

Economic Impact of Switching From Partially Combined Vaccine “Pentaxim ® and Hepatitis B” to Fully Combined Vaccine “Hexaxim ® ” in The Malaysian National Immunization Program

Syed Mohamed Aljunid (✉ saljunid@gmail.com)

Kuwait University

Lama Al Bashir

National University of Malaysia

Aniza Binti Ismail

University Kebangsaan Malaysia

Azimatun Noor Aizuddin

National University of Malaysia

S A Zafirah

National University of Malaysia

Amrizal Muhammad Nur

Kuwait University

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Abstract

Background: The decision to implement new vaccines should be supported by public health and economic evaluations. Therefore, this study was primarily designed to evaluate the economic impact of switching from partially combined vaccine (Pentaxim[®] plus hepatitis B) to fully combined vaccine (Hexaxim[®]) in the Malaysian National Immunization Program (NIP) and to investigate healthcare professionals (HCPs)' and parents/caregivers' perceptions.

Methods: In this economic evaluation study, 22 primary healthcare centers were randomly selected in Malaysia between December 2019 and July 2020. The baseline immunization schedule includes switching from Pentaxim[®] (four doses) and hepatitis B (three doses) to Hexaxim[®] (four doses), whereas alternative scheme includes switching from Pentaxim[®] (four doses) and hepatitis B (three doses) to Hexaxim[®] (four doses) and hepatitis B (one dose) administered at birth. Direct medical costs were extracted using a costing questionnaire and an observational time and motion chart. Direct non-medical (cost for transportation) and indirect costs (loss of productivity) were derived from parents/caregiver's questionnaire. The vaccine societal cost was calculated as cost per dose, per fully immunized child and per birth cohort, and then the net cost savings were calculated upon the total cost of Hexaxim[®] and Pentaxim[®] plus hepatitis B. Also, HCPs' and parents/caregiver's perceptions were investigated using structured questionnaires.

Results: The cost per dose of Pentaxim[®] plus hepatitis B vs. Hexaxim[®] was Malaysian ringgit (RM) 31.90 vs. 17.10 (direct medical cost), RM 54.40 vs. RM 27.20 (direct non-medical cost), RM 221.33 vs. RM 110.66 (indirect cost), and RM 307.63 vs. RM 155.00 (total cost). Similar trend was observed for alternative scheme. Compared with Pentaxim[®] plus hepatitis B, total cost savings per dose of Hexaxim[®] were RM 137.20 and RM 104.70 in the baseline and alternative scheme, respectively.

Conclusions: Incorporation of Hexaxim[®] within Malaysian NIP is highly recommended because the use of Hexaxim[®] has demonstrated substantial direct and indirect cost savings for healthcare providers and parents/caregivers with high percentage of positive perceptions, compared with Pentaxim[®] plus hepatitis B.

Trial registration: Not applicable

Background

Childhood vaccination programs have been a vital public health intervention that reduced the incidence of vaccine-preventable diseases by more than 95% for every pediatric vaccine recommended in the immunization schedules [1]. In Malaysia, the immunization schedule included administration of hepatitis B (Hep B) vaccine at birth, 1 and 6 months and of Pentaxim[®] (combination vaccines) at 2, 3, 5, and 18 months. Pentaxim[®] is a pentavalent vaccine that confers protection against the following five infectious diseases: diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenzae* type b (DTaP-IPV/Hib). It is administered as a pre-filled liquid syringe that contains DTaP-IPV and must be mixed or reconstituted with Hib vial (white lyophilized powder) immediately before injection. Nevertheless, even though the National Immunization Program (NIP) incorporates many combination vaccines, the immunization schedule is still somehow crowded and complex. This situation will worsen in the future as new diseases emerge and/or new

vaccines are developed [2]. Therefore, development of new combination vaccines that can simplify the vaccination schedule safely and efficiently is the unmet need [3]. A new, fully liquid, ready-to-use hexavalent DTaP-IPV-Hep B-Hib combination vaccine (Hexaxim®, Sanofi Pasteur) has been developed and administered at 2, 3, 5, and 18 months of age, with no reconstitution needed prior to administration [4]. Ready-to-use combination vaccines could reduce costs, simplify logistics and delivery infrastructure, and improve coverage with fewer injections [5]. Madhi et al. demonstrated that a fully liquid, hexavalent DTaP-IPV-Hep B-Hib vaccine (Hexaxim®) is highly immunogenic and safe in South African infants under the Expanded Programme on Immunisation [6]. In addition, similar safety profiles of Pentaxim® plus monovalent Hep B and Hexaxim® vaccine were found in Korean infants [7]. Mogale et al. recommended implementation of Hexaxim® within the South African Expanded Programme on Immunisation because it reduces healthcare providers' cost [5].

