Arch. Inst . Razi **38, 39:** 1-9 (1988)

A PROGRESS-REPORT ON 18 YEARS OF CONTINUOUS MEASLES VACCINATION IN RURAL AREAS OF IRAN*

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SUMMARY

A comprehensive-type report is given on recent 18 years continuous anti-measles vaccination in Iran, describing the problems connected with the live vaccine—strains applied during manufacturing of vaccines and also with the eeffectiveness of vaccinations mainly in rural areas of the Iran Islamic Republic.

On the basis of results of field trials performed, — two home-produced vaccines' (SUGIYAMA 5F100 and AIK-HDC) reactogenicity and efficacy was compared to the results achieved by three other live vaccines (SCHWARZ, Leningrade-16, and BIKEN—CAM). Since 1981—however—only AIK virus-strain is being applied for both, the vaccine production and immunizations performed throughout the country amounting 3 to 4 million doses per year.

INTRODUCTION

Measles has been recognized in Iran as well as in other Eastern countries as an independent clinical disease of childhood from the ancient times. Records in Iran go back at least to 1000 years ago. RHAZES (ABU BAKRE MOHAMMAD ZAKARIYA RAZI), a 10th century Iranian physician, receives credit for the first recorded reference to measles. In his book, Smallpox and Measles (21) he described 19 diseases with exanthema, among them smallpox, measles and varicella. In his famous book, AL-HAWI (Continens-Razi, translated first from Arabic to Latin in 1486 in Brescia, Italy and published in 1509 and 1542 in Venice, Italy), RHAZES cited several physicians of ancient time, among them CRITON (117-152), ORIBASE DE PERGAMON (325-400), AARON (650) and MASARJAWAY (722) and described the observations of these physicians about smallpox and measles. He specially assigned priority for the initial description of the

* Reprinted from: Ann. Immunol. hung., 26· 153-161; 1986

clinical picture of measles to MASARJAWAI, and Iranian Jewish physician, professor of Gunde Shapur University, as claimed by RHAZES, AL-YEHUDI (12).

Fatal waves of measles devastate from ancient time to the pre-vaccination era, most of infants of our country. In those days, as we know, there was no way to prevent the disease, therefore people relates it to Divine Dstiny. Although accurate statistics before 1967, when vaccination campaigns against measles started in Iran, are largely unavailable, it is evident that measles was responsible for widespread ravages in rural regions of Iran, causing over 50 per cent of deaths among infants between 5 months and 4 years of age. The poor nutritional and socioeconomic status of children, together with the lack of health center were the main factors causing great loss of children's life. The case-fatality in eight outbreaks which were followed up by the Department of Preventive Medicine of Iranian ministry of Health in 1962 and 1963 was 2 and 6 per cent (1). In 1965 more than 10,000 deaths due to measles were estimated by the mentioned Department(22).

VACCINATION TRIALS

After the development of the live attenuated measles vaccine by ENDERS (3), Iran immediately launched mass vaccination campaigns with imported vaccines. In the first trial, the imported vaccines were prepared with EDMONDSTON, B, SCHWARZ and BECKENHAM 31 strains. The clinical reactions of these vaccines were more severe in mountainous areas probably because of cold climates (22). The high cost and the vulnerability of the live vaccine constrained expansion of the vaccination program. However vaccination was carried out, at a limited scale, in the far remote rural areas. In 1969 another investigation was carried out (10) with two Japanese measles vaccines "DENKEN" and "BIKEN". The clinical reactions following vaccination with both vaccines were mild. The seroconversion-rate was over 90% in susceptible children. Following these trials, the Ministry of Health decided to use "DENKEN" vaccine, which was planned to be produced locally, for mass immunization in rural regions.

SUGIYAMA VACCINES

It is worthy to be mentioned that this vaccine was first manufactured in Chiba Serum Institute, Japan in primary baby calf kidney cells (CK) by using SUGIYAMA strain of measles virus attenuated by MATUMOTO et al. (9) in baby calf kidney cells. This vaccine, at

the 73-rd passage level in bovine renal cells, was one of the two further attenuated vaccines which have been considered by the Japanese Measles Vaccine Research Commission (25) to be safe and could be used without immune-globulin.

