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Benefit of Inactivated Influenza Vaccine in Infants in Iran: A Community based Randomized Control Trial

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Abstract

Background: Influenza in infants and young children is a major medical problem which causes excess medical visits, antibiotic prescriptions and hospitalization even in otherwise healthy children. Many of the developed countries have recommended influenza vaccination for all children (>6month old), but the economic benefit of this strategy is not clear especially for developing countries.
Objectives: To find the difference in the incidence of influenza-like illness (ILI) and economic cost related to it between TIV vaccinated and non-vaccinated infants in Mashhad, Iran.
Methods: This was a community randomized controlled trial which was started in November 2005 and ended up at May 2006. Each of the study and control groups were composed of 500 infants between 6 month and 20 months old who were brought for routine vaccination. The study group was given two doses of TIV; the control group received routine care without any extra intervention. Both groups were followed by monthly telephone calls (up to six months after the vaccination) and were asked about signs and symptoms of flu like illnesses and any cost related to them. SPSS 11.5 was used for statistical analysis, P<0.05 is considered as statistically significant.
Results: There was no significant difference in the monthly occurrence of ILI between the vaccinated and non-vaccinated groups (P: 0.06-0.97). The costs related to ILI were similar between vaccine and control groups, except for physicians visit cost in the third month, which was more in the control group (P<0.05).
Conclusion: In influenza season of 2005-06, TIV vaccination did not decrease the rate of influenza-like illnesses and was not cost saving in infants (6- 20 months old) in Mashhad.

Keywords: Cost-effectiveness, Infants, Influenza, Iran, Vaccine

1. Background

Influenza in infants and young children is a significant medical condition which causes medical visits, antibiotic prescriptions and hospitalization in healthy children (1). In Iran, influenza vaccination of toddlers and young children is not part of national program of immunization, although TIV (trivalent inactivated influenza vaccine) is provided by ministry of health (free of charge) for some highly susceptible groups like organ transplanted patients, HIV positive persons and health care personnel. In Iran a minority of parents vaccinate their young children by directly purchasing TIV from pharmacies or indirectly by asking from physicians.

In the United States, TIV vaccination of healthy infants and toddlers (6–23 Months old) for the first time was officially recommended in 2003, and in2008, the recommendation was gradually expanded to universal vaccination of all children younger than 18 years (2). In Europe, the Central European Vaccination Advisory recommended the universal influenza vaccination for all children from the age of 6 months firstly in 2010 (3). At least until 2010 Finland was the only country in Europe which executed flu immunization for all children aged from 6months to 35 months (3). In Australia Seasonal influenza vaccination is not funded under the national immunization program for normal infants and children (4).

There are different strategies for infants TIV vaccination. In US, CDC recommendation (which is practiced in Iran) is giving half of the usual dose (0.25 cc) for children below 36 months and two doses (one month apart) for children younger than 9 years who receive TIV for the first time. In Finland even the infants receive the usual dose of 0.5cc (which is shown to be more immunogenic), and in Japan all infants and children receive two doses of TIV each year, regardless of the previous vaccination (5,6).

In cost benefit analysis studies the correct use of *effectiveness and efficacy* in the study methods are commonly missed. Efficacy (which is not evaluated by the present study) is measured under ideal situations like a randomized controlled trial and shows the percentage reduction of the rate of laboratory-confirmed influenza in immunized persons in comparison to unimmunized. Effectiveness (which is a secondary goal in the current study) measures the effect of vaccine against a clinical case definition such as influenza-like illness (ILI). Effectiveness usually is lower than the corresponding estimates of efficacy because the clinical diagnosis of influenza especially in infants is unreliable and very nonspecific, and even during the peak days of an influenza outbreak the majority of ILI in outpatient children are caused by

non-influenza viruses (6,7). The Efficacy and effectiveness of TIV changes year by year, mainly depending on the similarity between the vaccine and the circulating strains of influenza.

