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International Journal of Vaccines and Vaccination

Live Attenuated Measles Mumps and Rubella Vaccines: An Over View

Abstract

Vaccination against Measles, Mumps and Rubella (MMR) of children early in life is established worldwide, and recommended by international organisations such as WHO and UNICEF. Elimination of measles and congenital rubella remains of the major objectives of WHO-UNICEF, albeit the failed plans of eradication by the early 2000. Therefore, the demand for safe and immunogenic MMR vaccines remains of a high priority in the next decade, both in affluent and less affluent countries. MMR vaccine has a documented history of safety and efficacy irrespective of the conflicting reports on the side effects, which was shown unrelated to the vaccination itself. Therefore, MMR vaccine remains the highest saviour of lives worldwide. The use of MMR or the recently developed MMR-V (Varicella) vaccine combination benefited from the established clinical surveillance, efficient-technology transfer and proper manufacturing, in addition to the cost effectiveness of these vaccines.

Keywords: Measles; Mumps; Rubella; Varicella; MR; MMR; MMRV; Vaccines; Vaccination

Review Article

Volume 1 Issue 1 - 2015

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Received: June 16, 2015 | **Published:** July 07, 2015

Abbreviations: MMR: Measles, Mumps and Rubella; WHO: World Health Organization; SSPE: Subacute Sclerosing Panencephalitis; PAHO: Pan American Health Organization; CRS: Congenital Rubella Syndrome; MR: Measles-Rubella; GSK: GlaxoSmithKline; EZ: Edmonston Zagreb; CEF: Chicken Embryo Fibroblast; IBD: Inflammatory Bowel Disease; CDC: Centers for Disease Control and Prevention; SSPE: Subacute Sclerosing Panencephalitis

Introduction

The Global eradication of small pox encouraged other mass vaccination campaigns to take place to eradicate other diseases, like poliomyelitis and measles. Poliomyelitis was readily eliminated from the American continent and its programmed eradication worldwide is steadily progressing. Measles elimination campaigns were implemented yet the eradication was difficult and thus the deadline to its elimination is now set for the year 2020. Currently vaccination programs remain the major means of protection from the sequel of wild-type virus infections and to reduce the rates of mortalities worldwide especially children in developing countries.

Industrialized countries experienced measles epidemics despite a fair vaccination coverage. With the advent of the trivalent measles-mumps-rubella (MMR) vaccine many developed countries adapted this type of vaccination in their programs. An extremely thorough approach for immunization allows containment of epidemics towards eradication of the disease. A documented experience in Finland and Sweden shows that with two dose vaccination campaign, in the early 80s, allowed Finland to claim elimination of "indigenous MMR" in 1994 [1] demonstrating that with rigorous approach, including a 2 dose schedule and high coverage (97% or more) the target of elimination of MMR was achievable. Anglo-Saxon and some other countries do now recommend a two dose MMR vaccination (e.g. USA 1st dose at 12-15 months, 2nd dose at 4-5 years or at 11-12 years) [2]. The occurrence of serious meningitis due to insufficiently attenuated mumps vaccine strains complicated the trivalent MMR approach in the 90s [3]. However, with the use of a more reliable mumps strains and the development of others (Table 1) boosted the further usage of MMR vaccine. Many countries, however, implement own vaccination policies and recommendations. Nevertheless, the perception of post-vaccination side-effects haunted this field for some time and had a negative effect on the public views concerning vaccines and vaccination, whose echo persisted even with the solid safety reports that assured the effectiveness of the vaccines.

Non-industrialized countries experienced yet another problem. Measles infection strikes there at an earlier age (usually in the first year of life) than in industrialized nations (from second year of life onward). The differences are explained by the fact that the fading of the maternal (protective) antibodies that usually occur 6-9 months and the presence of the "circulating" infectious agent, measles virus, in the neighbourhood allow an earlier infection and progression of the disease. Monovalent measles immunization in such countries is recommended at approximately 9-12 months followed by the trivalent MMR or Bivalent MR vaccines [4,5].

An overview of the benefits versus risks and the concerns raised against vaccination with live attenuated viral vaccines are summarized.

Table 1: Licensed MMR vaccine formulations excluding the local vaccines of Japan, Russia and China.