Based on the above-mentioned facts, Hexaxim® vaccine appears to be a better choice to replace Pentaxim® plus Hep B in the Malaysian NIP, especially within the context of growing financial burden on the Malaysian healthcare system. Since the decision to implement new vaccines should be supported by public health and economic evaluations that are becoming increasingly important for policymakers, this study was primarily designed to estimate the economic impact (direct medical costs, direct non-medical costs, and indirect costs) of using Hexaxim® vaccine compared with Pentaxim® plus Hep B vaccines in the Malaysian NIP and to investigate healthcare professionals (HCPs)' and parents/caregivers' perceptions.

Methods

Study Design and Participants

In this study, three types of study design namely economic evaluation, observational time & motion and cross-sectional study were employed to achieve the study objectives. A total of 22 primary healthcare centers (PHCs), which provide childhood vaccination services, were selected using stratified sampling method from the states of Selangor (18 PHCs) and the federal territory of Kuala Lumpur and Putrajaya state (4 PHCs). The study was conducted between December 2019 and July 2020. The following study participants were included in this study: (1) physicians and nurses who had at least 1 year of experience in the field of childhood vaccinations and were in charge of counseling or prescribing, administering and/or reconstituting Pentaxim® and Hep B injections, or supervising the vaccination process in PHCs and (2) parents (aged ≥ 18 years) of infants/toddlers who aged between 1 and 24 months.

The study was approved by the University Kebangsaan Malaysia ethics committee, Medical Research and Ethics Committee, Selangor and Federal Territory of Kuala Lumpur state health office, and Districts health department. The study was performed according to the local and national regulations. Also, it was consistent with the standards established by the Declaration of Helsinki and compliant with the International Council for Harmonization guidelines for Good Clinical Practice. An informed consent form was signed by each participant's parent(s) or legally acceptable representative(s) before enrollment into each study. If the parents were illiterate, an independent witness fully explained and signed the informed consent form. Also, informed consent form was signed by physicians and nurses (healthcare practitioners).

Outcome Measures and Data Collection

Economic evaluation:

The economic evaluation study was conducted using a costing questionnaire, time and motion chart, and parents/caregiver's questionnaire. The costing questionnaire had two versions: one directed to the PHCs (Supplementary Table 1) and the other to the district health office (Supplementary Table 2). The costing questionnaire was designed to extract raw data, transformed to vaccines' direct medical costs, from 22 PHCs and multiple district health offices, whereas time and motion chart (Supplementary Table 3) was designed to record the time spent by 46 nurses to accomplish tasks associated with vaccination process; this recorded time was used to calculate the cost of vaccine administration time. Parents/caregivers' questionnaire (Supplementary Table 4) was used to extract data that were used to calculate direct non-medical and indirect costs. Direct medical cost borne by the provider includes vaccine cost of consumables, hazardous waste disposal, vaccine wastage, cold chain storage, and vaccine administration time. On the other hand, the cost of the vaccine borne by the parents/caregivers includes the cost for transportation (direct non-medical cost) and loss of productivity (indirect cost). Economic evaluation was based upon two immunization schemes: (1) baseline scheme – the immunization schedule had a transition from four doses of Pentaxim® and three doses of Hep B to only four doses of Hexaxim® and (2) alternative scheme – it involves moving from Pentaxim® (four doses) and Hep B (three doses) to Hexaxim® (four doses) and one Hep B dose administered at birth.

Perceptions assessment:

This cross-sectional study of perceptions was conducted using a validated parents/caregivers' perceptions questionnaire (Supplementary Table 4) and healthcare practitioners' perceptions questionnaire (Supplementary Tables 5 and 6), where a five-point Likert scale (Strongly Disagree, Agree, Neutral, Disagree, and Strongly Disagree) was employed in the questionnaires [8, 9]. Reliability and validity of perceptions questionnaire were conducted based upon data extracted from the pilot study (Unpublished results). Reliability and validity of parents/caregivers' perceptions questionnaire were confirmed by the Cronbach's alpha of 0.91 and Kaiser–Meyer–Olkin's value of 0.88 ($p < 0.001$). The Cronbach's alpha for nurses' and physicians' perceptions questionnaire ranged from 0.87 to 0.92, and the validity was confirmed by Kaiser–Meyer–Olkin's value of 0.69 ($p < 0.001$) and 0.74 ($p < 0.001$) for nurses' and physicians' perceptions questionnaire, respectively.