Mau and colleagues analyzed the results of 11 studies about efficacy and effectiveness of TIV in healthy children (6 M to 18 Y) through the 20 years before 2007, with a focus on age groups of 6–23 months. The studies had been performed in US, Japan, Europe and Turkey. Despite the methodological differences, TIV efficacy was confirmed for any age in all studies except one of them which shows no significant difference between the vaccinated and the controls. The effectiveness of TIV (reduction rate of ILI, AOM, and other clinical outcomes) was inconstantly demonstrated, especially in infants and toddlers (7).

2. Objectives

The main goal of this study is to find the difference in the total economic cost related to influenza-like illness (ILI) between the vaccinated and non-vaccinated infants in Mashhad.

3. Methods

This was a community randomized controlled trial which was started in November 2005 and ended up at May 2006.The study and control groups each were composed of 500 infants between 6 month and 20 months old who were brought for routine vaccination. The cases were randomly collected from all 46 vaccination centers of the city (from each center compatible with the number of under 2 years old population of the region), for randomization, the first infant in each vaccination center was allocated to the TIV group, the second case put in control group and this order was repeated.The sample size was calculated according to the frequency of flu like illness in similar studies and a=0.05 and B=0.2. Ten health care workers were educated and performed the questioner job; two managers were managing and rechecking the data collection phase of the study.

The study group were given two doses of TIV (Influvac® or Inflexal® one month apart).Following administration of TIV, the mothers were called after two weeks from each shot and were asked about any adverse reaction to the vaccine (according to a check list). Both the study and control groups were called monthly (up to sixth month) and were asked about the signs, symptoms and costs of flu like illnesses.

In this study, "ILI" is referred to signs of influenza based on mothers report, including fever (based on mothers perception irrespective of thermometer usage) plus rhinorrhea and/or cough and/or dysphonia and/or red eye and/or otitis media and/or vomiting (8). Diagnosis of Acute otitis media (AOM) in this study was based on physician diagnosis of AOM or mothers' report of new onset otorrhea or mothers' report/ perception of earache (irritability plus ear rubbing).

Study Endpoints: The primary endpoint was the difference in total economic cost related to ILI between the vaccine and control group. Secondary endpoints were: 1) The difference in the incidence of ILI (combination of the signs and symptoms of a single episode of flu) between the two groups 2) The difference in the incidence of each of the signs of ILI between the two groups 3) The incidence of TIV adverse reactions.

Costs of ILI: For measuring the cost of ILI we have considered the medical care expenses (including hospital admission, physician visit, laboratory and X-ray studies and medicines) and non-medical costs(e.g. special food for the sick baby, temporary nurse for home care, number of days off work by parents to care and transport costs). The charges for general practitioner visits and pediatrician visit in Mashhad (at the time of study) was 3.5USD (35000 IRR) and 5USD (50000R) in public and 5USD (50000IRR) and 7USD (70000 IRR) in private sector, respectively.

Cost of vaccination: The cost of first time infants TIV vaccination (two doses one month apart) includes the cost of vaccine [4-5 USD (40000-50000 Rial/dose) depending on the brand of vaccine], injection [0.3-0.5 USD (3000-5000 R/shot)] and finally the cost of TIV adverse reactions. All costs were adjusted to 2005 US dollar rates (The costing year of the analysis was 2005).

The study protocol was approved by ethics committee of Mashhad University of Medical Sciences and enrollment of all subjects was following voluntary and awareness of their parents about the study objectives. The parents were free to leave the study at any time during the study. There was no conflict of interest.

The statistical analysis was conducted by SPSS version 11.5. For descriptive statistics the mean and standard deviation was measured. For the qualitative or quantitative data chi-square or Mann-Whitney and T-test were used based on data type. In all calculations P-value less than 0.05 was considered significant.

4. Results

Study population: Total population of the city of Mashhad at the time of study was 2650000 and under 2 years old population was 87400 people. In Table 1 the baseline characteristics of the vaccine and control group is demonstrated. As the table shows both groups were similar to each other except that the vaccine group were 1.52 month older ($p<0.001$) and 408 gram heavier ($p<0.001$) than control group at the time of TIV vaccination.

