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PROPHYLACTIC EFFECTIVENESS OF LIVE INFLUENZA VACCINE IN 1965

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SUMMARY Mass vaccination with live influenza vaccine developed in our laboratory, was carried out in Osaka in November, 1964. Febrile reactions were observed in 262 of the 13,894 vaccinated persons (1.9 per cent). Of these 101 had to stay away from work (0.7 per cent). A four fold or higher increase in HI (hemagglutination inhibition) antibody against the homologous strain of influenza A2 virus was observed in 42 of 131 vaccinated persons (32 per cent). In February, 1965, an epidemic of influenza A2 was observed. The morbidity rate among 3,464 vaccinated persons was 13.2 per cent while that of 1,429 unvaccinated persons was 26.6 per cent. Thus the coefficient of effectivenss was 2.0. The epidemic was less severe in schools where children had been vaccinated with live influenza vaccine than in neighbouring schools where children had been vaccinated with inactivated vaccine. The average period of absence from school or work of infected persons was 2.3 days in the vaccinated group and 3.0 days in the unvaccinated group.

INTRODUCTION

Studies were made on live influenza vaccine and vaccines differing from the Soviet one were obtained. (NAKAMURA, 1961 a, b; OKUNO, 1963; OKUNO and NAKAMURA, 1964).

Field trials with live influenza vaccine have been carried out since 1960 (NAKAMURA and OKUNO, 1961; NAKAMURA, 1964; NAKAMURA, 1966; NAKAMURA and UEDA, 1965) but few data were obtained about its epidemiological effectiveness (NAKAMURA, 1964; NAKAMURA, 1966). A large epidemic of influenza A2 was observed in February and March, 1965 and so some data on the effectiveness of our live influenza vaccine could be obtained.

MATERIALS AND METHODS

1. *Live influenza vaccine*

The supernatant fluid after low speed centrifugation of allantoic fluid infected with influenza A2/Okuda/57 E277 or influenza B/Setagaya/3/56 E120 was used as live influenza vaccine after two fold dilution with 0.2 per cent gelatin PBS. The titers of the vaccine of influenza A2 were $10^{8.5}$–$10^{9.0}$ EID_{50}/0.1 ml and 1024 HAU/ml and those of influenza B were $10^{7.5}$-$10^{8.0}$ EID_{50}/0.1 ml and 1024–2048 HAU/ml. Combined vaccination with influenza A2 and B (1:1 in volume) was done by spray with a nebulizer and inhaled by adult for 10 seconds and by children for 6 seconds as previously described (NAKAMURA, 1966).

2. *Vaccination*

Vaccination was carried out in primary schools, a factroy, a hospital and a housing site. Ages of vaccinated persons varied from 1 year to old adults. Vaccination was started at the end of October and ended at the beginning of December, 1964.

3. *Collection of serum specimens*

Serum specimens were collected at the time of vaccination and 3–5 weeks after vaccination from about 10 persons in one group. In this way, 87 paired sera were collected from children of 11–13 years of age and from adults of various ages.

4. *Investigation of clinical reactions*

All persons inoculated with live influenza vaccine were requested to record clinical reactions on cards and these cards were subsequently collected.

5. *Hemagglutination inhibition (HI) test*

Sera were stored at −15°C before antibody titrations. Paired sera were heated at 56°C for 30 minutes. No additional inhibitor treatment was used. Volumes of 0.25 ml of serial two fold dilutions of sera were prepared in saline and then 4 units of hemagglutinin in 0.25 ml saline was added. The mixtures were mixed with 0.5 ml of 0.5 per cent chicken red blood cells. Titers were expressed as the reciprocals of the highest dilution at which hemagglutination was completely inhibited.

6. *Investigation of epidemiological effectiveness*

An acute respiratory disease during the epidemic period was taken as a case of influenza. The morbidity rates of the vaccinated and unvaccinated persons in the same groups were investigated by questionaires. In the primary schools, absence from school was judged as a case of influenza. Other studies showed that the rate of absence from school for other reasons than an acute respiratory disease, was fairly constant at about 1 per cent.

RESULTS

1. *Clinical reactions*

The reports of 13,894 persons on their clinical reactions were examined and 101 of these (0.73 per cent) were found to have been absent from work for an average of 1.4 days. 366 persons had found some difficulty in doing their work. Febrile reactions were observed in 262 persons (1.9 per cent) and the mean maximal fever was 37.6°C. The mean incubation period and duration of fever were 20 and 13 hours respectively. Lassitude, headache and chilliness were observed in 3.0 per cent, 4.4 per cent and 1.8 per cent of the persons respectively. Rhinorrhea, nasal obstruction, throat pain and cough were observed in 1.6 per cent, 1.6 per cnet, 1.7 per cent and 1.7 per cent of the people respectively. (Table 1). The reaction rate varied from one group to another but children did not always show more clinical reactions than adults.

