

ORIGINAL ARTICLE

COST OF MANAGEMENT OF ADVERSE EVENTS OF PERTUSSIS VACCINE

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ABSTRACT

Whole-cell Pertussis (wcPertussis) vaccines combined with diphtheria and tetanus toxoids are effective in preventing clinical pertussis. The study aimed at determining the cost of managing fever and convulsions and cost of adverse events associated with wcPertussis. Parents who brought their children to health clinics and parents of children who were admitted for febrile convulsions were interviewed using structured questionnaire and the information were used to determine the cost of managing adverse events. Mean cost of managing mild fever per case was RM249, mean cost of managing high fever per case was RM1,036 and mean cost of managing convulsions was RM1,225. Total cost of managing adverse events was RM261 million for mild fever, RM66.7 million for high fever and RM1.3 million for convulsions. Costs of managing mild and high fever were less than the cost of managing convulsions. Total cost of managing mild fever was highest at RM261 million compared with RM66.7 million for high fever and RM1.3 million for convulsions. Thus, lower risk of adverse events actually contributed to higher costs of managing the adverse event.

Key words: wcPertussis, cost, adverse events.

INTRODUCTION

Pertussis (whooping cough) is a highly contagious acute bacterial respiratory tract disease caused by *Bordetella pertussis* (*B. pertussis*). It is the sole cause of epidemic pertussis and the usual cause of sporadic pertussis. Each year, between 20-40 million cases of pertussis occur throughout the world. Pertussis vaccine was introduced in 1956 in Malaysia, given together with diphtheria and tetanus (DT). The disease is one of the notifiable diseases in Malaysia and cases have been notified since then and the incidence rate was 0.11 (per 100,000 populations) in 2001 - 2003 and 0.17 (per 100,000 populations in 2004¹.

The availability of wcPertussis vaccines had been highly effective in reducing the burden of disease. The common occurrence of minor adverse reactions, the rare occurrence of more severe reactions, and public anxiety about the vaccine, had stimulated the development of less reactogenic pertussis vaccines.

For several decades inactivated wcPertussis vaccines have been part of national childhood vaccination programmes, dramatically reducing the considerable public health impact of pertussis. Access to health services typically requires out-of-pocket (OOP) payments. According to WHO (2003) data, out-of-pocket payments account for 1/3 of total health care spending in 2/3 of all low-income countries. In most African countries the amount of-out-of-

pocket is well above this average¹. Such payments can well lead individuals or households to reduce their expenditures for basic needs such as for food, housing and clothing, to borrow money, and to sell household assets. Some households as a result inevitably slide into poverty. Furthermore, out-of-pocket payments may lead to denied access to needed services or prevention from receiving a full course of needed treatment.

Frequent (but usually mild) adverse reactions and a fear of rare but serious acute or chronic neurological events associated with wcPertussis vaccination have prompted the development of a new generation of pertussis vaccines, the acellular (ac) vaccines. However, despite thorough investigations, the link suspected between wcPertussis vaccines and rare cases of permanent neurological damage has not been confirmed.

Concern about the safety of the wcPertussis vaccine had made routine pertussis vaccination of infants quite controversial in some countries, and led to the development of a new generation of pertussis vaccines based on selected bacterial components, rather than on inactivated whole cells.

What Are the Adverse events Associated with Pertussis Vaccine?

Although adverse events associated with Pertussis vaccines were noted to be numerous, the occurrence and intensity of the adverse events of wcPertussis are redness, swelling, pain and fever can occur in children after vaccines were given.

Convulsions

A convulsion is a medical condition in which a person's body appears to shake in an uncontrollable fashion. When person experiences convulsions, his or her muscles quickly contract and relax in a repeated fashion. This causes the appearance of rapid shaking movements. ²In most cases, convulsions last anywhere from 30 seconds to two minutes, though much longer convulsions may also occur. If convulsions last for a long period of time or if a person has several episodes of convulsions and does not appear to awaken between these episodes, ⁴they may be considered a medical emergency.

