever, one case in 12 500 does administered) (Farrington et al., 1995).
- Hypotonic-hyporesponsive episodes (one case in 1750 doses administered)(Cody, 1981).

Anaphylactic reactions are rare (two cases in 100 000 doses administered) (Edwards et al., 1999; CDC, 1996).

Convulsions are more frequent when there is a personal history (with a relative risk of 6.4) or a family history (relative risk of 2.4) of convulsions in the child (Edwards et al., 1999; Livengood, 1989). There was an increased relative risk for convulsions 0–3 days after DTP vaccination (Farrington, 1995).

Systematic administering of acetaminophen or any appropriate antipyretic at the time and at 4 and 8 hours after immunization decreases the subsequent incidence of febrile and local reactions (AAP, 1997). It may also be of benefit if there is a personal or family history of convulsions (Ipp et al., 1987; CDC, 1987).

The US Vaccine Safety Committee agreed in 1994 that there was insufficient evidence to conclude that pertussis vaccine could cause permanent brain damage (Edwards et al., 1999). Furthermore, the experts rejected the alleged causal link between DTP vaccine and autism, infant spasms, Reye syndrome and sudden infant death syndrome.

f) DPT COMBINED VACCINES CONTAINING ACELLULAR PERTUSSIS VACCINE

Mild adverse events

In general, vaccines containing the acellular pertussis component causes the same adverse effects, but less frequently, than vaccines containing whole cell pertussis component. (Edwards et al., 1999; CDC, 1997). Studies tend to show that the frequency of reactions containing the acellular component of pertussis does not exceed the frequency following injection of a vaccine without the pertussis component (DT or Td vaccines) (Gustafsson, 1996). Studies show considerable differences between children receiving first doses (at two, four and six months), for all slight to moderate reactions except vomiting (see table 4) (Mills et al., 1998; Decker et al., 1995; Decker & Edwards, 1996).

Table 4: Percentage of mild to moderate reactions within 24 hours following a dose of DTP

Adverse reactions	Acellular vaccines ^{a)}		Whole cell vaccine ^{b)}
	Range	Average	
Redness of 1 to 19 mm	15.1–44.0	31.4	56.3
Redness of 20 mm and more	1.4–5.9	3.3	16.4
Oedema of 1 to 19 mm	7.5–28.6	20.1	38.5
Oedema 20 mm and more	0.8–8.0	4.2	22.4
Pain	1.6–13.2	6.9	40.2
Temperature of 37.8°C to 38.3°C	16.0–29.2	20.8	44.5
Temperature of 38.4°C and above	1.6–5.9	3.7	15.9
Irritation	12.6–24.4	17.1	41.5
Drowsiness	29.4–59.2	42.7	62.0
Loss of appetite	17.7–27.2	21.7	35.0
Vomiting	7.4–21.6	12.6	13.7

^{a)} 13 different acellular pertussis vaccines, each containing 1 to 4 antigens, all combined with diphtheria and tetanus toxoids.

^{b)} Whole-cell pertussis vaccine combined with Lederle diphtheria and tetanus toxoids.

Source: Decker et al. (1995).

Severe adverse events

Studies to estimate the frequency of severe and rare reactions are continuing. Even when convulsions, persistent weeping, temperature in excess of 40°C and episodes of hypotonia and hyporeactivity have occurred after injection of acellular vaccines, minor and major reactions are reduced by more than half when whole-cell vaccine is used (Edwards et al., 1999).

Several studies have demonstrated the safety of substituting a vaccine containing the acellular pertussis component as a booster for a child who began the course of vaccination with a vaccine containing the whole cell component (Pichichero et al., 1997; Halperin et al., 1996; Feldman et al., 1992). In particular, administering a booster (fourth dose) of acellular pertussis vaccine to children whose course of vaccination had begun with acellular vaccine produced more local reactions than when they had previously been given whole-cell vaccines. However, even though the frequency of local and systemic reactions related to acellular vaccine tends to rise with the number of doses administered, they are less frequent than when a whole-cell vaccine is used.

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5. Adverse events associated with *Haemophilus influenzae* type b (Hib) vaccine

Vaccine preparation

Several *Haemophilus influenzae* type b (Hib) conjugate vaccines have been developed and licensed, resulting in extensive experience in their use in Europe and the Americas. All these vaccines utilize the same hapten, polyribosylribitol phosphate (PRP). However, the vaccines differ in the protein carrier used, the size of the polysaccharide, the type of linkage and immunogenicity (Ward & Zangwill, 1999). Four different types of carrier have been used – diphtheria toxoid (PRP-D), tetanus toxoid (PRP-T), a non-toxic variant of diphtheria toxin (HbOC), and the outer membrane protein complex of serogroup B *Neisseria meningitidis* (PRP-OMP). Thiomersal is used as a preservative in some preparations and adjuvant is added in some.

Mild adverse events

Localized reactions are common following administration of Hib vaccines. Within 24 hours of vaccination, recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required (Fritzell & Plotkin, 1992). Mild systemic reactions, including fever, rarely occur following administration of Hib vaccines (2%) (Valdheim et al., 1990).

Serious adverse events

Serious adverse events following administration of Hib vaccine are uncommon, making it one of the safest vaccines currently available. In a study including 4459 Navajo infants, there were no differences in the type and frequency of serious adverse reactions occurring among those receiving Hib conjugate vaccine and those receiving a placebo (CDC, 1991). Research has also shown the use of Hib vaccines to be safe in HIV-infected individuals (Leroy et al., 1996; Dockrell et al., 1998).

Anaphylaxis

Anaphylaxis was not reported during the pre-licensure clinical trials. Since then, post-marketing surveillance has identified five possible cases of anaphylaxis (Milstien et al., 1987; Stratton et al., 1994). However, no reports of anaphylaxis following Hib vaccination have been published. After reviewing available data, the Institute of Medicine (IOM) concluded that there is not enough evidence to accept or reject a causal relationship between Hib vaccines and anaphylaxis (Stratton et al., 1994).

Guillain–Barré syndrome

No controlled studies have been conducted to explore the risk of GBS following Hib vaccination. GBS was not reported in any of the pre-licensure clinical trials. The Institute of Medicine identified seven cases of GBS that occurred following Hib vaccination, however, three of the individuals had received multiple vaccines and one had an implausible onset interval. Therefore, the IOM concluded there was inadequate evidence to accept or reject a causal relationship between Hib vaccines and GBS (Stratton et al., 1994).

Thrombocytopenia

During one Hib conjugate vaccine trial, a case of thrombocytopenia was reported; however, a subsequent study found the vaccine had no effect on platelet count (Lepow et al., 1984; Stratton et al., 1994). Since that time, post-marketing surveillance has identified several possible cases of thrombocytopenia following Hib vaccination (Milstien et al., 1987; Stratton et al., 1994). The Institute of Medicine reviewed available data and concluded there was inadequate evidence to accept or reject a causal relationship between Hib vaccines and thrombocytopenia (Stratton et al., 1994).

Transverse myelitis

The vaccine adverse event reporting system has identified in the USA three possible cases of transverse myelitis (TM) following Hib vaccination (Stratton et al., 1994). However, there have been no reports of TM following Hib vaccination published in the literature and no cases of TM were reported in pre-licensure trials. Therefore, the Institute of Medicine concluded that the data was inadequate to accept or reject a causal relationship between Hib vaccines and TM (Stratton et al., 1994).

Vaccination of persons with human immunodeficiency virus infection was well tolerated except for mild soreness at the site of injection that was reported by some individuals (Kroon et al., 1997)

Combined Hib vaccines

- **Hib–DPT:** A combination of Haemophilus influenzae type b vaccine–diphtheria toxoid conjugate with diphtheria–tetanus–acellular pertussis vaccine did not result in significant differences in safety (Kovel et al., 1992). The rates of local and systemic adverse events did not differ according to the site of injection, arm versus thigh, or the concurrent or combined administration of DTP (Scheifele et al., 1992).
- The safety profile of combined HbOC–DTP is comparable to that of the vaccines co-administered at separate injection sites. The incidence of local and systemic reactions is similar (Madore et al., 1990; Paradiso et al., 1993; Black et al., 1993; CDC, 1993). One exception is for swelling after the first dose, which is more common with the combined product Hb–OC, 8.0% versus 4.3% with separate products (Black et al., 1991). This has not been found in other studies.

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- The administration on the same day of either MMR vaccine or DPT+OPV vaccine together with PRP-OMPC did not result in an increase in the rates of fever or irritability (Dashefsky et al., 1990). After PRP-T vaccine, no serious side-effects were observed and the rate of adverse reactions was consistent with the concurrent administration of diphtheria–tetanus–pertussis vaccine in Gambian infants (Mulholland et al., 1994), French children (Fritzell & Plotkin, 1994), and in a British accelerated schedule (Booy et al., 1992; Begg et al., 1995).
 - **Hib–DPT–IPV:** PRP-T vaccine mixed in the same syringe with diphtheria–tetanus–pertussis–enhanced inactivated poliovirus vaccine resulted in the same rate of local and systemic side-effects as for children receiving DTP–IPV only, except for irritability and use of acetaminophen after the second dose. These were slightly but significantly more frequent in the DTP–IPV–PRP-T group (Dagan et al., 1994). PRP-T was given concurrently or combined with PTP and IPV to healthy children at two, four and six months (Gold et al., 1994). Combination resulted in more local redness (18% vs. 11%, $p<0.001$), tenderness (27% vs. 24%) and swelling (15% vs. 13%), whereas systemic reaction occurred at similar rates in both groups.

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6. Adverse events following hepatitis A vaccine

The vaccines

Inactivated hepatitis A vaccine is prepared from a cell-culture-adapted virus, purified from cell lysates by ultrafiltration and exclusion gel chromatography or other methods, formalin inactivated, adsorbed to an aluminium hydroxide adjuvant, and prepared with or without 2-phenoxyethanol as a preservative. The antigen content of one vaccine is determined by reactivity in a quantitative immunoassay for HAV antigen and final vaccine potency (per dose) is expressed as an enzyme-linked immunosorbent assay (ELISA) units (El.U.). The titer varies from 360 El.U for children to 1440 El.U for adults. For other vaccines, the antigen content is expressed as units (U) of hepatitis A antigen (CDC, 1996) and varies from 25 to 160 antigen units. Several live attenuated hepatitis A vaccines are currently under development and two are licensed in China, but additional controlled trials with attenuated vaccines are needed for better assessment of both safety and efficacy (WHO, 1995).

Mild adverse events

Data concerning adverse events are derived from pre-licensure clinical studies. No serious adverse events have been attributed definitively to hepatitis A vaccine.

Among adults, the most frequently reported side-effects occurring within 3 days after the 1440 El.U. dose were (CDC, 1996):

- Soreness at the site of injection (56%).
- Headache (14%).
- Malaise (7%).

In clinical studies among children, the most frequently reported side-effects were

- Soreness at the injection site (15%).
- Feeding problems (8%).
- Headache (4%).
- Injection site induration (4%).

Balcarek et al., (1995) found minor local reactions (erythema, induration, soreness) in 29.8% of the pre-school children immunized with 360 El.U., most of them after the first dose. Minor systemic side-effects that resolved spontaneously were reported by parents of 47% of the children, including fever, malaise, anorexia and headache. All objective adverse events normalized within 48 hours.

Among the 9200 persons who have received the other vaccine, no serious adverse events were reported. Among adults the most frequent side-effects that occurred within 5 days following vaccination include tenderness (53%), pain (51%), and warmth (17.3%) at the injection site (53%) and headache (16.1%). Among children, the most common side-effects reported were pain, (19%), tenderness (17%) and warmth (9%) at the injection site (CDC, 1996).

Systemic reactions that include fatigue, fever, diarrhoea and vomiting occur in less than 5% of vaccine recipients (Feinstone et al., 1999).

The safety of hepatitis A vaccine during pregnancy has not been established. Since the vaccine is prepared from inactivated virus, the risk to the developing fetus is likely to be negligible. However, it should not be given to pregnant women unless there is a definite risk of infection. Safety of hepatitis A vaccine in patients with chronic liver disease has been assessed during a five-site survey, with a control group of healthy people. Symptoms were generally categorized as mild to moderate in severity and all resolved spontaneously (Keefe et al., 1998)

Severe adverse reactions

Post-licensure reports of severe adverse events, without regard to causality, received by the vaccine manufacturer, have included anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, and erythema multiforme. Most of these events have occurred among adults, and approximately one third have occurred among persons receiving other vaccines concurrently. For serious adverse events for which background incidence data are known (e.g. Guillain-Barré syndrome and brachial plexus neuropathy) the rates for vaccine recipients are not higher than would be expected for an unvaccinated population.

