



# Measles Vaccines in Iran: A 50-Year Review of Vaccine Development, Production and Effectiveness (1967 - 2017)

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## Abstract

**Context:** Information on the measles vaccine is important for future measles control policies. Vaccination history and laboratory confirmation during the development of the AIK measles vaccine in Iran is surveyed in this article. In addition, the production results and effectiveness of the Razi AIK-C/MRC-5 measles strain are compared with other vaccine strains.

**Evidence Acquisition:** The current study was carried out to aim local measles vaccine manufacturing and consequences of that in Iran, using various search engines. Almost complete search carried out in medical databases including PubMed, Scopus, Web of Science, Scientific Information Database, IranMedex, Magiran and Google Scholar.

**Results:** The morbidity rate of measles during the pre-vaccine era of this disease was 10,000 cases/year in 1970 - 1972. In 1997, the rate was 24 in 1000 cases. After using the high quality Razi measles vaccine between 1995 and 2013, the number of measles-positive cases declined to a maximum of 35 cases per year, while the country's population increased by more than 2.5 times. The median of the Razi measles vaccine efficacy (VE) was > 92.1% compared with that of the pre-vaccine era. For patients who received 2 doses of the measles vaccine at either 6 and 12 months or 9 and 18 months of age, the median VEs were > 90.0% (interquartile range [IQR], 83% - 97%) and 92.0% (IQR, 86% - 98%), respectively. The age at vaccination and strain type used in the vaccines are reviewed in this article.

**Conclusions:** The effectiveness of the local Razi measles vaccine resulted in a significant decline in measles mortality and morbidity in Iran. Two doses of the Razi measles (MR) or measles combination (MMR) vaccine provided excellent protection against measles. The seroprevalance of the measles vaccine in Iran revealed that more than 90% of Iranians are seropositive for the measles virus.

**Keywords:** Measles, Vaccine, Iran

## 1. Context

Measles is a common contagious disease can cause important public health problem worldwide. The ancient Iranian scientist, Mohammad Ibn Zakaria AlRazi, is the first who differentiated between smallpox and measles in the ninth century, AD (1). Measles is an infectious disease caused by an RNA virus from the genus *Morbillivirus* in the *Paramyxoviridae* family that easily spreads by air and causes severe clinical symptoms. It is characterized by high fever (up to 105°F), malaise, cough, coryza, and conjunctivitis (the three "C"s), and a pathognomonic exanthema (Koplik spots) followed by a maculopapular rash. The rash usually appears approximately 14 days after exposure; however, the incubation period ranges from 7 to 21 days. The rash spreads from the head to the torso and finally to the lower extremities. Patients are contagious from 4 days be-

fore to 4 days after the rash appears. Measles is caused by a single-stranded, enveloped RNA virus with 1 serotype. Humans are the natural host for the measles virus. Common complications include otitis media, bronchopneumonia, laryngotracheobronchitis, and diarrhoea. Measles can cause a serious illness requiring hospitalization (2).

One in 1,000 measles cases may develop sequelae such as encephalitis, which can result in constant brain damage. One to two in 1,000 children who become infected will die from measles complications. Subacute sclerosing panencephalitis (SSPE) is an uncommon delayed complication that results in a degenerative disease of the central nervous system (CNS) which characterized by intellectual deterioration that develops a few years after the measles infection. Subacute sclerosing panencephalitis incidence decreased significantly after the measles vaccine was developed (2). Isolation of the measles virus in 1954 by Enders

and Peebles led to the development of the first measles vaccines in the early 1960s (3), and in 1963, the Edmonston B strain was licensed in the United States. Two additional live attenuated measles vaccine were derived from the Edmonston strain: the Schwartz strain in 1965 and the Moraten strain in 1968. In 1973, the AIK-C strains (2, 3) became available for measles vaccine production. Three other attenuated measles vaccines used internationally are unrelated to the Edmonston strain and are produced from locally derived wild-type measles virus strains including the Leningrad-16 strain (Russian Federation), the Shanghai-191 strain (People's Republic of China), and CAM-70 (3) (Table 1).

## 2. Evidence Acquisition

The current study was carried out to aim measles vaccine manufacturing and consequences of that in Iran, using various search engines. Almost complete search conducted in medical databases including PubMed, Scopus, Web of Science, Scientific Information Database, Iran Medex, Magiran and Google Scholar.