It is believed that the high levels of endotoxin of about 3,000 different proteins found in the wcPertussis are a potential cause for concern. It has been demonstrated in several studies that endotoxins can cause severe brain reaction such as allowing blood brain barrier to leak and this could potentially be a cause for the neurological adverse reactions following whole-cell DTP vaccination³. The risk of convulsions was noted to be 6 per 10,000 doses for wcPertussis⁴.

High Fever

Fever is defined as the elevation of core body temperature above normal; the average oral temperature in adult is 37°C⁵. High fever is defined as a child developing a fever of more than 40.5°C⁶. Unwanted components such as endotoxins which were believed to be very high in wcPertussis, are correlated with a higher incidence of fever. The risk of high fever for wcPertussis was noted as 35 per 1,000 doses³. Based on a study by Donnelly et al⁷, it was noted that there was an increase in mean body temperature in mice, after vaccination with wcPertussis.

Mild Fever

Mild fever is when the child develops fever with a temperature of 38°C but less than 40.5°C⁸. The risk of mild fever for wcPertussis was noted to be 56.9 per 100 doses³. Donnelly et al⁷ carried out a study in mice and noted that there was an increase in mean body temperature in mice, after wcPertussis vaccination. The induction of fever was associated with the elevated Interleukin-1B production in the brain. The evidence suggested that the systemic effects of local exposure to live or killed bacteria may be mediated through pro-inflammatory cytokine

induction within the central nervous system. In this research, the vaccinated child developed fever and was considered mild in which the parents described it as being relieved with syrup paracetamol and the fever lasted for not more than five days.

A DT-wcPertussis vaccine is a combined vaccine which is a whole cell vaccine, composed of a suspension of formalin-inactivated *B.Pertussis* cells grown in an enriched broth. During growth, unwanted components such as endotoxins cannot be eliminated. It is believed that these unwanted components cause the side effects of the whole-cell Pertussis such as fever and convulsions.

METHODOLOGY

Two cross sectional sub-studies were undertaken to obtain the cost of managing the wcPertussis vaccine adverse events. Firstly, a total of 400 respondents were selected using systematic sampling from 16 August until 23 September 2004. The respondents were parents who brought their children for immunization in three government health clinics. Parents with children who fulfilled the inclusion and exclusion criteria were interviewed by trained interviewers using questionnaires. This data collection captures the cost of managing high and mild fever. Secondly, parents of 46 cases of children with convulsions admitted to two government hospitals between 8 October and 11 December 2004 were interviewed using a set of questionnaires and thus the information were used to determine cost of managing convulsions.

In this study, the child admitted to the selected hospitals for febrile fits with episodes of seizures of not more than 10 times during the hospital admission was taken as a proxy measure to determine the cost of managing adverse events due to convulsions. In this research, the fever in the vaccinated child was considered high in which the parents described it as not being relieved with syrup paracetamol and required the parents to seek further medical attention. The parents also mentioned that the fever lasted for five days or more. Also in this research, the vaccinated child developed fever and was considered mild in which the parents described it as being relieved with syrup paracetamol and the fever lasted for not more than five days.

Determining the Cost of Managing Fever

Cost of managing the wcPertussis vaccine adverse events include both the costs incurred by the patients and by the health care providers. Costs incurred by the health care providers and the patients included direct medical costs. Cost of loss of productivity was indirect costs borne by the patients.

The total costs were calculated based on the estimated live birth of 514,178 children in Malaysia for 2004. This figure was based on the year 2004 figures of crude birth rate of 20.1 per 1,000 populations and the population in Malaysia at the time of study which was 25,581,000⁸.

The sample size calculation for the survey on adverse events due to vaccination used the formula by Lwanga and Lemeshow⁹, and data collection was carried out from 16 August until 23 September 2004. A total of 400 respondents were selected in which every fourth attendance at either the three government health clinics, was interviewed. The respondents were parents who brought their children for immunization in those clinics. Parents with children who fulfilled the inclusion and exclusion criteria were interviewed by trained interviewers using questionnaires.

