



The Vaccines

Monovalent vaccines:

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

More than ten live attenuated *mumps vaccine* strains (Jeryl Lynn, Urabe, Hoshino, 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 µg of neomycin per dose. Several manufacturers in Japan and Europe produce a 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 live attenuated *rubella vaccines* used throughout the world contain the RA 27/3 virus strain (Plotkin, 1965). Exceptions are vaccines produced in China (BRD2 virus strain) and Japan (Matsuba, Takahashi, and TO- 336), produced on rabbit kidney cells, and the Matsuura strain, 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-attenuated virus produces viraemia and pharyngeal excretion, but both are of low magnitude and are non-communicable (Plotkin & Orenstein, 1999).

Combination vaccines:

The most frequently used combination is the Measles, Mumps and Rubella vaccine (MMR); the MR vaccine is also used in few countries as well. More recently the MMR vaccine has been combined with the Varicella vaccine (MMRV).

Types of vaccines

Route	Vaccine antigens	Excipients
Monovalent		
Measles	Vaccine strains include; <ul style="list-style-type: none"> • Edmonston strain and • Non-Edmonston derived strains include Leningrad-16, Shanghai-191, CAM-70 and TD97 	Antibiotics (e.g. 25 µg of neomycin), Sorbitol and gelatin
Mumps	Vaccine strains include - Jeryl Lynn, Urabe, Hoshino, Leningrad-3, L-Zagreb, Miyahara, Torii, NK M-46, S-12 and RIT 4385.	Neomycin 25 µg of per dose.
Rubella	Most vaccines contain the RA 27/3 virus strain Japanese derived strains include - Matsuba, Takahashi, and TO- 336 China - BRD2	
Combination		
MMR	Various combinations of above strains in different vaccines	
MR	The vaccine is prepared from the live, attenuated strains of measles virus and RA 27/3 rubella virus.	
MMRV	Various combinations of above strains in different vaccines and the Oka strain of the Varicella Zoster virus	

Adverse events

Measles vaccines

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 which is generally mild, transient and resolves within 2-3 days.

Systemic reactions includes fever $>103^{\circ}/39.4^{\circ}\text{C}$ occurs in about 5 to 15% of vaccine recipients between the 7th to 12th day after vaccination and lasts approximately 1 to 2 days. In some cases, the fever may be coincidental, due to other infections. Measles vaccination also causes a rash to occur in approximately 2% - 5% of vaccines. The rash typically occurs 7–10 days after vaccination and lasts about 2 days.

Mild adverse events 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 (approximately 90%) will already be fully protected by the first dose, 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 thought to be extremely rare. The rate of anaphylaxis has been documented to be variable with a rate of 3.5 to 10 per million doses of following a measles-containing vaccine (Bohkle K et al 2003). This variability is accounted for the different case definitions used for anaphylaxis and the variable methods used for case ascertainment – such as passive or active surveillance. Recent studies indicate that anaphylactic reactions to measles vaccine are not caused by residual egg proteins but by other vaccine components. Case reports have shown that about one-half of 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 do not predict reaction to these vaccines which have been given safely to people with serious 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 a measles-containing vaccines.

Seizures:

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 3,000 doses). Other studies have found a seizure rate of 1 per 2,941 and 1 per 1,150 doses (Barlow WE et al 2001, Miller E et al 2007). 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). In pre-licensure studies for MMRV vaccines, fevers were transient and there was no difference in the incidence of febrile seizures. However in post licensure studies, there were significant differences. This is outlined in the MMRV vaccine section.

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, Rajantie J et al 2007, France EK et al 2008). 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. There is no increased risk of thrombocytopenia after the second MMR dose (Stowe J et al 2008).

Other vaccine safety issues

Encephalopathy/encephalitis

Natural measles virus infection causes post-infectious encephalomyelitis in approximately 1 per 1,000 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 1 per million doses, or about 1,000 times less than the risk from measles infection.

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). Vaccine strain measles virus has never been identified in patients with SSPE. Genetic sequencing of viruses obtained from the brains of patients with SSPE to date, including patients with no history of having had measles, has revealed only viruses of wild-type origin.

Guillain–Barré Syndrome (GBS)

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). Subsequently published studies have not found evidence of a causal association between vaccination and GBS (Hughes et al., 1996; Silveira et al., 1997).