## 3. Results

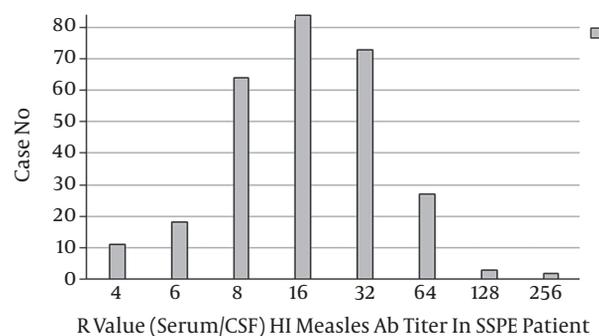
### 3.1. Measles Epidemiology, Pathogenicity and Complication in the Pre-Vaccination Era, Iran

In the period before the measles vaccine was licensed in 1963, an average of 150,000 - 500,000 measles cases and 10,000 measles deaths were reported in Iran annually. Although it is likely that most cases of measles were unreported, (4). In the early 1980s, the pre-vaccine era mortality rate from measles was 10 - 15%. Most of these cases were in children under 2 years old. Due to the lack of efficient and accessible health care services throughout Iran, many cases went unreported, and patients passed through the disease period at home. Before 1983, measles vaccination were not routine in the public health sector. Because of low socioeconomic status (SES) and poor health, particularly in low income families, disorders such as malnutrition and vitamin A deficiency led to the marked severity of measles in Iran and other developing countries (5).

The annually reported cases included progressive chronic disability from SSPE and acute encephalitis in many people with the disease. Measles strains were isolated and maintained by co-cultivation of infected brain cells with fresh Vero cells. The biological characteristics of the isolated strains showed that these strains remained cell-associated after repeated co-cultivations with Vero cells and that they produced plaques under fluid medium or traga-canth overlay (5). The data indicated the

existence of the viral (measles) antigen and antibody in the salivary glands of all SSPE patients in Iran. Unusual clinical and laboratory features among these patients were the occurrence of chorioretinitis in 25% and papilledema in 10% of the patients. The coexistence of cerebellar cystic astrocytoma with SSPE was described in one SSPE patient (6).

These complications had a relatively high incidence in Iran. The results of a 10-year study on SSPE found that more than 66.6% of 424 measles patients were 7 to 9-year old children who were diagnosed as SSPE-positive from just one hospital between 1975 and 1984 (Figure 1). The SSPE gender distribution was 76% male and 24% female (7).



**Figure 1.** Correlation of measles HI antibody titre of Serum and Cerebrospinal Fluid (CSF) [R Value (Serum / CSF)] in SSPE patients from one hospital during 1975 - 1984 in Iran

### 3.2. Available Vaccines and Vaccination Campaigns in Iran

The first measles vaccination was administered using three imported vaccines in 1967 (4). A comparative study of the clinical information for these vaccines indicated that there were more severe reactions from the attenuated measles vaccine than from the further attenuated vaccines and there was a high conversion rate for Edmonston B, Schwartz and Bikenham-31 vaccines in rural areas of Iran during the first measles immunization program. Two other measles vaccination strains, "Denken" and "Biken", were designed to evaluate clinical and serological reactions to explore the possibility of their large-scale use in Iran (8). Both vaccines resulted in serological responses showing that they were highly effective. However, rashes appeared in 26.5% of patients who received the Denken vaccine, compared with 8.7% of patients who received the Biken vaccine (8).

The first local production of the live attenuated measles vaccine began in 1967 at the Razi Institute using the Sugiyama strain, a Japanese measles strain adapted and attenuated with new-born calf kidney cells (CK) (9). In two separate field trials (10, 11) the vaccine was found

to be safe and highly immunogenic, inducing a seroconversion of approximately 95% in susceptible children. By the end of 1971, the number of vaccines in rural Iran was more than 3.5 million, which accounted for almost 37% of the susceptible age group (11). By the end of 1972, approximately 5 million children received this vaccine. This vaccine progressively decreased the incidence of measles and largely reduced infant mortality (12, 13). Another more attenuated strain, Sugiyama or 5F100, was cloned in AIPo4 and passaged in CK cells to use for the large-scale production of live measles vaccines (14). This new vaccine was more attenuated than the previous one. Because of its lower thermal reaction, short sporadic rash duration, and high level of protection with low production costs, it was largely produced in Razi and used in the mass immunization program. By the end of 1975, over 7.5 million children from 9 months to 5 years of age were vaccinated in Iran.

By the large-scale production and application of more than six million vaccines at the Razi institute, the measles epidemic and its associated paediatric problems were drastically reduced (11). From 1967 to 1976, the Razi institute produced more than 12,000,000 live attenuated lyophilized measles vaccines, using a highly attenuated Sugiyama strain, for mass vaccinations in south and west Iran. The vaccine's effectiveness on the measles epidemic conferred more than 50% immunity to more than 12,000,000 vaccinated children during this era (12). Although hyperattenuation of the Sugiyama strain provided a new and efficient vaccine in Iran, it was often impossible to determine if a resulting widespread rash was caused by the vaccine or a modified case of measles. Clinical reactions following inoculation with this vaccine were common, and some physicians were reluctant to continue using it. Therefore, Razi decided to change cellular substrate and viral strain.