2. *Antibody response*

When the pre-vaccination antibody titer was 32 or lower, the HI antibody response against the Okuda strain of influenza A2 virus was observed in 42 out of 131 persons (32 per cent). When the titer was higher than 32, no antibody

TABLE 1 *Clinical reactions by live influenza vaccine in November and December, 1964*

	Clinical reactions	
	Number	Per cent
Subjects	13,894	100
Disturbance of work	366	2.6
Absence from work	101	0.7
Fever	262	1.9
Lassitude	414	3.0
Headache	620	4.4
Feeling of cold	247	1.8
Dizziness	26	0.02
Pain in lower back or joints	66	0.05
Exanthema	28	0.02
Rhinorrhea	216	1.6
Nasal obstruction	227	1.6
Throat pain	237	1.7
Cough	245	1.7
Diarrhea	53	0.04
Others*	44	0.03

* Include dry feeling of the throat, stomach-ache, nausea etc.

response was observed. (Table 2). No remarkable antibody response was observed against the Setagaya strain of influenza B virus.

3. *Epidemiological effectiveness*

The epidemic of influenza A2 began in February 1965. The morbidity rate among 3,464 vaccinated persons was 13.2 per cent and in 1,429 unvaccinated persons was 26.6 per cent and so the effectiveness coefficient was 2.0 (Table 3). The period of absence from school or work of infected persons was 2.3 days in the group vaccinated with live influenza vaccine and 3.0 days in the unvaccinated group and so was 0.7 days shorter in the vaccinated group. (Table 4). The mean maximal fever was 38.4°C in the vaccinated group and 38.6°C in the unvaccinated group.

The epidemic was remarkably mild among the pupils of primary schools in the Minato Ward in which children had been vaccinated with live influenza vaccine for 4 consecutive years. In primary schools in neighbouring districts, namely the Taisho and the Konohana Ward, in which children were vaccinated with inactivated vaccine as ordinary prophylactic procedure in shcools, a servere epidemic of influenza was observed in most schools. (Figs. 1 and 2). The vaccination rates in the schools are shown in Table 5.

TABLE 2 *HI antibody response by live influenza vaccine against influenza A2 Okuda strain in November and December, 1964 in Osaka district*

Prevaccination HI antibody titer (log_2)	No. of subjects	Postvaccination HI antibody titer (log_2)							4 fold or more rise	
		<4	4	5	6	7	8	9≤	No.	%
<4	29	5	9	8	6	1			15	52
4	44		6	22	13	3			16	36
5	58			21	16	9	2		11	19
6	57			7	40	10			0	0
7	26				5	14	7		0	0
8	11					1	10		0	0
Total	225	5	15	58	90	38	19		42	19

TABLE 3 *Epidemiological effectiveness of live influenza vaccine*

Group	Age	Vaccinated		Unvaccinated		Coefficient of effectiveness
		No. of subjects	Morbidity rate (%)	No. of subjects	Morbidity rate (%)	
Primary school-I	6–13	647	8.2	280	28.9	3.5
Primary school-II	6–13	927	11.6	409	14.7	1.3
Primary school-III	6–13	918	14.4	514	30.3	2.1
Nursery school	1–6	434	11.0	66	25.8	2.6
Primary school-IV	6–13	296	23.6	35	51.5	2.2
Housing site-I	Adult	87	22.0	52	36.5	1.7
Housing site-II	Adult	155	18.1	73	39.7	2.2
Total		3464	13.2	1429	26.6	2.0