According to the history (obtained from mothers) 2.7% of the subjects (11 infants in vaccine and 16 in

control group, P=0.43) had developmental delay (moderate to severe). Four infants (two in each groups) had congenital heart disease.

Main findings: Ten infants in the control group dropped out during the study. Table 2 shows the monthly incidence of each of the signs of ILI during the study. During the second month the incidence of fever (P=0.03), clear rhinorrhea (P=0.04) , and purulent nasal discharge (P=0.04), were significantly more in non-vaccinated group while in the 5th month the vaccine group had more clear rhinorrhea (P=0.01) and cough (P=0.01). The two groups did not show any significant difference in the incidence of red eye, vomiting, dysphonia and otitis during whole follow up period. Table 3 shows the number of infants who had at least one of the signs of ILI during each month, from this view there was no significant difference between vaccinated and non-vaccinated groups. Table 4 demonstrates the number of infants who were visited for ILI by a physician, received any kind of medicine, underwent laboratory test and/or CXR and finally the number of admissions. There is no significant difference between the two groups except that vaccine group received more medicine for ILI in the sixth month (P=0.03).

Figure 1 demonstrates the costs related to ILI which includes physician visit, paraclinical studies, other costs (medicine, extra-nursing and specific food) and the total costs. The only difference was in the third month in which the control group had significantly more payments for physician visit (P<0.05). These expenses are showed in Figure 2 in

Table 1. Demographic characteristics of the vaccine and control groups

Characteristics		Vaccine (n=500)	Control (n=490)	P
Age(month)		14.61 ± 5.42	13.01 ± 5.0	< 0.001
Birth weight (gram)		3305.77 ± 1934.79	3196.96 ± 536.04	0.93
Current weight (gram)		10089.75 ± 4942.02	9666.96 ± 3725.85	0.001
birth rank		1.89 ± 1.16	1.87 ± 1.27	0.9
Nutrition type	Breast milk	466 (94)	458 (94)	0.95
	Formula	30 (6)	29 (6)	
Day care center		30 (6)	29 (6)	0.19
Medical insured		226 (45.7)	193 (39.6)	0.06
Mother's age		26.94 ± 5.67	26.51 ±5.06	0.18
Father's job				
Jobless		8 (1.6)	6 (1.2)	
Simple worker		100 (20.4)	105 (21.7)	0.31
Governmental jobs		88 (17.9)	65 (13.5)	
Non-governmental jobs		295 (60.1)	307 (63.6)	
Mother's job				
Housewife		460 (93.7)	463 (95.7)	
Governmental jobs		19 (3.9)	16 (3.3)	0.35
Non-governmental jobs		12 (2.4)	5 (1)	

Table 2. The frequency of each of the symptoms of ILI in the vaccine and control groups

symptoms		first month		second month		third month		fourth month		fifth month		sixth month	
		N (%)	P	N (%)	P	N (%)	P	N (%)	P	N (%)	P	N (%)	P
fever	Vaccine	132 (26.2)	0.53	143 (28.8)	0.03	170 (34.3)	0.54	165 (33.3)	0.13	135 (27.2)	0.88	134 (2.7)	0.04
	control	121 (24.8)		171 (35.1)		176 (36.1)		140 (28.7)		130 (26.7)		104 (21.4)	
Nasal discharge	Vaccine	97 (19.6)	0.23	83 (16.7)	0.04	109 (22)	0.11	114 (23)	0.14	92 (18.5)	0.09	83 (16.7)	0.29
	control	81 (16.6)		106 (21.8)		128 (26.3)		93 (19.1)		71 (14.6)		69 (14.2)	
Red eye	Vaccine	31 (6.3)	0.84	20 (4)	0.1	35 (7.1)	0.76	21 (4.2)	0.42	29 (5.8)	0.57	10 (2)	0.17
	control	29 (6)		31 (6.4)		32 (6.6)		26 (5.3)		24 (4.9)		17 (3.5)	
Coughs	Vaccine	143 (28.8)	0.28	157 (31.7)	0.25	161 (32.5)	0.54	154 (31)	0.94	139 (28)	0.01	116 (23.4)	0.08
	Control	156 (32)		171 (35.1)		167 (34.3)		150 (30.8)		103 (21.1)		92 (18.9)	
Ear pain	vaccine	33 (6.7)	0.84	24 (4.8)	0.36	27 (5.4)	0.95	26 (5.2)	0.77	18 (3.6)	0.72	20 (4)	0.14
	Control	34 (7)		30 (6.2)		27 (5.5)		23 (4.7)		15 (3.1)		11 (2.3)	