### 3.3. Development of a New Measles Vaccine in Iran

The successful development of a measles vaccine using viral strains developed by Makino et al., in 1973 at the Kitasato Institute in Japan with cooperation of IRAN (Razi) (14) marked the beginning of research that made available the new live attenuated measles vaccine (MV), AIK-C. The strain was named AIK to represent the three countries that collaborated to develop it. The "A" represents America because the Edmonston strain became licensed in the United States as the first live isolate of measles virus (MV) in 1963. The "I" represents Iran for the Iranian researcher, Dr. Nazari's, idea to use sheep fibroblasts. Finally, the "K" represents the Kitasato Institute in Japan, where the viral strain was developed. This live attenuated vaccine became licensed for production in Japan. AIK-C was manufactured by being cultured, adapted and cloned in chicken

embryos derived from AIK, and it achieved excellent serological and epidemiological results in Japan when administered to children aged 8 months to 8 years (15).

#### 3.2.1. AIK-C/HDC: An Iranian Measles Vaccine Strain

Due to the development of the live attenuated measles vaccine by Enders and his colleagues in 1960 (1), Iran was among the countries that launched mass vaccination campaigns against measles in 1967. Razi was the only centre for production of the measles vaccine, but it had difficulty obtaining specific pathogen free (SPF) eggs because of sanction and the cost of importation of (SPF) eggs as well. This substrate was not readily available, and when eggs were imported, the cost per dose was prohibitive. Heterogeneity and viral contamination of the non-human primate cell cultures caused additional problems in producing the viral vaccine. There was an urgent need for production of large-scale viral vaccines that were readily available by establishing a "cell seed system".

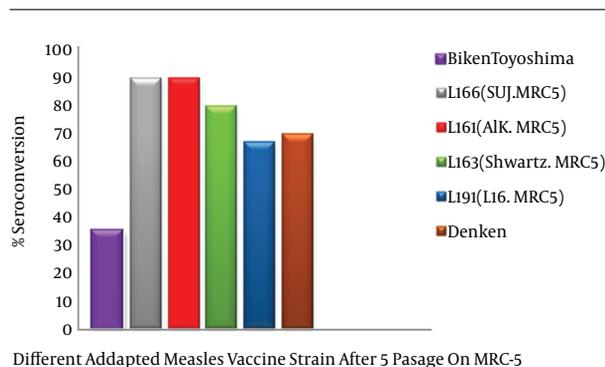
The stability and integrity of the human diploid cell strain, MRC-5, was established by Jacobs (16) and widely used as an alternative cell substrate for producing viral vaccines. This new cell system approach to producing the measles virus vaccine was widely accepted, and allowed for the safe and effective large-scale production of different human viral vaccines at Razi. Development of human diploid cell MRC-5 stock in 1960 was largely used to produce the Sabin polio vaccine (TOPV types I, II, III) by the Razi institute (17) and was essential for changing the cell substrate from CHEF to MRC-5 to develop the new measles vaccine strain. AIK-C was adapted to the human diploid cells (HDC), MRC-5, at the Razi Institute, and named AIK-C/HDC. This new measles strain was evaluated in a comparative field trial in which five different measles vaccine strains adapted to MRC-5 cell were tested (18).

#### 3.2.2. Production and Comparative Study of AIK-C/HDC (MRC-5) Measles Vaccine

After adapting the AIK-C to MRC-5, the results of the new vaccine were compared with four other experimental measles vaccines had been adopted and produced in human diploid cells, Biken-CAM, Leningrad-16, Schwarz, and Sugiyama SF100. The purpose of this experiment was to ensure that changing the cell substrate from chicken to human fibroblast HDCs did not affect the reactogenicity and immunogenicity of the new vaccine (AIK-C/MRC-5). The control viruses for this study was the Edmonston-Zagreb, adopted in human diploid cell (HDC) strain. In production and quality control of the measles vaccine, the safety, efficacy, neurovirulence, and genetic stability of the five measles vaccines were tested, based on WHO requirements (18). The neurovirulence in baby hamsters for all viruses

adapted to HDC were not significantly changed, and all attenuated and virulent viruses, both before and after adaptation to HDC/MRC-5, were virulent in the baby hamsters except the Sugiyama virus.

The neurovirulence of the Sugiyama virus was increased for the day-old baby hamsters after 5 passages in HDC, although they were not virulent before adaptation. The high neurovirulence of the Sugiyama strain may have been due to either the new host cell membrane coating the virus or an increase in the multiplication of the more virulent particles (12). The plaque size increased after 20 passages in the MRC-5 cells for all viruses except the AIK-C strain. This indicated that the AIK-C measles vaccine strain was stable and homogenous. The vaccines were evaluated in a field trial using seronegative children in Iran (18, 19). The lowest clinical reactions to the AIK-C vaccine were compared to those of 5 other measles vaccine strains. The seroconversion was high for all vaccines, ranging between 95.5 and 100%, and the hemagglutination inhibiting (HI) antibody titre in the recipients' sera ranged from 25.2 to 26.5 (Figure 2) (19). The comparative field trial results for the five vaccines produced in the human diploid cells, MRC-5, showed that those produced on the HDC substrate had a higher capacity for growth and replication in the human body and showed more immunogenicity than those produced on the other cell substrates (Figure 2) (20).