A case of leukocytoclastic vasculitis has been described after vaccination, which resolved without therapy (Cone et al., 1996).

No serious adverse events were reported from approximately 40 000 children who were administered a dose of 360 El.U. hepatitis A vaccine in a protective efficacy study (Innis et al., 1994; Sandman et al., 1995).

Combined vaccines

When hepatitis A and B vaccines are given in a combined form, the incidence of adverse events has generally been similar to that for hepatitis B vaccine.

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7. Adverse events associated with the hepatitis B vaccine

Vaccine preparation

Hepatitis B vaccines (HBV) are composed of highly purified preparations of hepatitis B “s” antigen (HBsAg). This is a glycoprotein that is a component of the outer envelope of hepatitis B virus, and is also found as 22-nm spheres and tubular forms in the serum of people with acute and chronic infection. Vaccines are prepared by harvesting HBs Ag from the plasma of people with chronic infection (plasma derived vaccine) or by inserting plasmids containing the viral gene in yeast or mammalian cells (recombinant DNA vaccine). An adjuvant, aluminium phosphate or aluminium hydroxide, is added to the vaccines that are sometimes preserved with thiomersal. The concentration of HBs Ag varies from 2.5 to 40 µg per dose, according to which manufacturer is used and the target population (CDC, 1996; Mahoney et al., 1999). More than half a billion people have been immunized in the world since the beginning of the implementation of the universal programmes, with a very effective vaccine which is considered extremely safe.

Mild adverse reactions

In general, there are minimal reactions, such as local pain, myalgia and transient fever, mostly within 24 hours. Children have fewer adverse reactions than adults (<10% vs. 30%). In summary (Zajac, 1986; Andre, 1989; Stevens, 1987; Szmuness, 1980; Francis 1982), mild adverse events occur with an approximate frequency of:

Temperature greater than 37.7°C	1–6%
Pain	3–29%
Erythema	3%
Swelling	3%
Headache	3%

Several studies compare reactions after different vaccines (Greenberg, 1996), different concentrations of the same vaccine (Pooverawan, 1993; Tan 1990), different schedules (Goldfard, 1994; Giammanco, 1998), or describe the reactions of a single vaccine (Soulie, 1991; McMahan, 1992; Leroux-Roels, 1997) or novel adjuvant system (Thoelen, 1998) without placebo group. All report mild local and general reactions, lasting less than 48 hours. In placebo-controlled studies, these side-effects were reported no more frequently among vaccine recipients than among individuals receiving a placebo.

Severe adverse events

Anaphylactic reactions

The estimated incidence of anaphylaxis among vaccine recipients is one per 600 000 vaccine doses distributed. No serious, severe or fatal anaphylactic reaction has been reported. Further vaccination with hepatitis B vaccine is contraindicated in people with a history of anaphylaxis to a previous dose (CDC, 1996).

Guillain–Barré syndrome

There has been a suggested possible association between Guillain–Barré syndrome (GBS) and receipt of the first dose of plasma-derived vaccine in the US (CDC, 1991). In 1991, Guillain–Barré syndrome was reported at a very low rate (0.5 per 100 000 vaccine recipients), with no deaths in all reported cases among adults. An estimated 2.5 million adults received one or more doses of recombinant vaccine during the period 1986–1990. Current available data indicate no demonstrable association between receipt of either plasma-derived or recombinant vaccine and GBS.

There are at least three controversial adverse events associated with hepatitis B vaccines: the relationship of hepatitis B vaccine to diabetes, to demyelinating diseases (e.g. multiple sclerosis) and chronic fatigue syndrome (Mahoney et al., 1999). Establishing a causal relationship between these adverse events and hepatitis B vaccine is difficult: these events are rare, occur in the absence of hepatitis B vaccination and have their peak incidence in the older age groups who did not receive hepatitis B vaccine as part of routine childhood vaccination. A recent review by the Food and Drug Administration (FDA) of case reports in the Vaccine Adverse Events Reporting System for the years 1991 to 1994 concluded that there were no unexpected adverse events in neonates and infants given hepatitis B vaccine. This was despite the use of at least 12 million doses of vaccine in these age groups (Mahoney et al., 1999).

Demyelating disorders

A few articles mention isolated demyelinating cases following hepatitis B vaccination (Shaw, 1988; Herroelen, 1991; Mahassin, 1993; Trevisani 1993; Nadler, 1993; Tartaglino, 1995). In France, over the years up to 1999, popular press and television programmes raised concern that hepatitis B immunization might be linked with new cases or flare-ups of multiple sclerosis or other demyelinating diseases.

A position paper from WHO was published pointing out the “Lack of evidence that hepatitis B vaccine causes multiple sclerosis” (Wkly Epidem Rec, 1997). Compared to the background rate of multiple sclerosis in France, which is 1 to 3 cases per 100 000 persons, the notification rate of demyelinating diseases in temporal association with hepatitis B vaccination was 0.6 per 100 000 during the period from December 1994 and December 1996. Observations in other countries show similar patterns to that observed in France: 0.1 to 0.8 cases of demyelinating disease per 100 000 vaccine recipients (Australia, Belgium, Canada, Germany, India, United Kingdom, United States).

A national pharmaco-vigilance survey was initiated in France in 1994, after the report to the National Agency for Drugs of several neurological disorders evoking multiple sclerosis after hepatitis immunization. Three studies have been conducted in adults, two in neurology wards in France, the third one based on the "General Practitioners Research Database" of the United Kingdom Ministry of Health. The three studies did not find a statistically significant increase in the risk of the first episode of central demyelination after immunization. The possibility of an association is being explored with further studies. No adverse event of this type has been reported so far in infants (Levy-Bruhl et al., 1999).

The Viral Hepatitis Prevention Board's activities are incorporated into the WHO Collaborative Centre on Prevention and Control of Hepatitis at the University of Antwerp, Belgium. A meeting of the Board organized in September 1998 made the following conclusions: "the available data, although limited, did not demonstrate a causal association between hepatitis B immunization and central nervous system demyelinating disease, including multiple sclerosis". Therefore, the group supported the WHO recommendations that all countries should have universal infant and/or adolescent immunization programmes, and continue to immunize adults when facing increased risk of hepatitis B, as appropriate (Hall et al., 1999; Halsey et al., 1999).

Chronic fatigue syndrome

In Canada, during 1993–94 a rumour was also raised that vaccination against hepatitis B was responsible for chronic fatigue syndrome (Delage, 1993) but no epidemiological data have ever confirmed this allegation (Canadian Medical Association, 1993).

Hair loss

Hair loss has been reported after routine immunization, especially hepatitis B (Wise et al., 1997). Hair loss is a common event; it may be extremely difficult to confirm a causal association with HBV administration.

Diabetes

Claims have been made that administration of vaccines including hepatitis B vaccine can cause type I diabetes (juvenile or insulin-dependent diabetes mellitus – IDDM) in rats (Classen, 1996) and children (Classen, 1997). The consensus of current professional opinion accepts there is no link (Karvonen 1999; Jefferson, 1998). In Finland, elimination of mumps by immunization has coincided with a decrease in IDDM (Hyoty, 1993). Studies in Sweden failed to find an increase in diabetes after stopping BCG (Dahlquist, 1995) or pertussis immunization (Heijbel, 1997). Similar studies and results have been documented in Sweden (Blom, 1991) and Canada (Parent, 1997). A panel review of all the evidence to date was held in the United States. This also found no association (Institute, 1999).

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8. Adverse events following influenza vaccine

Vaccine preparation

The vaccine is made from highly purified, egg-grown viruses that have been inactivated. Whole-virus, subvirion and purified surface antigen (split virus) preparations are available. Split virus preparation contains viruses that have been treated with an organic solvent to remove surface glycoproteins and thus reduce vaccine reactogenicity or capability to reduce side-effects.

Influenza vaccine contains 15 µg of each antigen per 0.5 ml dose of the three virus strains (usually two type A and one type B) that are likely to circulate during the upcoming influenza season (CDC, 1999). In February of each year, the World Health Organization (WHO) makes recommendations concerning the virus strains to be included in vaccine production for the forthcoming winter in the Northern Hemisphere. A second recommendation is made in September which relates to vaccines to be used for the winter in the Southern Hemisphere (WER, 1999). These recommendations are based on information collected from more than 100 laboratories worldwide that conduct influenza surveillance.

All the vaccines are comparable because of similar composition and production methods. Antibiotics including neomycin or gentamicin may be used in production along with sodium bisulfite. All manufacturers use thiomersal as a preservative and some gelatin as a stabilizer. In addition, the vaccines contain low levels of residual egg proteins.

Mild adverse events

In general, influenza vaccines are well tolerated by recipients. These vaccines are inactivated, meaning they contain only non-infectious viruses that clearly cannot cause the disease. Respiratory disease after vaccination therefore represents coincidental illness unrelated to influenza vaccine (CDC, 1999). Analysis by gender of 14 studies has revealed that females (both young and elderly) report significantly more local reactions (Beyer, 1996).

Local reactions

In placebo-controlled blinded studies, the most frequent side-effect of vaccination is soreness at the vaccination site (affecting 10–64% of patients); which lasts up to two days following administration of influenza vaccine (Govaert et al. 1993; Margolis et al., 1990; Nichol et al. 1996). Within 24 hours of vaccination, recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they resolve spontaneously within two to three days and further medical attention is not required.

Systemic reactions

Mild systemic reactions may also occur. Fever, general discomfort and muscle pain can affect those individuals without previous exposure to the antigens in the vaccine (e.g. children) (Barry et al., 1976). These reactions occur within 6–12 hours of vaccination and generally persist 1–2 days (CDC, 1999).

The frequency of febrile reactions to whole-virus vaccine in infants is prohibitive at 8–50%. A two-dose schedule or the use of split virus vaccine overcomes this problem (Gross, 1977).

Severe adverse events

Anaphylaxis

Immediate – presumably allergic – reactions (e.g. hives, angioedema, allergic asthma and systemic anaphylaxis) rarely occur after influenza vaccination (Bierman et al., 1997). It is generally thought that these reactions result from hypersensitivity to residual egg protein in the vaccine. However in one study, vaccine containing various small doses of egg protein was safely administered to individuals with egg allergies (James et al., 1998; Murphy et al., 1985). The majority of egg-allergic individuals can be immunized safely, although immunization of an individual with a definite history of egg allergy should be approached with caution.

Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thiomersal can lead to induction of hypersensitivity, most patients do not develop reactions when administered as a component of vaccines. When reported, hypersensitivity to thiomersal usually has consisted of local, delayed-type hypersensitivity reactions. Thiomersal-containing vaccines such as influenza are to be avoided during pregnancy, as there is a theoretical risk to the fetal brain.

Guillain–Barré syndrome

The 1976 swine influenza vaccine was associated with an increased risk of GBS (Hurwitz et al., 1981). Among those who received this vaccine, the rate of GBS that exceeded the background rate was slightly less than 10 cases per million vaccinated (CDC, 1998).

The risk of GBS associated with subsequent influenza vaccines (prepared from different virus strains) is less clear. It is difficult to detect a small increase in risk for a rare disease such as GBS. The annual incidence rate of GBS is approximately 10–20 cases per million adults (CDC, 1998). In four influenza seasons studied between 1977 and 1991, the relative risk of GBS following influenza vaccination was not statistically significant in any of the studies (Kaplan et al., 1982; Hurwitz et al., 1981). However there was a small excess risk of GBS in vaccine recipients aged 18 to 64 years in the 1990/91 vaccine season in the United States (CDC, 1993). A recent study found an elevated overall risk for GBS of 1.7 in the 6 weeks following influenza vaccination during the 1992–1993 and 1993–1994 seasons (Lasky et al., 1998). This represented an excess of one to two cases per million vaccine recipients (Lasky et al., 1998). Even if GBS is a true side effect of influenza vaccine, the estimated risk of one to two cases per million vaccinated is less than that for severe influenza (Lasky et al., 1998). Influenza vaccine does not predispose to Reye syndrome.

Rare sequelae

Rarely, the following reactions have been temporally associated with immunization: vasculitis (Mader, 1993), uveitis (Blanche, 1994), and delirium (Boutros, 1993), optic neuritis, brachial neuritis and cranial palsies. No causal effect has been demonstrated.

Asthma

Concern has been expressed that the vaccine might exacerbate asthma. This has not been proven, although recent studies (Park, 1998; Nicholson, 1998; Reid, 1998) suggested there might be a small risk.

