

Original Article

## Failure of inactivated influenza A vaccine to protect healthy children aged 6–24 months

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### Abstract

**Background:** The efficacy of inactivated influenza vaccine in healthy infants and children younger than 24 months has not been confirmed. The aim of the present study was to determine the prophylactic effect of inactivated influenza vaccine against influenza A in healthy children aged 6–24 months.

**Methods:** Healthy infants and young children (6–24 months old) were immunized by subcutaneous injection of inactivated influenza vaccine before influenza seasons. Age matched children were randomly assigned as the control. These children were followed up from January to April in each year (2000, 2001 and 2002). The attack rates of influenza A infection was compared and statistically assessed.

**Results:** The attack rate of influenza A virus infection in the vaccine group and the control group were 14.8% ( $n = 27$ ) vs 12.5% ( $n = 32$ ) in 2000 ( $P = 0.526$ ); 2.8% ( $n = 72$ ) vs 7.2% ( $n = 69$ ) in 2001 ( $P = 0.203$ ); and 3.4% ( $n = 52$ ) vs 8.9% ( $n = 56$ ) in 2002 ( $P = 0.205$ ). The attack rates of influenza A between the two groups were not significantly different.

**Conclusion:** Inactivated influenza vaccine did not reduce the attack rate of influenza A infection in 6–24 month old children.

### Key words

influenza, vaccine, children, infant.

Different countries have selected a range of different programs for influenza vaccine recommendations. In the United States, inactivated influenza vaccine is recommended for any person aged >6 months old who is at increased risk for complications.<sup>1</sup> In Japan, the inactivated influenza vaccine had been administered to schoolchildren, but because of the lack of supporting studies for this approach at the time the government discontinued the program in 1994.<sup>2,3</sup> Many cases of influenza-associated encephalitis-encephalopathy have been reported in Japan since the discontinuation of the program, and the major target of the complication is children <5 years old.<sup>4,5</sup> Two recent studies have shown increased rates of influenza-related hospitalizations among children <2 years old.<sup>6,7</sup> Subsequently, it is now being debated whether inactivated influenza vaccine should be given to young children and infants.

We have previously reported that inactivated influenza vaccine is effective in preventing influenza A infection in preschool children in the 2–7-year-old age group, as well as in adults.<sup>8</sup> However, in the same article we also suggested that vaccination of children <2 years old is not effective for prevention of influenza.<sup>8</sup>

Our current objective was to estimate the clinical prophylactic effect of inactivated influenza vaccine in healthy infants and children <24 months old.

### Methods

#### Study population

Healthy infants and young children who were 6–24 months old at the time of recruitment were enrolled in the study. Informed consent was obtained from parents. A total of 175 children were given inactivated influenza vaccine between November and December in 1999, 2000 and 2001 at Public Shisou General Hospital (Shisou-Gun, Japan) or Rokko Island Hospital (Kobe City, Japan). As the control group, 171 age matched infants and children in good health, who did not

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receive influenza vaccine within 1 year of enrolment, were randomly assigned from medical records of the hospitals.

Children with any congenital disorders or chronic illnesses were excluded from the study. Patients who were taking medications that might interfere with the study were also excluded.

### Immunization

The immunization protocol was begun early in November and ended in December in 1999, 2000 and 2001. The vaccine group received commercial inactivated influenza vaccines provided by the Research Foundation for Microbial Disease of Osaka University. The vaccine for the 1999/2000 influenza season contained 200 chick cell agglutination units per mL (CCA/mL) of A/Beijing/262/95 (H1N1), 350 CCA/mL of A/Sydney/5/97 (H3N2) and B/Shandong/7/97. The vaccine for the 2000/2001 influenza season included >15 µg hemagglutinin per 0.5 mL of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) and B/Yamanashi/166/98. The vaccine for the 2001/2002 influenza season contained >15 µg hemagglutinin per mL of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) and B/Johannesburg/5/99.

Each dose of subcutaneous injection were administered as follows. Infants younger than 12 months old were given 0.1 mL of the vaccine, and young children from 12–24 months old were given 0.2 mL of the vaccine. They received two doses of the vaccine 14 days apart.

For ethical reasons, we did not use placebo injections as a substitute for the vaccine in the control group.

### Diagnosis of influenza A virus infection

Influenza A virus infection was defined by a positive result of the enzyme immunoassay membrane test (Directigen FLU-A antigen test, Becton Dickenson Microbiology Systems, Cockeysville, MD, USA) of specimens from patients' pharynges. The test was performed according to the direction of the manufacture. The Directigen FLU-A utilizes enzyme-conjugated monoclonal antibodies that are specific for conserved regions of influenza A nucleoprotein. The test detects influenza A virus but not influenza B.

### Follow-up

The follow-up period was from January to April in each year (2000, 2001 and 2002). The participating children were asked to come to the hospitals within 48 h if they ever developed a febrile illness. When the children were seen for a febrile illness (>38.0°C), in addition to the physical examination, throat swabs from the children were examined by the enzyme immunoassay membrane test to detect influenza A virus antigen. The results of the examinations were recorded.

**Table 1** Characteristics of the study infants and children

	Vaccine group	Control group
1999–2000		
<i>n</i>	27	32
Male (%)	8 (29.6)	14 (43)
Female (%)	19 (70.4)	18 (56)
Age (months) <sup>†</sup>	14.2 ± 4.6	16.4 ± 4.9
2000–2001		
<i>n</i>	72	69
Male (%)	39 (54.2)	33 (47.8)
Female (%)	33 (45.8)	36 (52.2)
Age (months) <sup>†</sup>	15.9 ± 5.5	14.6 ± 5.0
2001–2002		
<i>n</i>	58	56
Male (%)	37 (63.8)	30 (53.6)
Female (%)	21 (36.2)	26 (46.4)
Age (months) <sup>†</sup>	16.7 ± 4.6	15.8 ± 4.4

<sup>†</sup>mean ± SD.