**Figure 2.** Comparative seroconversion between different measles vaccine strains after adaptation (5 passages) on human diploid lung cell strains (MRC-5)

These findings were confirmed by further investigation and epidemiological studies, which indicated that administering AIK-C may be more effective than the other measles vaccine strains. Tidjani surveyed the serological effects of the Edmonston-Zagreb, Schwarz, and AIK-C measles vaccine strains in children at ages 4 - 5 months or 8 - 10 months (21). The detailed results of this seroepidemiological study showed that high-dose Edmonston-Zagreb strains at 4 - 5 months of age is at least as effective as vaccinations with the standard strains at 8 - 10 months.

The 55% of cases who were negative before vaccination at age 4 - 5 months, seroconversion rates were 96% with the AIK-C, 94% with the Edmonston-Zagreb, and 50% with the high-dose Schwarz vaccines. The children who were seropositive before the vaccination were estimated to be approximately 50% with the high-dose Edmonston-Zagreb and AIK-C strains and 10% with the Schwarz strain. Seroconversion rates for the vaccination at 8-10 months were 87% for the AIK-C and 68% for the Schwarz strains. Thus, vaccination with the high-dose Edmonston-Zagreb or the AIK-C strain at 4-5 months was as effective as the vaccination with the AIK-C strain at 8 - 10 months and more effective than the vaccination with the standard-dose Schwarz strain at 8 - 10 months (20). Immunizing 6 and 9 month old infants with AIK-C, Edmonston-Zagreb, Leningrad-16 and Schwarz strains of the measles vaccine also revealed standard-titres. AIK-C was more effective than the other measles vaccine strains for early immunization, efficacy, long-term immunogenicity, and long-term safety (21, 22).

The effects of the dosage and strain of live attenuated measles vaccines on serological responses in young infants was surveyed by Cutts et al. (23). They found that among children under 9 months of age, Edmonston Zagreb and AIK-C vaccines produced higher seroresponse rates than the Schwarz vaccine of an equivalent titre. Based on previous research, the AIK-C/MRC-5 was declared to be as potent and more immunogenic for controlling the measles epidemics which were common among Iranian children in 1950. The study of new vaccine viral strains began in 1963 and ended in late 1966. Production of pathogen-free, local calf serum was cost-effective and safe and helped to stabilize a working cell bank of HDCs for future vaccine production (24, 25).

### 3.2.3. Maternal Antibody, Age at Vaccination, and Immune Response

The effectiveness of the measles vaccine is impacted by the level of maternal antibodies to the measles virus during infancy and at the age of vaccination. The presence of maternally derived transplacental antibodies is important in evaluating the immunogenicity of the live measles vaccine in early infants because maternal antibodies interfere with the live measles vaccine virus. In Iran between 1967 and 1983, 1 dose of the monovalent AIK-C/RAZI vaccine was recommended for all children; however, the measles vaccination was not routinely offered in the public sector. To determine the maternal antibody level, the best age for vaccination, and the duration of passive immunity, the measles serum antibody (IgG) was measured by an HI assay in the cord blood at the time of birth (26, 27). The data showed that the maternal measles antibody protects the infant at a young age and then decreases as the child

grow, suggesting that the measles vaccine should be given when the maternal immunity disappears. This study recommended 6 - 9 months as the optimal age to administer the measles vaccine. The second dose, given 3 - 4 months later, showed an increased humeral response after administration (26). These results were presented at the Congress of Vaccinations in tropical countries under WHO supervision and was accepted by Africa in 1977 (Guadeloupe vaccination in the tropics). Based on these data, vaccinating before 1 year could lead to a high risk of primary vaccine failure and subsequent infection in recipients. After the Islamic revolution in 1979, the recommended vaccination age was 12 months, based on the Ministry of Health & Education Program for Immunizations. Seroepidemiological surveys showed that 90 - 95% of the population at this age seroconverted after vaccination, compared with 55% in those aged less than 9 months. At present, the measles vaccination in Iran contains 2 doses of measles (MMR).

### 3.3. Measles Vaccine Efficacy

Vaccination age, passively acquired measles antibodies, immunological immaturity at vaccination, immunosuppressive conditions such as infection with human immunodeficiency virus type 1 (HIV-1) or, and in some circumstances, concurrent acute infections have critical roles in efficacy of measles vaccine (3). Frequently cited figures are that 90% of children develop protective antibody levels when given 1 dose of MV at 9 months of age, whereas 90 - 95% respond when vaccinated at 12 months (2, 3).

Surveys related to AIK-C measles-containing vaccines showed that this vaccine, either monovalent or combined with Rubella and Mumps, is generally recognized as safe and effective (1). Many serologic evaluations have demonstrated that over 50 years of using attenuated RAZI AIK-C/HDC MCVs elicits immune responses in most susceptible vaccine recipients particularly when handled and administered under ideal conditions. Epidemiological results of the measles vaccination in Iran changed the seroepidemiological picture of this disease. If a measles reinfection occurs in a population with an HI antibody titre  $\leq 1:16$  (4 log<sub>2</sub>), it acts as a booster for increasing the antibody titre (28). Shafiyi et al. reported that mass vaccination and EPI programs led to a natural circulation of the virus; therefore, reduced and natural boosting did not occur in the population. This phenomenon significantly reduced maternal antibody levels between 1990 and 1991 (28).