The parents' questionnaire was distributed among 346 parents of vaccinated children, who were chosen by systematic random sampling and provided information about their sociodemographic characteristics and expressed their opinion and perceptions regarding the employment of Hexaxim® vaccine in the immunization schedule. Healthcare practitioners' questionnaire had two versions, one directed to nurses and the other toward physicians who are working in the maternal and child health (MCH) units in PHCs. Nurses' version was collected from 100 nurses, who provided information about their sociodemographic and clinical practice profile and conveyed their perceptions regarding Pentaxim® vaccine and about switching to fully combined vaccine. Moreover, 50 physicians participated in the physicians' perceptions questionnaire answered the questions regarding their perception of incorporating Hexaxim® vaccine in the NIP transparently and vividly.

Statistical Analyses

The costing method employed in the economic evaluation study was based upon the societal perspective that is the sum of costs paid by providers and parents/caregivers. The vaccine societal cost was calculated as cost per dose, per fully immunized child (FIC), and per birth cohort, and then the net cost savings were calculated for each. The costing analysis method of calculation and the specific formula and inputs for each cost component are summarized in Supplementary Table 7. Sensitivity analyses were conducted to investigate how sensitive the findings of an economic evaluation are to changes in the assumptions used in the study and to examine variations in the parameter estimates. Sensitivity analyses were calculated based on vaccine wastage rate (2.5% and 10%) and administration time as both are the key variables that affect the cost saving.

Data were analyzed using Excel Microsoft Office spreadsheet (version 2013) and SPSS (version 22) where descriptive tables with frequencies and percentages for all the categorical variables were generated. Mean and standard deviation were calculated for all continuous variables.

Results

Economic Evaluation

A summary of cost borne by providers (direct medical), parents (direct non-medical and indirect cost), and total vaccine cost by immunization schemes are shown in Tables 1, 2, and 3, respectively. In the baseline scheme, the cost per dose of partially combined vaccine vs. Hexaxim® was Malaysian Ringgit (RM) 31.90 vs. 17.10 (direct medical cost), RM 54.40 vs. RM 27.20 (direct non-medical cost), RM 221.33 vs. RM 110.66 (indirect cost), and RM 307.63 vs. RM 155.00 (total cost). Cost savings of Hexaxim® were RM 137.20 per dose, RM 458.00 per FIC, and RM 267,977,435 per birth cohort. In alternative scheme, cost per dose for both partially and fully vaccines were the same as in the baseline scheme since the additional vaccine effect was added to the cost per FIC. The cost per FIC of partially combined vaccine vs. Hexaxim® was RM 112.91 vs. 83.10 (direct medical cost), RM 190.40 vs. RM 136.00 (direct non-medical cost), and RM 774.64 vs. RM 553.31 (indirect cost). Cost savings per dose of Hexaxim® were RM 104.70 per dose, RM 305.50 per FIC, and RM 204,540,947 per birth cohort.

Table 1
Summary of cost borne by provider (direct medical) by immunization schemes.

Cost components	Cost (RM) per dose of vaccine					
	Baseline scheme ^a			Alternative scheme ^b		
	Pentaxim	Hepatitis B	Hexaxim®	Pentaxim	Hepatitis B	Hexaxim®
1.a Swabs	0.03583	0.03583	0.03583	0.03583	0.03583	0.03583
1.b Syringe	0.32579	0.32579	0.32579	0.32579	0.32579	0.32579
1.c Needles	0.18537	0.18537	0.18537	0.18537	0.18537	0.18537
1.d Safety box	0.00109	0.00073	0.00073	0.00109	0.00073	0.00073
2 Hazardous waste disposal	0.15000	0.10000	0.10000	0.15000	0.10000	0.10000
3 Vaccine wastage ^c	2.60450	0.21460	2.60450	2.60450	0.21460	2.60450
4.a Refrigerator	0.00212	0.00020	0.00016	0.00212	0.00020	0.00016
4.b Cold box	0.00056	0.00001	0.00001	0.00056	0.00001	0.00001
5 Administration time	13.91216	13.82024	13.81065	13.91216	13.82024	13.81065
Total per dose	17.21742	14.68276	17.06303	17.21742	14.68276	17.06303
Total per FIC	68.86968	44.04828	68.25211	68.86968	44.04827941	68.25211
Comparison of cost (RM)	Pentaxim® + Hepatitis B		Hexaxim®	Pentaxim® + Hepatitis B		Hexaxim®
Cost per dose	31.90		17.10	31.90		17.10
Cost per FIC	112.91		68.40	112.90		83.10
Cost saving per FIC	44.50			29.80		
Cost per birth cohort (2019) ^d	55,142,582		33,402,593	55,142,582		40,581,220