Tradename	Manufacturer	Measles Strain	Mumps Strain	Rubella Strain	Excipients
MMR II	Merck	Edmonston- Enders	Jeryl-Lynn	Wistar RA 27/3	Neomycin, HSA, gelatine
Priorix	GSK	Schwarz	RIT 4385 (Jeryl-Lynn derived)	Wistar RA 27/3	Neomycin, HSA
Morupar[1]	Chiron	Schwarz	Urabe AM9	Wistar RA 27/3	Neomycin, kanamycin
Trimovax	Aventis	Schwarz	Urabe AM9	Wistar RA 27/3	Antibiotics, HSA
Tresivac[2]	Serum Institute of India	Edmonston-Zagreb	Leningrad-Zagreb	Wistar RA 27/3	Not known
Triviraten[3]	Berna Biotech	Edmonston- Zagreb EZ-19*	Rubini	Wistar	HSA
MMR Berna[4]	Berna Biotech	Edmonston- Zagreb EZ-19*	S12 Razi-strain	Wistar RA 27/3	HSA, gelatine

Notes:

[1]Morupar was discontinued after the acquisition of Chiron.

[2-4]Vaccines that have all of the three components produced in HDC.

[2]The frequency of aseptic meningitis after the use of Tresivac has been reported makes this vaccine not marketable in Europe, where concerns of safety are the highest among parents.

*The measles vaccine originated from the Edmonston Zagreb seed 19, called later MVb (20).

HSA=Human Serum Albumin

Risks of Infection and Benefits of Vaccination

Measles is a highly contagious viral infection that affected almost every person by adolescence during the pre-vaccine era. Transmission occurs primarily by large respiratory droplets and contact. The disease is typically characterized by high fever, cough, runny nose and generalized maculopapular rash. Approximately 30% of Measles cases have one or more of the following complications: diarrhea, otitis media and pneumonia. Rare but fatal complications are acute encephalitis (0.1%) with onset of about a week after the appearance of rash, and subacute sclerosing panencephalitis (SSPE) with onset sometimes years after the acute disease [6]. SSPE occurs in 5 to 10 per million reported measles cases. Deaths caused by measles have been reported in 1-2 per 1,000 affected in the U.S. Prior to the introduction of measles vaccine 3,000 - 5,000 deaths occurred annually in the U.S. alone, primarily in children aged 2-5 years old. In developing countries, the rate of deaths was much higher. The most common causes of death are pneumonia in children and acute encephalitis in adults [7-9].

The global use of measles vaccines in infant immunization programs has led to a significant reduction in measles cases and deaths. Measles vaccination is recommended in the second year of life (12-15 months) in developed countries and at 9 months in developing countries. In developed countries a second dose is generally recommended before school entry (4-6 years) or during adolescence according to different national vaccination schemes [10]. This vaccination strategy has successfully eliminated endogenous measles in Finland, Denmark, and U.S. and is actively pursued by the Pan American Health Organization (PAHO) to eliminate measles from the Americas [11].

Mumps is a viral infection primarily affecting the salivary glands. Up to 20% of mumps infections are asymptomatic. Although mostly a mild childhood disease, mumps virus may also affect adults among whom complications are relatively common. Symptomatic meningitis occurs in up to 15% of patients and generally resolves without sequels. Encephalitis is rare occurring in <2 cases per 100,000 affected. Orchitis is the most common complication occurring in up to 20-50% of post pubertal males [12], where as Oophoritis occurs in only 5% of post pubertal females. In the pre-vaccine era deafness caused by mumps was the leading cause of deafness in childhood; with an incidence of 1 per 20,000 mumps cases [13,14]. Extensive use of mumps vaccines in industrialized countries has led to a significant decrease in the incidence of mumps. In order to achieve mumps control, large-scale vaccination is recommended in countries with an efficient childhood vaccination programs and sufficient resources to maintain high-level vaccination coverage. In these countries the combination of Mumps with Measles and Rubella vaccines (MMR) is recommended [14,15].