Table 3. The total frequency of the symptoms of ILI in the vaccine and control groups

follow up time after vaccination (month)	Vaccine N (%)	Control N (%)	P	RR (95%, CI)
1	247 (49.8)	242 (49.7)	0.97	1.01 (0.78-1.29)
2	231 (46.6)	255 (52.4)	0.07	0.79 (0.62-1.02)
3	233 (47)	227 (46.6)	0.91	1.01 (0.79-1.3)
4	219 (44.2)	193 (39.6)	0.15	1.2 (0.93-1.55)
5	198 (39.8)	163 (33.5)	0.4	1.32 (1.02-1.71)
6	195 (39.3)	163 (33.5)	0.06	1.29 (0.99-1.67)
Total	453 (91.3)	430 (88.3)	0.12	1.39 (0.92-2.12)

Table 4. The frequency of medical service and medicine usage for ILI in the vaccine and control groups

services		first month		second month		third month		fourth month		fifth month		sixth month	
		N (%)	P	N (%)	P	N (%)	P	N (%)	P	N (%)	P	N (%)	P
Physician	Vaccine	143 (28.6)	0.78	150 (30)	0.03	161 (32.2)	0.64	151 (30.2)	0.63	126 (25.2)	0.26	114 (22.8)	0.54
	Control	145 (29.6)		191 (39)		161 (33.7)		141 (28.8)		108 (22)		103 (21)	
Medicines	Vaccine	131 (26.2)	0.94	139 (27.8)	0.03	152 (30.4)	0.31	147 (29.4)	0.48	123 (24.6)	0.15	110 (22)	0.53
	Control	127 (25.9)		168 (34.3)		164 (33.5)		134 (27.3)		101 (20.6)		99 (20.2)	
Lab test or CXR	Vaccine	6 (1.2)	0.68	5 (1.1)	0.14	7 (1.6)	0.74	8 (1.8)	0.89	5 (1.2)	0.52	4 (0.8)	0.69
	Control	9 (2.1)		11 (2.5)		9 (2.1)		7 (1.6)		7 (1.7)		2 (0.4)	
Hospital admission	Vaccine	0 (0)	0.12	0 (0)	0.5	0 (0)	–	0 (0)	–	0 (0)	0.24	1 (0.2)	0.5
	Control	3 (0.8)		1 (0.2)		0 (0)		0 (0)		2 (0.4)		0 (0)	

