

MEASLES IMMUNIZATION IN IRAN*

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Mass immunization with live measles vaccine has been carried out in rural Iran since 1968. Two strains have been used: primary baby calf kidney cell-adapted Sugiyama strain and human diploid cell-adapted AIK strain. More than 94% of the susceptible children experimentally vaccinated with either of the two vaccines have shown seroconversion. Mass immunization in rural regions has covered about 80% of susceptible children. It is now recommended that the live vaccine be administered twice: the first dose at six to nine months and the second at 12-15 months of age. In all of 100 cases of subacute sclerosing panencephalitis (SSPE) observed in the Tehran region between 1977 and 1982, the patient had a history of measles infection in childhood; there was no indication that SSPE developed after vaccination. Most of the patients with SSPE have had a high titer of antibody to measles virus in serum and cerebrospinal fluid, and antibody has commonly been demonstrated in saliva as well.....

During the last two decades, an immunization program against measles has received top priority in Iran; the vaccination campaign started in 1967. Although accurate statistics are not available for the preceding years, 150,000 cases of measles were reported in 1965, and in rural regions more than 10,000 deaths due to measles complications were estimated by the Department of Preventive Medicine of the Iranian Ministry of Health [1]. The 60,000 villages affected were scattered throughout the country and contained much of Iran's population of 49 million.

The financial resources of the developing world generally do not permit adequate allocations for a normal immunization program. However, in the case of measles in our country, health authorities were ready to provide financial support for the control of this major hazard to children's health.

After the development of the live attenuated measles vaccine

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by Enders [2], Iran immediately launched mass vaccination campaigns with imported vaccine. However, the high cost and the vulnerability of the live vaccine constrained expansion of the vaccination program. In 1968 a domestically produced potent and effective vaccine became available, and a program for mass vaccination in rural areas was planned by the Department of Preventive Medicine. The Ministry of Health provided air transport of vaccines to the major cities and refrigerated trucking for transfer of the vaccines to the vaccination centers; installed refrigerators in most of the health centers; made available mobile teams of health personnel trained in mass vaccination for missions to remote rural communities; and maintained a stock of lyophilized live vaccine at -20 C. Whenever possible vaccines were delivered in boxes containing enough dry ice for dispatch to vaccination centers in mountainous regions. Large stocks of disposable syringes and jet injectors were distributed to health centers before performance of operations.

In this report we briefly present some details about production of measles vaccine in Iran and the results of our mass campaigns. A short report on the late neurologic complications associated with measles will also be presented.

Vaccine Production

Sugiyama vaccine. The Sugiyama strain of measles virus was adapted by Matumoto et al. [3] to cultured baby calf kidney (CK) cells in 1962 and was tested in Japan as a live attenuated vaccine [4]. The strain was kindly given to us as its 78th passage in CK cells, grown at 30 C, by Dr. S. Hashizume of the Chiba Serum Institute in Japan. For production of a seed lot, this virus was passed three times in CK cells. The quality controls of our seed lot (CK82) were made according to the World Health Organization requirements for live measles vaccine [5]. The vaccine was produced in CK cells according to the procedure developed by the Chiba Serum Institute.

A further-attenuated form of the same strain of virus was isolated by Myamura et al [6] in 1971 after elution of virus from aluminum phosphate. The new strain, called 5F100, was also given to us by Chiba Serum Institute. With use of these two strains, between 1968 and 1981 more than 20 million doses of measles vaccine were produced and lyophilized in multidose vials.

Gelatin-sodium glutamate was used as stabilizer. Each dose of vaccine contained at least 3 log TCID₅₀ virus after lyophilization.

AIK vaccine. AIK-C vaccine lot TV-12 was generously supplied by Dr. S. Makino of the Kitasato Institute in Tokyo. This is a still further attenuated virus derived from the Edmonston virulent strain by Makino et al. [7]. The Edmonston strain was passed 12 times in primary sheep kidney cells at 33 C. The virus was then inoculated into specific pathogen-free chick embryo cultures. Isolated plaques were cloned in chick embryo cells, and one clone was selected as seed virus for vaccine. This clone was called AIK-C strain. the seventh passage of the AIK-C strain in chick embryo cells was used for vaccine lot TV-12 [8, 9]. The AIK-C vaccine lot TV-12 was directly subcultured (0.1-0.01 TCID₅₀/cell) five times in human diploid cells, line MRC-5, in roller bottles at 33 C. A CPE consisting of the appearance of small giant cells was observed at the second and third passages, seven to nine days after inoculation. At the fifth passage, the CPE appeared five to six days after inoculation. The maintenance medium was TC199 supplemented with 0.2% gelatin, 50ug of neomycin/ml, and 50 ug of kanamycin/ml at pH 7.6. The medium was changed five days after infection, when the CPE was first observed. Two days later, the fluid was harvested and fresh maintenance medium was added. It was possible to make three to five harvests from each batch. Those harvests having a titer of 4.0 log were pooled and aseptically passed through Millipore filters of 5-um pore size or centrifuged 30 min at 2,660 g for removal of cellular debris.

The viral suspension was blended with human albumin-lactose stabilizer, distributed into vials of five or 10 doses, and lyophilized. The viral content per dose was 4.0-4.5 log TCID₅₀ of virus. Four million doses of this vaccine have been used in Iran.

