VARICELLA EPIDEMIOLOGY AND COST-EFFECTIVENESS ANALYSIS OF UNIVERSAL VARICELLA VACCINATION PROGRAM IN TAIWAN

HF Tseng[1], HF Tan[2] and CK Chang[3]

[1]Institute of Medical Research, Chang-Jung Christian University, Taiwan; [2]Department of Healthcare Administration, Chang-Jung University, Taiwan; [3]Department of Sport Management, National Taiwan College of Physical Education, Taiwan

Abstract. Varicella zoster virus is highly contagious and affects people worldwide. In this study, we collected local epidemiological data and evaluated the cost-effectiveness of varicella vaccination program in Taiwan. To examine the economical consequences of universal vaccination, a model of the incidence and the associated costs in a hypothetical cohort was created each year for 30 years. The incidence increased sharply after the infancy and peaked in children aged 5 years. The hospitalization rate among cases was the highest in infants, followed by adults 30 to 44 years old. The benefit-cost analysis showed that one dollar invested in the program would cost extra 46 cents in direct medical expense, but would save extra 45 cents considering the societal expenses. Substantial economical benefits can occur due to the averted unproductive days for parents. Sensitive surveillance of both varicella and zoster is essential in countries that have implemented or are about to implement varicella vaccination.

INTRODUCTION

Varicella zoster virus (VZV) is a highly contagious virus that affects people worldwide. This virus has kept almost a 100% rate of consistent prevalence from generation to generation. Varicella epidemics are caused by the transmission of VZV through respiratory secretions and contacts of the virus-filled lesions. The incidence of varicella appears to vary among regions with different climates, population densities, and degrees of development (Fairly and Miller, 1996; Yawn *et al*, 1997; Gershon *et al*, 1999). However, morbidity and mortality statistics are almost non-existent in Taiwan and other tropical or less developed regions.

In temperate countries, the number of annual incidence case approximately equals to the size of birth cohort in the pre-vaccination era. As a result, the annual incidence in the US was about 3.9 million. These cases resulted in approximately 10,000 hospitalizations and 100 deaths (CDC, 1999). In the US, the incidence was the highest among the 5-9 years old in 1980-1992 (approximately 91-105 per 1,000) (Finger *et al*, 1994; CDC, 1996). The peak shifted to the 1-5 years old in 1995 (approximately 130 per 1,000) while the incidence among the 5-9 years old dropped slightly to 86 per 1,000 (Yawn *et al*, 1997). It suggested that pre-school children might have become the major target in varicella prevention.

Although varicella is a generally mild disease, occasionally severe complications do occur. In addition, its very high incidence among healthy children gives rise to considerable morbidity. It triggers the implementation or recommendation of universal vaccination program against varicella in the US and several other industrialized countries.

More than 650,000 varicella vaccines were imported in Taiwan in private market from 1998 to 2001. Starting from 2004, varicella vaccine has been included in the routine vaccination program in Taiwan. The preliminary studies in several countries have shown that the varicella vac-

Correspondence: Dr Hung-Fu Tseng, Institute of Medical Research, Chang-Jung Christian University, 396, Sec 1, Chang-Jung Road, Kway Jen, Tainan 711, Taiwan.
Tel: +886-6-2785110
E-mail: tsenghf@yahoo.com.tw

cination program was cost-effective (Thiry *et al*, 2003). However, cautions should be taken in applying this result to countries with different health status, social and economical structures, and healthcare costs. In addition, with an apparently different epidemiological pattern than those in temperate regions, the countries with different climates would need local data to evaluate the appropriateness of their own varicella vaccination strategies. In the 17 studies of economic evaluations of varicella vaccination reviewed by Thiry *et al,* (2003), none of them was done in Asian countries. In this study, we collected local epidemiological data and evaluated the cost-effectiveness of implementing varicella vaccination program in Taiwan.

MATERIALS AND METHODS

Varicella epidemiology

Population-based data were obtained using the year 2000 annual outpatient claims and hospitalization discharge claims from the Southern branch and Kaoping branch of the Bureau of National Health Insurance (NHI), which covered 3,246,949 and 3,629,444 populations, respectively. Varicella cases were identified according to the International Classification of Disease code of varicella (ICD-9), including 052.0 (Postvaricella encephalitis), 052.1 (Varicella hemorrhagic pneumonitis), 052.7 (Varicella with other specified complications), 052.8 (Varicella with unspecified complication), and 052.9 (Varicella without mention of complication).