Abbreviations: FIC: Fully immunized child; RM, Malaysian ringgit.

^aBased on four doses of Hexaxim®.

^bPer four doses of Hexaxim® + 1 dose at birth for Hep B.

^cVaccine wastage rate: 5%, according to WHO for single dose vaccines.

^dBirth cohort (2019): 488,342 live birth according to the Department of Statistics, Malaysia.

Cost components	Cost (RM) per dose of vaccine					
	Baseline scheme ^a			Alternative scheme ^b		
	Pentaxim	Hepatitis B	Hexaxim®	Pentaxim	Hepatitis B	Hexaxim®
Cost savings per birth cohort	21,739,989			14,561,362		
Cost saving per dose	11.10			7.50		
Abbreviations: FIC: Fully immunized child; RM, Malaysian ringgit.						
^a Based on four doses of Hexaxim®.						
^b Per four doses of Hexaxim® + 1 dose at birth for Hep B.						
^c Vaccine wastage rate: 5%, according to WHO for single dose vaccines.						
^d Birth cohort (2019): 488,342 live birth according to the Department of Statistics, Malaysia.						

Table 2
Summary of cost borne by parents (direct non-medical and indirect cost) by immunization schemes

Comparison of cost saving (RM)	Perspective	Baseline scheme ^a		Alternative scheme ^b	
		Pentaxim® + Hepatitis B	Hexaxim®	Pentaxim® + Hepatitis B	Hexaxim®
Cost per dose	Transportation	54.40	27.20	54.40	27.20
	Loss of productivity	221.33	110.66	221.33	110.66
	Total	275.73	137.86	275.73	137.86
Cost per FIC	Transportation	190.40	108.80	190.40	136.00
	Loss of productivity	774.64	442.65	774.64	553.31
	Total	965.04	551.45	965.04	689.31
	Saving	413.60		275.73	
Cost per birth cohort (2019) ^c	Transportation	92,980,317	53,131,610	92,980,317	66,414,512
	Loss of productivity	378,288,574	171,899,835	378,288,574	214,874,794
	Total	471,268,891	225,031,445	471,268,891	281,289,306
	Saving	246,237,446		189,979,585	
Cost savings per dose of Hexaxim®		126.06		97.26	
Abbreviations: FIC, fully immunized child; RM, Malaysian ringgit.					
^a Based on four doses of Hexaxim®.					
^b Per four doses of Hexaxim® + one dose at birth for hepatitis B.					
^c Birth cohort (2019): 488,342 live birth according to the department of statistics Malaysia					

Table 3
Summary of total vaccine cost by immunization schemes

Comparison of cost saving (RM)	Cost perspective	Baseline scheme ^a		Alternative scheme 1 ^b	
		Pentaxim® + Hepatitis B	Hexaxim®	Pentaxim® + Hepatitis B	Hexaxim®
Cost per dose	Direct medical	31.90	17.10	31.90	17.10
	Direct non-medical	54.40	27.20	54.40	27.20
	Indirect	221.33	110.66	221.33	110.66
	Total	307.63	155.00	307.63	155.00
Cost per FIC	Direct medical	112.91	68.40	112.91	82.93
	Direct non-medical	190.40	108.80	190.40	136.00
	Indirect	774.64	442.65	774.64	553.31
	Total	1077.95	619.90	1077.95	772.40
	Saving	458.00		305.50	
Cost per birth cohort (2019) ^c	Direct medical	55,142,582	33,402,593	55,142,582	40,581,220
	Direct non-medical	92,980,317	53,131,610	92,980,317	66,414,512
	Indirect	378,288,574	171,899,835	378,288,574	214,874,794
	Total	526,411,473	258,434,038	526,411,473	321,870,526
	Saving	267,977,435		204,540,947	
Cost savings per dose of Hexaxim®		137.20		104.70	
Abbreviations: FIC: fully immunized child; RM, Malaysian ringgit.					
^a Based on four doses of Hexaxim®.					
^b Per four doses of Hexaxim® + 1 dose at birth for hepatitis B.					
^c Birth cohort (2019): 488,342 live birth according to the Department of Statistics, Malaysia.					