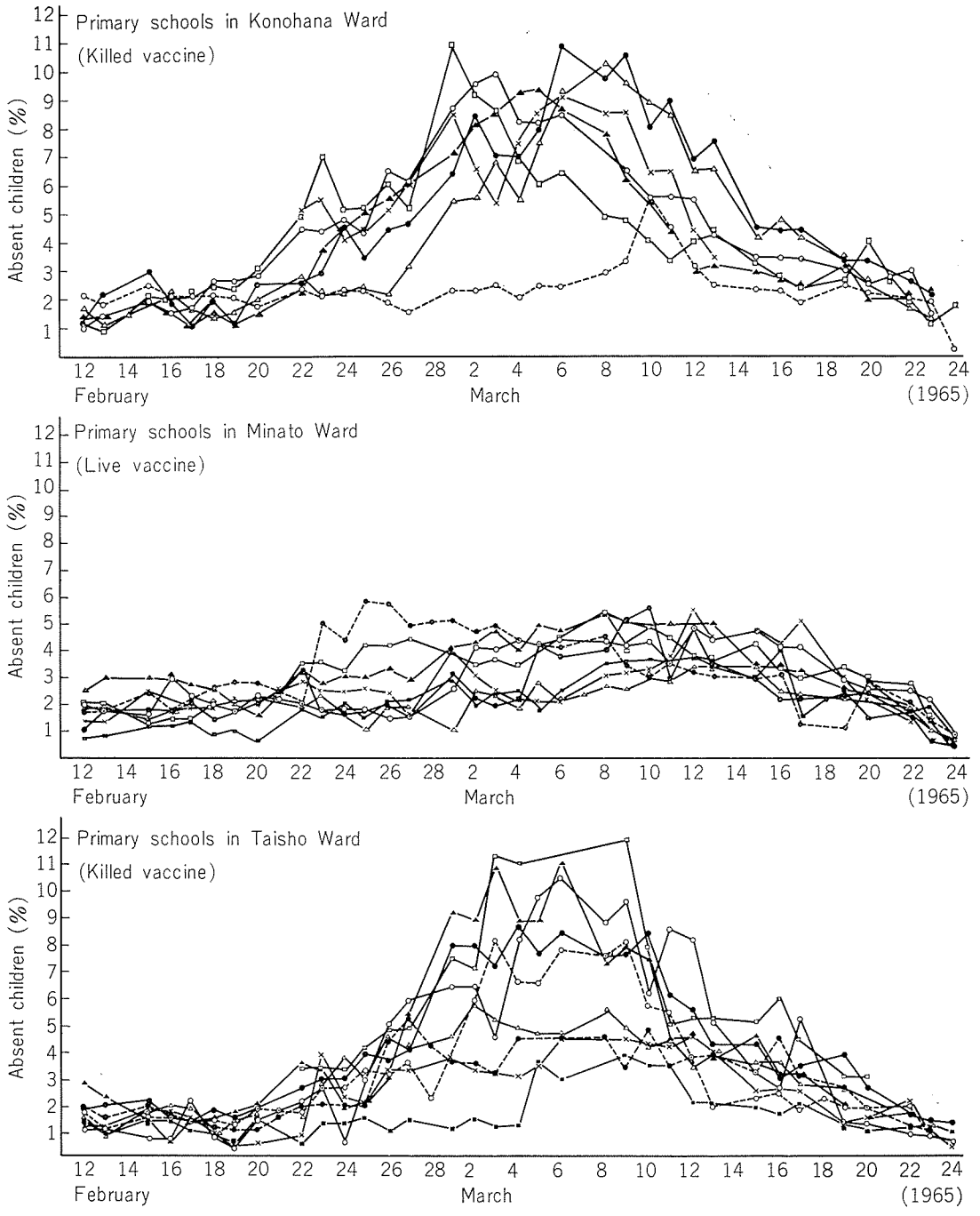

FIGURE 1 Influenza epidemic in primary schools in Minato Ward and in neighbouring Wards.(One line indicates the absence rate of children in one school during the epidemic period)

TABLE 4 *Days of absence from work due to epidemic influenza*

	No. of subjects	Days absent from work											
		1	2	3	4	5	6	7	8	9	10	11 or more	Mean
Vaccinated	419	168	128	51	27	23	11	5	2	1	1	2	2.3
Unvaccinated	383	95	85	83	41	37	32	5		1	4		3.0

TABLE 5 *Vaccination rate in schools*

Ward	No. of Schools	No. of children		Vaccination rate (%)	
		A school	Total	A school	Mean
Konohana	7	730–1238	7245	56–80	71
Minato	8	756–1556	9217	56–92	69
Taisho	9	720–1679	6965	66–96	81

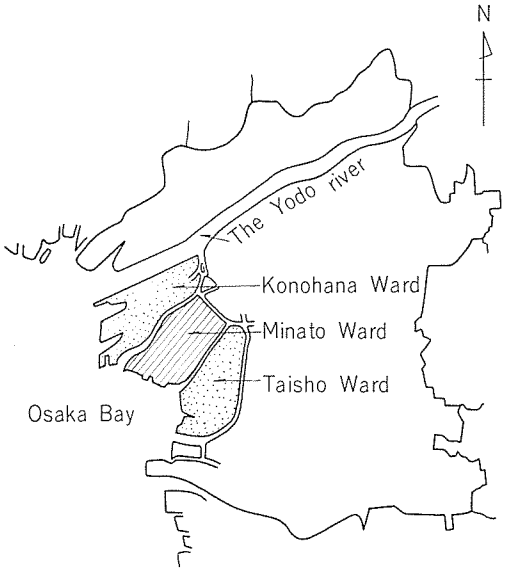

FIGURE 2 Map of Osaka city

DISCUSSION

1. *Method of vaccination*

From the practical point of view, the inhalation method is very convenient and better than the intranasal spraying method used in Soviet Russia, although it needs the special apparatus. No feeling of discomfort was felt in vaccinees and a very small volume of vaccine was consumed per person by the inhalation method. (NAKAMURA, 1961 a). Soviet workers say that febrile reactions were inevitable by the inhalation method (SMORODINTSEV, 1957), but they were rarely experienced when we used this method.