The outpatient claim files included an encrypted personal identification number, date of birth, date of service, ICD-9, fee for medications, fee for physician visit, and the total costs claimed to the NHI. Multiple outpatient claims with the same personal identification number were counted only once in order to measure the incidence.

The hospitalization discharge claims contained data from both acute and long-term stay hospitals. Data included an encrypted personal identification number, date of birth, length of stay, ICD-9, fee for treatment, fee for physician visit, fee for hospitalization, and total costs claimed to the NHI.

The age-specific incidence and hospitalization rates (express as 1/10,000 total population) were calculated by dividing the respective incidence cases and the hospitalization numbers of each age group by 95% of the total age-specific population published by the Department of Internal Affairs, Executive Yuan, Taiwan, assuming 95% NHI coverage. The hospitalization rate among the reported cases (expressed as per 100 cases) of each age group was calculated by dividing the hospitalization numbers by the total incidence cases of the group.

Cost-benefit and cost-effectiveness analyses of universal vaccination program

To examine the economical consequences of universal childhood vaccination against varicella, a model of the incidence and cost of varicella in a new 300,000 hypothetical birth cohort was created each year in the next 30 years. These children were assumed either to have received 80% varicella vaccination coverage (as provided by the government) or 10% private coverage (current situation). For each scenario, we calculated the expected number of cases of varicella and the associated expected costs that would occur in the next 30 years.

The costs of varicella were assumed to include the expense for medical treatment as well as the value of illness-related work loss. The former included outpatient visits and hospitalization, while the latter included the work loss from the diseased employee and the parents who had to provide care for the sick children.

Direct medical cost. According to the NHI claims data, on average, each varicella outpatient visit cost NHI 324 NT dollars (1 US$ = 35 NT dollars) and 150 NT dollars out-of-pocket payment. Each varicella case needed 1.53 outpatient visits. Therefore, the direct cost for each varicella outpatient visit was 734 NT dollars. Each varicella hospitalization cost 10,755 NT dollars on average.

It was estimated by the Department of Health that the price for the vaccine could be further reduced to no more than 800 NT dollars per dose, which is half of the current price, after the vaccination program begins. The price for each dose in our calculation was 800 NT dollars and discounted 2% annually.

According to the previous results, the efficacy of varicella vaccine was assumed to be 85% (Vazques *et al*, 2001). Based on our study on varicella vaccine safety in Taiwan, 2% of the vaccinated children would need one outpatient visit for adverse events (Tseng *et al*, 2003). It was estimated that the cost of each adverse event was 474 NT dollars (324 by NHI and 150 out-of-pocket).

Indirect costs of work loss. We estimated the expected cost of work loss as the product of the percentage of cases involving work loss, the average number of days of work loss per case, and the value of a day of work.

The cost of additional care for 0-2 years old was assumed to be 0 as children at this age would require the care regardless of their health status. Care for cases aged 3-12 years required 1 person with 3.7 days loss of work (Huse *et al*, 1994). While care for cases aged 13-17 years require no additional cost. Forty percent of the cases aged 18-22 and 100% of 23-29 year-old cases would lose 5.5 work days on average (Huse *et al*, 1994). The daily salary was estimated to be 1395.8 by dividing the monthly salary published by the Council of Labor Affairs of Executive Yuan, Taiwan, by 30.

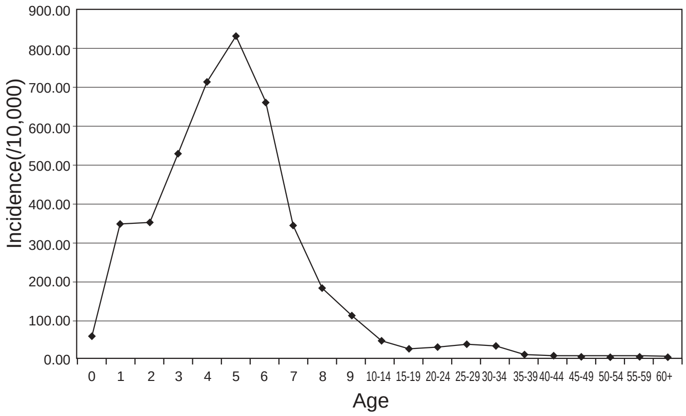

Fig 1–Incidence of varicella in Taiwan, 2000.