Inclusion criteria were parents with children aged between 3 months and 5 years old as this was the age group for children to receive the four doses of vaccination against diphtheria, tetanus, pertussis and poliomyelitis. The respondents who consented to participate in the sub-study were interviewed. The exclusion criteria were parents with children presenting with severe chronic disease or immunodeficiency, history of seizures or epilepsy, other medical illnesses such as asthma or other congenital abnormality and receiving immunosuppressive treatment over the previous six months.

The necessary data were converted to monetary values. The questionnaires were used to obtain direct and indirect costs to parents. The indirect costs such as loss of productivity were derived by converting the time spent in the health clinic to monetary values by using annual per capita income of Malaysia in 2004 which was RM15,375.60¹⁰.

Determining the Cost of Managing Convulsions

This second sub-study which was a cross-sectional survey was conducted in two tertiary government hospitals to obtain costs of managing convulsions from patients' or caregivers' and health care providers' perspectives. A sample size of around 30 is adequate for costing analysis. Within the time frame of about four weeks, which was from 8 October to 11 December 2004, parents of 46 cases of children

with convulsions admitted to these two hospitals were included in the sub-study and interviewed using a set of questionnaires.

Inclusion criteria for this survey were parents of children aged between 3 months to 8 years old, as children in this age group are those who should receive either the first to fourth doses of OPV-DTP and a booster dose at the age of 7 and those children who presented with convulsions associated with fever, who consented to participate in the study. Exclusion criteria were children with history of seizures or epilepsy, and children with other medical illness such as asthma or other congenital abnormalities. The costing data obtained were direct cost incurred by parents, including admission charges and other expenses incurred during admission such as for buying of food or milk. Indirect costs incurred in this sub-study were determined by obtaining the number of days the parents had to spend in hospital during admission. The cost was derived by converting the number of days admitted to monetary values by using the annual per capita income. This cost was the cost of loss of productivity that was the indirect cost borne by the patients from the patient's perspective.

Cost of Managing wcPertussis Vaccine Adverse Events

The costs per dose of wcPertussis vaccine adverse events were derived from the survey, which were costs of managing fever and convulsions. The total costs of adverse events per year were calculated based on the incidence rate of wcPertussis vaccine adverse events from the published literature.

The collected data from the surveys in health clinics and hospitals were coded and entered in Excel for Windows 2000 as well as Statistical Package for the Social Science (SPSS) version 11.0.

RESULTS

A. Survey for the wcPertussis Adverse Events (Mild Fever and High Fever) at the Health Clinics

From the survey on the three health clinics, out of 400 respondents, 300 (75%) stated that their children had developed adverse events after the last episode of immunization of wcPertussis-Polio (Table 1).

Table 1. Distribution of Respondents of Post wcPertussis-Polio Immunization by Gender and Ethnicity

Variables	Yes (%)	No (%)	Total (%)
Adverse events	300 (75)	100(25)	400(100)
Gender			
Male	166 (55.3)	57 (57)	223(55.8)
Female	134 (44.7)	43 (43.0)	177(44.2)
Total	300 (100)	100(100)	400 (100)
Race			
Malay	214	72	286 (71.5)
Chinese	43	13	56 (14.0)
Indian	38	12	50 (12.5)
Others	5	3	8 (2.0)
Total	300	100	400 (100)

Of these, 44.2 % were female infants/children and 55.8% males. It was also noted that the majority of the respondents (71.5 %), were

Malays, 14.0% Chinese, 12.5 % Indians and 2.0 % others. The other ethnic groups interviewed were Ibans and Indonesians (Table2).