Figure 1 demonstrates the percentages of the different direct medical cost components to the total vaccine cost per dose. The major contribution in direct medical cost per dose for both vaccines was the cost of administration time, followed by the cost of vaccine wastage per dose. Sensitivity analysis results of direct medical cost by immunization schemes, which are consistent with the results of the primary analysis,

indicated that the direct medial cost savings per FIC and per birth cohort of Hexaxim® were higher as compared with Pentaxim® plus Hep B (Table 4). Overall, the use of Hexaxim® demonstrates direct and indirect cost savings as compared with Pentaxim® and Hep B, irrespective of implementing immunization schemes.

Table 4
Sensitivity analysis of direct medical cost by immunization schemes

Cost components	Cost (RM) per dose of vaccine					
	Baseline scheme ^a			Alternative scheme ^b		
	Pentaxim® + Hepatitis B	Hexaxim®		Pentaxim® + Hepatitis B	Hexaxim®	
Scenario 1^d						
Cost per dose	29.48	15.31		29.48	15.31	
Cost per FIC	103.84	61.25		103.84	75.35	
Cost per birth cohort (2019)	50,711,216	29,912,990		50,711,216	36,796,952	
Scenario 2^e						
Cost per dose	37.62	21.17		37.62	21.17	
Cost per FIC	134.29	84.70		134.29	100.90	
Cost per birth cohort (2019)	65,584,301	41,364,947		65,584,301	49,277,207	
Comparison of cost saving (RM)	Baseline scheme			Alternative scheme		
	Baseline case ^c	Scenario 1 ^d	Scenario 2 ^e	Baseline case ^c	Scenario 1 ^d	Scenario 2 ^e
Cost saving per FIC	44.7	42.59	49.60	29.98	28.49	33.39
Cost saving per birth cohort	21,812,210	20,798,226	24,219,354	14,642,002	13,914,263	16,307,093
Cost savings per dose of Hexaxim®	11.1	10.56	12.40	7.50	7.12	8.35
Abbreviations: FIC, fully immunized child; RM, Malaysian ringgit.						
^a Based on four doses of Hexaxim®.						
^b Per four doses of Hexaxim® + 1 dose at birth for hepatitis B.						
^c Baseline: Wastage Rate 5%, mean administration time.						
^d Scenario 1: Wastage rate 2.5%, minimum administration time (Pentaxim® + Hepatitis B: 98.2 minutes; Hexaxim®: 48.56 minutes).						
^e Scenario 2: Wastage rate 10%, maximum administration time (Pentaxim® + Hepatitis B: 112.23 minutes; Hexaxim®: 55.29 minutes)						

Perceptions Assessment

A summary of parents/caregivers' and HCPs' perceptions is presented in Table 5. A total of 346 parents/caregivers (mean age: 31.90 years [range: 19–59 years], 70.5% female) participated in the perception study. Majority of parents/caregivers had positive perceptions toward Hexaxim® vaccine, where 94.2% of them thought that Hexaxim® usage would reduce their child's pain and discomfort due to less injection administered compared with the current immunization schedule. In addition, 99.1%, 97.1%, and 95.6% of parents/caregivers agreed that Hexaxim® could reduce their visits to PHCs, decrease their transportation expenses to reach PHCs, and increase their compliance to the vaccination schedule, respectively. Moreover, 97.1% of parents/caregivers supported the idea of reviewing the current schedule and incorporating Hexaxim® in it. One hundred nurses completed the perceptions questionnaire, with the mean age of 34.85 years and mean experience of 8.39 years in childhood vaccination. In all, 70.0%, 78.0%, 79.0%, and 74.0% of nurses believed that Pentaxim® vaccine reconstitution is a time loss, requires too many steps compared with other vaccines, could lead to handling errors, and has a greater chance of needlestick injury, respectively. On the other side, 91.0% and 87.0% of nurses agreed that Hexaxim® usage could reduce their daily work burden and patient influx (arrival) to the PHCs, respectively. This could be the reason why 95.0% of nurses supported Hexaxim® employment in the NIP. A total of 50 physicians (mean age: 32.70 years and average experience in childhood vaccination: 4.47 years) participated in the study. In all, 80.0% of physicians thought that Hexaxim® replacement instead of Pentaxim® and Hep B could yield cost savings to the provider or government. In all, 60.0% of physicians believed that parents would support Hexaxim® incorporation, and 84.0% of physicians believed that Hexaxim® incorporation would increase their compliance. Also, 82.0% of physicians agreed that Hexaxim® could reduce the daily patient influx and crowdedness at PHCs. In addition, 82.0% of physicians also thought that Hexaxim® would ease the incorporation of pneumococcal conjugate vaccine into the immunization schedule. Lastly, 84.0% of physicians supported Hexaxim® employment in the Malaysian NIP.