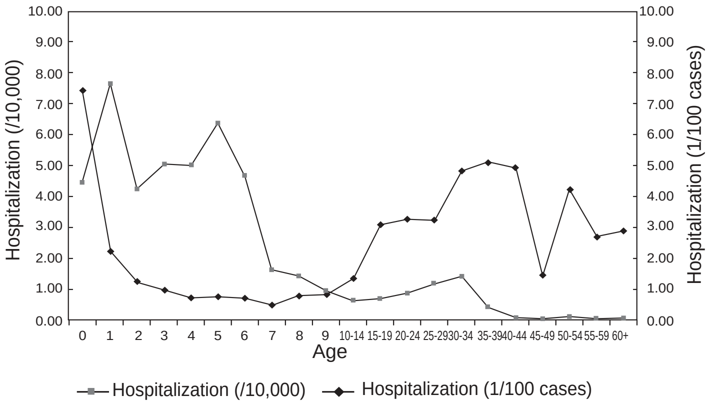

Fig 2–Hospitalization of varicella in Taiwan, 2000.

RESULTS

The incidence of varicella in both branches increased sharply after infancy and peaked in children aged 5 years, then decreased gradually. While children under 10 years old accounted for 81.4% and 78.6% of total varicella cases in Southern and Kaoping branches, respectively, they only accounted for 64.5% and 49.5% of total hospitalization. For both branches combined, hospitalization rate among cases was the highest in infants, followed by adults 30 to 44 years old. For children aged between 3 and 9 years, the hospitalization rates were all below 1 per 100 cases (Table 1, Figs 1 and 2).

In a cohort of 300,000 population with 10% private vaccine coverage for 30 years, we estimated that there would be 2,717,060 cases of varicella and 28,647 hospitalizations, at a total direct medical cost of 2,856,826,406. The expected work loss related to the disease would amount to 7,623,313 days, at a total cost of 10,640,620,980. If the vaccine coverage rate reaches 80%, the cases of varicella would be reduced to 1,047,230 and the number of hospitalization would be reduced to 12,839, at a total direct medical cost of 5,326,826,439. The expected work loss related to varicella would amount to 2,868,303 days, at a total cost of 4,003,578,475. Overall, a vaccination pro-

Table 1
Age-specific incidence of varicella in Taiwan, 2000.