Simultaneous administration of other vaccines, including childhood vaccines

The target groups for influenza and pneumococcal vaccination overlap considerably. For persons at high risk who have not previously been vaccinated with pneumococcal vaccine, health care providers should strongly consider administering pneumococcal and influenza vaccines concurrently. Both vaccines can be administered at the same time at different sites without increasing side-effects (Grilli et al., 1997; Fletcher et al., 1997). However, influenza vaccine is administered each year, whereas pneumococcal vaccine is administered once only.

Children at high risk of influenza-related complications can receive influenza vaccine at the same time they receive other routine vaccinations, including pertussis vaccine and using, if possible, DTaP which is less frequently associated with fever.

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9. Adverse events following Japanese encephalitis vaccine

The vaccines

Three types of Japanese encephalitis (JE) vaccine are currently in large-scale production and use in the world:

Mouse brain-derived inactivated vaccine is produced in several Asian countries, China – province of Taiwan – India, Japan, Korea, Thailand and Vietnam (WHO, 1994). It is inactivated by formaldehyde, and contains gelatin as a stabilizer and thiomersal as a preservative.

Cell culture-derived inactivated vaccine: primary hamster kidney cells are used in China and may well be used more widely in the near future.

Cell culture-derived live attenuated SA14-14-2 vaccine is based on a stable neuro-attenuated strain of JE virus prepared in China

Mild adverse events

Mouse brain-derived inactivated vaccine

Local reactions such as tenderness and swelling occur in about 20% of the vaccine recipients. A similar percentage may experience mild systemic symptoms including headache, low-grade fever, myalgia, malaise and gastrointestinal symptoms are reported 10 to 30% of vaccine recipients (Poland et al., 1990, WHO, 1998).

Cell culture-derived inactivated vaccine

Local reactions, including swelling at the injection site are observed in about 4% of vaccine recipients, and mild systemic symptoms, such as headache and dizziness are reported by fewer than 1% of vaccine recipients.

Cell culture-derived live attenuated vaccine

Clinical monitoring of experimentally immunized subjects has documented the absence of local or systemic symptoms. In a study of 867 children in whom fever was monitored over a 21-day period after immunization, temperatures above 37.6°C were recorded in less than 0.5% of vaccine recipients (Yu et al., 1988).

Severe adverse events

Mouse brain-derived inactivated vaccine

The manufacturing process purifies the infected mouse brain suspension extensively, and myelin basic protein content is controlled below 2 ng per ml. Vaccine-related neurological complications were not observed more often in vaccine recipients than in control groups in the Japanese studies in 1955–66. However, since 1992, several cases of acute encephalitis temporally linked to JE vaccination have been reported. From the Republic of Korea, three such cases were recently reported, of which two were fatal.

Hypersensitivity reactions, serious generalized urticaria, facial angio-oedema or respiratory distress have been observed in adult Western vaccine recipients (Anderson & Ronne, 1991; Plesner & Ronne, 1997; Ruff et al., 1991; CDC, 1993). The frequency of these reactions ranges between 1 and 64 per 10 000 vaccine recipients (Tsai & Chang, 1999). Although not clearly explained, these reactions may be in connection with gelatin, used as a stabilizer.

Cell culture-derived inactivated vaccine.

Fever higher than 38°C was previously a complication in 12% of the vaccine recipients, but after a reduction of bovine serum in the currently formulated vaccine, febrile convulsions have halved. An urticarian allergic reaction was observed in 1 of nearly 15 000 vaccine recipients surveyed (Tsai & Chang, 1999).

Cell culture-derived live attenuated vaccine

A block randomized cohort study of 13 266 vaccinated and 12 951 non-vaccinated one to two-year-old children followed prospectively for 30 days confirmed the vaccine safety. No cases of encephalitis or meningitis were detected in either group, and rates of hospitalization were similar in the two groups. The observations excluded a vaccination-related encephalitis risk above 1 in 3400 (Liu et al., 1997).

As a precaution, vaccine recipients should be observed for 30 minutes after vaccination. Epinephrine and other medications and equipment to treat anaphylaxis should be available. Vaccine recipients should be warned about the possibility of delayed urticaria and angioedema of the head and the respiratory track and advised to remain in areas with ready access to medical care in the 10 days after receiving a dose of JE vaccine.

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10. Adverse events following Lyme disease vaccine

The vaccine

Lyme vaccine is made from lipidated recombinant outer surface protein A (rOspA) of *Borrelia burgdorferi sensu stricto*. The rOspA protein is expressed in *Escherichia coli* and purified. Each 0.5-ml dose contains 30 µg of purified rOspA lipidated adsorbed onto aluminum hydroxide adjuvant. Another producer is using a lipidated and purified rOspA preparation based on *Borrelia burgdorferi* B isolate. (Telford & Fikrig, 1995; CDC, 1999). Two doses are usually required, a year apart. Preparations are generally monodose and do not contain thiomersal, but may contain an alum-based adjuvant.

Mild adverse reactions

In a randomized, controlled clinical trial (phase III), a total of 10 936 subjects aged 15–70 years living in Lyme disease-endemic areas were recruited at 31 sites. They were randomized to receive three doses of vaccine or placebo (Steere et al., 1998). 5469 subjects received at least one 30 µg dose of rOspA vaccine, and 5467 subjects received at least one injection of placebo. The subjects were followed for 20 months. Information was available from 4999 subjects in each group regarding adverse events that were thought to be related to injection of the vaccine.

Soreness at the injection site was the most frequently reported adverse event, which was reported without solicitation by 24,1% of vaccine recipients and 7,6% of placebo recipients ($p < 0.001$). Redness and swelling at the injection site were reported by <2% of either group but were reported more frequently among vaccine recipients than among those who received placebo ($p < 0.001$).

Myalgia, influenza-like illness, fever and chills were more common among vaccine recipients than placebo recipients ($p < 0.001$), but none of these was reported to occur in more than 3.2% of subjects. Reported rates of arthritis were not significantly different between vaccine and placebo recipients, but vaccine recipients were significantly ($p < 0.05$) more likely to report arthralgia or myalgia within 30 days after each dose. No statistically significant differences existed between vaccine and placebo groups in the incidence of adverse events more than 30 days after receiving a dose and no episodes of immediate hypersensitivity among vaccine recipients were noted.

Mild local reactions were common in trials published to date and appear more often in vaccine recipients than in placebo recipients. The most common was local pain, tenderness or both at the injection site, which occurred in up to 85% of subjects (Keller D et al., 1994; Schoer et al., 1995).

Safety in patients with previously diagnosed Lyme disease

The safety of three different dosage strengths of rOspA vaccine with adjuvant in 30 adults with previous Lyme disease was evaluated in an uncontrolled safety and immunogenicity trial (Schoen et al., 1995). Second, third and fourth doses were administered at monthly intervals. Follow-up of subjects was conducted one month after the third dose. No serious adverse events were recorded during the study period.

In the randomized, controlled clinical trial (phase III), the incidence of adverse events among vaccinees that were seropositive at baseline was similar to the incidence among those who were seronegative. The incidence of musculo-skeletal symptoms within the first 30 days after vaccination was higher among vaccinees with a self-reported previous history of Lyme disease compared with vaccinees with no such history. This difference was not statistically significant. No statistically significant difference existed in the incidence of late musculo-skeletal adverse events between vaccine and placebo recipients with a self-reported previous history of Lyme disease.

Severe adverse reactions

There were no significant differences between the groups in the frequency of severe side-effects in two studies (Keller D et al., 1994; Schoer et al., 1995). Preliminary analysis revealed no excess of serious or rare adverse events in the vaccinees when compared with results in placebo recipients.

Risk of possible immunopathogenicity of rOspA vaccine

The phase III trial did not detect differences in the incidence of neurological or rheumatological disorders between vaccine recipients and their placebo control during the 20 months after the initial dose. However, because the association between immune reactivity to OspA and treatment-resistant Lyme arthritis is poorly understood, the vaccine should not be administered to persons with a history of treatment-resistant Lyme arthritis.

There remain certain unanswered questions about the vaccine. Does vaccination alter the clinical presentation of Lyme disease? Does it delay the onset of infection? Does it modify the initial infectious process?

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11. Adverse events following meningococcal polysaccharide vaccine

Vaccine preparation

Licensed meningococcal vaccines are prepared from purified bacterial capsular polysaccharides, according to standard requirements (WHO, 1976a). Products available are monovalent group A or C, bivalent A+C, or tetravalent A+C+Y+W135 polysaccharide vaccines. Lyophilized preparations are reconstituted before administration and the diluent may include a very low dose of thiomersal. One vaccine dose usually contains 50 mg of each antigen and is administered subcutaneously. Immunization elicits a serogroup-specific antibody response and is indicated for the control of widespread epidemics and local outbreaks, and for the prevention of sporadic cases of meningococcal disease in high-risk individuals. A conjugate vaccine against meningococcus C has recently been introduced and used in mass campaigns in the United Kingdom.

Mild local reactions

The “gold standard” for assessing the frequency of adverse reactions to vaccines is the double-blind randomized trial, in which the control group receives a placebo injection containing an inactive substance. For obvious ethical reasons, such a study design has never been used for meningococcal vaccine trials, and control groups received either another vaccine or no injection. In all the controlled trials, using a one or two-dose schedule, polysaccharide vaccines were well tolerated and no serious reaction was observed (WHO, 1976b). Local reactions were frequent (up to 71% of recipients in one study) but mild, consisting principally of local erythema lasting 1–2 days (Mäkelä et al., 1975; Mäkelä et al., 1977; Peltola et al., 1978; Griffiss et al., 1981; Hankins et al., 1982; Ambrosch et al., 1983; Peltola et al., 1985; Lepow et al., 1986; Lieberman et al., 1996; King et al., 1996).

Systemic reactions

Fever is the most consistent systemic reaction to polysaccharide vaccines. In controlled trials, the reported frequency of transient febrile reaction with temperature equal to or higher than 38.5°C was between 0.6% and 3.6% (Mäkelä et al., 1977; Hankins et al., 1982; King et al., 1996; Lieberman et al., 1996). A correlation has been found between the frequency and severity of systemic reactions and the residual bacterial endotoxin content of vaccine lots (Peltola et al., 1978). However, current polysaccharide vaccines are highly purified, and systemic reactions are less frequent. In Quebec, during a mass immunization campaign in 1993, using mainly a bivalent A+C vaccine, the reported frequency of fever was 1.9% but

the real figure could be lower (Saintonge, 1995). During the same campaign, the frequency of all allergic reactions was 9.2 per 100 000 doses, and only one non-fatal case of anaphylaxis occurred among approximately 1.2 million vaccinees (Yergeau et al., 1996). In New Zealand, there were 92 reports of transient peripheral motor and sensory nerve symptoms after 130 000 children were vaccinated (Hood et al., 1989). However, the reports were gathered from parents after a media announcement was made seeking reports of reactions to meningococcal vaccines and only a few cases had medical assessment. Causality was thus difficult to establish.

There are few published data on repeated vaccination. In two small studies in children, the frequency of local and systemic reactions was no higher after second and third doses, than after primary immunization (Gold et al., 1979; MacDonald et al., 1998).

Other effects

Polysaccharide vaccines induce a relatively poor immune response in young children. In a recent study in Canada, children immunized at 15–23 months of age showed evidence of serologic hypo-responsiveness to group C polysaccharide when given a second dose 12 months later (MacDonald et al., 1998). Immunological refractoriness to group C polysaccharide has also been observed in adults (Granoff et al., 1998). However, the clinical significance of this phenomenon is not clear. To date, no increase in the risk of group C meningococcal disease has been observed in vaccinated individuals, even in those who received a first dose before the age of two years (Taunay et al., 1978; De Wals et al., 1996). Inactivated vaccines are considered safe for the fetus. No adverse effect has been documented among 51 newborns whose mother was vaccinated against meningococcal disease during pregnancy (McCormick et al., 1980).

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12. Adverse events following measles, mumps and rubella vaccines

Vaccine preparations

Numerous attenuated *measles vaccines*, most derived from the Edmonston strain, are currently produced worldwide. Four vaccines containing non-Edmonston derived strains are also in use including Leningrad-16, Shanghai-191, CAM-70 and TD97. In most cases, the virus is cultured in chick embryo cells. However, a few vaccines are attenuated in human diploid cells. Most vaccines do contain small doses of antibiotics (e.g. 25 mg of neomycin per dose), but some do not. Sorbitol and gelatin are used as stabilizers (Redd et al., 1999).