Table 5
Summary of parents/caregivers' and healthcare professionals' perceptions

Perception item	Agree (%) (strongly agree or agree)	Neutral (%)	Disagree (%) (strongly disagree or disagree)
Parents/Caregivers' perception			
Hexaxim® Reduced Pain and Discomfort	94.20	5.20	0.60
Hexaxim® Reduce Number of Visits	99.10	0.90	0.00
Hexaxim® Reduce Transportation Expenses	97.10	2.90	0.00
Hexaxim® Increase Compliance	95.60	4.10	0.30
Current Immunization Schedule Should be Reviewed	97.10	2.30	0.60
Nurses' perceptions			
Pentaxim® Cause Time Lost	70.00	17.00	13.00
Pentaxim® Has Too Many Steps in Reconstitution.	78.00	11.00	11.00
Pentaxim® May Lead To Handling Errors	79.00	6.00	15.00
Pentaxim® May Cause More Needle Stick Injury	74.00	9.00	17.00
Hexaxim® Can Reduce Staff Work Load	91.00	7.00	2.00
Hexaxim® Can Reduce Patient Overcrowding in Clinics	87.00	9.00	4.00
Support Hexaxim® Employment	95.00	3.00	2.00
Physicians' perceptions			
Support Hexaxim® Employment	84.00	6.00	10.00
Parents Interested to Replace Pentaxim® with Hexaxim®	60.00	32.00	8.00
Hexaxim® Lead to Cost-Saving	80.00	20.00	0.00
Hexaxim® Can Reduce Patient Overcrowding in Clinics	82.00	10.00	8.00
Hexaxim® can ease Incorporation of other vaccines e.g. PCV	82.00	18.00	0.00
Hexaxim® may enhance compliance to Immunization Schedule	84.00	8.00	8.00

Discussion

To the best of our knowledge, this study is the first to evaluate the cost implications and HCPs/parents' perception of a switch from the current combination of Pentaxim® plus Hep B injections to a single Hexaxim® injection in the Malaysian NIP.

The economic evaluation results demonstrated that Hexaxim® had a lower cost per dose, per FIC, and per birth cohort (2019) and significant cost savings with regards to direct medical cost borne by HCP and direct non-medical cost (transportation) and indirect cost (loss of productivity) borne by parents/caregivers, compared with Pentaxim® plus Hep B. These results are supported by the results of a similar cost minimization study (from the public sector perspective only) conducted in South Africa in 2014 that also analyzed replacing Pentaxim® and Hep B vaccine with Hexaxim® vaccine [5]. The direct medical cost saving per dose of Hexaxim® for the present study was RM 11.10 (in baseline scheme) compared with RM 7.4 (29.4 African rand) in the South African study [5]. Moreover, based upon the costing profile generated in this study, it appeared that administration time was the cost component that contributed the most to the total direct cost per dose for Pentaxim® plus Hep B (86.9%) and Hexaxim® (80.9%). In contrast, Mogale et al. showed that cold chain storage was the major costing component for both partially and fully combined vaccines [5]. This inconsistency arose due to the different methods used to calculate the administration cost. To assess the cost of cold chain storage, Mogale et al. have used the capital costs, which means that the researcher calculated how much space each vaccine would occupy compared with the refrigerator cost or cost of appliance. This method yielded a higher cost because of the expensive purchase price of vaccines appliances. In the current study, cold chain storage cost calculation was based upon the recurrent cost of energy for each dose of the vaccine, which resulted in a relatively minor contribution in the cost per dose compared with the other cost components for partially (0.009%) and fully combined (0.0009%) vaccines.