Age	Southern Branch[a]				Kaoping Branch[b]				Combined		
	Incidence cases (%)[c]	Hospitalized cases (%)[c]	Incidence (/10,000)	Hospitalized (/10,000)	Incidence cases (%)[c]	Hospitalized cases (%)[c]	Incidence (/10,000)	Hospitalized (/10,000)	Incidence (/10,000)	Hospitalized (/10,000)	Hospitalized (/100 cases)
0	263 (1.1)	16 (6.1)	67.24	4.09	220 (0.9)	20 (4.8)	52.51	4.77	59.63	4.44	7.45
1	1,421 (7.1)	33 (18.7)	370.96	8.61	1,341 (6.4)	28 (11.5)	323.24	6.75	346.15	7.64	2.21
2	1,718 (14.4)	17 (25.2)	371.40	3.68	1,657 (13.1)	24 (17.3)	329.04	4.77	349.32	4.24	1.21
3	2,569 (25.3)	20 (32.8)	571.26	4.45	2,445 (23.1)	28 (24.0)	482.83	5.53	524.42	5.02	0.96
4	3,481 (40.0)	24 (42.0)	773.19	5.33	3,391 (36.9)	24 (29.8)	666.26	4.72	716.45	5.00	0.70
5	4,061 (57.2)	28 (52.7)	928.61	6.40	3,774 (52.3)	32 (37.5)	745.22	6.32	830.20	6.36	0.77
6	3,025 (70.1)	14 (58.0)	689.76	3.19	3,241 (65.6)	30 (44.7)	639.62	5.92	662.88	4.65	0.70
7	1,459 (76.2)	10 (61.8)	344.58	2.36	1,695 (72.5)	5 (45.9)	344.00	1.01	344.26	1.64	0.48
8	756 (79.4)	4 (63.4)	177.07	0.94	902 (76.2)	9 (48.1)	182.20	1.82	179.83	1.41	0.78
9	471 (81.4)	3 (64.5)	104.46	0.67	604 (78.6)	6 (49.5)	116.24	1.15	110.77	0.93	0.84
10-14	911 (85.3)	5 (66.4)	40.54	0.22	1,194 (83.5)	23 (55.0)	47.34	0.91	44.14	0.59	1.33
15-19	573 (87.7)	13 (71.4)	20.67	0.47	733 (86.5)	27 (61.5)	23.14	0.85	21.99	0.67	3.06
20-24	779 (91.0)	24 (80.5)	26.71	0.82	851 (90.0)	29 (68.5)	25.10	0.86	25.84	0.84	3.25
25-29	989 (95.2)	18 (87.4)	38.20	0.70	1,042 (94.2)	47 (79.8)	33.92	1.53	35.88	1.15	3.20
30-34	822 (98.7)	22 (95.8)	30.48	0.82	886 (97.8)	60 (94.2)	28.89	1.96	29.63	1.42	4.80
35-39	187 (99.5)	4 (97.3)	6.76	0.14	265 (98.9)	19 (98.8)	8.53	0.61	7.70	0.39	5.09
40-44	17 (99.6)	2 (98.1)	0.67	0.08	44 (99.1)	1 (99.0)	1.48	0.03	1.11	0.05	4.92
45-49	17 (99.6)	0 (98.1)	0.78	0.00	52 (99.3)	1 (99.3)	1.95	0.04	1.42	0.02	1.45
50-54	20 (99.7)	1 (98.5)	1.38	0.07	27 (99.4)	1 (99.5)	1.60	0.06	1.50	0.06	4.26
55-59	11 (99.8)	1 (98.9)	0.79	0.07	26 (99.5)	0 (99.5)	1.77	0.00	1.29	0.03	2.70
60+	57 (100.0)	3 (100.0)	1.23	0.06	118 (100.0)	2 (100.0)	2.74	0.05	1.96	0.06	2.86
Total	23,607	262	72.71	0.81	24,508	416	67.53	1.15	69.97	0.99	1.41

[a]Estimated total insured population 3,246,949
[b]Estimated total insured population 3,629,444
[c]Cumulative percentage

Table 2
Thirty-year cost-benefit and cost-effectiveness analysis for routine varicella vaccination program for children in Taiwan.

	Option 1 (80% coverage, 7,200,000 vaccinated)	Option 2 (10% private coverage, 900,000 vaccinated)	Differences averted by Option 1 cf. Option 2
Consequences			
Chickenpox cases	1,047,230	2,717,060	1,669,830
Hospitalization cases	12,839	28,647	15,808
Costs (savings)			
Direct medical costs			
Vaccines	4,363,350,534	545,418,817	3,817,931,717
Vaccine adverse events	55,987,200	6,998,400	48,988,800
VZV outpatient visits	769,433,439	1,996,310,704	(1,226,877,265)
VZV hospitalization	138,075,316	308,098,485	(170,023,169)
Total direct medical costs	5,326,846,489	2,856,826,406	2,470,020,083
Indirect costs			
Work-loss (days)	2,868,303	7,623,313	(4,755,010)
Work-loss (money)	4,003,578,475	10,640,620,980	(6,637,042,505)
Total direct plus indirect	9,330,424,964	13,497,447,386	(4,167,022,422)
Benefit to cost ratios			
Dollars cost (saved) per dollar invested in vaccination program, health care payer's perspective			0.46
Dollars cost (saved) per dollar invested in vaccination program, societal perspective			(0.45)
Cost-effectiveness ratios			
Direct medical costs (savings) in dollars per:			
Child vaccinated			392
Case prevented			1,479
Hospitalization averted			156,251
Total costs (savings) in dollars per:			
Child vaccinated			(661)
Case prevented			(2,495)
Hospitalization averted			(263,602)

gram providing 80% coverage would save 4,167,022,422 over 30 years considering the direct and indirect costs (Table 2).