More than ten *mumps vaccine* strains (Jeryl Lynn, Urabe, Hoshino, Rubini, Leningrad-3, L-Zagreb, Miyahara, Torii, NK M-46, S-12 and RIT 4385), have been used throughout the world. The Jeryl Lynn strain is used in many countries. Most vaccines contain 25 mg of neomycin per dose. Several manufacturers in Japan and Europe produce a live mumps vaccine containing the Urabe Am9 virus strain. However, concerns about vaccine-associated meningitis prompted several countries to stop using Urabe vaccine strain (WER 1992). Other vaccines have more limited distribution. In most cases, the viruses are cultured in chick embryo fibroblasts (such as for the Jeryl Lynn and Urabe strain containing vaccines), however, quail and human embryo fibroblasts are also used for some vaccines.

Most *rubella vaccines* used throughout the world contain the RA 27/3 virus strain (Plotkin, 1965). The only exceptions are vaccines produced in Japan that use different virus strains (Matsuba, DCRB 19, Takahashi, and TO- 336 all produced on rabbit kidney cells and Matsuura produced on quail embryo fibroblasts. The RA 27/3 strain is used most often because of consistent immunogenicity, induction of resistance to reinfection, and low rate of side-effects (Plotkin et al., 1973). The live virus produces viraemia and pharyngeal excretion, but both are of low magnitude and are noncommunicable (Plotkin & Orenstein, 1999).

a) MEASLES VACCINE

Mild adverse events

Local reactions are not uncommon following administration of vaccines containing measles antigens. Within 24 hours of vaccination, recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required.

Mild systemic reactions may also occur with use of the vaccine. Measles vaccine is associated with moderate fever ($\approx 103^{\circ}\text{F}$) which occurs in up to 5% of recipients lasting 1-2 days. In most cases, these reactions are coincidental, with fever found in less than 2% on days 8–9 after vaccination in a placebo-controlled trial (Peltola & Heinonen, 1986). Measles vaccination also causes a rash to occur in approximately 2% of vaccinees. The rash typically occurs 7–10 days after vaccination and lasts 2 days.

Mild side-effects occur less frequently after the second dose of a measles-containing vaccine (Chen et al., 1991) and tend to occur only in those not protected by the first dose (Davis et al., 1997). For persons receiving a second dose of measles vaccine, it is likely that the vast majority will already be fully protected by the first dose. The actual figure depends on the age at which the first dose is given e.g. an estimated 9 out of 10 if vaccine was given at 12 months of age, leading to immediate and complete neutralization of the vaccine virus. Therefore, it is reasonable to assume that the risk of events will be decreased by a corresponding factor with the exception of allergic reactions. Likewise, there is no reason to believe that persons receiving more than 2 doses would be at higher risk for adverse reactions.

Severe adverse events

Allergic reactions, including anaphylaxis

Hypersensitivity reactions, including urticaria at the injection site, rarely occur following use of MMR, MR or its component vaccines. Anaphylactic reactions are extremely rare. Estimates of anaphylaxis range from 1 in 20 000 to 1 per million doses of measles-containing vaccine distributed (Stratton et al., 1994). Recent studies suggest that anaphylactic reactions to measles vaccine are not caused by residual egg proteins but by other vaccine components. Case reports have shown that individuals experiencing anaphylactic reactions following MMR vaccination had IgE antibodies to gelatin, a stabilizer used in vaccine production (Kelso et al., 1993; Sakaguchi et al., 1995). The risk for serious adverse reactions in those individuals allergic to eggs is low. The prick and intradermal testing with measles-containing vaccines have little bearing on the final reaction to these vaccines which have been given safely to people with severe egg allergy (Fasano et al., 1992; Kemp et al., 1990; James et al., 1995). A history of egg allergies is therefore no longer considered a contraindication to immunization with measles-containing vaccines.

Encephalopathy/encephalitis

Natural measles virus infection causes post-infectious encephalomyelitis in approximately one per 1000 infected persons. At least 50% of those affected are left with permanent central nervous system impairment. This syndrome is considered to be immunologically mediated because of the perivenular demyelinating lesions. While many have been concerned about the attenuated measles vaccine's ability to produce such a syndrome, the United States Institute of Medicine concluded there was not enough evidence to accept or reject a causal relationship (Stratton et al., 1994). In the United Kingdom, results from the British National Childhood Encephalopathy Study (NCES) 10 year follow-up did not identify an increased risk of permanent neurological abnormality following measles vaccination (Miller, 1997).

An analysis of claims for encephalitis following measles vaccine in the United States found clustering of events at 8–9 days after immunization, which supports but does not prove the possibility that the vaccine causes encephalitis (Weibel, 1998; Duclos, 1998). The risk was less than one per million doses, or about 1000 times less than the risk from measles.

Subacute sclerosing panencephalitis (SSPE)

Measles vaccination reduces the occurrence of SSPE as evidenced by the near elimination of SSPE cases after widespread measles vaccination (Dyken et al., 1989). Use of a vaccine containing live measles virus does not increase the risk for SSPE, even among those individuals with a prior history of measles disease or vaccination (Howson et al., 1991; Duclos & Ward, 1998).

Guillain–Barré Syndrome

GBS has been reported following receipt of MMR and its component vaccines, however, the United States Institute of Medicine reviewed the available research and concluded that there was not enough evidence to accept or reject a causal relationship (Stratton et al., 1994). Recently published studies have also been unable to show a causal association (Hughes et al., 1996; Silveira et al., 1997).

Seizures

On rare occasions, use of a measles-containing vaccine can cause febrile seizures. By linking vaccination records with computerized hospital admission records in five districts in the UK, Farrington et al. (1995) found that 67% of admissions for a febrile convulsion 6–11 days after MMR vaccination were attributable to the measles component of the vaccine (risk 1 in 3000 doses). An association between MMR vaccine and residual seizure disorders has not been established (Stratton et al., 1994). Children with a personal or family history of seizures are at greater risk for idiopathic epilepsy, however, febrile seizures after vaccination do not increase the likelihood that epilepsy or other neurological disorders will develop in these children. Children with a history of convulsions may be at increased risk for febrile convulsions after MMR vaccination, but the risk appears to be minimal (CDC, 1989).

Thrombocytopenia

On rare occasions, vaccines containing measles, mumps and rubella antigens can cause thrombocytopenia. The risk of thrombocytopenia following MMR vaccination is 1 in 30 000 to 1 in 40 000 vaccinated children (Bottiger et al., 1987; Nieminen et al., 1993; Farrington et al., 1995). The clinical course of these cases is usually transient and benign (Beeler et al., 1996). The risk for thrombocytopenia following MMR vaccination may be increased for those with a previous diagnosis of immune thrombocytopenic purpura, especially for those who have had it after an earlier dose of MMR vaccine (Stratton et al., 1994; Drachtman et al., 1994; Vlacha et al., 1996). The data support a causal relationship only with MMR and not with the measles component. In other words, it is impossible to attribute these reactions to either of the viral components of the vaccine. Although based on natural disease history, this is probably more likely to be connected to either the measles or rubella components.

Table 5 highlights the fact that natural measles is a serious disease with frequent complications, whereas vaccination with live attenuated virus is remarkably benign.

Table 5: Risk of complications from natural measles infection compared to known risks of vaccination with a live attenuated virus in immunocompetent individuals

(after Duclos & Ward, 1998)

Complication	Risk after natural disease* a)	Risk after vaccination b)
Otitis media	7–9%	0
Pneumonia	1–6%	0
Diarrhoea	6 %	0
Post-infectious encephalomyelitis	0.5–1 per 1000	1 per 1 000 000
SSPE	1 per 100 000	0
Thrombocytopenia	-c)	1 per 30 000 ^{d)}
Death	0.1–1 per 1000 (up to 5–15% in developing countries)	0

* Risk as measured in industrialized countries. Risk in developing countries is not as well defined but generally higher (Hussey et al., 1996).

a) Risks after natural measles are calculated in terms of events per number of cases

b) Risks after vaccination are calculated in terms of events per number of doses

c) Although there have been several reports of thrombocytopenia occurring after measles including bleeding, the risk has not been properly quantified.

d) This risk has been reported after MMR vaccination and cannot only be attributed to the measles component.

MMR = measles, mumps and rubella;

SSPE = subacute sclerosing panencephalitis.

Inflammatory bowel disease and autism

In recent years, researchers have hypothesized that measles vaccine may be associated with inflammatory bowel diseases (IBD), including Crohn's Disease (Ekbom et al., 1990; Wakefield et al., 1993; Ekbom et al., 1994; Thompson et al., 1995; Wakefield et al., 1995; Ekbom et al., 1996). One research group speculated that measles vaccine could be related to the development of IBD and autism (Wakefield et al., 1998). Within the scientific community, concerns have been raised about the methodological limitations in the studies upon which these hypotheses are based (Patriarca & Beeler, 1995; Farrington & Miller, 1995; MacDonald, 1995; Miller & Renton, 1995; Chen & DeStefano, 1998). Other research does not support these hypothesized associations (Liu et al., 1995; Iizuka et al., 1995; Feeney et al., 1997; Haga et al., 1996). There is no evidence to indicate an association between MMR vaccine and IBD or autism. The alleged associations between measles vaccination and Crohn's disease and autism are based upon weak science and have been refuted by a large volume of scientifically sound work (Duclos & Ward, 1998).

b) MUMPS VACCINE

Mild adverse events

Localized reactions are common following administration of vaccines containing mumps antigens. Within 24 hours of vaccination, recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions may also occur with use of these vaccines. The most common side-effects include parotitis and low-grade fever. Parotitis typically occurs 10–14 days after vaccination (Fescharek et al., 1990).

Generally, the rates for mild events appear to differ little between strains. For instance, parotid and/or submaxillary swelling occurred in 1.6% of children who received Jeryl Lynn vaccine and 1–2% of those who received Urabe vaccine (Popow-Kraupp et al., 1986). Data from post-marketing surveillance in Canada, however, have shown a much higher rate of parotitis with the Urabe strain than with the Jeryl Lynn strain.

Mumps vaccine is also associated with rash, pruritus and purpura but these reactions are uncommon. It is biologically plausible that orchitis (Kuczyk et al., 1994), arthritis (Nakayama et al., 1990; Nussinovitch et al., 1995), sensorineural deafness (Stewart & Prabhu, 1993; Nabe-Nielsen & Walter, 1988) and acute myositis (Rose et al., 1996) may also occur following mumps vaccination, however, these reactions are rare. Canadian data from post-marketing surveillance show an increased risk, albeit small, of orchitis for the Urabe versus Jeryl Lynn strain.

Severe adverse events

Aseptic Meningitis

Several attenuated mumps vaccines have been associated with aseptic meningitis. The incubation period following immunization is 2–3 weeks and the clinical course is similar to that of the natural disease (McDonald et al., 1989). The risk of developing this complication varies depending on the vaccine strain and the manufacturer:

- **Jeryl Lynn strain.** This strain has not been shown to cause aseptic meningitis. In the United States, a 10-year retrospective study of hospitalized cases of mumps found only one case of aseptic meningitis per 100 000 doses of Jeryl Lynn-containing MMR vaccine in children aged 12–23 months (Black et al., 1997). Another study found 1 per 1.8 million doses administered (Nalin, 1992). In yet another study, it was associated with 0.1 cases per 100 000 doses (Fescharek et al. 1990). It is such a rare event that when it does occur in association with the vaccine administration, it probably represents a coincidental occurrence.
- **Leningrad-3 strain.** A causal relationship has been established between the Urabe, Leningrad-3 and L-Z strains of mumps vaccine and aseptic meningitis (Miller et al., 1993; Stratton et al., 1994; Black et al., 1997, Galazka et al., 1999). In Slovenia, passive surveillance over the period 1979–85 identified 20–100 cases of aseptic meningitis per 100 000 doses of MM vaccine containing Leningrad-3 strain. (Kraigher 1990, Cizman M et al., 1989).

- **Leningrad-Zagreb (LZ) strain.** An outbreak of aseptic meningitis was reported in Brazil after using this strain in 1998 during a campaign. An incidence rate of 4.22-1.36 per 100 000 population was observed during the peak week of the outbreak, a rate 70 times higher than the pre-campaign period (Dourado 2000). A rate of 20 per 100 000 doses was recorded in Slovenia (Fescharek et al., 1990). In Slovenia, 2 cases of aseptic meningitis per 100 000 doses were reported (A. Kraigher, unpublished data). In Croatia 90 cases per 100 000 doses were reported (Tesovic et al., 1993).
- **Rubini strain.** Immunogenicity is relatively low with this strain, and aseptic meningitis has not generally been reported to be a problem following Rubini strain administration. However in Italy, a case-control study found that children vaccinated with Rubini strain had a higher risk of contracting mumps compared with Urabe or Jeryl Lynn vaccine use (Benevento 1998). In Portugal, large mumps epidemics continued despite high coverage with MMR. The peak incidence of mumps occurred after Portugal switched to MMR containing Rubini strain (Dias et al., 1996).
- **Urabe strain.** Following reports of aseptic meningitis cases temporally associated with administration of MMR vaccine containing Urabe strain, Canada withdrew the vaccine from the market (Furesz et al., 1990). A study in Nottingham, UK, showed 9 cases of aseptic meningitis per 100 000 doses (Miller et al., 1993). As a result, the product was no longer purchased by UK. A Japanese study demonstrated a rate of 49 cases of aseptic meningitis per 100 000 doses of Urabe strain produced locally (Sugiura et al., 1991). A subsequent study put the rate at 100 cases per 100 000 doses (Ueda et al., 1995).

c) **RUBELLA VACCINE**

Mild adverse events

Localized reactions are common following administration of vaccines containing rubella antigens. Within 24 hours of vaccination, recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required.