The necessity of measles immunizations in women before marriage was suggested by Shafiyi A at the CVI conference in Geneva and was accepted for developing countries in Africa and Asia in 1992. In 2004, MR (Measles and Rubella) mass vaccinations of all Iranian women under 25 years of age helped to resolve this problem. Currently, Iran

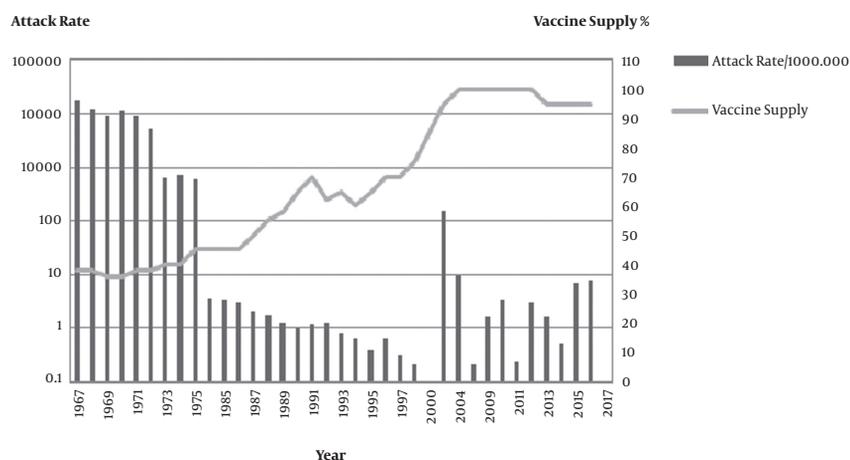
is trying to establish a target date for measles elimination. Although cases that have been imported from neighbouring countries affected by security conflicts in recent years pose a major challenge for eliminating measles in Iran.

### 3.4. Comparative Epidemiology of Measles; Pre- and Post-Vaccine Era in Iran

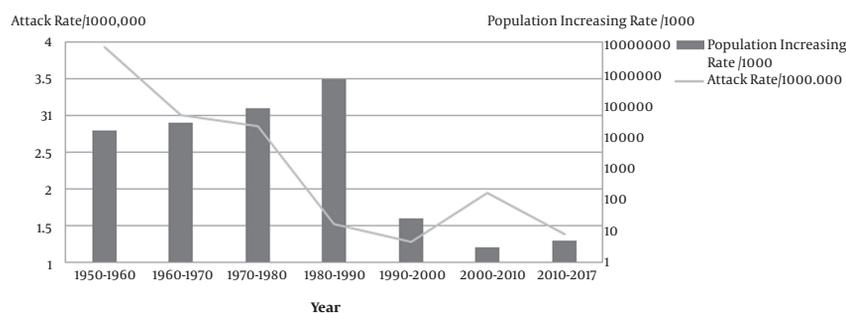
From the time of the vaccine licensure in 1963 until the end of 2016, over 88 million doses of the measles vaccine were produced at the Razi institute in Iran, and an estimated 95% of the 1- to 25-year-old population was vaccinated. Widespread vaccine production and administration during this period was followed by a 99% decrease in reported measles cases, resulting in large economic savings (Figures 1 and 2). In the pre-vaccine era, measles was a common infectious disease with high incidence, morbidity and mortality (29).

In the USA in 1958, with a population of 200 million, the number of measles-related deaths was 552, while in India there were 85,400 measles-related deaths in a population of 400 million. This means that for 1 death in the USA, there were 17 measles-related deaths in India. At the same time in Africa, Asia and Latin America there were 50 deaths per 100,000 residents (29). Immunization against measles in Iran started in 1967 with a population of 30 million. The annual incidence of measles over the period of 1967 - 1976 was 150,000 - 500,000, and the mortality was 5 - 10% with a higher rate of  $\geq 10\%$  in urban areas. In the early 1980s, there were 30,000 - 50,000 cases of measles annually. Between 1967 and 1983 there was no clear and efficient strategy for measles vaccinations. In 1979, after the Islamic revolution, the primary health system (PHC) with 95% accessibility in rural areas was established. Since 1984 systematic vaccinations against measles, which were initially monovalent and then became trivalent with MMR, for all children was initiated in Iran. The identified measles cases decreased significantly from 11,604 in 2002 to 724 in 2004 and to 1.6 cases per 1,000,000 persons in 2009 (30) (Figure 3).