The benefit-cost analysis showed that one dollar invested in the vaccination program would cost extra 46 cents in direct medical expense. However, it would save extra 45 cents if the direct and indirect expenses were considered together. The cost-effectiveness analysis revealed that the vaccination program would increase medical expenses of 392 (NT) dollars per vaccinee, 1,479 dollars per cases prevented, and 156,251 dollars per hospitalization averted. It would, however, yield net economical benefits of 661, 2,495, and 263,602 dollars per vaccinee, per case prevented, and per hospitalization averted, respectively, if both expenses were combined (Table 2).

DISCUSSION

Beginning from the year of 2000, the NHI in Taiwan has requested health care providers, from primary care clinics to medical centers, to provide ICD-9 coding when claiming for reimbursements. Given the availability of health care services and health seeking behaviors of the public, this requirement has made the NHI claim data a very good source for varicella surveillance. The fact that each varicella case had visited physicians 1.5 times on average demonstrated that nearly all cases would be seen by doctors in Taiwan. The diagnosis of varicella is relatively simple in clinical practice without being confused with other conditions causing vesicles. Therefore, the completeness of NHI data was acceptable and the proportion of unreported cases was minimum. Our estimated incidences, which were completed 2-3 years after the vaccine was available in the private market, were lower than those published pre-vaccination era data in western countries (Finger *et al,* 1994; Fairley and Miller, 1996; CDC, 1996, 1999; Yawn *et al,* 1997; Gershon *et al,* 1999; Boelle and Hanslik, 2002). In addition to the availability of the vaccine, life styles and climates might also explain the differences in incidence among these countries.

The trend of the age-specific incidence, increasing in the pre-school years and declining thereafter, is consistent with other countries and that of other childhood infections such as measles, mumps, and rubella (Finger *et al,* 1994; Halloran *et al*,1994; Fairley and Miller, 1996; Brisson *et al*, 2001; Edmunds and Brisson, 2001). This suggested that pre-school and school-age mixing plays an important role in varicella transmission, similar to other childhood infections. The high pre-school attendance rate in Taiwan might be responsible for the significantly high risk in pre-school children due to the increased opportunity for effective contact. Similar trends have been observed in the US and the United Kingdom (Finger *et al,* 1994; Fairley and Miller, 1996; Brisson *et al*, 2001).

It has long been observed that the epidemiology of varicella varies remarkably between temperate and tropical climates (Wharton, 1996). Seroepidemiology showed that the lifetime risk of varicella was indeed close to 100% in temperate countries. However, a seroepidemiology study in Taipei city, the largest city in Taiwan, showed that the proportion of seropositivity for adults over 20 years old was less than 90%, indicating that the varicella transmission in Taiwan might not be as common as that in temperate countries (Lin *et al*, 1996). In the pre-vaccination era, susceptibility to varicella was 34% for children aged 4-5 years and 18% for children aged 6-10 years in the US (Van Loon *et al*, 1993), while these numbers were 61% and 31% in Taiwan, respectively (Lin *et al*, 1996). In tropical areas like Singapore and India, susceptibility of the young adult population was even higher (42.8% and 68.2%, respectively) (Ooi *et al*, 1992; Lokeshwar *et al*, 2000).

It is well known that the complications of varicella tend to be more severe in adults than in children. In our study, only about 10% of the incidence cases occurred in adults over 20 years old, while 20-30% of the hospitalizations occurred in this population. In the US, the risk of dying of varicella was 25 times greater in adults than in children aged 1-4 years (CDC, 1999; Meyer *et al*, 2000) and the risk of hospitalization was 14 times greater (Guess *et al*, 1986; Choo *et al*, 1995). In France, the risk of death was 30 times greater in subjects over 15 years old than in children aged 1-4 years, while the risk of hospitalization was 7 times greater (Boelle and Hanslik, 2002). Our estimation showed that the hospitalization rate was the highest in infants, which was 10 times greater than the lowest group of 3-9 years old. The second peak occurred in adults 30-44 years old, which was about 6.5 times greater than the lowest group. Unlike in France, the case hospitalization rate in adults over 55 years old was not particularly high in Taiwan, similar to that of children 1 to 2 years old.