Mild systemic reactions may also occur with the use of rubella vaccine. Those vaccinated sometimes develop a mild case of the disease that includes fever, rash, lymphadenopathy, sore throat and headache. The risk of experiencing adverse events following rubella vaccination varies with age.

Severe adverse events

Arthralgia, arthritis and arthropathy

Rubella vaccines may be associated with joint symptoms. Transient joint pain develops in up to 25% of post-pubertal females (Freestone et al., 1971). Arthritis accounts for only 10% of these cases. However, such adverse reactions are very rare in children receiving MMR vaccine (less than 1%) (Rowlands & Freestone, 1971). Symptoms typically begin one to three weeks after vaccination and last one day to three weeks.

The United States Institute of Medicine (IOM) reviewed available research and found that while data supported a causal relationship between rubella vaccine and chronic arthritis among adults, the findings were limited in scope (Howson et al., 1991). Most recently published research, however, has shown no increased risk of chronic arthropathies among women receiving 27/3 rubella vaccine and do not support the conclusion of the IOM (Slater et al., 1995; Frenkel et al., 1996; Ray et al., 1997). One study found a borderline statistically significant slight increase in risk (Tingle et al., 1997).

Despite the risk of transient arthralgia or arthritis in post-pubertal females, efforts should be made to identify and vaccinate susceptible women of childbearing age. This will help prevent the birth defects associated with congenital rubella syndrome (CRS). Natural rubella infection can have a devastating impact on pregnancy, leading to fetal death, premature delivery and an array of congenital defects. Approximately 85% of pregnancies will be negatively affected when rubella infection occurs during the first trimester. Administration of rubella vaccine during pregnancy is of no consequences for the fetus.

The attenuated virus strain in the current rubella vaccine can rarely infect the fetus but there is no evidence that fetal infection with the vaccine virus is harmful. The theoretical maximum risk for CRS after administration of the vaccine at 1.6%, is much lower than the risk of major non-CRS induced congenital defects during pregnancy (Plotkin & Orenstein, 1999). The observed risk has been zero. Therefore, because of an unsubstantiated theoretical risk, and because it is impossible to prove that the risk is zero, known pregnancy remains a contraindication to administration of rubella-containing vaccine. It is recommended that pregnancy be deferred for a month after vaccination. If vaccination is given to a pregnant female, this should *not* be considered as an indication for termination of the pregnancy.

d) COMBINATION VACCINES

In many countries, children typically receive a combination vaccine that contains either the measles, mumps and rubella (MMR) or measles and rubella (MR) antigens. The combination vaccine produces an immunological response equal to that of the single antigen shots (Decker & Edwards, 1999). A recent study compared the reactogenicity and immunogenicity of two MMR vaccines produced by two manufacturers (Usonis et al., 1999). The researchers found differences in the incidence of localized reactions (pain, redness and swelling at the injection site) among the vaccines that were most likely the result of varying pH levels. The safety and immunogenicity of these vaccines appears to be similar.

Mild adverse events

When combination vaccines (MR or MMR) are used, mild reactions are similar to those described above. The use of MR can result in mild lymphadenopathy, urticaria, rash, malaise, sore throat, fever, headache, dizziness, nausea, vomiting, diarrhoea, polyneuritis, arthralgia and arthritis.

Fever is the most common reaction reported following MMR vaccination. Approximately 5–15% of children develop a temperature of $^{3}103^{\circ}\text{F}$ within 12 days of vaccination (CDC, 1998). In most cases, these reactions are coincidental,

with fever found in less than 2% on days 8–9 after vaccination in a placebo-controlled trial (Peltola & Heinonen, 1986). Measles vaccination also causes a rash to occur in approximately 2% of vaccine recipients. The rash typically occurs 7–10 days after vaccination and lasts 2 days. On rare occasions, transient lymphadenopathy and parotitis have also been reported following administration of MMR vaccine (CDC, 1998).

Severe adverse events

The type and rate of severe adverse reactions do not differ significantly from the measles, mumps and rubella vaccine reactions described separately.

Altered immunocompetence

In individuals who are immunocompromised, including those suffering from HIV infection, a transient enhanced replication of vaccine viruses may occur. Case reports have linked the deaths of some severely immunocompromised individuals to vaccine-associated measles infection (Stratton et al., 1994; CDC, 1996) but there are no data on mumps or rubella. Vaccines containing measles, mumps or rubella antigens pose a theoretical threat to severely immunocompromised individuals. When feasible, a physician should determine whether an individual is severely immunocompromised based on clinical and laboratory assessment. In most situations in developing countries, screening for HIV status and degree of immunodeficiency is impossible. Immunization policy must find a balance between the remote risk of enhanced replication and the known high risk of death or severe complications in the event that an HIV-infected individual should contract measles infection.

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13. Adverse events following pneumococcal vaccine

Vaccine preparations

The current pneumococcal vaccine, available since 1983, includes either the 14 or 23 purified capsular polysaccharide antigens of *Streptococcus pneumoniae*, serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. One dose (0,5 ml) of the 23-valent vaccine contains 25 µg of each capsular polysaccharide antigen, dissolved in isotonic saline solution with phenol (0.25%) or thiomersal (0.01%) added as preservative and no adjuvant.

Extensive clinical trials are now under way with a new generation of pneumococcal vaccines. These protein-polysaccharide combinations, known as conjugate vaccines, contain 7-11 selected polysaccharides bound to a protein carrier, and induce immunological memory. These vaccines are likely to be protective even in children aged <2 years, and may reduce pneumococcal transmission through a herd effect (WHO, 1999).

Mild adverse events

Pneumococcal polysaccharide vaccine is generally considered safe, based on clinical experience since 1977, when the pneumococcal polysaccharide vaccine was licensed. Approximately half of persons who receive pneumococcal vaccine develop mild, local side-effects (e.g. pain at the injection site, erythema and swelling). These reactions usually persist for < 48 hours. Moderate systemic reactions (e.g. fever and myalgias) and more severe reactions (e.g. local induration) are rare. Intradermal administration may cause severe local reactions and is inappropriate. In a meta-analysis of nine randomized controlled trials of pneumococcal vaccine efficacy, local reactions were observed among approximately one third of 7531 patients receiving the vaccine (Fine, 1994).

Severe adverse events

Severe systemic adverse effects (e.g. anaphylactic reactions) have been reported rarely after administration (CDC, 1989; Fedson, 1994). Fine et al. did not report severe febrile or anaphylactic reactions in the meta-analysis mentioned before (on 7531 patients). No neurological disorders (e.g. Guillain-Barré syndrome) have been associated with administration of pneumococcal vaccine. Although preliminary data have suggested that the pneumococcal vaccine may cause transient increases in HIV replication (Brichacek et al., 1996), the importance of this observation is unknown.

Adverse events following revaccination

Early studies have indicated that local reactions (i.e. Arthus type reactions) among adults receiving the second dose of 14-valent vaccine within two years after the first dose are more severe than those occurring after initial vaccination (CDC, 1989; Borgono et al., 1978). However, subsequent studies have suggested that revaccination after intervals of >4 years is not associated with an increased incidence of adverse side-effects. (CDC, 1989; Mufson, 1984; Rigau-Perez, 1983). One study showed an increased rate in local reactions of large dimension in those receiving more than one dose of the vaccine (Snow et al., 1995). An evaluation of 1000 elderly Medicare enrollees who received a second dose of pneumococcal vaccine indicated that they were not significantly more likely to be hospitalized in the 30 days after vaccination than were approximately 66 000 persons who received their first dose of vaccine (Snow et al., 1995). No data are available to allow estimates of adverse reaction rates among persons who received more than two doses of pneumococcal vaccine.

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14. Adverse events following poliomyelitis vaccine

a) ORAL POLIOVIRUS VACCINE

Vaccine preparation

Approximately 18 manufacturers, located around the world, produce OPV using Sabin vaccine seeds provided by the World Health Organization. Most manufacturers grow the viruses in cultures containing monkey kidney cells and continuous cell lines (Vero or diploid cells). OPV contains the three poliovirus strains that are known to infect human beings. The titers for human dose are as follows:

- 10^6 TCID₅₀ for type 1
- 10^5 TCID₅₀ for type 2
- $10^{5.7}$ TCID₅₀ for type 3

Each dose of OPV contains residual amounts (less than 25 µg) of antibiotics including streptomycin and neomycin. In addition, MgCl₂ is added as a stabilizer. No adjuvants or preservatives are used (Sutter et al., 1999).

Mild adverse events

In general, OPV is well tolerated by vaccine recipients. OPV is not associated with any common side-effects.

Severe adverse events

Vaccine-associated paralytic polio (VAPP)

The major adverse event associated with OPV is VAPP. The case definition of this condition is “an acute flaccid paralysis 4–30 days following receipt of oral polio vaccine (OPV), or within 4–75 days after contact with a recipient of OPV, with neurological deficits remaining 60 days after onset, or death”. The precise rate of VAPP varies with the study and methodology used to measure it. The rate of VAPP is higher for the first dose of OPV than subsequent doses, ranging from one case per 1.4 million to one case per 3.4 million first doses administered. A 1969 WHO Collaborative study found VAPP rate to be one in every 5.9 million doses administered for vaccine recipients and one in every 6.7 million doses administered for contacts.

Studies have found no significant differences in VAPP rates between developing and industrialized countries. In countries where wild poliovirus transmission has been extensive until recently, VAPP occurs more commonly in children and vaccine recipients than in adults and contacts. Reasons for this include a smaller number of adult susceptibles because of recently acquired natural immunity, and the immunization of all children simultaneously in mass eradication campaigns. VAPP is more common in individuals who are immunocompromised. No study has demonstrated transmission from a VAPP case resulting in another VAPP case.

Table 6: Rates per million doses of vaccine-associated paralytic poliomyelitis

Study (Reference)	Rate for recipient of 1 st dose* (number of VAPP cases)	Recipient overall rate (number of VAPP cases)	Rate for contacts (number of VAPP cases)	Overall
Canada (Varughese, 1989)	-	1:9.5 (4)	1:3.2 (12)	-
England & Wales (Joce, 1991)	1:0.7 (6)	1:2.0 (9)	1:4.5 (4)	1:1.4
FR Germany (Maass, 1987)	-	1:4.4 (21)	1:15.5 (6)	1:3.4
Italy (Novello, 1987)	-	1:8.1 (1)	1:4.1 (2)	1:2.7
Latin America (Andrus, 1995)	1:1.2 (24) 1:1.1 (27)	1:3.6 (85) 1:2.7 (114)	1:5.6 (54) 1:3.3 (91)	1:2.2 1:1.5
USA (CDC, 1996)	1:1.4 (40)	1:6.2 (72)	1:5.7 (53)	1:2.4
WHO Collaborative study of 13 countries (Esteves, 1988)	-	1:5.9	1:6.7	1:3.2

* Data are probably most complete and comparable for rates for recipients of first doses, comparison of rates for other doses being methodologically more complex.

Guillain-Barré syndrome

Current data do not indicate an increased risk of GBS following receipt of OPV (CDC, 1996). Research conducted in Finland during the 1980s suggested an increased incidence of GBS following mass OPV vaccination (Kinnunen et al., 1989; CDC, 1997; Uhari et al., 1989). These findings led the US Institute of Medicine to conclude that there was an association between OPV and GBS (Stratton et al., 1994). Since the IOM review, the Finland results have been reanalysed and other factors have been identified as having contributed to the increase in the incidence of GBS. These factors include an influenza epidemic and widespread circulation of wild type-3 poliovirus (Kinnunen et al., 1998). During this time period, another observational study was completed in the United States. Research findings did not support a causal relationship between OPV and GBS (Rantala et al., 1994; CDC, 1996; Kinnunen et al., 1998).