Table 2. Distribution of Respondents by Adverse Events Post wcPertussis- Polio Immunization by Ethnicity

Variables		Malay	Chinese	Indian	Others
Adverse events	N (%)	N (%)	N (%)	N (%)	N (%)
No	100 (25)	72(25.2)	13(23.2)	12(24.0)	3(37.5)
Yes	300 (75)	214(74.8)	43(76.8)	38(76.0)	5 (62.5)
Total	400(100)	286(100)	56(100)	50(100)	8(100)

Of the respondents who experienced adverse events post immunization, 91.7% stated that their children experienced mild fever after the

DPT/Polio vaccination, 1.7% experienced high fever, 3.3% vomiting, 4.0% redness or skin rash and 41.7% pain (Table 3).

Table 3. Distribution of Respondents by Adverse Events Post wcpertussis- Polio Immunization (After first dose)

Variables	Yes N (%)	No N (%)	Total N (%)
Adverse events	300(75)	100(25)	400(100)
Type of Adverse Events			
Mild fever	275 (91.7)	25(8.3)	300 (100)
High fever	5 (1.7)	295 (98.3)	300 (100)
Vomiting	10 (3.3)	290 (96.7)	300 (100)
Redness/ skin rash	12 (4.0)	288(96.0)	300 (100)
Pain	125 (41.7)	175 (58.3)	300 (100)
Fits	1 (0.3)	299 (99.7)	300 (100)
Others	1 (0.3)	299 (99.7)	300 (100)

In this study, fever described by parents as relieved by taking syrup paracetamol and not lasting more than five days, were considered mild fever. Fever described as not being relieved by syrup paracetamol and required the infants or children to seek further treatment as outpatients or inpatients was considered high fever.

Cost from the provider’s perspective is the cost syrup paracetamol, the medication given on the day of vaccination. The direct cost from the patient’s perspective included the travelling and waiting time for the vaccination for parents who had recalled their waiting time and travelling time (Table 4).

Table 4. Mean Cost of Managing Mild Fever per Case

	Provider’s Perspectives	Patient’s Perspectives	
Cost (RM)		Direct	Indirect
Cost of Medication	0.90	-	-
Cost of Parents/patient waiting time	-	0.29	-
Cost of Parents/patient travelling time	-	0.35	-
Cost for Parents absent from work (loss of productivity)	-	-	248.34
Total cost (RM)	249.88		

The indirect costs from the patient’s perspective, which was the loss of productivity, was derived from the duration of illness of the child at home and converted to monetary values using the income stated and divided with working time (income per min). This income per min was multiplied by the duration that they had to wait for vaccination. For mothers who were

housewives, their income was taken as RM1281.30, the income per capita of Malaysia for the year 2004¹².

Due to the experience of high fever by the child, parents had to bear other costs such as fee-for-service of general practitioners, as well as toll cost when they had to travel to the nearest

clinic. The transportation cost was the cost borne when the parents sought outpatient treatment. The cost from the patients' perspective was as tabulated in Table 5, whereby the parents had to bear the costs of transportation, cost of waiting time, cost of travelling time and others as mentioned earlier. Others also included cost of paying for items such as toiletries and food during admission. Indirect cost from the patients' perspective was derived from the time the parents was absent from work while taking care of the child during admission to hospitals which was the cost of loss of productivity.

The cost of managing high fever was also looked at from the providers' perspectives. The providers' perspective was calculated using the step-down method for government health clinic. The cost per outpatient visit was RM4.77 from the provider's perspective as parents either brought their child to the nearest private clinic or the Casualty Department of the nearest hospital. The cost per outpatient visit was determined by direct allocation of overhead. The final cost centre was child per visit, whereby the cost was apportioned to the total number of child attendances which was 14,600 attendances in the year 2004(Table 5).

Table 5. Mean Cost of Managing High Fever per Case

	Provider's Perspectives	Patient's Perspectives	
		Direct	Indirect
Cost of Child Outpatient Visit	4.77	-	-
Parents/patient waiting time	-	4.43	-
Parents/patient travelling time	-	6.87	-
Transportation		6.50	
Miscellaneous/others		34.38	
Parents absent from work	-	-	979.07
Total cost (RM)	1,036.01		

B. Survey for the wcPertussis Adverse Events (Convulsions) at the Hospitals

A total of 48 convulsions cases were admitted during the study duration. However, 46 cases were interviewed as the other two cases did not meet the inclusion criteria. One of the children was more than 8 years old and the other had 14 episodes of convulsions.