Comparative Field Trials

Since 1968, several field trials have been designed to evaluate the domestically manufactured measles vaccines and to compare them with other commercial vaccines. In one field trial, 839 susceptible children were divided into five groups. Two groups were immunized with two domestically produced vaccines

(Sugiyama and AIK strains); and three groups, with three other live vaccines (Schwarz, Leningrad-16, and Biken-CAM). The clinical responses were not significantly different in the five groups. However, the children who received AIK vaccine exhibited milder reactions. Seroconversion rates were 95.5%-100 %, and the mean HAI titers ranged between 5.2 log₂ and 6.4 log₂ [10]. In another trial, 235 children aged 12 months to five years were immunized with Sugiyama 5F100 vaccine or with AIK vaccine. For both vaccines, about 50% of susceptible children showed a rise in temperature of 1 C for about one day. Respiratory disorders such as cough, coryza, and tonsillitis were more severe with Sugiyama 5F100 than with AIK vaccine. The seroconversion rates were 94.% and 97.8 for Sugiyama 5F100 and the AIK vaccines, respectively. The mean HAI titer was about 1 log₂ lower in children immunized with the AIK vaccine [11].

Mass Vaccination Campaigns

From 1965 to 1970, the measles vaccines used in Iran were imported derivatives of the Edmonston measles virus (Edmonston B, Schwarz, and Beckenham strains). By 1968, domestically produced vaccines were being used in expanded vaccination programs. The effect of the mass vaccination in reducing morbidity and mortality in rural Iran was remarkable (figure 1). At the end of 1971, coverage of only 37% had brought a 56% reduction in morbidity and a dramatic fall in mortality due to measles complications [12]. In 1975 the number of reported cases was 10% of that in 1966, when mass immunization was first being planned (table 1). By 1977, both Sugiyama and AIK vaccines were being widely used, and by the end of 1977 an 80% coverage had been achieved. During the past three years, mass immunization has been carried out in the remote districts of the country, especially in the mountainous regions.

Age of immunization. Until recently the age of immunization against measles in Iran was nine to 12 months. Revaccination with live vaccines was encouraged, especially when children were first immunized before 12 months of age. However, many deaths due to measles infection were reported among four- to eight-month-old infants of low socioeconomic strata [13]. As previously reported [14], most neonates have adequate levels of maternal antibody to measles virus. By four to six months after birth, this

antibody is not longer detectable in the blood of most infants. Evidently, many of these children still have a trace of maternal antibody that, in combination with cell-mediated immunity, probably protects them against measles infection. On the other hand, some children older than four to six months may lack the maternal antibody to measles and may become victims of the disease before their first birthday. Therefore, a new vaccination scheme has been introduced. It has been decided to vaccinate infants at six to nine months of age and to revaccinate them at 12 to 15 months of age.

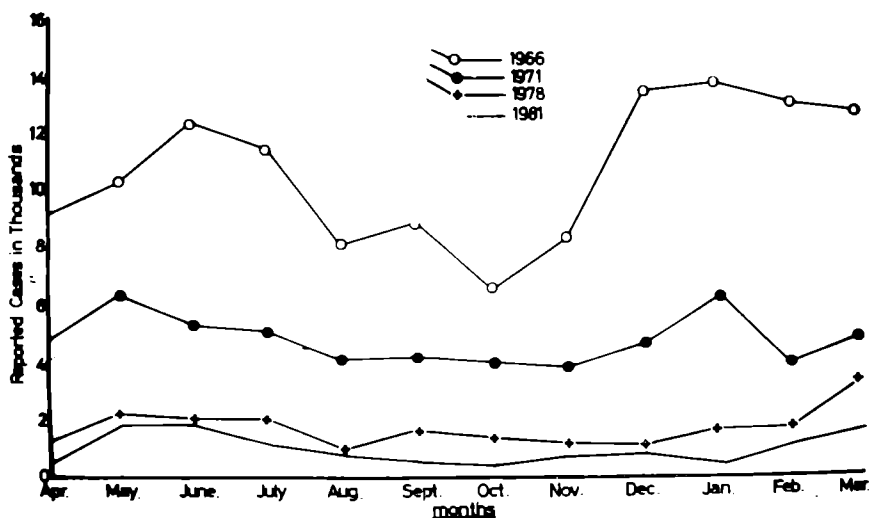


Figure 1. Effect of expanded immunization program on the number of reported cases of measles in Iran.

Already considerable progress has been achieved in eliminating measles infection in rural communities of Iran. Waves of measles epidemics are no longer observed, as they were before 1970. Deaths due to measles complications in rural areas in 1981 were negligible. A follow-up program, which is of primary importance for avoiding a return to the recent prevalence of measles in the rural sectors of Iran, is being planned.

Complications of Late Measles

Between 1977 and 1982, in collaboration with a team of neurosurgeons at a children's hospital in Tehran, we studied 100 cases of subacute sclerosing panencephalitis (SSPE). Boys ac-

counted for 60% of the patients. Patients were four to 20 years

Table 1. Morbidity due to measles in rural areas of Iran: 1966-1981.

Year	No. of cases reported
1966	127,514
1967	92,752
1968	94,365
1969	84,486
1970	63,751
1971	57,545
1972	50,142
1973	42,994
1974	16,589
1975	13,873
1978	13,250
1981	12,290

of age. The levels of HAI antibody in serum and in cerebrospinal fluid of patients, which were measured several times during the course of the disease, were very high in comparison to those in children immunized against measles. Antibody to measles virus was also detected in the saliva of all patients with SSPE at various stages of the disease. The relatively low titer of antibody in their saliva may indicate that antibody may have leaked from the circulating system into the saliva. But intense fluorescent staining of the cells lining the salivary ducts suggested the presence of viral antigen on the glandular cell membranes [15]. Cocultivation of saliva gland biopsies yielded no virus after 10 passages. However, in three of seven brain biopsies, it was possible to isolate cell-associated measles-like virus by cocultivation with Vero cells [16].

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