Inflammatory bowel disease and autism

In recent years, some researchers hypothesized that measles vaccine may be associated with inflammatory bowel diseases (IBD), including Crohn's Disease (Ekobom et al., 1990; Wakefield et al., 1993; Ekobom et al., 1994; Thompson et al., 1995; Wakefield et al., 1995; Ekobom et al., 1996). One research group speculated that measles vaccine could be related to the development of IBD and autism (Wakefield et al., 1998). However, most of the authors rescinded their support for this manuscript and the journal has withdrawn the publication because of serious unreported conflicts of interest and evidence indicating that the primary data did not match the published results and conclusions (Deer publications in BMJ). Within the scientific community, major concerns were raised about the methodological limitations in these studies (Patriarca & Beeler, 1995; Farrington & Miller, 1995; MacDonald, 1995; Miller & Renton, 1995; Chen & DeStefano, 1998; Duclos & Ward, 1998). Several other studies demonstrated no support for these hypothesized associations (Liu et al., 1995; Iizuka et al., 1995; Feeney et al., 1997; Haga et al., 1996; Farrington P et al 2001, Taylor B et al 2002, Madsen KM et al 2002, Wilson K et al 2003, Smeeth L et al 2004, Honda H et al 2005, Uchiyama T et al 2007). The overall evidence clearly indicates no association of MMR vaccine with either inflammatory bowel disease or with developmental disorders including autism.

Mumps vaccines

Mild adverse events

Local 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, transient and resolve within 2-3 days.

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 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 1 case per million 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 Leningrad-3 strain 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 1.4 – 4.2 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).

Urabe strain. A study in Nottingham, UK, showed 9 cases of aseptic meningitis per 100 000 doses (Miller et al., 1993, Miller E et al 2007). 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).

Rubella vaccine

Mild adverse events

Local reactions are common, occur within 24 hours of vaccination, and are generally mild and transient.

Serious adverse events

Arthralgia, arthritis and arthropathy

Rubella vaccines, in adults, may be associated with acute joint symptoms. Transient joint pain develops in up to 25% of post-pubertal females (Freestone et al., 1971). Arthritis (RA 27/3) accounts for only 12% of these cases. Symptoms typically begin 1-3 weeks after vaccination and last one day to three weeks. In a randomised placebo-controlled, double-blind study of rubella vaccination in sero-negative women there was a significantly higher incidence ($p = 0.006$; odds ratio = 1.73 [95% CI = 1.17-2.57]) of acute joint manifestations in rubella-vaccine recipients ($n=270$) compared with placebo recipients ($n=276$) (Tingle et al 1997).

The association between rubella vaccination and chronic arthritis is less clear. Most recently published research, has shown no increased risk of chronic arthropathies among women receiving RA27/3 rubella vaccine and do not support the conclusion of the IOM (Slater et al., 1995; Frenkel et al., 1996; Ray et al., 1997). These studies have included a large retrospective cohort analysis which showed no evidence of any increased risk of new onset chronic arthropathies and a double-blind historical cohort study. One randomised placebo-controlled, double-blind study of rubella vaccination in sero-negative women demonstrated that the frequency of chronic (recurrent) arthralgia or arthritis was marginally increased (1.58 [1.01-2.45], $p = 0.042$) (Tingle et al., 1997). In 2011, the United States Institute of Medicine (IOM) reviewed available research and concluded that the evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthralgia in women.

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. Studies on administration of rubella vaccine unknowingly during pregnancy in 6 countries showed an absence of risk of CRS associated with administering rubella vaccine shortly before or during pregnancy (Castillo-Solórzano et al).

Serious adverse events

The IOM review concluded that the evidence favours acceptance of a causal relationship between MMR vaccine and transient arthralgia in children with a moderate degree of confidence based on the epidemiologic evidence and the evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthropathy in children.

Other safety issues

Pregnancy

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. No cases of CRS have been reported in 2,894 susceptible women who were unknowingly pregnant and received a rubella vaccine in early pregnancy (Carlos Castillo - Solorzano 2011). 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). Although the observed risk has been zero, 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.

Combination vaccines – measles, mumps, rubella (MMR) vaccines

In many countries, children typically receive a combination vaccine that contains the measles, mumps and rubella antigens (MMR) or measles and rubella (MR) antigens. The combination vaccine produces an immunological response equal to that of the single antigens. The adverse effects are equal to the rates of adverse events associated with the single antigens.

Mild adverse events

When combination vaccines (MR or MMR) are used, mild reactions are similar to those described with the single antigens. The use of MR can result in mild lymphadenopathy, urticaria, rash, malaise, sore throat, fever, headache, arthralgia and arthritis.

Severe adverse events

The type and rate of serious adverse events do not differ significantly for the MMR or MR combinations compared with the individual antigens.