The seed material at CK-78 and the technology of production were kindly supplied by Dr. HASHIZUME, chief, Virus Unit of Chiba Serum Institute. Soon some 600,000 doses of lyophilized vaccine were made by Razi Institute and a new field trial was initiated in 1969 by the Department of Preventive Medicine in several rural areas of the couuntry (11).

MASS VACCINATION CAMPAIGNS

Soon locally manufactured vaccine was being used in expanded vaccination programs. The effect of the mass vaccination in reducing morbidity and mortality in rural Iran was remarkable. At the end of 1971, vaccination coverage of only 37% had brought a 56% reduction in morbidity and a dramatic fall in mortality due to measles complications (8). At the end of 1972, when about five million doses of vaccine prepared with SUGIYAMA strain at its 82nd passage in CK were used throughout rural Iran, the number of reported cases was 10% of that in 1966, when mass immunization was first being planned (table 1). At this time a further attenuated strain of SUGIYAMA called 5F100, developed by MYAMURA et al. (19) in Chiba Serum Institute of Japan by elution of virus from A1PO4, and further passage in CK cells of the cloned virus, was received and used for large-scale production of live further attenuated measles vaccine (13). In subsequent 4 years some 12 million doses of this vaccine were used in rural regions.

AIK VACCINE

AIK SEED VIRUS: AIK-C vaccine lot TV-12 was supplied by Dr. S. MAKINO, chief, Virus Research Department of the Kitasato Institute, Tokyo. This is a further attenuated virus derived from virulent EDMONDSTON-strain of measles virus developed by MAKINO et al. (5, 6). The virulent strain was passed 12 times in primary sheep kidney cell at 33°C. Plaques isolated in SPF chick embryo (CE) cultures were cloned in CE cells and one clone was selected as vaccine seed virus and was called AIK-C strain. The 7th passage virus of AIK-C strain in CE cells was used for vaccine lot TV-12 (7).

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	63,715
1971	57,545
1972	50,142
1973	42,994
1974	16,589
1975	13,873
1978	13,250
1981	12,290

Table 2.

Comparative Infective Titers of Serial Harvests of Measles Virus AIK-C Strain, in Human Diploid Cells MRC-5 and R-17

No of Experiment	Type of Cell	Harvest No	Days Post Inoculation	TCID 50 (Log 10)
1	MRC-5	1	5	5.0
		2	6	5.0
		3	7	5.2
		4	8	5.5
2		1	5	5.0
		2	6	5.3
		3	7	5.3
		4	8	5.7
3		1	5	5.5
		2	6	5.7
4		1	5	4.5
		2	6	5.5
5	R-17	1	5	5.5
		2	6	5.5
		3	7	5.5
		4	8	5.5
6		1	5	5.0
		2	6	5.5
		3	7	5.5
7		1	5	5.25
		2	6	5.0
		3	7	5.5
		4	8	5.5
8		1	5	5.5
		2	6	5.5

AIK VACCINE PRODUCTION IN IRAN

The AIK-C vaccine lot TV-12 was directly subcultured (0.1-0.01 PFU/cell) 5 times in human diploid cells HDC MRC-5 at 33°C. The cytopathogenic effect (CPE) consisted of the appearance of small giant cells, as observed at the 2nd and 3rd passage, 7-9 days post inoculation. At the 5th passage the time for the appearance of CPE was 5-6 days. The maintenance medium was TC199 supplemented with

0.2% gelatin, 50% g/ml of erythromycin and 50% g/ml of kanamycin, at pH 7.6. This medium was changed 5 days post infection when the first CPE was observed. Two days later the fluid was harvested and fresh maintenance medium was added. It is possible to make 2 to 4 harvests for each batch.

This virus pool, after having met the requirements, was blended with stabilizer and freeze-dried in single or multi-dose vials. The virus content per dose, after lyophilization was 3.6 to 4.2 log10 TCID50.

AIK VACCINE IN NEW HDC.

