Short Communication

Diarrhea as a Minor Adverse Effect Due to Oral Polio Vaccine

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SUMMARY: Using the adverse events monitoring system of Japan, we observed diarrhea cases in approximately 10% of patients who received oral poliovirus vaccine (OPV). This study was conducted to investigate whether diarrhea among children aged 0 to 1 is caused by OPV or by other factors such contact at the doctor's office and/or with others outside the home. We conducted a survey of the health of children after regular health check-ups and after the administration of the OPV. The data from the health check-ups were used as a control for the OPV case group. We compared the first-OPV dose vaccination group as well as the second-OPV dose vaccination group to the health check-up group. For cases of diarrhea, the odds ratio of the OPV group to the health check-up group was 1.776. Our findings strongly suggest that post-OPV cases of mild diarrhea are closely related to the administration of the OPV.

Oral poliovirus vaccine (OPV) is a highly effective vaccine for the prevention of poliomyelitis and is recognized as very safe vaccine with almost no major severe adverse side-effects, with the exception of rare cases of vaccine-associated paralytic poliomyelitis (VAPP) due to the administration of live poliovirus vaccines. On the other hand, minor adverse effects, especially diarrhea, have been noted in a clinical process report (1). In Japan, the Ministry of Health, Labour and Welfare requested a report of health status after routine vaccination during a given period every year in order to monitor adverse effects resulting from the vaccination (2,3). As many as 8,000 children are monitored for 1 month after receiving the poliovirus vaccination. Among those, diarrhea is reported for approximately 10% at 1-3 days post-OPV administration.

However, since no statistical analyses including a control group have been included in such reports, it has not yet been established whether diarrhea is indeed caused by the OPV or by other factors such as contact during a doctor's visit or contact with others. Nevertheless, the reported symptoms have been mild and therefore have not influenced the vaccination policy itself. Some caregivers in Japan remain concerned about even these mild adverse effects, and very often doctors are asked about a possible relationship between the onset of diarrhea and the administration of the OPV. Thus, we examined the issue in more detail in order to clarify whether or not diarrhea is indeed an adverse effect of the OPV (4).

In order to compare the health status of children who received a check-up only with that of those who received a first or second dose of the OPV, we asked parents to monitor their child's health after a visit to the doctor for a health check-up and to monitor the child's status post-OPV; the same questionnaire was used in both cases.

We conducted the survey in six cities (Sakai, Kanazawa, Adachi, Bunkyo, Matsuyama, and Echizen) from November 2005 to March 2006. In these cities, the OPV was delivered via group vaccination. We asked the parents of children who received the OPV or who underwent health check-ups to monitor their children for 2 weeks. The reports were recorded on postcards; 8,700 cards were sent to the OPV group, and 4,130 cards to the health check-up group. The details of this survey are summarized in Table 1.

For the purpose of comparison, the questionnaire was designed to be similar to the post-vaccination health survey conducted by the Ministry of Health, Labour and Welfare. Questions included those regarding the date of fever onset, convulsions, vomiting, diarrhea, and other symptoms.

We excluded those children for whom the observational period was shorter than 2 weeks, those who were more than 3 years old, and those for whom complete relevant information was not provided or available. Moreover, the observation period for children in the health check-up group who received any vaccination within the 2-week period was ended on the day before the vaccination was received.

We adopted three analytical methods. First, we compared

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Table 1. Number of postcards sent and rate of returned postcards by area