Rubella occurs worldwide and is normally a mild childhood disease. Complications are rarely seen in children and mainly affect adults. Arthritis occurs in up to 70% of adult women contracting rubella. Encephalitis occurs in 1 per 5,000 cases in adult females, and hemorrhagic manifestation

(thrombocytopenic purpura being the most common) may occur in 1 per 3,000 cases. Most importantly, rubella virus infection in early pregnancy (<12 weeks of gestation) leads to fetal infection in an astounding 90% of the cases; resulting in fetal death (25%) or Congenital Rubella Syndrome (CRS, 75%). CRS can be characterized by deafness, cataracts, congenital heart anomaly, microcephaly, mental retardation and bone spleen and liver alterations. Prior to the introduction of the rubella vaccine, thousands of CRS cases occurred annually in the U.S. alone. Vaccination against rubella is aiming at the control of rubella and elimination of CRS; rubella vaccination in large-scale programs has led to the disappearance of CRS in many countries [15]. Most industrialized countries and most countries in the region of the Americas include the rubella vaccine in their national immunization programs, usually as combined Measles-Mumps-Rubella (MMR) or Measles-Rubella (MR) vaccines. Some countries conduct selective immunization of adolescent females with rubella-containing vaccines.

Trivalent MMR Vaccines and Beyond

The MMR vaccine is a mixture of live attenuated measles, mumps and rubella vaccine viruses and administered by a single injection. It was first developed by Maurice Hilleman while at Merck [16]. The monovalent vaccines to prevent measles, mumps and rubella became available in 1963 then 1968, for measles, then in 1967 and 1969 for mumps and rubella respectively. The three vaccines were combined in 1971 to generate the MMR vaccine.

Two vaccination doses are recommended at the age of one year, and the second at the age of 4-5 years (before school). MMR is widely used around the world; since introduction of its earliest versions in the 1970s. More than 500 million doses have been used worldwide. Currently only few vaccine manufacturers are marketing this combination, MMRII by Merck Priorix by GlaxoSmithKline (GSK), Tresivac by Serum Institute of India and Trimovax by Sanofi Pasteur (Table 1). Although MMR is usually considered a childhood vaccination, it is also recommended for use in some cases of adults with HIV [17].

Components of the MMR Vaccines

Different strains of the measles and mumps vaccine-viruses and one strain of rubella vaccine are used in the formulation of MMR vaccine (Table 1). Whereas most of the current measles vaccines originated from the Edmonston strain, developed by Enders and Peeples in the early 60s (excluding the Leningrad strain), the mumps vaccines originated from various isolates and were developed and attenuated separately, leading to a variable stability, efficacy and protection.

An overview of registered MMR vaccines is shown in Table 1. MMR Vaccine Berna, in the last row, contained the new mumps strain (S12) that replaced the Rubini strain, and has been shown to induce strong seroconversion and immune response without serious side effects, which was comparable to Jeryl-Lynn strain (Not shown). This product did not proceed to registration.

Measles vaccines

The vaccine is generally safe even to those with HIV infections. Side effects are usually mild and short lived, which includes pain at the site of injection and mild fever [18]. Anaphylaxis has been documented in about one per hundred thousand people. Rates of Guillian-Barre syndrome, autism and inflammatory bowel disease do not appear to be increased [18]. Attenuated Measles virus vaccines diverged from the Edmonston seed upon serial cell culture passages on different mammalian or avian cell lines, among those are the Edmonston Zagreb (EZ), Schwarz, AIK-C, MVb (derived from EZ) and Moraten [19]. All of the vaccine strains have a long record of safety, tolerability and efficacy as injectable vaccines. Additionally, the EZ and MVb strains were used successfully and safely as aerosol vaccines [20,21]. This is likely because this type of vaccines is propagated on HDCs resulting with a product that is devoid of avian contaminants.

Mumps vaccines

The mumps vaccines are safe and side effects are generally mild [22-24]. It may cause mild pain and swelling at the site of injection and mild fever. More significant side effects are rare. Evidence is insufficient to link the vaccine with complications such as neurological effects [23]. The vaccine should not be given to people who are pregnant or have severe immunosuppression [22]. Even though the vaccine is developed in chicken cells, it is given to those with egg allergies [23].

Components of the MMR vaccines consisted of either one of the mumps strains:

I. Jeryl-Lynn strain vaccine is the Merck brand [24]and is the mumps vaccine standard in the United States. The Jeryl-Lynn strain has been in use since 1967, and was believed to be a single strain until 2002. Upon the cloning and sequencing of the mumps cDNA Jeryl-Lynn was found to be a mix of two strains [25].