The successful and high-quality local measles vaccine resulted in  $< 1$  case per million residents during 2004 - 2009. From 2009 until now, the number of measles cases that were laboratory-confirmed but not epidemiologically linked (positive and equivocal), as reported by the National Reference Laboratory, were approximately 1456 cases. The total population has doubled over the past 4 decades to an estimated 78 million in 2017. Recent surveys have revealed a greater than 92% seropositivity in Iranian children (31, 32) (Figure 4).



**Figure 3.** Supply and production of a local measles vaccine and its effect on the significant reduction of confirmed reported measles cases during the pre- and post-vaccine era in Iran, 1967 - 2017



**Figure 4.** The increased population size/1000 and decreased number of confirmed reported measles/1000000 cases over seven decades

#### 4. Conclusions

During the last 50 years, vaccine production, implementation and the widespread use of local EPI vaccines have all contributed to the decreased incidence of numerous preventable diseases and associated mortality in Iran. The development process of viral vaccine is a complex combination of knowledge and technology side along experience. Its development need to follow a fixed and standard pattern that fits the process well in general. We have described this complex process for Local measles vaccine in some standard details in this review, contains a schematic explaining the usual set of steps along the way from Isolation of virus to new local measles vaccine approval. Measles was introduced in population with a very high incidence and morbidity. This local vaccine production besides high coverage has led to a significant decrease in disease cases In Iran (Figure 3) (30, 32). A comparison between the period prior to the Local Vaccine production and implementation of national vaccination in Iran and

2017 showed a greater than 99% decline in the number of, measles (99.9%) cases. However, the result of seroepidemiology survey in some urban area reported that more effective national program needed to be organised for control and elimination of measles (33, 34). This production also had a major effect on economic and societal welfare. Eliminating the physical and disability defects caused by disease, making the healthy body for longer working years and higher productivity besides good educational results, and reducing healthcare costs.

Reductions in morbidity and mortality of measles disease have been so great that eradication has been proposed and believed to be feasible soon. Razi, as a member of the immunization family, hopes it will happen in Iran's near future.

**Table 1.** The Historical Development of Different Measles Vaccine Strains

Country of Origin Wild Isolate	Vaccine Strain	Cell Substrate	Reference
United State of America (Edmonston origin)	Edmonston B (1963) USA	Chicken Embryo Fibroblast	(35)
	Edmonston-Zagreb	WI-38 (Human Lung Diploid)	(36)
	Beckenham & further attenuated Beckenham 31	Chicken Embryo Fibroblast	(3)
	Schwarz (1965) USA	Chicken Embryo Fibroblast	(37)
	Moraten (1968) USA	Chicken Embryo Fibroblast	(38)
	AIK-C JAPAN	Chicken Embryo Fibroblast	(14)
	AIK/MRC5 IRAN	Human Lung Diploid cell (MRC-5)	(39)
Russia Federation	Leningrad 16 (L16), USSR-58	quail embryo cells (QEC), Chicken Embryo Fibroblast	(40, 41)
Yugoslavia	Milovanovic's strains	Chicken Embryo Fibroblast	(41)
People's Republic of China	Shanghai 191	Chicken Embryo Fibroblast	(42)
JAPAN	CAM 70	chorioallantoic membrane of chick embryo	(43, 44)
	Sugiyama attenuated. Sugiyama178 (More attenuated)	Bovine Kidney	(9)
	Denken-Toyoshima, Biken-Sugiyama	chick-embryo amniotic membrane. Bovine Kidney	(45)