Aseptic meningitis/encephalitis

On rare occasions, particularly in immunodeficient infants, aseptic meningitis and encephalitis have been reported after OPV (Andronikou et al., 1998; Yeung et al., 1997; Rantala et al., 1989).

Transverse myelitis

Seven cases of transverse myelitis have been reported after OPV, but five occurred following the administration of multiple vaccines. TM was not observed in the clinical trials that occurred prior to licensure of the polio vaccine and no other controlled studies have been conducted. Therefore, the data is inadequate to determine whether a causal relationship exists between OPV and TM (Stratton et al., 1994).

Simultaneous administration

OPV can be administered with other vaccines, there being no evidence of increased rates of adverse events nor reduced immunogenicity. OPV is frequently administered simultaneously with diphtheria–tetanus–pertussis (DTP) vaccines and therefore side effects from the latter may often be falsely attributed to OPV.

Provocation polio

In persons incubating wild polio virus infection, intramuscular injections (e.g. DTP) may provoke paralysis in the injected limb (Sutter et al., 1992; Strebel, 1995).

b) INACTIVATED POLIOVIRUS VACCINE

Vaccine preparation

Like OPV, inactivated poliovirus vaccine (IPV) contains three poliovirus strains. The viruses are grown either on Vero cells or human diploid (MRC-5) cells and then concentrated, purified and inactivated with formaldehyde. Each dose of vaccine contains 40 D antigen units of type 1, eight D antigen units of type 2 and 32 D antigen units of type 3. Trace amounts of antibiotics are also found in the vaccines, including neomycin, streptomycin and polymyxin B. Some manufacturers use 2-phenoxyethanol as a preservative (Plotkin, 1999). Thiomersal is not used.

Mild adverse events

Localized reactions are common with IPV use. Within 24 hours of vaccination, recipients frequently experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions may also occur.

Severe adverse events

IPV contains small amounts of streptomycin, polymyxin B and neomycin which can theoretically cause reactions in persons allergic to these antibiotics – but no confirmation of such reactions has been found in post-marketing surveillance (Plotkin et al., 1999; CDC, 1997). No reports of anaphylaxis, thrombocytopenia or transverse myelitis (Stratton et al., 1994) after IPV have been published.

Table 7: Adverse events associated with poliovirus vaccines

Vaccine type	Mild reactions	Serious reactions
Oral polio vaccine	None reported	Aseptic meningitis/encephalitis vaccine-associated paralytic polio No evidence to support association with Guillain–Barré syndrome or transverse myelitis
Inactivated polio vaccine	<i>Localized</i> Pain and tenderness at the injection site <i>Systemic</i> Allergic reactions to streptomycin, polymyxin B and neomycin	No evidence to support association with thrombocytopenia, transverse Myelitis or anaphylaxis

Source: CDC, 1996

Other

Simian papovavirus SV40

From 1954 to 1962, both the inactivated and live attenuated forms of polio vaccine were prepared in primary cultures of rhesus monkey kidney cells, some of which were derived from monkeys that were naturally infected with SV40. This is a live simian papovavirus 40 (SV-40) which may cause neural tumour in animals, and viruses from the same papovavirus family may cause neural tumours in human beings. Some studies tried to investigate possible causation between the receipt of polio vaccine and the development of tumours (Dittmann, 1992). Long-term follow-up studies do not support such an association. Butel & Lednicky, 1999). A meeting convened at the National Institute of Health in 1997 concluded that “no measurable increase in neoplastic diseases has occurred in humans exposed to SV40 contaminated polio vaccines” (Plotkin et al., 1999). All currently-produced oral polio vaccine is now tested for SV40 and none has been found positive.

Simultaneous administration

IPV is frequently administered simultaneously with diphtheria–tetanus–pertussis (DTP) vaccines. Side-effects from the combined vaccine are often falsely attributed to the IPV component. The combination of IPV with other vaccines, including DPT and Hib, does not appear to increase adverse reactions (Murdin et al., 1996; Vidor et al., 1994).

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15. Adverse events following rabies vaccine

The vaccine

There are three main types of rabies vaccine:

Vaccines containing animal brain tissues

- Rabies virus phenol-inactivated vaccines using as a substrate sheep, goat or rabbit brain. It contains nerve tissue and is used in Asia and Africa.
- Rabies virus inactivated vaccines, using as a substrate suckling mouse brain, with a decreased myelin content. It is used in South America.

Avian vaccines

They use as a substrate duck embryo, are inactivated by β propiolactone, and purification is done by ultracentrifugation. This vaccine is used in Europe.

Cell-cultured vaccines

- Human diploid cell culture vaccine (HDCV) is grown on human fibroblast, inactivated by β propiolactone and used in Europe and USA.
- Primary hamster kidney cells rabies vaccine is grown on hamster kidney cells, inactivated by formalin.
- Purified chick embryo cells culture vaccine (PCEC) is inactivated by β propiolactone purified by ultracentrifugation and has been licensed in the United States since October 1997.
- Purified Vero rabies vaccine (PVRV) is grown on Vero cells, inactivated by β -propiolactone and purified by ultracentrifugation.
- Rabies vaccine adsorbed (RVA) vaccine uses a Kissling strain of rabies virus adapted to a diploid cell of fetal rhesus monkey lung fibroblast, inactivated by β -propiolactone, and containing alum phosphate (Plotkin et al., 1999; CDC, 1998).

Mild adverse events

(i) *Vaccines containing animal brain tissues (Wiktor, 1980)*

General systemic reactions

The various minor disorders that may develop during and after a course of antirabies treatment includes fever, headache, insomnia, palpitations and diarrhoea. Sensitization to proteins contained in older vaccines can cause a sudden shock-like collapse, usually toward the end of the course of treatment.

Local reactions

Erythematous patches may develop approximately 7 to 10 days after the beginning of anti-rabies treatment. Lesions appear on the skin a few hours after administration and fade in 6 to 8 hours, reappearing after the next dose.

(ii) *Cell-cultured vaccines*

Cell-cultured vaccines are widely accepted as well-tolerated rabies vaccines, although reported reaction rates to primary immunization have varied with the monitoring system. In a large-scale testing of the safety and immunogenicity of human diploid cell vaccine performed on American veterinary students, adverse reaction rates observed in more than 1770 volunteers are shown in Table 8.

Table 8: Adverse events following cell-cultured rabies vaccine

Adverse event	Percentage
Significant sore arm	15–25%
Headache	5–8%
Malaise, nausea or both	2–5%
Allergic oedema	0.1%

Source: Plotkin 1980

In another study of post-exposure vaccination, 21% had local reactions, 3.6% had fever, 7% had headache, and 5% had nausea. The most common local reactions are erythema, pain and induration (Anderson et al., 1980). A comparative study of HDCV and PVRV vaccines in 144 volunteers did not show serious adverse events with either vaccine, although some vaccinees complained of redness, induration or local pain and, exceptionally, fever (Ajjan & Pilet, 1989)

Allergic reactions are reported mostly after booster doses (CDC, 1984; Dreesen et al., 1986). The overall incidence was 11 per 10 000 vaccinees (0.11%), but rose to 6% after boosters (Fishbein et al., 1993). These reactions have been attributed to antigenicity conferred on the stabilizer – human albumin – by the b-propiolactone used to inactivate the virus. The b-propiolactone increases the capacity of albumin to form immune complexes (CDC, 1984; Anderson et al., 1987; Swanson et al., 1987). Respiratory symptoms are mild; there have been no fatalities. Epinephrine, antihistamines and occasionally steroids have been used in successful treatment of these reactions, which have resolved in 2 to 3 days.

Severe adverse events

(i) Vaccines containing animal brain tissues

Severe and fatal reactions

A patient may suffer from serious and often fatal illness after nerve tissue vaccine. These accidents are of two types: (1) *rage de laboratoire*, a disease no longer occurring, induced by the living “fixed virus” present in the old Pasteur vaccine, and (2) neuroparalytic accidents, which present the greatest danger from rabies vaccination. All types of vaccines containing adult mammalian nervous tissues exhibit similar capacities for inducing neuroparalytic reactions. The neuroparalytic reactions usually develop between the 13th and the 15th days of treatment and may assume one of the following three forms:

1. Landry type. In this type of accident, the patient rapidly becomes pyrexial and suffers pain in the back. Flaccid paralysis of legs begins and, within one day, the arms become paralysed. Later, the paralysis spreads to the face, tongue and other muscles. The fatality rate is about 30%; in the remaining 70%, recovery usually occurs rapidly.
2. Dorsolumbar type. Less severe than Landry type, this is the most common form of neuroparalytic accident. Clinical features are explicable by the presence of dorsolumbar myelitis. The patient may be febrile and feel weak, with paralysis of the lower limbs, diminished sensation and sphincter disturbances. The fatality rate does not exceed 5%.
3. Neuritis type. In this type of accident, the patient may be pyrexial and usually shows a temporary paralysis of the facial, oculomotor, glossopharyngeal or vagus nerves.

Neuroparalytic accidents are caused by allergic “encephalomyelitis”, attributable to sensitization to adult nerve tissue antigen (myelin-based protein). The incidence of these reactions varies widely from 0.0017% to 0.44% and is definitely lower in people receiving DEV and in people receiving properly manufactured vaccine of newborn rodent brain.

(ii) Cell-cultured vaccines

Neurological reactions

Five cases of central nervous system disease, including transient neuroparalytic illness of Guillain–Barré type, have been reported among the millions of individuals given human diploid cell vaccines (Bernard et al., 1982; Boe & Nyland, 1980; Knittel et al., 1989; Tornatore & Richert, 1990; Moulignier et al., 1991). But this rate is too low to be positively related to vaccination, because the background incidence of such diseases is about 1 per 100 000 per year. This low incidence after human diploid cell vaccine compares well with a neurological complication rate of 1:1600 people for nerve tissue vaccine, 1:8000 for suckling mouse brain vaccine and 1:32 000 for duck embryo vaccine.

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16. Adverse events following rotavirus vaccine

The vaccines

Two rotavirus vaccines are currently available:

- Rhesus rotavirus tetravalent vaccine (RRV-TV) containing 10^5 plaque-forming units (PFU) of each serotype, G1, G2, G4 RRV reassortants and the RRV-G3 strain in a liquid form. This vaccine licensed in 1998 but was subsequently withdrawn by the manufacturers in July 1999 following reports of intussusception following administration (see below).
- Bovine strain WC3x human reassortant rotavirus vaccine containing 10^7 PFU OF WC3 reassortants of G2, G2, G3 and P1a specificity. This vaccine is not yet licensed and is undergoing evaluation in industrialized countries.
- Human paediatric oral serotype G1 monovalent strain is not yet licensed.

Mild adverse events

No major adverse reactions have been associated with administration of the RRV-TV vaccine among more than 17 000 children who have received it, but a significant increase in mild fever has been observed three to five days after immunization. Low-grade fevers of temperature less than 38°C have been the most common (up to 15%), and a small group of children have had temperature higher than 39°C .

In a randomized double-blind study, infants aged 6 to 24 months received RRV-TV, RRV-S1 or placebo (Santosham et al., 1997). The proportion of children who had diarrhoea or vomiting during the five-day period after each of the doses of the vaccine or placebo ranged from 3% to 7% and did not differ significantly among the groups. The only statistically significant difference occurred after the second dose, at which time 18% of the RRV-TV recipients had a temperature greater than 38°C , in comparison with 12% among placebo recipients ($p=0,02$). In a randomized, double-blind, placebo-controlled trial in Venezuela, 2207 infants received either three oral doses of RRV-TV or placebo. The vaccine was safe, although 15% of the vaccinated infants had febrile episodes ($>38,1^{\circ}\text{C}$) during the six days after the first dose, as compared with 7% of the controls ($p<0;001$) (Perez-Schael et al., 1997). Only a small group of children (1 to 2%) had a temperature higher than 39°C (Bernstein et al., 1995; Rennels et al., 1996; Santosham et al., 1997).

Bovine strain WC3 safety has been evaluated in a multi-site study. There was a slight excess (8%) of mild diarrhoea noted in the vaccine group after the first dose only (Clark et al., 1995).

Severe adverse events

Intussusception has been reported in recipients of the tetravalent rhesus-based rotavirus vaccine (CDC, 1999). The exact attributable risk is still being estimated. The significance of this finding is still being evaluated (WHO 2000), but there was sufficient concern that the vaccine was withdrawn by the manufacturers. Other rotavirus vaccines may not present the same risk.