II. Studies in the industrialized countries demonstrated that a single dose immunization with the Jeryl-Lynn vaccine results in seroconversion rates of approximately 80-100%. Outbreak-based studies from the United States have demonstrated that the effectiveness of the Jeryl-Lynn vaccine against clinical mumps ranges from 63% to 96% [26].

III. RIT 4385 is a newer strain derived from the Jeryl-Lynn strain [27]and was invented by Maurice Hilleman. Comparative studies of the RIT 4385 and Jeryl-Lynn vaccines showed similar seroconversion rates (96% for RIT 4385 and 97% for Jeryl-Lynn). Since no controlled clinical trials of efficacy have been conducted to compare the two vaccines, the clinical significance of this observation is not known [27].

IV. Leningrad-3 strain was developed by Smrodintsev and Klyachko in guinea pig kidney cell culture and further passaged in Japanese quail embryonic culture. It has been used in former Soviet Union, since 1980 in the national immunization program [26,28]. The Leningrad-3 vaccine strain has achieved seroconversion rates of 89-98% in children aged 1-7 years and protective efficacy ranged from 92% to 99%. Furthermore, a trial involving 113'967 children aged 1-12 years demonstrated a protective effectiveness of 97% when used as urgent prophylaxis during mumps outbreak.

V. L-Zagreb strain used in Croatia and India was derived from the Leningrad-3 strain by further passaging on chicken embryo fibroblast (CEF) cell culture [26,28]. Studies of Leningrad-Zagreb in Croatia have demonstrated clinical protection equivalent to that of the Leningrad-3 strain.

VI. Urabe strain was introduced in Japan, and later licensed in Belgium, France and Italy [26]. It has been associated with a higher incidence of meningitis (1/143'000 versus 1/227'000 for Jeryl-Lynn) [28] and abandoned in several countries. It was formulated in the MMR in United Kingdom.

VII. Rubini strain was developed and used mainly in Switzerland as of 1985. This strain was attenuated by a higher number of passages on CEF cell culture then on HDC. A number of studies demonstrated substantially lower rates of seroconversion and effectiveness than the Jeryl-Lynn and Urabe AM9. Based on these data, WHO recommended that the Rubini strain vaccine NOT be used in national immunization programs [26,29]. A replacement for the Rubini with a more potent vaccine strain was progressing by the same producer however, this effort was discontinued immaturely.

VIII. S79 mumps strain have been manufactured and administered to more than 100 million individuals in China. The other attenuated mumps virus strains that are used on a limited scale include the Hoshino, Torii, Miyahara, and NKM-46 strains. S79 was reported to possess similar immunologic properties as the Urabe Am9 strain [26]. However, controlled clinical trial of efficacy has not been conducted to compare the two vaccines, the clinical significance of this observation is not clear.

Rubella vaccine

Most of the licensed rubella vaccines used worldwide is based on the live attenuated Wistar RA27/3 strain that is propagated in HDC. Other attenuated rubella vaccine strains used primarily in Japan and China are the Takahashi, Matsuura, TO-336 strains and the BRD-2 strain respectively. Rubella vaccines are available either as monovalent formulations or in combinations with measles (MR), measles and mumps (MMR), or measles, mumps and varicella (MMR-V) [30]. Each dose contains a defined number of infectious units [31]. The immunization program using the rubella vaccine has been quite successful. Cuba declared the disease eliminated in the 1990s, and Centers for Disease Control and Prevention (CDC) announced that both the congenital and acquired forms of rubella had been eliminated from the United States in 2004.

Vaccine safety and adverse effects

Generally, the adverse reactions following vaccination with MMR vaccine, whether monovalent (single vaccines) or in fixed combinations (MR or MMR) include pain, redness and induration at the site of injection. Low-grade fever and rash, irritability, lymphadenopathy, myalgia and paresthesia are commonly reported.

As part of the strategy to eliminate rubella and CRS in the Region of the Americas, >250 million adolescents and adults were vaccinated in mass campaigns with MR. Vaccine-safety surveillance conducted in those countries did not identify any serious measles or rubella vaccines associated adverse reactions or chronic disease [32,33]. Thrombocytopenia has been reported in 1/30'000 vaccinees (as compared with 1/3000 cases in wild rubella disease).