Whether febrile episodes of all children were recorded was confirmed by questionnaires during the follow-up period sent to all participants, or direct interviews at the end of the study period.

### Statistical analysis

The outcome was compared by Fisher's exact test. Differences were considered significant if  $P < 0.05$ .

## Results

### Study participants

The number of infants and young children aged 6–24 months who received inactivated influenza vaccine in each time period were as follows: 30 in 1999–2000; 79 in 2000–01; and 66 in 2001–02. The numbers of children enrolled in the control groups for each year were: 36 in 1999–2000; 74 in 2000–01; and 65 in 2001–02. Among the vaccine group, 27 participants in 1999–2000, 72 in 2000–01 and 58 in 2001–02 completed the trial. Thirty-two infants and children in the control group in 1999–2000, 69 in 2000–01 and 56 in 2001–02 completed the trial. The characteristics of the vaccine group and the control group were not statistically different (Table 1).

### Prophylactic efficacy

The numbers of influenza A infection patients were: four of 27 children (14.8%) in the vaccine group and four of 32 (12.5%) in the control group in the 1999/2000 influenza season ( $P = 0.526$ ) (Table 2); two of 72 (2.8%) in the vaccine

**Table 2** Attack rate of influenza virus A infection in children <24 months old

	Vaccine group	Control group	<i>P</i>
1999–2000			
attack rate	14.8%	12.5%	0.526
Influenza patients/subjects	4/27	4/32	
2000–2001			
attack rate	2.8%	7.2%	0.203
Influenza patients/subjects	2/72	5/69	
2001–2002			
attack rate	2.1%	9.1%	0.154
Influenza patients/subjects	2/52	5/56	
Total			
attack rate	4.8%	9.0%	0.117
Influenza patients/subjects	8/157	14/157	

group and five of 69 (7.2%) in the control group in the 2000/2001 influenza season; and two of 58 (3.4%) in the vaccine group and five of 56 (7.2%) in the control group in the 2001/2002 influenza season. The results in the latter two influenza seasons were not statistically significant ( $P = 0.203$ ,  $P = 0.205$ , respectively) (Table 2). Attack rates of influenza A over the three influenza seasons in the vaccine group and the control group were, respectively, 5.1% (8 of 157) and 8.9% (14 of 157), which was statistically not significant ( $P = 0.117$ ) (Table 2).

### Influenza patients

A total of 24 children were infected with influenza A (eight in the vaccine group, 14 in the control group). The mean ( $\pm$ SD) age of the patients infected with influenza A were  $14.3 \pm 5.7$  months in the vaccine group and  $15.7 \pm 4.9$  months in the control group ( $P = 0.608$ ). None of these patients required hospitalization or developed serious influenza complications.

### Discussion

The attack rate of influenza A virus infection in 6–24 months old healthy infants and children was not significantly different between the vaccine group and the non-vaccine group. That is to say, the inactivated influenza vaccine was of little or no benefit in the prevention of influenza A virus infection among these young children.

It is difficult to distinguish influenza virus infection from other respiratory viruses infections, particularly respiratory syncytial virus, which has clinical manifestations resembling those of influenza, is prevalent in the winter, and is often

coincident with influenza.<sup>9,10</sup> In the present study, to separate the effects of cocirculating viruses from influenza virus A, an enzyme immunoassay membrane test (Directigen FLU-A test) was used for making a diagnosis of influenza infection. The negative predictive value and the false-negative rate of the test were 100% and 0%, respectively, and there was no evidence of cross-reactivity with non-influenza A antigen.<sup>11</sup> Hence, the reliability of the results of the test were comparable to the other diagnostic methods such as virus isolation.

Although sero responses of infants and young children to the influenza vaccines were identified, the responses vary with the vaccine immunogen in this population.<sup>12</sup> The study of Innocent *et al.* showed that vaccination with inactivated influenza A virus vaccine dose not invariably induce detectable cytotoxic T lymphocyte activity in infants 6–24 months old.<sup>13</sup> For these reasons or others, the prophylactic effect of the vaccine in 6–24 month old children may be limited.

Recent studies have shown increased rates of influenza-related hospitalizations among <24 months old children and suggest that routine influenza vaccination should be considered in these children.<sup>6,7</sup> For this reason, influenza vaccination of all children in this age group is encouraged when feasible in the United States.<sup>1</sup> The utility of the vaccine should be considered from many perspectives. The prophylaxis effect of the vaccine against influenza is one of the important factors to consider in making a decision about recommending the vaccine. The vaccine efficacy of reducing the risk for influenza-related complications and hospitalization is also important. However, it is uncertain whether influenza vaccination is effective in preventing secondary complications or reducing the risk for influenza-related hospitalization among 6–24 months old children, although the vaccination among older persons can reduce the risk for hospitalization and death.<sup>14,15</sup>

To justify influenza vaccination of healthy infants and young children, a high benefit-risk ratio is required. Taking these factors into consideration, together with the results of the present study, additional studies to confirm the vaccine benefit among infants and children <24 months of age are needed before implementation of the proposed recommendations.

### Conclusion

We conclude that inactivated influenza vaccine did not reduce the attack rate of influenza A virus infection in 6–24 months old children. This negative vaccine result suggests that the strategy for controlling influenza viruses infection in this age group may need to be different from that in older children and adults.

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