It was noted that 58.7% of the children studied were males and 41.3% were females. The majority (71.7%) was of the Malay ethnic group, 15.2% were Chinese and 13.0% were of Indian ethnicity. The majority of the respondents (57.4%), stated that their children experienced only one episode of convulsions. The minimum number of convulsions episode reported was one and maximum was six. The average age of the children admitted during the study period was 22 months (1 year 10 months), with a minimum age of 5 months and maximum age of 54 months (4 years 6 months). The minimum length of stay was one day and maximum length of stay was

seven days, while the average length of stay for convulsions was three days.

This survey contributed to the costing of managing the adverse event of convulsions that was calculated as in Table 6. Cost of managing convulsions consisted of cost from the providers' perspective. Cost from the providers was calculated using the step-down method for the tertiary hospital. This step-down method was carried out in view of the time constraint in the study. The final cost center was the paediatric ward which received the allocated cost based on the patient days and the cost per hospital admission for paediatric patient was RM 233. The average length of stay for patients in the ward for one episode of hospital admissions was 3 days. Therefore the total cost of hospital admission for patients with convulsions was RM 699 (Table 6).

Table 6. Mean Cost of Managing Convulsions per Case

Cost (RM)	Provider's Perspective		Patient's Perspective	
			Direct	Indirect
Cost of Hospital Admission	699.00		-	-
Parents/patient waiting time	-		14.04	-
Parents/patient travelling time	-		7.15	-
Others (diapers, milk powder etc)			74.73	
Parents absent from work	-		-	431.04
Total cost (RM)	1,225.96			

Determining the Cost of managing the wcPertussis Adverse Events per Case

Table 7 shows the unit cost of managing wcPertussis vaccine adverse events from the

patients 'and the providers' perspectives. The adverse events involved were mild and high fever and convulsions (Table 7, Table 8).

Table 7. Unit Cost of wcPertussis Adverse Events per Case

Type of AE	Providers' Perspective				Patients' Perspective			
	Direct (RM)	Cost	Indirect Cost (RM)	Direct (RM)	Cost	Indirect (RM)	Cost	Total cost per case (RM)
Mild fever	0.90			0.64		248.34		249.88
High fever	4.77			52.17		979.07		1,036.01
Convulsion	699.00			95.92		431.04		1,225.96

Table 8. Costs per Case of Adverse Events following wcPertussis Vaccination from Providers' and Patients' Perspectives

Cost per case of adverse events	Providers' Perspective				Patients' Perspective			
	RM	%	RM	%	RM	%	Total %	
Mild fever	0.90	0.36	0.64	0.26	248.34	99.38	100	
High fever	4.77	0.46	52.17	5.03	979.07	94.51	100	
Convulsion	699	57.02	95.92	7.82	431.04	35.16	100	

The cost of adverse events such as mild fever for wcPertussis, took into consideration the loss of productivity of both parents during the duration of five days and 99.3% of costs were derived from the indirect cost from the patients' perspective. For the adverse events of high fever, the majority of the indirect costs, 94.51% (Table 8), was borne from the patients'

perspective which was loss of productivity for parents whose children developed high fever because it was expected that both parents would not be fully productive when their child was taken ill.

Risks of wcPertussis Adverse Events

Data associated with the incidence of adverse events associated with wcPertussis containing vaccines (such as fever and convulsions) was not

available; therefore the risks of adverse events following immunization were obtained from published literature as shown in Table 9.