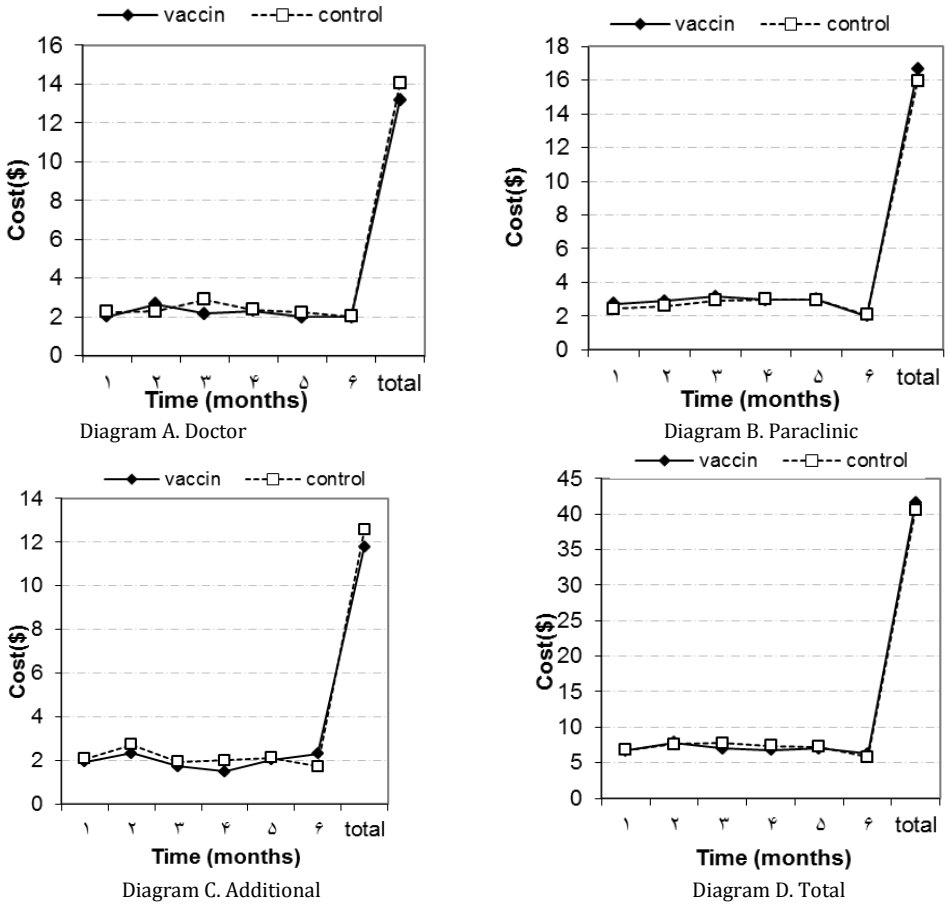

Figure 1. The costs of ILI in control and case groups based on type of expense in USD during 6 months

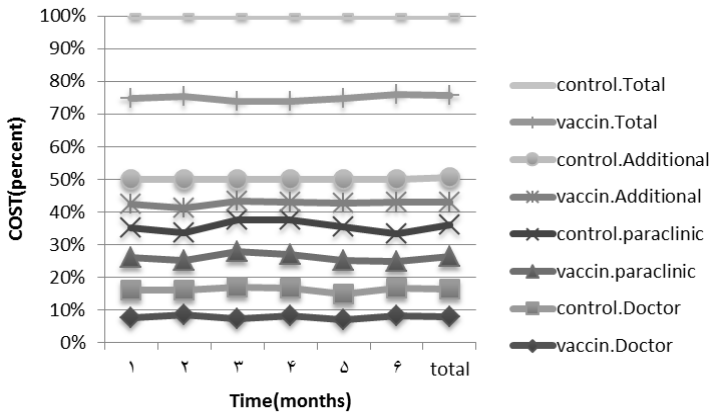

Figure 2. The costs of ILI in control and case groups based on type of expense in term of percentage during 6 months follow up

term of percentage of the costs in two studied groups.

5. Discussion

Pure economic benefit of TIV vaccination in healthy children depends on many factors including: The children's age-groups, health system setting, and methodological variations (more or less optimistic assumptions about epidemiological, medical, and economic cost factors, including considering or ignorance of influenza related death and vaccine adverse events). Cost-effectiveness of infants TIV vaccination in each society depends on the degree of mothers employment out of home and the national social and labor laws regarding parental care of a sick child mainly (7). Consequently, routine vaccination of all children is not cost saving in every society.

The results of studies on influenza vaccine efficacy and effectiveness in infants and young children are conflicting. The latest published Cochrane review has shown that in children less than two years the efficacy of TIV is similar to the placebo (2). In Hoberman study (a randomized, double-blind, placebo-controlled trial in children 6 to 24 months old) TIV efficacy (against culture-confirmed flu) was 66% and-7% in two successive flu season with influenza attack rate of 15.9% and 3.9%, respectively (the sample size of this study was close to ours, 786 and 375 children in the first and second year respectively) (9).