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17. Adverse events following tick-borne encephalitis virus vaccine

The vaccines

Vaccines used in Europe are usually inactivated by formalin, prepared from a tick-borne encephalitis (TBE) virus (subtype Central Europe) grown on chicken embryo cells and purified. Each dose contains 0.35 mg of viral antigen, 1 mg of aluminum hydroxide as an adjuvant, thiomersal as a preservative, and 0.5 mg of human albumin as a stabilizer.

Mild adverse events

As with all intramuscularly administered vaccines, occasional local reactions may occur, such as reddening and swelling around the injection site; swelling of the regional lymph nodes or general reactions, such as fatigue, pain in the limb, nausea and headache. On rare occasions, temperature higher than 38°C for a short time, vomiting or temporary rash may occur. In children, the reduced dosage results in a decrease of local reactions (19% vs. 30% for temperature above 38°C (Girgsdies, 1996). However, an accumulation of notifications of allergic reactions in children resulted in a withdrawal of that product from the market. The reactions appear to be due to IgE responses to the gelatin stabilizer. After removal of thiomersal and human albumin from the product recently, an apparent rise occurred in the number of children under 3 years of age who developed fever after the first dose. The reasons for this remain unclear.

Serious adverse events

In very rare cases, neuritis of a varying degree of severity may be present, although the etiologic relationship to vaccination is uncertain (Kunz, 1992). The vaccination is suspected of causing an aggravation of autoimmune diseases such as multiple sclerosis or iridocyclitis in some patients.

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18. Adverse events following typhoid vaccine

The vaccines

Several typhoid vaccines are currently available:

- An oral live attenuated vaccine, supplied as liquid or enteric-coated capsules containing lyophilized Ty21a, a mutant strain of *Salmonella typhi*;
- A newly licensed capsular polysaccharide vaccine (ViCPS) for parenteral use which is an injectable solution of Vi (virulence) antigen prepared from the polysaccharide (ViCPS) of *S. typhi* strain TY2. Each dose contains 25 µg of polysaccharide;
- A parenteral heat-phenol-inactivated whole-cell vaccine that has been widely used for many years;
- An acetone-inactivated parenteral vaccine.

Mild adverse events

Ty 21a vaccine

Ty 21a produces fewer adverse reactions than either ViCPS or the parenteral inactivated vaccine. During studies in volunteers and field trials with oral live-attenuated Ty 21a vaccine, side-effects were rare and consisted of abdominal discomfort, nausea, vomiting, fever, headache, and rash or urticaria (Gilman et al., 1977; Simanjuntak et al., 1991; Cryz, 1993).

Results of three double-blind, placebo controlled studies that utilized active surveillance methods to assess the reactogenicity of Ty21a in adults and children are shown in Table 5. The rates of adverse reactions in the vaccine recipients were not significantly higher than those for the placebo group for any symptom or sign.

Table 9: Typhoid vaccine trials

Randomized, placebo-controlled, double-blind clinical trials of three doses of Ty21a in enteric-coated capsules, in milk with NaHCO₂, or in buffer suspension to assess reactogenicity of the vaccine in adults, school children and preschool-aged children (Levine, 1999)

Adverse reaction %	Adults, Chile		6 and 7-year-olds		All ages, Indonesia			
	Enteric-coated vaccine (385)*	Placebo (367)	Enteric-coated vaccine (172)	Placebo (172)	Enteric-coated vaccine (311)	Placebo (291)	Liquid suspension vaccine (333)	Placebo (255)
Diarrhoea	1.8	1.1	1.2	9.9	3.9	3.1	3.8	5.5
Vomiting	0.5	0.3	2.3	11.0	1.0	1.7	1.5	0.8
Fever 0.3	0.5	0.6	0.6	4.8	1.7	4.8	3.5	
Rash 0.5	0.5	ND	ND	1.0	0.3	1.2	0.4	

* total number of subjects
ND = Not determined

Data from Levine et al., 1986; Black et al., 1983; Simanjuntak et al., 1991)

In large-scale field trials with Ty 21a, involving 555 000 schoolchildren in Chile (Black et al., 1990), 32 000 in Egypt (Wahdan et al., 1980) and 20 000 subjects ranging from three years to adulthood in Indonesia (Simanjuntak et al., 1991), passive surveillance failed to identify vaccine-related adverse reactions.

ViCPS

In several trials, ViCPS produced fever (occurring in 0– 1% of vaccinees), headache (1.5– 3% of vaccinees), and erythema or induration >1 cm (7% of vaccinees) (Klugman et al., 1987; Cumberland et al., 1993; Keitel et al., 1994). In the study conducted in Nepal, the ViCPS vaccine produced fewer local and systemic reactions than did the control (the 23-valent pneumococcal vaccine) (Acharya et al., 1987). Among school children in South Africa, ViCPS produced less erythema and induration than did the control bivalent meningococcal vaccine (Klugman et al., 1987). In a direct comparison, ViCPS produced reactions less than half as frequently as parenteral inactivated vaccine, probably because ViCPS contains negligible amounts of bacterial lipopolysaccharide (Cumberland et al., 1993).

Parenteral inactivated vaccines

Parenteral inactivated vaccines produce several systemic and local adverse reactions, including fever (occurring in 6.7–29% of vaccinees), headache (9–10% of vaccinees) and severe local pain and/or swelling (3–35% of vaccinees). 21–23% of vaccinees missed work or school because of adverse reactions (WHO, 1964; Aschcroft et al., 1964; Hejfec et al., 1966; Levine, 1999). Table 10 summarizes the common adverse reactions of the current typhoid fever vaccines.

Table 10: Common adverse reactions of typhoid fever vaccines

Vaccine	Reactions		
	Fever	Headache	Local reactions
Ty21a	0– 5%	0– 5%	Not applicable
Vi CPS	0– 1%	1.5– 3%	Erythema or induration >1 cm: 7%
Parenteral inactivated	6.7– 24%	9– 10%	Severe local pain or swelling: 3– 35%

Source: CDC, 1994

Severe adverse events

Hypotension, chest pain and shock, have been reported sporadically after administration of parenteral typhoid inactivated vaccines (CDC, 1994). Rarely, more significant reactions have been attributed to this vaccine. These include thrombocytopenic purpura, acute renal disease, dermatomyositis, appendicitis, erythema nodosum, multiple sclerosis, and a syndrome of high fever, severe malaise and toxæmia. There is also a report of sudden unexpected death after typhoid–cholera vaccination (Pounder, 1984). No serious adverse event has ever been reported with the Ty21a, nor with the Vi CPS.

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19. Adverse events following varicella vaccine

The vaccine

The varicella vaccine is composed of the Oka strain of live attenuated varicella-zoster virus (VZV). The Oka strain was isolated in Japan from a healthy child with natural varicella, and was attenuated through sequential propagation in cultures of human embryonic lung cells, embryonic guinea-pig cells and human diploid cells (WI-38). The virus underwent further passages through human diploid-cell cultures (MCR-5) for one of the available vaccine. Varicella virus vaccine is lyophilized and, when reconstituted, the vaccine contains >1350 plaque forming units (PFUs) of Oka VZV in 0.5 ml. Each 0.5 mL dose also contains 12.5 mg of hydrolyzed gelatin, trace amounts of neomycin and fetal bovine serum, 25 mg of sucrose, and traces residual components of MRC-5 cells (including DNA and protein). The vaccine does not contain preservatives (CDC, 1996).

Mild adverse events

Varicella vaccine has been well tolerated when administered to more than 11 000 healthy children, adolescents and adults during clinical trials. Inadvertent vaccination of persons immune to varicella has not resulted in an increase in adverse events. In a double-blind placebo-controlled study of 914 healthy, susceptible children and adolescents (Kuter et al., 1991), pain and redness at the site were the only adverse events that occurred significantly more often ($p < 0.05$) in vaccine recipients than in placebo recipients.

In children aged 12 months to 12 years, uncontrolled clinical trials of approximately 8900 healthy children who were administered one dose of vaccine and then monitored for up to 42 days, 14.7% develop fever (oral temperature $\geq 39^{\circ}\text{C}$), usually associated with intercurrent illness. A total of 19.3% of vaccine recipients had complaints regarding the injection site (e.g. pain/soreness, swelling, erythema, rash pruritus, haematoma, induration and stiffness). 3.4% had a mild, varicella-like rash at the injection site consisting of a median number of two lesions and occurring at a peak of 5–26 days post-vaccination. Febrile seizures following vaccination occurred in <0.1% of children; a causal relationship has not been established.

In persons ³13 years of age, uncontrolled studies of approximately 1600 vaccinees who received one dose and 955 who received two doses of varicella vaccine were monitored for 42 days for adverse events. After the first and the second dose, 10.2% and 9.5% of vaccinees, respectively, develop fever (e.g. oral temperature ³37.7°C), usually associated with an intercurrent illness. After one or two doses, 24.4% and 32.5% of vaccinees, respectively, had complaints regarding the injection site, (e.g. soreness, swelling, erythema, rash, pruritus, haematoma, pyrexia, induration and numbness). A varicella-like rash at the injection site consisting of a median number of two lesions and occurring at a peak of 6–20 days and 0–6 days post-vaccination developed in 3% and 1% of vaccinees, respectively. A non-localized rash, consisting of a median number of five lesions, developed at a peak of 7–21 days and 0–23 days in 5.5% and 0.9% of vaccinees, respectively. (CDC, 1996).

Data on potential adverse events are available from the Vaccine Adverse Event Reporting System. During March 1995–July 1998, a total of 9.7 million doses of varicella vaccine were distributed in the United States. During this time (CDC, 1999), VAERS received 6,580 reports of adverse events, 4% of them serious. Approximately two thirds of reports were for children aged < 10 years. The most frequently reported adverse event was rash (rate: 37/100 000 vaccine doses distributed). Polymerase chain reaction (PCR) analysis confirmed that most rash events occurring within 2 weeks of vaccination were caused by wild-type virus.

Serious adverse events

The post-licensure vaccine adverse events reporting system in the United States and vaccine manufacturer reports of serious adverse events, without regard to causality, have included encephalitis, ataxia, erythema multiforme, Stevens Johnson syndrome, pneumonia, thrombocytopenia, seizures, neuropathy, and herpes zoster. For serious adverse events for which background incidence data are known, VAERS reporting rates are lower than the rates expected after natural varicella or the background rates of diseases in the community. However, VAERS data are limited by under-reporting and unknown sensitivity of the reporting system, making it difficult to compare adverse event rates following vaccination reported to VAERS with those from complications following natural disease. Nevertheless, the magnitude of these differences makes it likely that serious adverse events following vaccination occur at a substantially lower rate than following natural disease. In rare cases, a causal relationship between the varicella vaccine and a serious adverse event has been confirmed (e.g. pneumonia in an immunocompromised child or herpes zoster). In some cases, wild-type VZV or other causal organisms have been identified. However, in most cases, data are insufficient to determine a causal association. Of the 14 deaths reported to VAERS, eight had other definite explanation for death, three had other plausible explanation for death, and three had insufficient information to determine causality. One death from natural varicella occurred in a child aged nine years who died from complications of wild-type VZV 20 months after vaccination.

Association with other vaccines

Introduction of varicella vaccination for public health use in young children would be facilitated if the live attenuated varicella vaccine could be combined with a measles–mumps–rubella (MMR) vaccine. The safety of two dose levels (5300 and 200 PFU) of varicella vaccine combined or not with standard MMR vaccine was studied. Single varicella vaccine at both titer levels was found safe, although 10% of the children had minor skin reactions, possibly attributable to the vaccine. Reactions typically associated with MMR vaccination did not significantly increase after the combined varicella plus MMR vaccination (Vesikari et al., 1991). The same safety was observed in combination of MMR–Varicella and Hib vaccines (Reuman et al., 1997), and even DPT Hib, MMR and Varicella vaccine (Shinefield et al., 1998).

Vaccination of HIV-positive persons

Varicella vaccine is not currently indicated for HIV-infected (Gershon et al., 1999) but studies are in progress to determine safety and possible indications (AAP, 1997).

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20. Adverse events following vitamin A supplementation

The vitamin

Vitamin A supplementation is recommended in countries where vitamin A deficiency (VAD) and xerophthalmia are a public health problem. In such situations, combining the administration of vitamin A with immunization services is a safe and effective strategy. Ideally, any programme linking vitamin A supplementation with immunization services should be part of an overall national plan for control of VAD that may include food fortification and dietary approaches.

Preparations of vitamin A can be supplied as retinyl palmitate, retinyl acetate or retinol, although retinyl palmitate is the form most widely available from commercial sources.¹ As long as the recommended dose is administered, the chemical form is not important. Typically,² these preparations are diluted with high quality vegetable oil, usually peanut oil, with vitamin E included as an antioxidant and to promote absorption and retention of vitamin A by the body.