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## References

- Kaadan AN. *Al-Razi on smallpox and measles*. 2017. Available from: <http://muslimheritage.com/article/al-razi-smallpox-and-measles>.
- Griffin DE. *Measles virus*. In: *Knipe DM, Howley PM, editors. Field's virology*. Philadelphia: Lippincott Williams Wilkins; 2013. p.1042-69.
- Plotkin SA, Orenstein W, Offit P. *Vaccines*. 6th ed ed. Philadelphia: Saunders; 2013.
- Nafyici K, Saidi S, Nategh R, Mostatab A, Akbarshahy E. Comparative study of live attenuated and further attenuated measles vaccines in rural areas of Iran. *Archiv für die gesamte Virusforschung*. 1967;22(1-2):11-22. [PubMed: 4879874].
- Mirchamsy H, Bahrami S, Shafiyi A, Shahrabady MS, Kamaly M, Ahourai P, et al. Isolation and characterization of a defective measles virus from brain biopsies of three patients in Iran with subacute sclerosing panencephalitis. *Intervirology*. 1978;9(2):106-18. doi: 10.1159/000148928. [PubMed: 412813].
- Derakhshan I, Lotfi J, Abbasioun K, Shakib N. Subacute sclerosing panencephalitis in Iran: new immunologic, virologic and clinical observations. *Iran J Med Sci*. 1980;11(1):97-110. Persian.
- Shafiyi A, Lotfi J, Mirchamsy H. Subacute sclerosing panencephalitis in Iran. *Kitasato Arch Exp Med*. 1984;57(4):267-71. [PubMed: 6543890].
- Mirchamsy H, Shafiyi A, Bassali Y, Bahrami S, Nazari F. A comparative study of two live measles vaccines in Iran. *J Hyg (Lond)*. 1970;68(1):101-10. [PubMed: 5266577].
- Matumoto M, Mutai M, Saburi Y, Fujii R, Minamitani M, Nakamura K. Live measles-virus vaccine: clinical trial of vaccine prepared from a variant of the Sugiyama strain adapted to bovine kidney cells. *Jpn J Exp Med*. 1962;32:433-48. [PubMed: 13933923].
- Mirchamsy H, Shafiyi A, Bahrami S, Nazari P, Mirzadeh M, Bassali Y. Mass immunization of children in Iran with live attenuated Sugiyama measles virus adapted to calf kidney cell cultures. *Jpn J Exp Med*. 1971;41(1):39-48. [PubMed: 5313449].
- Mirchamsy H, Manteghi A, Saleh H. Efficacy and safety of live attenuated Sugiyama strain of measles virus in mass vaccination children in rural region of Iran. *Arch Razi Ist*. 1976;28:3-10. doi: 10.22092/ARI.1976.108782.
- Mirchamsy H, Shafiyi A, Rafiyi MR, Bahrami S, Nazari P, Fatemie S. Experimental study of a further attenuated live measles vaccine of the Sugiyama strain in Iran. *J Hyg (Lond)*. 1974;72(2):273-9. [PubMed: 4522721]. [PubMed Central: PMC2130516].
- Manteghi A. *Minist Health Rrport*. The epidemiological survey of measles in Iran following mass vaccination. 49. 1971. p. 1-49.
- Makino S, Sasaki K, Nakamura N, Nakagawa M, Nakajima S. Evaluation of the live AIK measles virus vaccine. *Kitasato Arch Exp Med*. 1973;46(3-4):83-92. [PubMed: 4805362].
- Makino S, Sasaki K, Nakamura N, Nakagawa M, Kasahara N. Field trial with a further attenuated live measles virus vaccine. *Jpn J Microbiol*. 1973;17(1):75-9. [PubMed: 4540649].
- Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res*. 1961;25:585-621. doi: 10.1016/0014-4827(61)90192-6.
- Mirchamsy H, Shafiyi A. The expanded program in immunization against measles and poliomyelitis, Iran's experience. *Arch Razi Ist*. 1984;34:1-8.
- Mirchamsy H, Shafiyi A, Bahrami S, Kamali M, Nazari P, Razavi J. A comparative field trial with five live measles virus vaccine produced in HDC/MRC5 of Iran. *Arch Inst Razi*. 1977;29:11-32.
- Mirchamsy H, Shafiyi A, Nazari P, Ashtiani MP, Sassani A. Evaluation of live attenuated measles vaccines prepared in human diploid cells for reimmunization. *Epidem Inf*. 1988;101:437-43.
- Tidjani O, Grunitsky B, Guerin N, Levy-Bruhl D, Lecam N, Xuereff C. Serological effects of Edmonston-Zagreb, Schwarz, and AIK-C measles vaccine strains given at ages 4-5 or 8-10 months. *Lancet*. 1989;2(8676):1357-60. doi: 10.1016/S0140-6736(89)91967-3.
- Tidjani O, Grunitzky B, Guerin N, Levy-Bruhl D, Lecam N, Xuereff C, et al. [Comparative serological efficacy of the measles vaccine strains Edmonston-Zagreb, Schwarz and AIK-C in Togolese infants of 4-5 months and 8-10 months]. *Bull Soc Pathol Exot*. 1991;84(5 Pt 5):873-84. [PubMed: 1819435].