Combination vaccines – measles, mumps, rubella, varicella (MMRV) vaccines

Mild adverse events

Compared with MMR and Varicella vaccines administered separately the MMRV vaccine is more likely to result in transient fever (temperature ≥ 38.9 degrees C) between 0 and 42 days following vaccination (39.1% versus 33.1%, $P = 0.001$ among children 12 to 23 months of age). The incidence of adverse experiences following a second dose of MMRV was lower than that following the initial dose (Kuter BJ et al 2006).

Serious adverse events

Febrile seizures

In pre-licensure studies, (with smaller sample size) rates of fever (temperature $\geq 38.9^{\circ}\text{C}$ oral equivalent or tactile) were greater in recipients of MMRV than in recipients of MMR + V (39.1% versus 33.1%, $P = 0.001$). Fevers were transient and there was no difference in the incidence of febrile seizures. (Lieberman JM et al 2006, Kuter BJ et al 2006).

Post-licensure surveillance studies, using the Vaccine Safety Datalink and company initiated studies (Merck), have documented a rate of febrile seizure after MMRV which is higher than the rate after MMR vaccine.

Serious adverse events

The final results of the two post-licensure studies indicated that among children aged 12–23 months, one additional febrile seizure occurred 5–12 days after vaccination per 2,300–2,600 children who had received the first dose of MMRV vaccine compared with children who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit. The Vaccine Safety Datalink study among 12–23 month old showed that 7–10 days after vaccination, the rate of febrile seizures was 8.5 per 10,000 vaccinations among MMRV vaccine recipients and 4.2 per 10,000 vaccinations among those who received MMR vaccine and varicella vaccine (MMR &V) at the same visit. The company initiated study among 12–60 months old (99% of whom were aged 12–23 months) showed that 5–12 days after vaccination, the rate of febrile seizures was 7.0 per 10,000 vaccinations (MMRV) and 3.2 per 10,000 vaccinations (MMR &V) respectively.

Data from post-licensure studies do not suggest that children aged 4–6 years who received the second dose of MMRV vaccine had an increased risk for febrile seizures after vaccination compared with children the same age who received MMR vaccine and varicella vaccine administered as separate injections at the same visit.

Other safety issues in combination vaccines

Immunocompromised including HIV - 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 seriously immunocompromised individuals to vaccine-associated measles infection (Stratton et al., 1994; CDC, 1996) but there are no data on mumps or rubella vaccine associated infection. Rubella vaccines should not be given to persons suffering from severe immunodeficiency, including advanced HIV infection and AIDS, congenital immune disorders, malignancies and aggressive immunosuppressive therapy. Thus, vaccines containing measles, mumps or rubella antigens pose a theoretical threat to seriously immunocompromised individuals. MMRV vaccine has not been tested in any immunocompromised populations and should not be substituted for MMR vaccine in any of these populations including HIV+ persons.

In developing countries screening for HIV status and the degree of immunodeficiency is seldom possible. Immunization policy must find a balance between the remote risk of enhanced replication following immunisation and the known high risk of death or serious complications in the event that an HIV-infected individual should contract measles infection. Current recommendations are to immunise asymptomatic HIV infected children and adults with a measles containing vaccine and to consider immunisation for those HIV infected symptomatic individuals who do not have serious immunosuppression according to standard definitions (anonymous 1999, WER 2004).

Table 2: Summary of mild and serious adverse events after Measles, Mumps and Rubella vaccines

	Description	Rate/doses
Measles		
Mild	Injection site reactions Systemic reactions Fever Rash	17-30 per 100 5 - 10 per 100 5 per 100
Serious	Encephalomyelitis Thrombocytopenia Anaphylaxis Febrile Seizures	1 per 10 ⁶ 1 per 30 000 1-3.5 per 10 ⁶ 1 in 2000 to 3000
Mumps		
Mild	Injection site reactions Systemic reactions Parotid swelling (depending on strain)	17-30 per 100 1 to 2 per 100
Serious	Aseptic meningitis <ul style="list-style-type: none"> • Jeryl Lynn • Leningrad-3 • Leningrad-Zagreb • Urabe Orchitis, sensorineural deafness, acute myositis	1-10 per 10 ⁶ 200-1000 per 10 ⁶ 13-900 per 10 ⁶ 90-490 per 10 ⁶ Case reports
Rubella		
Mild	Injection site reactions Systemic reactions Fever Acute arthralgia	17-30 per 100 2 per 100 25 per 100
Serious	Acute arthritis	10%

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