The number of reports on neurological disorders is very small. An evidence for an association between a form of the MMR vaccine that contains the Urabe mumps strain and the rare adverse events of aseptic meningitis, a transient mild form of viral meningitis, had been suspected [34,35]. The UK National Health Service stopped using the Urabe mumps strain in the early 1990s due to cases of transient mild viral meningitis, and switched to a form using the Jeryl-Lynn mumps strain instead [36]. The Urabe strain remains in use in a number of countries; may be because the Urabe strain is easier to manufacture and that a strain with higher efficacy along with a somewhat higher rate of mild side effects may still be cost effective [36].

Exposure to MMR was unlikely to be causally associated with Crohn's disease or ulcerative colitis. In addition, no evidence has shown a causal relationship between autism and MMR [37]. This is due to the fact that autism is a complex disorder of uncertain and probably multiple etiologies. Genetic predisposition to autistic spectrum disorder (ASD) may involve as many as 10 genes and that the abnormal brain development in autism occurs before 30 weeks' gestation in most instances [38].

Measles, Mumps, Rubella and Varicella (MMR-V) Vaccines

The MMRV vaccine combines the live attenuated MMR vaccine with the chickenpox vaccine varicella (V) [39] and is given to children between 1 and 2 years of age, instead of the MMR vaccine.

MMR-V vaccines are supplied by Merck and GSK. The ProQuad (Merck) was approved in the US by FDA in 2005 for children ages twelve months through twelve years; Priorix Tetra (GSK) was approved in Germany and Australia. The rationale for implementing this combination in the U.S. and a few other countries was that MMR and varicella vaccines are given at roughly the same time and a booster injection is recommended for both. Thus, MMRV vaccine simplifies administration of the vaccines and is cost effective [39].

Adverse effects of MMR-V

Rare but serious adverse events reported following ProQuad vaccination including allergic reactions, swelling of the lips, tongue, or face; difficulty breathing or closing of the throat; hives; paleness; weakness; dizziness; a fast heart beat; deafness; long-term seizures, coma, or lowered consciousness; permanent brain damage; seizures (jerking or staring) caused by fever; or temporary low platelet count.

For children age two and younger, the MMR-V vaccine is associated with more adverse events compared to separate administration of MMR and varicella vaccinations on the same day [40]. There are 4.3 additional febrile seizures per 10,000

vaccinated children, 7.5 additional mostly mild fever episodes per 100 vaccinated children and 1.1 additional measles-like rashes per 100 children [41].

Conclusion

Although the possible association with MMR vaccine has received much public and political attention and there are many who have derived their own conclusions based on personal experiences, the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or inflammatory bowel disease (IBD). Separate administration of measles, mumps, and rubella vaccines to children provides no benefit over administration of the combination MMR vaccine and would result in delayed or missed immunizations.

Due to the urgent medical need for a further efficacious vaccine against MMR with negligible side effects, methods of manufacturing and formulations might require certain refinement to reduce the impurities from the preparation. The vaccines currently marketed in Europe that use measles and mumps components are grown on chicken-derived cell lines. These cells bear the theoretical risk of harboring avian derived retroviruses and showing reverse transcriptase (RT) activity. Additionally, these vaccines contain traces of avian proteins representing a theoretical risk to children with allergies against these compounds. A vaccine entirely produced with human diploid cells (HDC) technology should by definition be safe concerning these risks. More importantly, systemic (non-serious) Adverse Events, such as fever, occur in a significant number of recipients of the leading MMR vaccines. An MMR vaccine with equivalent efficacy, but an improved safety and tolerability profile, could provide tangible advantages to parents, doctors and health care policy makers.

Combining MMR and varicella (MMR-V) into a single vaccine increased risk of febrile seizures following MMR-V compared with MMR (+V) but the absolute level of risk was small [42]. The vaccine may have advantages for the following aspects:

(i) It allows a decreased pain for children (one injection instead of two or four),

(ii) Decreases distress for parents

(iii) Decreases cost and

(iv) Improves vaccination coverage. However, it might be advisable to counsel parents in advance regarding the expected transient side-effects and, perhaps, the policy-makers need to balance the potential risk-to-benefit of administering the combination vaccine and determine whether the vaccine remains to be the choice of clinicians and/or parents.

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Citation: Naim HY (2015) Live Attenuated Measles Mumps and Rubella Vaccines:An Over View. Int J Vaccines Vaccin 1(1): 00005. DOI: 10.15406/ijvv.2015.01.00005