

## EFFICACY AND SAFETY OF LIVE ATTENUATED SUGIYAMA STRAIN OF MEASLES VIRUS IN MASS IMMUNIZATION OF CHILDREN IN RURAL REGIONS OF IRAN (\*)

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Since the development of the live attenuated measles vaccine by John F. Enders, (2) Iran was among those countries which launched without delay mass vaccination campaigns against measles. What led to this decision was the high mortality due to measles or its effects in rural parts of the country. The situation regarding the high incidence of complications and mortality due to measles in urban areas of Iran was also a matter of concern. As a matter of fact, since the eradication of malaria, smallpox and diphtheria, measles remained the major hazard of childhood in populated urban regions.

### *Measles mortality in the cities*

To illustrate the mortality in urban population we shall report here on the mortality cases in the workers community in the city of Tehran for years 1969-1971. The figures on which Table 1 is based comes from a report of the Children's Hospital of Workers Community of the Teheran City, sponsored by the Health and Medical Section of Workers Social Security, Ministry of Labor, Tehran. The figures are most probably representative of the general trend in other cities of the country. The children of this community are admitted to the hospital when the complications of measles are severe. It is believed that during measles outbreaks not more than 10 per cent of very sick children are hospitalized. From the data in Table 1 we can assume that a significant number of cases occur in children under 12 months of age. These are mostly infants 5-9 months old, who together with the children aged less than two years are the main victims of the disease.

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Table 1  
*Measles complications and mortalities in children of the workers community — Teheran city*

Years	Cases						Deaths								
	< 12 months	1-2 years	2-5 years	5 > years	total	< 12 months	1-2 years	2-5 years	5 > years	total	< 12 months	1-2 years	2-5 years	5 > years	total
1970	511	307	265	—	1083	51	26	10	—	87	10	8.4	3.7	—	8.0
1971	309	475	245	73	1102	22	31	14	2	69	7.1	6.5	5.7	2.7	6.2
1972	365	521	288	100	1274	23	26	8	3	60	6.3	5.0	2.7	3.0	4.7

### *Measles mortality in the rural areas of Iran*

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 remote rural regions of Iran, causing over 50 per cent of the deaths among infants between 5 months and 4 years of age. The poor nutritional and socio-economic status of children, together with the lack of health centers 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 reported to be 2 and 62 per cent (1). In 1965, more than 10,000 deaths due to measles were estimated by the mentioned department (6).

### *Vaccination trials*

The first field trials was carried out under the auspices of the Ministry of Health in July-September 1966. According to Naficy et al. (6), 1484 children were inoculated in this trial with Edmonston B, Schwarz or Beckenham 31 strains of attenuated measles virus without need of human gamma globulin. The reactions to these vaccines were more severe in mountainous areas, probably because of colder climate.

The serological conversion rates for Edmonston B, Beckenham 31 and Schwarz strains of vaccine were 89,94 and 93 per cent respectively.

Two other investigations were carried out by Mirchamsy et al. (4, 5) with substantial help of the Ministry of Health. In the first study the results of immunization of 523 children 9 months to 5 years of age, with two attenuated Japanese measles vaccines, "Denken" and "Biken", were described. The clinical

reactions following vaccination with both vaccines were mild, but Denken vaccine produced rash more often than the Biken vaccine. The serological conversion was satisfactory for both vaccines.

In the second trial Denken vaccine, which consisted of Sugiyama live attenuated measles vaccine, produced at Razi Institute in bovine renal cells, was administered to 1365 susceptible children in three different regions. Clinical observations of immunized children revealed a mild fever lasting 3-4 days, which was accomplished by the appearance of a morbilliform rash which faded in 2 days.

The duration of pyrexia was longer on the plateau than in mountainous regions, especially when the vaccine was inoculated intra-muscularly. The seroconversion rate was 95 to 100 per cent.

In order to illustrate the clinical symptoms observed in mass vaccination campaigns in Iran, the results of our second study group will be reported on briefly here (5).