	OPV group		Health check-up group	
	No. of post-cards sent	Rate of returned postcards (%)	No. of post-cards sent	Rate of returned postcards (%)
Sakai	1,400	44.36	1,400	35.79
Kanazawa	1,200	55.50	1,200	24.67
Adachi	5,500	41.24	1,000	29.50
Matsuyama	0		360	38.33
Echizen	0		50	58.00
Bunkyo	600	46.00	120	40.00
	8,700	44.03	4,130	31.65

the incidence rate for each day among the two groups. Second, we estimated the survival function (i.e., the rate of children showing no symptoms in the two groups), and we determined by log-rank test and Wilcoxon's test the null hypothesis showing that the two lines representing the two groups would be identical. Third, when there was a significant difference between the characteristics of the two groups, we estimated the incidence rate of the two groups using Cox's proportional hazard model controlling for differences in characteristics among the two groups, and thus we tested for the potential effects of vaccination. In our estimation, the following explanatory variables were used: vaccination status, age classification, gender, and geographical region. We also examined the first-dose vaccination group versus the health check-up group as well as the second-dose vaccination group versus the health check-up group, and all available samples were included in the analysis.

Table 1 shows the number of returned postcards with the rate of return. A total of 3,831 records were received for the OPV group, and thus the rate of return was approximately 44.0%. For those in the health check-up group, we received 1,307 records, and thus the latter rate of return was approximately 31.7%. The rates of return for each city were as follows: 40.1% for Sakai, 40.1% for Kanazawa, 39.4% for Adachi, 38.3% for Matsuyama, 58.0% for Echizen, and 45.0% for Bunkyo.

Table 2 summarizes the descriptive statistics. There appears to have been no gender bias in either group, and we confirmed this using a *t* test (where probability under the null hypothesis = 0.421). Conversely, we found a significant difference in age (probability under the null hypothesis <0.0005). Therefore, to the need to control for the effect of age was established.

The survival function for those lacking symptoms and the 95% confidence interval (CI) for the two groups were calculated for the following symptoms: fever (Fig. 1), vomiting (Fig. 2), and diarrhea (Fig. 3). The statistical test for these survival functions indicates that there was a significant difference among the two groups only in the category of diarrhea.

We also calculated the survival function of those showing no symptoms according to each dose of OPV, i.e., for the first dose (Fig. 4) as well as the second dose (Fig. 5).

Table 3 shows the estimated results of Cox's proportional hazard model for diarrhea. The estimated numbers of each variable represent the odds ratio comparisons with a default status, i.e., a 3- to 5-month-old boy in Sakai who was seen for a health check-up. We found that for diarrhea, the odds

ratio of the OPV group compared to the health check-up group was 1.776 (95% CI, 1.274-2.476). We also estimated Cox's proportional hazard model by each symptom.

There were no statistical differences in terms of the incidence of fever, convulsions, or vomiting among the OPV and health check-up groups; thus children in both groups showed similar incidence rates. However, the OPV group had a statistically significant higher incidence of diarrhea than the health check-up group. Since diarrhea appears to be rare in wild-type poliovirus-infected patients, post-OPV diarrhea has been considered to be either a coincidental event or caused by
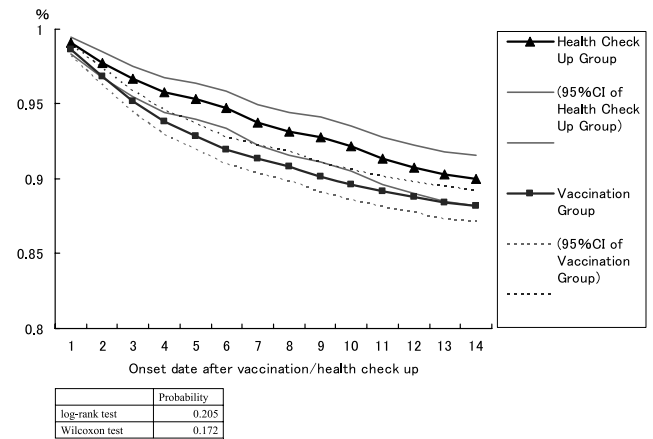