When given as a prophylactic with immunization, high-dose³ vitamin A is usually presented in an oil-based solution (either in soft-gelatin capsules or liquid form) and given at a dosage and frequency according to age⁴:

- Children between 6–11 months: 100 000 IU orally, every 4–6 months;
- Children 12 months and older: 200 000 IU orally, every 4–6 months;
- Women within 6–8 weeks after delivery: 200 000 IU orally, *once* during safe infertile time

¹ Although the International Unit (IU) for vitamin A (which expresses biological activity and not chemical quantity) was officially discontinued in 1954, vitamin A preparations are still conveniently labelled in IU with equivalence in mg or µg of retinol or its esters also indicated. A dose of 200 000 is equivalent to 110 mg of retinyl palmitate, 69 mg of retinyl acetate or 60 mg of retinol.

² Compressed powder tablets also exist but are more rarely used.

³ For vitamin A supplementation “high dose” refers to amounts greater than 25 000 IU per dose.

⁴ Children < 6 months of age, non breast-fed or breast-fed infants whose mothers have not received supplement vitamin A within 6-8 weeks of delivery, 50 000 IU orally.

For administration with immunization services, the above are the currently recommended age-specific dosage guidelines. For children, one high-dose supplement is sufficient to fully increase their stores of vitamin A for a period of 4–6 months. Ideally, children at risk of VAD should receive supplements at least twice a year (i.e. every 4–6 months). Giving vitamin A more often is not necessary, however, it is safe and there are no risks *if a minimum interval of one month* between doses is observed.

The interval and frequency of dosage is different when vitamin A supplements are given to pregnant women or used for treatment of measles or xerophthalmia/clinical vitamin A deficiency, or integrated management of child illness (IMCI) (WHO/UNICEF/IVACG Task Force, 1997).

The administration of excessive amounts of vitamin A can lead to toxicity, known as hypervitaminosis A. The amount required to cause toxicity will vary among individuals. The manifestations of toxicity will depend on the individual's age and hepatic function and on the dose and duration of administration (Bauernfeind, 1980).

Worldwide, the incidence of vitamin A excess (hypervitaminosis A) is a very minor problem compared with the incidence and effects of vitamin A deficiency. An estimated 200 cases of hypervitaminosis A occur annually, an estimated 3 million individuals develop clinical vitamin A deficiency each year, 250 000–500 000 children become blind, and many more suffer an increased risk of mortality and morbidity (Bauernfeind, 1980; Beaton et al., 1994; Glasziou & Mackerras, 1993; WHO, 1995).

Mild adverse events

Side-effects or adverse events are rare when the correct age-specific dose of vitamin A is given with immunization. Occasionally, some children experience loose stools, headache, irritability, fever, nausea and vomiting. Depending on age and the dosage given, the excess rate of occurrence of these mild symptoms of intolerance has been shown to be in the range of 1.5–7% (Florentino et al., 1990; West et al., 1992; Agoestina et al., 1994). These transient side-effects disappear in practically all children within 24–48 hours (Florentino et al., 1990; West et al., 1992; Agoestina et al., 1994). Beneficial reactions following administration of vitamin A have also been reported by mothers and documented. These positive reactions included improved appetite, more sound sleep, and change in behaviour (children became more active and lively) (Florentino et al., 1990).

In neonates and young infants under the age of 6 months, vitamin A supplementation has been associated with an increased incidence of transient bulging fontanelle. This resolves itself within 24–72 hours (Florentino et al., 1990; West et al., 1992; Agoestina et al., 1994; Rahman et al., 1995; Baqui et al., 1995). Depending on age and dosage, the excess rate of occurrence has been found to be between 0.5–10% (West et al., 1992; Agoestina et al., 1994; de Francisco et al., 1993; WHO/CHD, 1998). Two studies have investigated the long-term developmental effects and found no long-term developmental abnormalities as a result (Agoestina et al., 1994; van Dillen & de Francisco, 1996). Although a definitive statement cannot be made, it has been postulated that while intracranial volume may increase to a small degree due to vitamin A supplementation, the compliance of the neonatal cranium is sufficient to prevent an increase in pressure (Agoestina et al., 1994).

Clinical toxicity resulting from overdose

Hypervitaminosis

This does not result from public health intervention programmes. Rather, toxicity has been associated with the abuse of vitamin A supplements and with diets extremely high in preformed vitamin A (i.e. foods of animal origin). Toxic reactions provoked by large doses of vitamin A are well-known to occur following either intake of liver rich in vitamin A (e.g. polar bear, halibut or whale) or by excessive administration of vitamin A preparations (Miller & Hayes, 1982). It is useful to differentiate between the acute vitamin A-intoxication caused by short-term ingestion of excessive amounts of vitamin A and the chronic hypervitaminosis resulting from long-term intake of more moderate vitamin A doses:

(i) **Acute vitamin A toxicity** (*single ingestion of 25 000 IU per kg or more*)

Signs and symptoms may be delayed for 8 to 24 hours and include irritability, drowsiness, dizziness, lethargy, nausea and vomiting, diarrhoea, erythema, pruritus, desquamation, headache and increased intracranial pressure (resulting in bulging of fontanelles in infants), diplopia, papilloedema. Peeling of skin around mouth may be observed from one to several days after ingestion and may spread to the rest of the body (Miller & Hayes, 1982; Bendich & Langseth, 1989; Hathcock et al., 1990; CPS, 1999; Parfitt, 1999).

(ii) **Chronic vitamin A toxicity** (*excessive ingestion of 4 000 IU/kg daily for 6 to 15 months*)

This may produce symptoms of fatigue, irritability, anorexia and loss of weight, vomiting and other gastro-intestinal disturbances, low-grade fever, hepatosplenomegaly, skin changes (yellowing, dryness, sensitivity to sunlight), alopecia cracking and bleeding lips, brittle nails, hair loss, anaemia, headache, hypercalcaemia, subcutaneous swelling, nocturia and pains in the bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, tinnitus, visual disturbances which may be severe blindness, and painful swelling of the long bones. Increased plasma concentrations of vitamin A occur but do not necessarily correlate with toxicity (Miller & Hayes, 1982; Bendich & Langseth, 1989; Hathcock et al., 1990; CPS, 1999; Parfitt, 1999).

Harmful effects during pregnancy

Excessive or high-dose vitamin A should be avoided during pregnancy because of potential teratogenic effects to the fetus (birth abnormalities or birth defects). Where vitamin A deficiency is endemic, current recommendations advise that the safe vitamin A supplementation of pregnant women should not exceed 10 000 IU per day, or 25 000 IU per week (WHO, 1998). During the safe infertile period 6–8 weeks post-partum, depending on breast feeding status, it is safe to give women one high-dose supplement of vitamin A. This raises the content of vitamin A in the breast milk and benefits the breast feeding infant under the age of 6 months.

Prevention

Avoid overdoses by following the recommended age-specific dosage schedule as appropriate for prevention or treatment.

Treatment

For an acute overdose, empty stomach and follow with activated charcoal and a cathartic. Treat symptomatically. For chronic ingestion, discontinue vitamin A. Toxicity is slowly reversible but may persist for several weeks.

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21. Adverse events following yellow fever vaccine

The vaccine

The only yellow fever vaccine available in the world is the live-attenuated 17D virus strain. The vaccine is recommended for use from six months of age. Each dose contains at least 1000 LD 50 (lethal dose for mouse, or equivalent in PFU – plaque forming units).

Mild adverse events

Over 300 million people have been immunized, with a remarkable record of tolerability and safety. Reactogenicity of 17D vaccine was monitored in 10 clinical trials conducted between 1953 and 1994 (Kouwenaar, 1953; Tauraso et al., 1972; Tauraso et al., 1972; Freestone et al., 1977; Moss-Blundell et al., 1981; Roche et al., 1986; Lhuillier et al., 1989; Mouchon et al., 1990; Soula et al., 1991; Ambrosh et al., 1994). Self-limited and mild local reactions (headache, headache and fever, and fever without symptoms) occurred in a minority of subjects five to seven days after immunization. The lack of placebo controls in all published reports makes interpretation of data on adverse events unreliable, although the lower incidence of adverse events in previously vaccinated subjects in one study suggests that these events are real. Reactogenicity in infants is no greater and may even be less than in adults; this conclusion was also made during the early studies in Brazil in 1937 to 1938. In subjects under daily surveillance, a higher frequency of adverse events was detected; headache in 10% and reactions of any type in 30%. On 370 travellers followed by a telephone survey, 25% of the vaccinees reported one or more reactions, generally mild, characterized by systemic flu-like symptoms (22%) or local reaction (5%, typically pain) (Pivetaud et al., 1986).

Severe adverse events

Post-vaccination encephalitis

The 17D vaccine retains a degree of neurovirulence as demonstrated by intracerebral inoculation of mice and monkeys and by the occurrence of rare cases of post-vaccination encephalitis in humans. These cases have occurred principally, but not exclusively, in very young infants. From 1952 to 1960, 15 cases occurred when there was no age restriction on the use of vaccine in infants. Of the 15 cases, 13 (87%) occurred in infants younger than four months and all were seven months of age or younger. The incidence of post-vaccination encephalitis in very young infants may be estimated at 0.5 to 4 per 1000, based on the two reports that provide denominator data. In contrast, the risk of developing encephalitis in people older

than nine months of age (the current minimum age recommended for routine immunization) is extremely low. Only three such cases have been reported among travellers. Surveillance for adverse events has been passive and insensitive. Further studies in large-scale campaigns are needed to clarify the risk of encephalitis following 17D vaccine.

Two deaths were recently reported from Brazil following yellow fever vaccine, the significance of which is not yet clear. There had been no genetic mutation to virulence (Silva 2000).

Immediate allergy reactions to egg proteins

Current yellow fever vaccines contain egg proteins and on rare occasions may induce immediate allergic reactions, including anaphylaxis. Vaccination of 242 people having allergic history were given 0.1 ml of 17D vaccine by intradermal route; if no reaction occurred within 45 minutes, they received the remaining 0.4 ml subcutaneously. Nine (3.7%) of the subjects experienced allergic reactions. Exacerbation occurred of known but dormant allergy – eczema, asthma, rhinitis - in four patients, urticaria in three patients, and “serum sickness-like disease” in three patients. In a control group of 465 persons without a history of allergy, only three had a late reaction to yellow fever vaccine (Kouvenaar, 1953).

More recent and definitive data on the incidence of allergic reactions are few, principally because a prior history of intolerance or allergy to eggs or to egg-based vaccines is considered a contraindication to the use of 17D vaccine. According to the preliminary assessment of data collected between 1990 and 1995 (CDC, 1990), the estimated incidence of allergic reactions is between 5 and 20 per million doses. Other components may also play a part in hypersensitivity to vaccine, for example hydrolyzed gelatin incorporated as a stabilizer by some manufacturers (Monath, 1999). Skin testing with yellow fever vaccine is recommended before administration to persons with a history of systemic anaphylactic symptoms (generalized urticaria, hypotension, and/or manifestations of upper or lower airway obstruction) after egg ingestion.

Vaccination of HIV-positive persons

Asymptomatic HIV infection is not considered a contraindication in the United States, but is in the United Kingdom. Preliminary studies indicate that asymptomatic HIV infection may reduce the immune response to 17D vaccine (Monath, 1999). The decision to immunize immuno-compromised patients is based on assessment of the patient’s risk of exposure and clinical status (AAP, 1997). WHO does not recommend vaccination of individuals symptomatic for HIV infection.

Vaccination of pregnant women

Pregnancy is a contraindication to administration of all live-virus vaccines, except when susceptibility and exposure are highly probable and the disease to be prevented poses a greater threat to the woman or fetus than does the vaccine. Yellow fever vaccine may be given to pregnant women who are at substantial risk of imminent exposure to infection.

Simultaneous administration

Yellow fever vaccine may be administered simultaneously with poliomyelitis vaccine (oral or inactivated). It can also be administered at the same time (but not from the same syringe) as injected vaccines such as measles vaccine, BCG (Gateff et al., 1973), DTP, hepatitis A and hepatitis B vaccines (Yvonnet B et al., 1986) without affecting the immunogenicity of these vaccines nor increasing vaccine reactions to each component. Several studies have shown that a combination of measles and yellow fever vaccines given in the same syringe at the same time resulted in the same antibody titers as when the vaccines were given separately, with no unforeseen adverse events (Lhuillier et al., 1989; Mouchon et al., 1990; Soula et al., 1991). However, WHO does not recommend reconstituting the two vaccines together as each vaccine must be reconstituted with the diluent provided. To do otherwise is to risk damaging the vaccine.

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