The site of this study was a privately owned textile factory located in a suburb of Karaj, a district 30 miles to the west of Teheran. In this area 2,013 susceptible children were immunized and some of them were selected for follow up of postvaccinal reactions and serological studies. A total of 354 children, ranging in age from 9 months to 5 years, without a history of measles, constituted this study group. They were vaccinated subcutaneously with a double dose of vaccine and were under the care of physicians and attendant personnel of the Health Department of the Teheran Region.

We can assume from Tables 2 and 5 that a mild fever (37-38° C) was observed in more than 55 per cent of inoculated children; 16.8 per cent of vaccinees manifested a pyrexia of 38-39°C and only 1.75 per cent of infants had fever exceeding 39°C. The onset of fever was 8-11 days after inoculation and the mean duration of pyrexia was 4.22 days. The variations of the mean duration and maximum fever based on age group were not significant in 285 vaccinated children. Forty-one per cent had a moderate morbilliform rash and 20 per cent a marked rash (Table 6). A slight cough or coryza were also seen in many subjects. Anxiety was the main disorder observed by mothers during the second week after vaccination. Other Signs such as otitis, diarrhoea or convulsions were not recorded during the period of follow-up. The results of serological studies are summarized in Table 7. In sera tested by the seroneutralization (SN) test, the seroconversion was 97.7 per cent with a mean titre of 7.1 log 2, with haemagglutination inhibition (HI) test, a seroconversion of 95.05 per cent with a mean titre of 7.5 log 2 was recorded.

Table 2  
Age and sex distribution of inoculated children

Total inoculated	Sex		Age (years)			
	Female	Male	9—12 months	> 1—2	> 2—5	> 5
354	165	189	62	133	121	38

Table 3  
Number of children developing fever

No. of children clinically assessed	Fever		
	37—38°C	38—39°C	> 39°C
	158 (55.4%)	48 (16.8%)	5 (1.75%)

Table 4  
Distribution of children by incubation period of fever

Onset (mean days)	8.11
Mean duration of pyrexia (days)	4.22
Mean duration of maximum temperature (days)	2.6

Table 5  
Pyrexia variation according to age group

Age	Mean duration (days)	Mean maximum fever (°C)
9—12 months	4.14	37.9
> 1—2 years	4.4	37.6
> 2—5 years	4.7	37.2
> 5 years	4.0	37.4

### *Mass immunization trial*

Following these observations a lot of 600,000 doses of Sugiyama live measles vaccine was made by Razi Institute using the Sugiyama strain received through the courtesy of Dr. S. Hashizume of Chiba Serum Institute, Japan. This vaccine lot as well as the subsequent batches of Sugiyama vaccine used thereafter in rural parts of Iran were prepared in Razi Institute with Sugiyama strain at the 82nd subculture in bovine renal cells.

In view of the satisfactory epidemiological and immunological results

obtained, a program was initiated by the Ministry of Health of Iran to protect the children at risk in the remote rural areas of the country where measles was ravaging the life of thousands of children .

The program of mass immunization in rural regions started in 1967, with the priority being given to rural areas and mountainous localities. By the end of 1971 the number of vaccinated children was about 3,517,547, which makes almost 37 per cent of the susceptible children (3).

The response of the population has generally been favourable. In most instances the vaccination was performed by health teams in a village along the street and door-to-door. Sometimes mothers were asked to bring their children to the places where vaccination was performed. They were also instructed to report on any complications or severe reactions that may occur during the two weeks following inoculation.

Table 6  
*Major symptoms observed in 285 children vaccinated with double doses of live Sugiyama strain, measles vaccine*

Symptom	Number	Percentage
Total inoculated	354	—
Total observed	285	80
Total reacting	175	61.4
Slight or moderate rash	118	41
Marked rash	57	20
Koplik spots	17	6
Corvza	153	54

#### *Evaluation of the results*

The remarkable effect of the mass vaccination program in reducing measles morbidity and mortality in rural parts of Iran became soon apparent. As it is reflected in Table 8 and Fig . 1, there was a close correlation between the reduced morbidity and deaths, and the initiation of the program of immunization. At the end of 1971, when a coverage of only 37 per cent was achieved, there was a 56 per cent reduction in morbidity and a dramatic decrease in mortality due to measles.