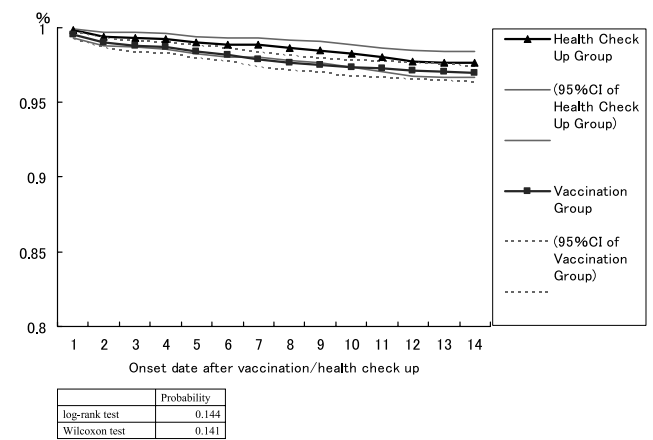|	Probability
log-rank test	0.205
Wilcoxon test	0.172

Fig. 1. Survival function for fever.

	Probability
log-rank test	0.144
Wilcoxon test	0.141

Fig. 2. Survival function for vomiting.

	Probability
log-rank test	0.000
Wilcoxon test	0.000

Fig. 3. Survival function for diarrhea.

Table 2. Descriptive statistics

		Total (*n* = 4,794) N (%)	OPV group (*n* = 3,579) N (%)	Health check-up group (*n* = 1,215) N (%)
Gender	Male	2,406 (50.19)	1,809 (50.54)	597 (49.14)
	Female	2,388 (49.81)	1,770 (49.46)	618 (50.86)
Age	3-5 m	777 (16.21)	171 (4.78)	606 (49.88)
	6-8 m	872 (18.19)	865 (24.17)	7 (0.58)
	9-11 m	864 (18.02)	843 (23.55)	21 (1.73)
	1 y	2,145 (44.74)	1,565 (43.73)	580 (47.74)
	2 y	136 (2.84)	135 (3.77)	1 (0.08)

"N" denotes the number of samples in the below analysis. Probability for *t* test under the null hypothesis that gender distributions are the same in the two groups is 0.421. Conversely, probability for *t* test for equal average age is less than 0.0005.
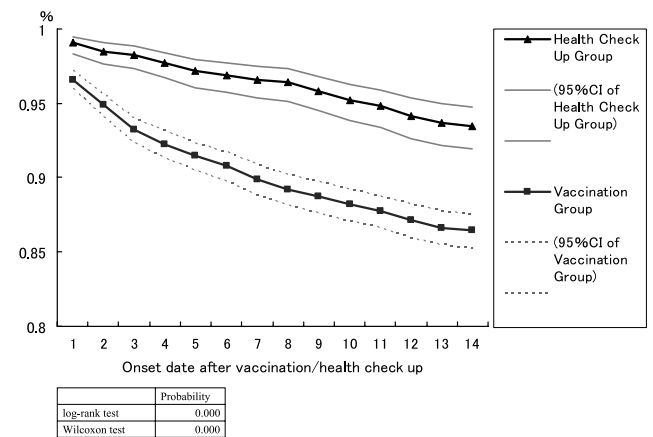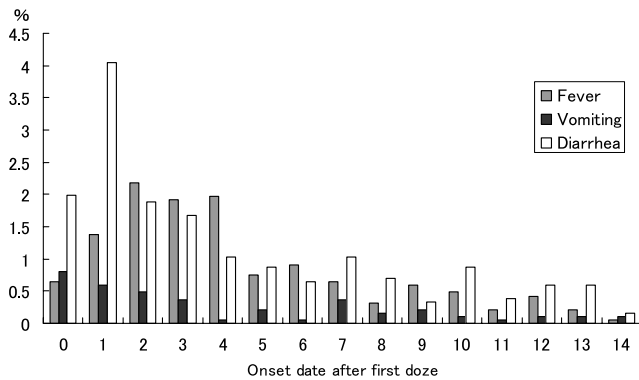
Fig. 4. Onset date for fever, vomiting, and diarrhea after first dose of polio vaccination.
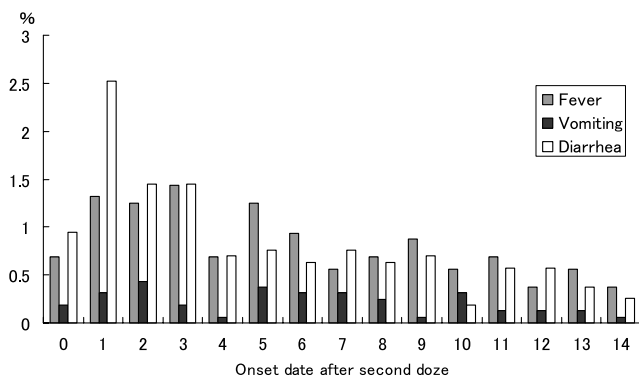
Fig. 5. Onset date for fever, vomiting, and diarrhea after second dose of polio vaccination.