In the present study, the majority of parents believed that using Hexaxim® vaccine could reduce their child's pain and discomfort compared with Pentaxim® plus Hep B. This was similar to a combination perception study conducted in the United States by Petraco and Judelsohn [10], where all parents wished that new childhood vaccinations would be available in a combination form, so that their infants do not have to get too many shots or injections to avert the extra pain they have to suffer. Per the Malaysian NIP, parents must make five vaccination visits during the first 6 months of their infants' life, which increases the direct non-medical cost (transportation) and indirect cost (loss of productivity). The parents who participated in this study "Agreed" unanimously that replacing Pentaxim® and Hep B with Hexaxim® could reduce the number of visits and, consequently, the transportation expenses. Based upon that, majority of parents in this study believed that Hexaxim® incorporation in the immunization schedule could lead to more vaccination compliance. According to Hull and McIntyre [11], vaccination delays increase with number of doses or visits, where the number of immunizations and the complexity of the schedule are the primary reasons for vaccine dose deferrals and non-compliance. Most of the parents in this study demanded an immunization schedule review if there is a new vaccine, such as Hexaxim®, that can simplify the schedule.

In the present study, more than three-quarter of nurses believe that Pentaxim® vaccine reconstitution is a time loss because it requires too many steps to prepare, whereas Hexaxim® vaccine usage could reduce the work burden as it does not need reconstitution like Pentaxim®, which can save nurses' time and efforts. Our finding is consistent with the result of a randomized, crossover, time and motion study conducted at Belgium

by De Coster et al. [12], which reported that preparation time for non-fully liquid vaccine (70.5 s) was double than that for fully liquid vaccines (36.0 s). Furthermore, Pellissier et al. stated that time saving due to fully liquid vaccine can allow more time for patient education over a broad range of healthcare issues and increases the quality of care that HCPs can offer [13]. Moreover, more than three-quarter of nurses in the current study believe that Pentaxim® reconstitution could lead to handling errors, which is consistent with the results of the time and motion study conducted by De Coster et al., where it was found that non-fully liquid vaccine reconstitution led to 24.48% of the immunization errors compared with 5.2% for the fully liquid vaccines [12]. In the present study, the majority of nurses supported Hexaxim® employment in the vaccination schedule, which is consistent with De Coster et al.'s study [12] in which 97.6% of HCPs participated in the study preferred the use of the fully liquid vaccine in their daily clinical practice.

In the present study, more than three-quarter of physicians believe that Hexaxim® incorporation in the Malaysian NIP can produce substantial cost savings for both healthcare providers and parents. This is supported by the high percentage of positive perceptions regarding Hexaxim® obtained from parents and healthcare providers. This high percentage of agreement is due to two reasons: (1) physicians are aware of the limited budget dedicated to the health sector and (2) all the physicians participated in the study are medical officers who often deal with the financial issues of the health center. In the present study, the physicians' perceptions analysis indicated that more than three-quarter of physicians' believe that Hexaxim® usage could increase the parents' compliance to the immunization program, which is a much higher percentage compared with the survey carried out in the United States in 2008 in which only 26.0% of physicians agreed that a combination vaccine would increase the parents' compliance [14]. This inconsistency is based upon the Malaysian physicians' previous experience with Pentaxim® vaccine where they noticed an increased parents' compliance to the NIP, compared with monovalent vaccines (Hep B or oral polio vaccine) used earlier. The current study finding is in line with the findings of Kalies et al. that the physicians' perceptions toward parents' better compliance if Hexaxim® is incorporated in the NIP [15]. Kalies et al. found that combination vaccines were shown to be associated with improved timeliness of vaccination, with the percentage of subjects completing the full immunization series in time increasing with the use of higher valence vaccines. As a result of their positive perception regarding Hexaxim®, more than three-quarter of physicians supported using Hexaxim® in the immunization schedule.

The followings are the limitation of this study: (1) data were collected only from the PHCs of the states of Selangor and the Federal Territory of Kuala Lumpur due to limited budget and short study duration; (2) due to accessibility issues, two PHCs were excluded from the study plan; and (3) systematic sampling of nurses for MCH that have more than five nurses was not employed appropriately in some health centers since some nurses were absent or transferred to other departments on the day of data collection, which forced the researchers to choose convenient sample.