2. *Clinical reactions*

Clinical reactions were rather few but some persons showed transient fever. Data in our preceding paper show that almost all symptom such as headache, lassitude or rhinorrhea are not due to vaccination (NAKAMURA and UEDA, 1965). Our live influenza vaccine does not provoke or only rarely provokes local catarrhalic sign. As shown in the preceding paper (NAKAMURA, 1964, 1966; NAKAMURA and UEDA, 1965) no remarkable differences were observed between the clinical reactions of children and adults with our live vaccine, which seems to show that our vaccine is preferable to Soviet vaccine which cannot be used for children (SMORODINTSEV, 1957; BAROYAN and BOLOTOVSKY, 1962). The observation that

local catarrhalic signs were rarely seen or were negligible, seems to show that our vaccine is more attenuated than the Soviet vaccine.

3. *Antibody response*

This year, the HI antibody response against influenza A2 was not so good as in past years. (NAKAMURA and OKUNO, 1961; NAKAMURA, 1966). This is probably due to the fact that the prevaccination antibody titer was relatively high. A remarkable HI antibody response against influenza B Setagaya strain was observed in Spring, 1961 (NAKAMURA, 1964), but it was not observed in December, 1961 (NAKAMURA, 1966) or subsequently because the prevaccination HI antibody titer was relatively high.

4. *Epidemiological effectiveness*

The coefficient of effectiveness this year was 2.0. A more effective vaccine is desirable but this coefficient is no worse than that of the killed vaccine. The coefficient of the Soviet vaccine (BERLYANT, 1960; SLEPUSHKIN, 1953) does not seem to exceed that of ours. The epidemiological data seem to show that this vaccine is better than the killed vacicne now commonly used in our country. Generally speaking, the live vaccine not only reduces the incidence rate, but also accelerates the recovery of infected persons. Similar data were also observed in field trials in December, 1961 (NAKAMURA, 1966). The strain isolated in 1957 was used for vaccine production and so the antigenicity of the vaccine strain seems to be somewhat different from that of the epidemic strains. Since even this vaccinal strain was effective, it may be possible to obtain more effective results with antigenically similar strains.

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REFERENCES

BAROYAN, O. V. and BOLOTOVSKY, V. M. (1962). Preliminary result of influenza vaccination. Communication I. The degree of immunogenicity and the intensity of reaction in response to administration of various anti-influenza preparatus. *J. Microbiol. Epidemiol. Immunobiol.* No. 11, 57–62. (in Russian, with English summary)

BERLYANT, M. L. (1960). Epidemilogical effectiveness of live influenza vaccines of A2 and A, A1, B types. *Vopr. Virusol.* No. 1, 50–52. (in Russian, with English summary)

NAKAMURA, K. (1961 a). Studies on the live influenza virus vaccine. *Igaku no Ayumi* **38**, 689–694. (in Japanese)

NAKAMURA, K. (1961 b). Studies on the live vaccine of the influenza A2. *Virus* **11**, 257–266. (in Japanese, with English summary)

NAKAMURA, K. (1964). Field trials of live influenza B vaccine carried out in January and February in 1961. *Igaku Hyoron* (*Japana Medicina Revuo*) No. 28, 24–28. (in Japanese)

NAKAMURA, K. (1966). Mass immunization with live influenza vaccine in Osaka from December, 1961 to February, 1962. *Igaku Hyoron* (*Japana Medicina Revuo*) No. 30, 26–33. (in Japanese, with English summary)

NAKAMURA, K. and OKUNO, Y. (1961). Vaccination with live attenuated influenza virus at the Osaka University Hospital in 1960. *Virus* **11**, 349–354. (in Japanese, with English summary)

NAKAMURA, K. and UEDA, S. (1965). Field trials of live influenza vaccine carried out from December 1962 to February 1963. *J. Japan Assoc. Infect. Dis.* **39**, 247–253. (in Japanese, with English summary)

OKUNO, Y. (1963). Prophylaxis of influenza. Especially on live influenza vaccine. *XVI Jap. Med. Congress.* No. 2, 211–221. (in Japanese)

OKUNO, Y. and NAKAMURA, K. (1964). On live influenza vaccine. *Nihon Iji Shinpo.* (*Japan Med. J.*) No. 2121, 15–21. (in Japanese)

SLEPUSHKIN, A. N. (1953). Comparative study of effectiveness of anti-influenza vaccine. *J. Microbiol. Epidemiol. Immunobiol.* No. 10, 46–49. (in

Russian, with English summary)

SMORODINTSEV, A. A. (1957). A living anti-influenza vaccine and anti-influenza serum for influenza prophylaxis and treatment. *Proceedings, Third International Meeting of Biological Standardization* 97–101.