In 1978 when because of general strikes during the Islamic revolution, and following a long-lasting current failures and other shortcomings, our stock of two diploid cells WI-38 and MRC-5 were lost, we developed 10 HDC from lung tissues of embryos obtained from the Central Maternity Hospital, Teheran. Details about the characteristics of the new cells will be published elswhere (18); we only mention here that five pilot lots of measles virus produced comparatively in MRC-5 and in one of these local HDC, called R17 (table 2) have had almost the same titers and therefore this local HDC could be considered as a candidate cell for production of measles virus vaccine in future if needed.

FIELD TRIALS AND MASS CAMPAIGNS WITH AIK-HDC VACCINE

In one field trial, 839 susceptible children were divided into five groups. Two groups were immunized with two home-produced vaccines (SUGIYAMA 5F100 and AIK-HDC) and three groups, with 3 other live vaccines (SCHWARZ, Leningrade-16 and BIKEN-CAM). The clinical responses were not significally different in the five groups. However, the children who received AIK vaccine exhibited milder reactions. Seroconversion rates were 95.5-100% and the mean HI titers between 5.2 log2 and 6.4 log2 for AIK and SUGIYAMA vaccines respectively (14). In another trial, children, aged 12 months to five years were immunized with SUGIYAMA 5F100 or with AIK-HDC vaccine. Respiratory disorders such as cough, coryza and tonsillitis were more severe With SUGIYAMA vaccine than with AIK vaccine. The seroconversion rates were 94.6% and 97.8 for SUGIYAMA and AIK vaccines respectively. The HI titer was about one log2 lower in children immunized with the AIK vaccine (15).

By 1977, both vaccines were being widely used, and by the end

of 1977 an 80% coverage had been achieved. AIK-HDC vaccine has gradually replaced SUGIYAMA vaccine and since 1981 only AIK vaccine-3 to 4 million doses are produced annually-is used throughout the country.

THE PRESENT SITUATION

It is worthy to be mentioned that following regular mass immunizations with mobile teams the high mortality due to measles or its effects - in rural areas of the country disappeared and no more waves of major epidemics are observed in remote rural areas.

The high incidence of measles-infection in urban regions of Iran has been a matter of concern during the last few years. Attention in the past had been focused to control the fatal epidemics in far remote regions of the country, while in cities people were asked to refer to the health centers for immunization of their children against measles, but most of people neglected this suggestion and this led to an increase of the number of susceptible children in urban areas where mass populations of low socioeconomic are living. Therefore measles epidemics have been frequent, during the last few years in the country. Fortunately, the Ministry of Health of Islamic Republic of Iran, in cooperation with WHO (Expanded Programme on Immunization: EPI) has planned to control measles in all cities and towns of the country. Both locally manufactured measles vaccine and some imported vaccines are being used in this new crusade against measles. In the same time a follow-up program, which is of primary importance for avoiding a return of measles in the rural sectors of the country is being planned.

AGE OF IMMUNIZATION

Until 1979 the age of vaccinees against measles in Iran was nine to twelve months. Revaccination was encouraged, especially when children were first immunized before 12 months of age. However, many deaths due to measles were reported among four to eight months old infants living among low socio-economic circumstances (12). As previously reported (16), most neonates have adequate levels of maternal antibody to measles virus. Four to six months after birth, this antibody is no longer detectable in most infants. Evidently, many of these children still have a trace of maternal antibody that probably, in combination with cell-mediated immunity, protect 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 schedule has been suggested. We believe in our country it is wise to vaccinate children at six to nine months of age and to revaccinate them six to nine months later.

FREQUENCY OF LATE COMPLICATIONS OF MEASLES IN IRAN

It is well known that DAWSON disease or subacute sclerosing panencephalitis (SSPE) is a rare disease which is known to be a late complication of measles infection of early childhood. This disease is relatively frequent in Iran. From 1975 to 1984, 200 cases were diagnosed as SSPE in our laboratory (2, 17, 24). Since there were controversial views regarding the influence of immunization with measles vaccine on the occurrence of SSPE (4, 19, 23), we were interested to investigate association of SSPE with measles vaccination. According to our study on 200 cases of SSPE, the disease hardly could-be attributed to measles vaccination but was clearly associated with natural measles infection (23).

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