22. Bolotovskii VM, Grabowsky M, Clements CJ, Albrecht P, Brenner ER, Zargaryantz AI, et al. Immunization of 6 and 9 month old infants with AIK-C, Edmonston-Zagreb, Leningrad-16 and Schwarz strains of measles vaccine. *Int J Epidemiol.* 1994;**23**(5):1069-77. [PubMed: 7860158].
23. Cutts FT, Grabowsky M, Markowitz LE. The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants. *Biologicals.* 1995;**23**(1):95-106. [PubMed: 7619443].
24. Mohammadi A, Mirchamsy H, Shafiyi A. Removal of viral pathogen from calf serum by Gamma Irradiation Techniques. *Arch Razi Ist.* 2002;**53**:97-104.
25. Mohammadi A, Shafiyi A, Mirchamsy H. Elimination of Mycoplasma from cell culture and establishment of mycoplasma free cell line. 2nd Iranian congress on virology. Tehran: Iranian society on virology; 2004. 345 p.
26. Mirchamsy H, Shafiyi A, Mahinpour M, Nazari P. Age of measles immunization in tropics. *Dev Biol Stand.* 1978;**41**:191-4. [PubMed: 572788].
27. Mirchamsy H, Shafiyi A, Bahrami S. The occurrence of SSPE in Iran. *Arch Razi Ist.* 1984;**34**:35-43.
28. Shafiyi A, Mirchamsy H, Yousefi I. Immunology and vaccine failure in measles vaccination. *Res Reconstruct Sci Educat Quarter Agricult Minist.* 1996;**31**:108-17. Persian.
29. Mirchamsy H, Neway T, Hamed M, Pilet C. Adjuvanticity of pGPL-Mc and LRS in the immune responses of monkeys to oral immunization with diphtheria and tetanus toxoids. *Comp Immunol Microbiol Infect Dis.* 1997;**20**(1):13-20. [PubMed: 9023036].
30. Zahraei SM, Gouya MM, Azad TM, Soltanshahi R, Sabouri A, Naouri B, et al. Successful control and impending elimination of measles in the Islamic Republic of Iran. *J Infect Dis.* 2011;**204** Suppl 1:S305-11. doi: 10.1093/infdis/jir076. [PubMed: 21666178].
31. Mokhtari Azad T, Ehteda A, Yavari P, Hamkar R, Safar Pour Z, Essalat M, et al. Comparative Detection of Measles Specific IgM Antibody in Serum and Saliva by an Antibody-Capture IgM Enzyme Immunoassay (EIA). *Iran J Allergy Asthma Immunol.* 2003;**2**(3):149-54. [PubMed: 17301372].
32. Esteghamati A, Gouya MM, Zahraei SM, Dadras MN, Rashidi A, Mahoney F. Progress in measles and rubella elimination in Iran. *Pediatr Infect Dis J.* 2007;**26**(12):1137-41. doi: 10.1097/INF.0b013e3181462090. [PubMed: 18043452].
33. Shakurnia A, Alavi SM, Norouzirad R, Sarajian AA, Shakerinejad G. Post-Vaccination Immunity Against Measles in Under Twenty-Five Year-Old Population of Ahvaz, Southwest of Iran. *Jundishapur J Microbiol.* 2013;**6**(10):1-5. doi: 10.5812/jjm.7707.
34. Shamsizadeh A, Nikfar R, Makvandi M, Hakimzadeh M, Alisamir M, Ziaei T. Seroprevalence of measles, mumps and rubella antibodies in 18 months and 6.5 years old children: six months after measles-mumps-rubella (mmr) vaccination. *Jundishapur J Microbiol.* 2012;**5**(4):578-81. doi: 10.5812/jjm.4563.
35. Enders JF, Peebles TC. Propagation in tissue cultures of cytopathogenic agents from patient with measles. *Proc Sot Exp Biol Med.* 1954;**86**:277-86. [PubMed: 1317653].
36. Ikic D, Juzbasic M, Beck M, Hrabar A, Cimbur-Schreiber T. Attenuation and characterisation of Edmonston-Zagreb measles virus. *Ann Immunol Hung.* 1972;**16**(0):175-81. [PubMed: 4679646].
37. Schwarz AJF. Extensive Clinical Evaluations of a Highly Attenuated Live Measles Vaccine. *JAMA.* 1967;**199**(1):26-30. [PubMed: 6071117].
38. Maurice R, Hilleman DS, Eugene B, Buynak P, Robert E, Weibel MD. Development and Evaluation of the Moraten Measles Virus Vaccine. *JAMA.* 1968;**206**(3):587-90. [PubMed: 5695578].
39. Makino S, Sasaki K, Nazari F, Nakagawa M, Akagawa M, Nakamura N. Cultivation of Measles Virus in Sheep Kidney Cells. 1970;**14**(6):501-4. [PubMed: 5312562].
40. Smorodintsev AA, Boichuk LM, Shikina ES, Batanova TB, Bystriakova IV, Peradze TV. Clinical and immunological response to live tissue culture vaccine against measles. *Acta Virol.* 1960;**4**:201-4. [PubMed: 13854875].
41. Fadeeva LL, Dadashyan MA, Lebedev DD, Zhdanov VM. Attenuated measles-virus strain in the U.S.S.R. *Am J Dis Child.* 1962;**103**:379-81.
42. Xiang JZ, Chen ZH. Measles vaccine in the People's Republic of China. *Rev Infect Dis.* 1983;**5**(3):506-10. [PubMed: 6879006].
43. Takaku K, Sasada T, Konobe T, Onishi K, Ueda S. Studies on further attenuated live measles vaccine. 3. Selection of less reactive variants of CAM measles vaccine virus. *Biken J.* 1970;**13**(3):163-8. [PubMed: 5530510].
44. Ueda S, Takahashi M, Kurimura T, Ogino T, Suzuki N. Studies on further attenuated live measles vaccine. IV. Clinical and serological evaluation of a clone of CAM-CEF measles vaccine virus. *Biken J.* 1970;**13**(3):169-74. [PubMed: 5530511].
45. Okuno Y, Sugai T, Toyoshima K, Takahashi M, Yamamura T, Hata S. Studies on prophylaxis of measles with attenuated living virus. IV. Inoculation tests in children with chick embryo passage measles virus in 1960. *Biken J.* 1960;**3**:293.