Cochran performed a case-control study on the same age-group from 2003 to 2006 (300 confirmed influenza cases and 1348 controls). He found no vaccine efficacy in the first two years of the study, probably because of the large mismatch between TIV and the circulating strains, but in the third year (with a much better antigen match) TIV efficacy was 59% (10). Heinonen in a prospective cohort study (of 96 vaccinated and 172 unvaccinated children < 2 years old) found that TIV was 66% effective against laboratory confirmed influenza (11). Katayose in an observational study of TIV efficacy found that TIV was 80% and 63% effective in preventing *Laboratory-confirmed* cases of *influenza* in 6-12M and 1-2Y old children, respectively. In Katayose's study vaccine efficacy was higher in infants(< 1 year)than in the 5-year olds (80% versus 35%), significantly (12). Ritzwoller performed a retrospective cohort study in which TIV effectiveness was 25% against ILI in 6 to 23 months old children (13). Allison in a similar study showed that TIV effectiveness was 69%for prevention of ILI (6-21M) (14).

In developing countries few studies about cost effectiveness of TIV vaccination has been performed. In Singapore, Lee analyzed the cost-benefit and cost-effectiveness of pandemic influenza vaccination by using a decision-based model (the age range of the study group was 6 M to more than 65Y). The study showed that pandemic vaccination is only cost-effective when there is a severe pandemic, high vaccine effectiveness and low vaccine cost. They concluded that the economic outcome of flu vaccination is different between countries and should be based on local data (15). In Colombia cost-effectiveness study of influenza vaccination in children younger than 2 years, which measured the yearly number of cases of acute respiratory infection (ARI), medical visits, hospitalizations and deaths by ARI, showed that although the vaccination was not cost saving but the incremental cost effectiveness ratio was less than 3000 USD per related mortalities and supported the Colombian government strategy for introducing yearly flu vaccination to young children (16). In Argentina cost-effectiveness study of influenza vaccination in high-risk children (6M-15Y) ,which considered direct medical costs of Flu management and indirect costs, related to lost parental working days, showed a net savings of 10.04 USD per vaccinated child (17).

In Hong Kong Fitzner performed a cost-effectiveness study of TIV (in children and adults, in a non-epidemic year with ILI incidence of 10%) and used an economic model to estimate the medical and social costs associated with influenza-like illness (ILI).The study showed that although the vaccine was cost-effective for individual person but it was not for the society, even with the most cost-effective strategy of limiting vaccination to the elder population. In Hong Kong, like Iran, the medical and social costs of ILI is not as high as more developed countries like US. Specially the lost productivity is relatively insignificant because the rate of absenteeism, wages, ILI related admission (< 1% in the mentioned study) and the cost of primary care are relatively low (18).

6. Conclusion

According to the current study, TIV vaccination of infants was not cost saving in city of Mashhad which may be referred to: A relatively mild season for influenza, antigen mismatch between TIV and the circulating influenza viruses, very low (≤%5) employment rate of the mothers, the low cost of medical care and medicines in Iran and finally the study design which measured nonspecific ILI (effectiveness study) and did not consider the cost of influenza related death (because of small sample size).

Limitations

One of the main limitations of the current study is lack of any information about the virology, severity and attack rate of the influenza in 2005-06 flu season in Mashhad (which could show the level of mismatch between the used TIV and the circulating wild virus and also can change the cost of influenza care). The national and local influenza watch stations have actively recorded influenza virus activity in whole

country including Mashhad since 2006 but the data about our study period is not sufficient.

Some studies of cost benefit analysis of TIV consider the cost of the time that parents get off their job for care of the sick baby, which is not included in our study, but this is not a major limitation because more than 90% of mothers in both vaccine and control group were housewives.

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Conflicts of interest

None.

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