Table 7

*Serological findings, 1 month after immunization of children, study group 2  
with double-dose live Sugiyama measles vaccine*

Type of test	No. of sera tested	No. positive before immunization	No. response	Titres (log 2)											Mean titre	Sero-conversion %	
				1.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5			10
S. N.	221	18	5	11	11	15	19	33	23	44	20	14	12	15	—	7.1	97.70
H. I.			11	7	7	8	15	32	18	40	23	29	8	13	3	7.5	95.02

Table 8

*Morbidity and deaths from measles in rural areas of Iran, 1966—1971*

Years	Total cases reported	Cases studied in outbreaks		Percentage of deaths due to measles to total deaths caused by communicable diseases
		morbidity	deaths	
1966	127514	21931	2420	11.0
1967	92752	9218	892	9.7
1968	94365	6898	527	7.6
1969	84486	2544	198	7.8
1970	63751	1829	74	4.0
1971	57545	2753	152	5.5

Fig. 1. Effect of Vaccination on reported measles cases in Rural Regions of IRAN



### Comment

The present investigation confirms that immunization with Sugiyama live attenuated virus vaccine is highly effective in protecting against measles, and its application in rural areas of Iran, where the mortality due to measles complications is very high, has already resulted in a large saving of lives. This vaccine, at the 73rd 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 (7) to be safe and could be used without gamma globulin. About six million doses of this vaccine have so far been used throughout Iran mainly in rural regions in children of 9 months to 5 years without any untoward reactions.

Because of the high level of protection conferred by this vaccine and the low cost of its production, the Ministry of Health in Iran has decided to expand the program of mass immunization and to cover most of the rural regions and also urban parts of the country where the population is dense and to maintain the level of immunity by regular immunization of newborn infants reaching 9 months.

### SUMMARY

The mortality due to complications of measles is the major cause of deaths of children in rural parts of Iran.

Since the introduction of live attenuated measles vaccine, Iran was among

those countries where mass immunization against measles was started without delay.

The production of large batches of Sugiyama live attenuated measles vaccine, grown in primary calf kidney cells in Razi Institute and the mass use of this vaccine in rural areas of the country, resulted in the reduction of morbidity and drop of mortality due to this infectious disease.

#### REFERENCES

1. Annual Report of the Ministry of Health (Iran) 1962–1963 49–51.
2. *Enders, J. F., S. L. Katz, M. V. Milovanovic and A. Halloway*(1960): Studies on an attenuated measles virus vaccine. I–Development and preparation of the vaccine: technics for assay of effects of vaccination. *New Eng. J. Med.* 263 153–184.
3. *Manteghi, A.* (1972): Measles and its epidemiological evolution following vaccination in Iran (1961–1971) (In Persian). Report No. 41 Ministry of Health Iran.
4. *Mirchamsy, H., A. Shafyi, Y. Bassali, S. Bahrami and F. Nazari* (1970): A comparative study of two live measles vaccines in Iran. *J. Hyg. Camb.* 68 101–110.
5. *Mirchamsy H., A. Shafyi, S. Bahrami, P. Nazari, M. Mirzadeh and Y. Bassali* (1971): Mass immunization of children in Iran with live attenuated Sugiyama measles virus adapted to calf kidney cell cultures. *Jap. J. Exp. Med.* 41 39–48.
6. *Nafyici, K., S. Saidi, R. Nategh, A. Mostatab and A. Akbarshahy* (1967): Comparative studies of live attenuated and further attenuated measles vaccines in rural areas of Iran. *Arch. ges. Virusforsch.* 22 11–22.
7. *Shishido, A.* (1969): A field trial of further attenuated live measles-virus vaccines in Japan. *Jap. J. Med. Sci. Biol.* 22 191–200.