Based upon the results of this study, the following are the proposed recommendations for the Ministry of Health (MOH): (1) Hexaxim® vaccine can be adopted by the MOH and replace Pentaxim® and Hep B starting with the next birth cohort; (2) an evaluation study should be conducted to explore the satisfaction level of parents, nurses, and physicians after Hexaxim® vaccine usage; (3) the immunization schedule can be modified to exclude extra routine visits that does not include vaccination based upon the desire of the

parents; (4) any current or future vaccines that need reconstitution can be replaced or not incorporated, since it can lead to handling errors or needlestick injury based upon nurses' perceptions.

Conclusion

The results of this study recommended incorporation of Hexaxim® within the Malaysian NIP because the use of Hexaxim® had a lower cost per dose and demonstrated substantial direct and indirect cost savings for healthcare providers and parents/caregivers, compared with Pentaxim® and hepatitis B. This is supported by the high percentage of positive perceptions regarding Hexaxim® obtained from parents and healthcare providers. In addition, Hexaxim® reduces clinic visits, handling errors, and number of injections, which translate to better acceptability, convenience, and increased compliance.

Abbreviations

DTaP: diphtheria, tetanus, and pertussis; FIC: fully immunized child; HCPs: healthcare professionals; Hib: *Haemophilus influenzae* type b; Hep B: hepatitis B; IPV: inactivated polio vaccine (poliomyelitis); MCH: maternal and child health; MOH: ministry of Health; NIP: national immunization program; PHCs: primary healthcare centers; RM: Malaysian Ringgit

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the University Kebangsaan Malaysia ethics committee, Medical Research and Ethics Committee, Selangor and Federal Territory of Kuala Lumpur state health office, and Districts health department. An informed consent form was signed by each participant's parent(s) or legally acceptable representative(s) before enrollment into each study. If the parents were illiterate, an independent witness fully explained and signed the informed consent form. Also, informed consent form was signed by physicians and nurses (healthcare practitioners).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

All author involved in these studies received grants from Sanofi-Aventis (Malaysia) Sdn Bhd through their respective institutions for the conduct of this study but did not receive any direct payment from Sanofi-

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Author's contribution

All authors were involved in the design of the study, data analysis and interpretation, and critical revision of the manuscript. All authors reviewed and approved the final draft of the manuscript.

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Figures

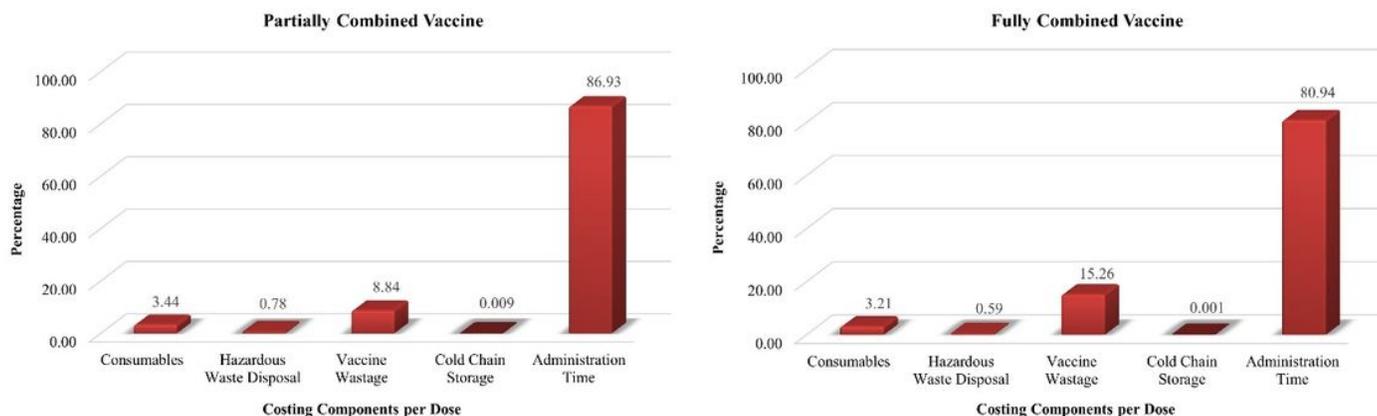


Figure 1

Direct medical cost profile. The relative contribution of cost components to the total cost per dose for partially combined vaccine (Pentaxim® + hepatitis B) vs. fully combined vaccine (Hexaxim®).

Supplementary Files

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