Table 9. Costs of wcPertussis Adverse Events per Dose

Type of vaccines	Type of adverse events	Total cost per case (RM)	Risk of adverse events after immunisation	Cost of adverse event per dose
			DPT-OPV	(RM)
wcPertussis				
	Mild fever	249.88	0.569 ¹	142.1817
	High fever	1,036.01	0.035 ¹	36.26
	Convulsion	1,225.96	0.0006 ²	0.74

Source : ¹Decker et al, Paediatrics, 1995

²WHO, Weekly Epidemiological Report, 2005

Total Cost of Managing wcPertussis Vaccine Adverse Events

The total cost of managing wcPertussis vaccine adverse events for four doses was calculated by

using a 95% coverage rate for the first three doses of DTwcPertussis given to the estimated live births for 2004 which was 514,178 and 73% coverage rate for the fourth dose (Table 10).

Table 10. Total Cost of Managing wcPertussis Adverse Events

	Type of adverse events	Cost adverse event per dose (RM)	Total Cost (RM)
wcP	Mild fever	142.1817	261,722,030.49
	High fever	36.26	66,746,501.79
	Convulsion	0.74	1,354,016.85

DISCUSSION

Cost of managing fever was divided into two components namely cost of managing mild fever and cost of managing high fever. Each of the components consisted of direct and indirect cost from the provider's and the patient's perspective. The mean cost of managing fever per case was RM249.88 while the total cost per case of managing fever was RM261 million. This means that for a child that was vaccinated with wcPertussis vaccine, and if the child develop fever the cost of managing the fever for each child is RM249.88 while taking the cohort of children in Malaysia as estimated live birth of

514,178 children in Malaysia for 2004, the cost of managing this number of children will be RM261 million.

Similarly with high fever, the mean cost of managing high fever per case was RM1,036.01 while the total cost per case of managing fever was RM66 million. This means that for a child that was vaccinated with wcPertussis vaccine, and if the child develop high fever the cost of managing the high fever for each child is RM1,036.01 while taking the cohort of children in Malaysia as estimated live birth of 514,178 children in Malaysia for 2004, the total cost of managing this number of children who developed

high fever post wcpertussis vaccine was about RM66 million.

Costs of managing convulsion were looked at from both the patients' and providers' perspective. Cost from the patients' perspective consisted of both direct and indirect cost. The direct cost from the patients' perspective included the travelling time and the waiting time for the admission of convulsion for parents who had recalled their waiting time and travelling time. The indirect cost from the patient's perspective, which was the loss of productivity, was derived from the duration of illness of the child during admission in which parents had to take leave in order to care for the child. The mean cost of managing convulsion per case was RM1225.96 while the total cost per case of managing convulsion was RM1.3 million. This means that for a child that was vaccinated with wcpertussis vaccine, and if the child develop convulsion the cost of managing the convulsion for each child is RM1225.96 and taking the cohort of children in Malaysia as estimated livebirth of 514,178 children in Malaysia for 2004, the total cost of managing this number of children who developed convulsion post wcpertussis vaccine will be RM1.3 million.

These findings provide an insight that although the cost of managing fever per case is only a small proportion to the cost of managing high fever and convulsions, if we calculate the total cost of managing these cases of managing fever to the total number of children and risk per dose, the amount of money needed is many times more than managing the total cases of convulsions and high fever.

LIMITATIONS

The study was conducted in a government health facility and not throughout the country. The risks of adverse events were obtained from published

REFERENCES

literature and thus might not reflect the true risk of occurrence.

CONCLUSION

It was found that although the mean cost of managing mild fever was RM249.88 per case, the risk of occurrence of fever was 1 in every 2 children (0.569) resulting in the total cost of managing mild fever due to wcpertussis vaccine to be at RM261 million. The mean cost managing high fever was RM1,036.01 per case and the mean cost of managing convulsions was RM1,225.90 but the total cost of managing high fever was RM66.7 million and managing convulsion was RM1.3 million respectively. Looking at the risks of adverse events, the total cost of managing the adverse events associated with wcpertussis, of mild fever was the highest at RM261 million as compared to RM66.7million (high fever) and RM1.3 million (convulsions). Therefore, although the mean cost of managing fever per case is less costly, the total cost of managing fever per case is very high. There is need to be an alternative of the possibility of a better vaccine with fewer risks of adverse events to reduce these total costs of managing the adverse events caused by wcpertussis.

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