Table 3. Estimation result of Cox's proportional hazard model for diarrhea

	Odds ratio	Probability	95% confidence interval
OPV	1.776	0.001	1.274 - 2.476
6-8 m	1.782	0.006	1.181 - 2.688
9-11 m	1.991	0.001	1.325 - 2.991
1 y	1.491	0.035	1.028 - 2.164
2 y	1.074	0.836	0.546 - 2.113
Female	1.015	0.866	0.858 - 1.200
Kanazawa	1.057	0.704	0.793 - 1.409
Adachi	1.158	0.232	0.910 - 1.474
Matsuyama	1.555	0.178	0.818 - 2.955
Echizen	3.036	0.013	1.265 - 7.286
Bunkyo	0.992	0.969	0.669 - 1.471
First-OPV dose	1.903	0.002	1.273 - 2.844
6-8 m	1.666	0.022	1.077 - 2.576
9-11 m	2.037	0.001	1.316 - 3.152
1 y	1.519	0.04	1.019 - 2.264
2 y	1.750	0.446	0.415 - 7.383
Female	1.182	0.118	0.958 - 1.457
Kanazawa	0.706	0.067	0.486 - 1.025
Adachi	1.113	0.48	0.827 - 1.498
Matsuyama	1.371	0.341	0.716 - 2.624
Echizen	2.726	0.03	1.103 - 6.737
Bunkyo	0.820	0.445	0.492 - 1.365
Second-OPV dose	1.701	0.007	1.155 - 2.505
9-11 m	1.413	0.323	0.712 - 2.805
1 y	1.744	0.029	1.059 - 2.869
2 y	1.149	0.736	0.512 - 2.58
Female	0.861	0.229	0.674 - 1.099
Kanazawa	1.413	0.077	0.963 - 2.074
Adachi	1.084	0.652	0.763 - 1.541
Matsuyama	1.560	0.191	0.801 - 3.04
Echizen	4.603	0.002	1.791 - 11.835
Bunkyo	1.132	0.665	0.646 - 1.983

contact during a visit to a doctor and/or with other people. Our results show a statistically significant higher incidence rate in the OPV group, and thus clearly refutes previous assumptions. However, it remains unclear whether or not the present cases of diarrhea were caused by the virus itself in the OPV or by another component of the vaccine.

Another potential explanation could be the use of different inclusion criteria for the vaccination and health check-up groups. Namely, parents may be more sensitive to adverse effects after a vaccination than they are after a regular health check-up, and thus they may be more vigilant about their children's health and in turn adopt a lower threshold for reporting certain symptoms. In this survey, we did not ask participants about the severity of symptoms, and aside from body temperature, no information was collected via objective measures. Moreover, it is quite difficult to comparatively evaluate the care with which parents assess a child's health status. Therefore, sensitivity may have differed among the two groups. A double-blind test using a placebo vaccine with-

out the live poliovirus would be needed to overcome this limitation of the analysis. However, as previously indicated (5), such a study would require clearance by an ethics board, would be difficult to carry out, and its benefit might remain limited.

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