In spite of the diversity in assumptions, our study is consistent with other studies (Preblud *et al*, 1985; Huse *et al*, 1994; Lieu *et al*, 1994; Beutel *et al*, 1996; Coudeville *et al*, 1999; Diez Domingo *et al*, 1999; Scuffham *et al*, 1999, 2000; Brisson and Edmunds, 2002; Getsios *et al*, 2002). Systematic vaccination of children aged 12-18 months seems advisable because large savings would occur from averted unproductive days of parents. However, for the healthcare payer, a universal vaccination program would not generate savings.

Two major components of the costs associated with the vaccination program are the vaccine price and the value of lost work time. Universal vaccination is no longer cost-saving when the vaccine price increases two to three folds versus the baseline in 3 other studies (Preblud *et al*, 1985; Diez domingo *et al*, 1999; Scuffham *et al*, 1999). The same strategy resulted in net costs to society if the value of a lost day decreased by 95% or if parents lost only one work-day per case (Beutels *et al*, 1996). In our study, the vaccine price was 800 NT dollars with 2% annual discount thereafter. Although it is only half of the current price in the private market, the estimate is conservative. According to the experience of influenza vaccination program for senior citizens in Taiwan, the Department of Health estimated that the vaccine price could be further reduced to as low as one fifth of the original price when the universal vaccination begins. The healthcare payer could anticipate savings if the vaccine price is further reduced through price negotiation with the suppliers. Similar finding has been reported by Coudeville *et al* (1999) using the lowest baseline values for the vaccination costs.

Although our assumption that one person was needed to take care of a 3 to 12 year-old case was slightly overestimated, it should not be off the reality too much. Over the past several decades, the economical growth and urbanization processes have significantly changed the life style of most families in Taiwan. Working parents are very common. Many children attended pre-school at as early as 3 years old, especially in the cities. Therefore, loss of work days is inevitable if children are infected and have to stay home.

Post-licensure studies of varicella vaccine have confirmed that under field conditions the efficacy of the vaccine appears to be high (around 85% at preventing any case of varicella). In addition, the vaccine appears to offer very good protection (95-100%) against severe diseases (Vazquez *et al*, 2001). We revealed in our previous study that the first 3-year risk of breakthrough in Taiwan was only 2.8% with over 80% of them being very mild in comparison with those seen in natural varicella (Tseng *et al*, 2003). Bernstein *et al* (1993) also showed that breakthrough varicella had fewer median numbers of total and vesicular lesions, lower incidence of fever, and shorter duration of illness. In our cost-benefit analysis, the assumption that the breakthrough cases were as severe as unvaccinated cases and thus cost equal amount of direct and indirect expenses was conservative. The cost associated with taking care of breakthrough varicella should be significantly less than what we have estimated.

Evidences appear to be accumulating that in places where the vaccine is widely used, the incidence may have also declined in unvaccinated children (Clements *et al*, 2001; Seward *et al*, 2002). The effect of herd immunity might also provide protection in high risk groups, such as immunocompromized populations, pregnant women, and healthcare workers. Furthermore, we omitted the number of death from natural varicella or vaccination in the analysis. Although the possibility of a fatal adverse reaction cannot be ruled out when the vaccine is widely used, it seems likely that fewer deaths would occur among vaccinated than unvaccinated persons. Finally, physical or psychological sufferings from painful experience of varicella were not quantified in our study.

There are three primary concerns with mass childhood vaccination that might lessen the benefit of it. Firstly, it may lead to an increase in adult cases, particularly if vaccine-induced immunity wanes over time. Secondly, significant numbers of breakthrough cases may occur. Thirdly, the loss of exogenous boosting may lead to an increase in the incidence of zoster (Edmaunds and Brisson, 2002). These situations need to be carefully evaluated as the vaccination program begins.

Due to the increase in preschool attendance rate, the incidence of varicella peaks in preschool children in Taiwan. Our analysis indicated that the varicella vaccination program is cost-effective. In countries like Taiwan where job attendance is common for both parents, substantial economical benefits can occur due to the averted unproductive days for parents. Sensitive surveillance of both varicella and zoster is essential in countries that have implemented or are about to implement varicella vaccination.

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